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Original Article

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Correction to: "Cardiovascular Outcomes Comparison of Dipeptidyl Peptidase-4 Inhibitors Versus Sulfonylurea as Add-on Therapy for Type 2 Diabetes Mellitus: A Meta-Analysis"

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The authors have no conflicts of interest to declare.

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ABSTRACT

Objective: Recent studies have raised concerns about the cardiovascular safety of dipeptidyl peptidase-4 (DPP4) inhibitors. We performed a systematic review and meta-analysis to compare the cardiovascular outcomes of sulfonylureas (SUs) versus DPP4 inhibitors in combination with metformin.
Methods: After searching for trials using combination therapy of metformin with an SU or DPP4 inhibitor in PubMed, Cochrane Library, and Embase, 1 prospective observational study and 15 randomized controlled studies were selected.
Results: Regarding the primary analysis endpoint, no significant differences were found in the risk of all-cause mortality between SUs and DPP4 inhibitors as add-on therapies to metformin (random-effect relative risk [RR], 1.14; 95% confidence interval [CI], 0.98–1.33; I^2=0%; p=0.097). Cardiovascular death was also similar between SUs and DPP4 inhibitors in the 5 studies that reported outcomes (random-effect RR, 1.03; 95% CI, 0.83–1.27; I^2=0%; p=0.817). Furthermore, there were no significant differences in major adverse cardiac events, coronary heart disease, myocardial infarction, and heart failure. However, the SU group showed a higher risk of ischemic stroke, more hypoglycemic events, and more weight gain than the DPP4 inhibitor group (ischemic stroke, random-effect RR, 2.78; 95% CI, 1.06–7.30; I^2=51.9%; p=0.039; hypoglycemia, random-effect RR, 3.79; 95% CI, 1.53–9.39; I^2=98.2; p=0.004; weight gain, weighted mean difference, 1.68; 95% CI, 1.07–2.29; I^2=94.7; p<0.001).
Conclusion: As add-on therapies to metformin, SUs and DPP4 inhibitors showed no significant differences in all-cause mortality and cardiovascular mortality. However, some of the favorable results of DPP4 inhibitors suggest good safety and feasibility of the drugs.

Keywords: Diabetes mellitus; Sulfonylurea compounds; DPP4 inhibitor; Cardiovascular risk

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Author Contributions

Conceptualization: Kang J, Park KW; Data curation: Jeon WK, Kang J; Formal analysis: Jeon WK; Methodology: Park KW; Supervision: Kim HS, Park KW; Validation: Kang J; Writing - original draft: Jeon WK, Kang J, Kim HS, Park KW; Writing - review & editing: Jeon WK, Kang J, Kim HS, Park KW.

INTRODUCTION

Guidelines recommend metformin and comprehensive lifestyle modifications as the first-line therapy in the treatment of type 2 diabetes mellitus (T2DM).[1-4] This recommendation is based on the benefits of metformin compared to other classes of oral hypoglycemic agents, such as sulfonylureas (SUs), thiazolidinediones, and dipeptidyl peptidase-4 (DPP4) inhibitors, with regard to its combined effects on hemoglobin A1c, weight gain, hypoglycemic side effects, socioeconomic burden, and long-term cardiovascular disease.[5]

In cases where the maximal dose of a single agent cannot maintain a hemoglobin A1c level below 6.5%, combination therapy is recommended.[6-8] Although the specific recommended agent differs according to baseline risk stratification, DPP4 inhibitors, SUs, thiazolidinediones, α-glucosidase inhibitors, and sodium-glucose cotransporter-2 inhibitors can be used as combination therapies with metformin.[9] When there is a compelling need to minimize hypoglycemia, DPP4 inhibitors can be considered. For patients whose major issue is cost, SUs or thiazolidinediones could be a good choice. For patients with atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease, treatment with glucagon-like peptide-1 (GLP1) receptor agonists or SGLT2 inhibitors as a combination therapy should be preferred according to the patient's individual status. In Korea, SUs and DPP4 inhibitors are the most commonly used drugs for add-on therapies to metformin.

DPP4 inhibitors act by decreasing the degradation of GLP1 and glucose-dependent insulinotropic peptide.[10] They have been shown to effectively control blood glucose levels and reduce hemoglobin A1c levels with minimal risk of hypoglycemia and good tolerability.[11,12] However, previous studies have reported concerns of increased risk of heart failure.[13,14] In contrast, SUs, which are insulin secretagogues, can effectively decrease blood glucose with neutral effects on the cardiovascular system, but hypoglycemia and weight gain are common side effects.[15,16] In this current study, we conducted a systematic review and meta-analysis to compare the cardiovascular risk of SUs with that of DPP4 inhibitors during combination therapy with metformin.

MATERIALS AND METHODS

1. Data sources and searches

We performed a systematic electronic search of MEDLINE, Cochrane Library, and Embase, with no language limits, using the following search terms: "diabetes mellitus," "sulfonylurea," "glimepiride," "glipizide," "gliclazide," "glibenclamide," "glyburide," "gliquidone," "dipeptidyl peptidase-4 inhibitor," "DPP4 inhibitor," "sitagliptin," "vildagliptin," "linagliptin," "saxagliptin," "alogliptin," and "dutogliptin."

2. Study selection

Two reviewers (W.K. Jeon and J. Kang) independently searched for articles with the following inclusion criteria: 1) both randomized control trials (RCTs) and non-randomized trials examining the efficacy of combination therapy of metformin with an SU compared to a DPP4 inhibitor, except case-control studies; 2) studies analyzing the cardiovascular risks of combination therapy, including cardiovascular death, myocardial ischemia, and heart failure; and 3) studies presenting the incidence rate of mortality or morbidities. Disagreements were resolved by discussion (**Supplementary Table 1**).

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3. Data extraction and quality assessment

Two reviewers independently extracted data from the included articles using a standardized form. Data from each reviewer were compared to examine internal consistency, and inconsistent data were corrected by discussion. The extracted data were all-cause mortality, cardiovascular death, ischemic stroke or transient ischemic attack, serious cardiovascular or cerebrovascular adverse events reported in the study, which were regarded as major adverse cardiac events (MACE), coronary heart disease, myocardial infarction, heart failure, hypoglycemic events, and weight change.

The quality of RCTs was assessed using the Cochrane Collaboration's Risk of Bias 2.0 tool. Random sequence generation, allocation concealment, blinding of participants, blinded outcome assessment, complete follow-up, and selective reporting were assessed. Non-randomized trials were assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

4. Data synthesis and analysis

Meta-analysis was performed based on the random-effect model. To qualitatively assess small study bias, funnel plots were constructed. As a quantitative assessment, the Egger linear regression method was used. If small-study bias was found, the trim-and-fill method was used. The Cochran Q via the chi-square test and the I^2 statistic were used to evaluate statistical heterogeneity. The *p*-values were two-tailed and statistical significance was considered when $p<0.05$. STATA/SE 12.0 (StataCorp LLC, College Station, TX, USA) was used for the statistical analysis.

RESULTS

1. Identification and selection of studies

Our first search yielded 4,753 studies from PubMed, Cochrane Library, and Embase (641, 388, and 3,724 studies, respectively). After removal of duplicated, irrelevant, or retrospective studies, as well as studies with a short follow-up duration (under 1 year), 15 studies were included in our current analysis. One was a prospective observational study and 14 were RCTs. The study selection process is summarized in **Fig. 1**.

2. Description of the included trials

The characteristics of the included studies are summarized in **Table 1**. Among the RCTs, 6 studies exclusively used glipizide as the SU, 6 used glimepiride, and 2 used gliclazide. For DPP4 inhibitors, 4 studies exclusively used vildagliptin, 3 used sitagliptin or linagliptin, and 2 used alogliptin or saxagliptin, respectively. The only non-randomized study permitted various SUs and DPP4 inhibitors. The duration of patient follow-up ranged from 52 weeks to over 312 weeks. All patients were diagnosed with T2DM, and 7 studies required a minimum dose of metformin of 1,500 mg before considering combination therapy.

The results of the Cochrane Collaboration's risk assessment are shown in **Table 2**. One prospective cohort study[17] was assessed by the STROBE checklist and scored 19.

3. Analysis endpoint outcomes

The primary analysis endpoint of the meta-analysis was all-cause mortality. All-cause mortality data were reported in 13 studies, while Rosenstock et al.[27] reported no mortality events during

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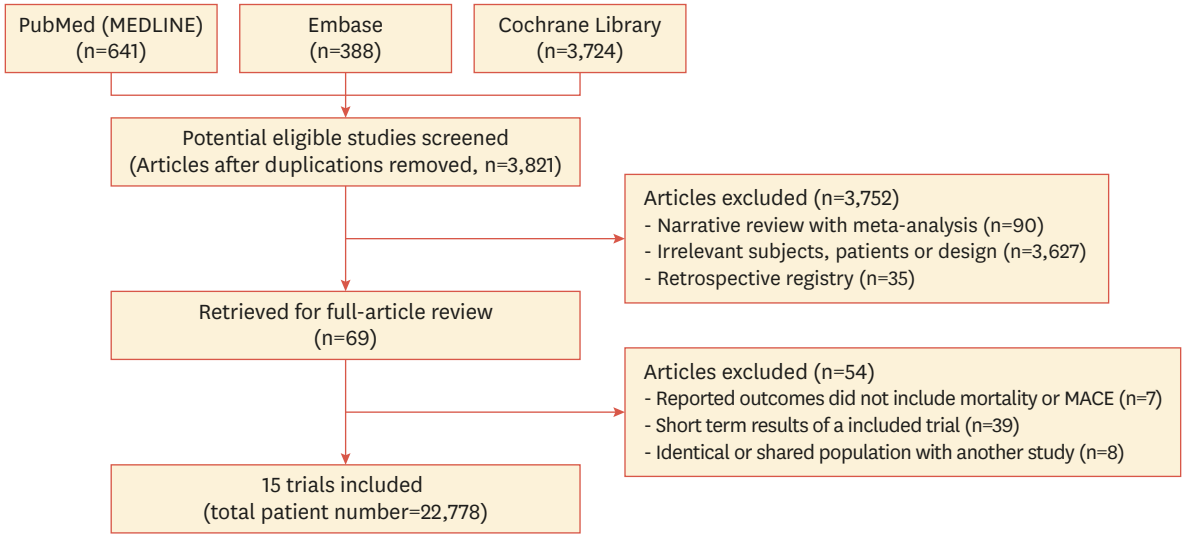

Fig. 1. Diagram of study selection.
MACE, major adverse cardiac events.

follow-up. There was no significant difference in all-cause mortality among the 13 studies comparing SUs and DPP4 inhibitors as add-on therapies to metformin (random-effect relative risk [RR], 1.14; 95% confidence interval [CI], 0.98–1.33; I^2=0%; p=0.098) (**Fig. 2**). Cardiovascular death also showed no significant difference in an analysis of 5 studies that reported cardiovascular death as an outcome (random-effect RR, 1.03; 95% CI, 0.83–1.27; I^2=0%; p=0.817) (**Fig. 2**).

Regarding morbidity events, SUs were associated with a higher risk of ischemic stroke or transient ischemic attack from an analysis of 6 studies that reported these outcomes (random-effect RR, 2.78; 95% CI, 1.06–7.30; I^2=51.9%; p=0.039) (**Fig. 3**). However, there were no significant differences in MACE (random-effect RR, 1.05; 95% CI, 0.91–1.23; I^2=0%; p=0.496), coronary heart disease (random-effect RR, 0.96; 95% CI, 0.79–1.17; I^2=0%; p=0.675), myocardial infarction (random-effect RR, 1.04; 95% CI, 0.83–1.29; I^2=0%; p=0.755), and heart failure (random-effect RR, 0.90; 95% CI, 0.73–1.12; I^2=0%; p=0.345) in an analysis of studies that reported these outcomes (**Fig. 3**).

Regarding the representative side effects of specific agents, SUs showed a significantly higher risk of hypoglycemic events, in an analysis of 12 studies that reported this outcome (random-effect RR, 3.79; 95% CI, 1.53–9.39; I^2=98.2%; p=0.004) (**Fig. 4**), and weight gain an in analysis of 8 studies that reported this outcome (weighted mean difference, 1.68; 95% CI, 1.07–2.29; I^2=94.7%; p<0.001) (**Fig. 4**).

4. Analysis of publication bias

The presence of small-study bias was analyzed for outcomes that were evaluated in more than 10 studies by funnel plot asymmetry and the Egger linear regression method. The analysis of all-cause mortality and hypoglycemia showed no publication bias (Egger test, p=0.238 and p=0.676, respectively). The funnel plot test of the primary analysis endpoint is presented in **Supplementary Fig. 1**.

https://doi.org/10.12997/jla.2022.11.1.89

Table 1. Characteristics of the included studies

Study	Type	SU dose	DPP4 inhibitor dose	Duration	Inclusion criteria	Primary outcome	Quality of evidence (grade)
Gitt et al.[17]	Prospective	Various	Various	52 weeks	· Aged ≥40 years · T2DM · Metformin monotherapy	Change in HbA1c from baseline	Low
Arjona Ferreira et al.[18]	RCT	Glipizide 10 mg bid	Sitagliptin 25 mg qd	54 weeks	· Aged ≥30 years · T2DM · ESRD with dialysis · HbA1c 7%–9%	Change in HbA1c from baseline	Moderate
Del Prato et al.[19]	RCT	Glipizide 20 mg qd	Alogliptin 12.5–25 mg qd	104 weeks	· Aged 18–80 years · T2DM · HbA1c 7%–9% · Metformin ≥1,500 mg	Change in HbA1c from baseline	High
Ferrannini et al.[20]	RCT	Glimepirid 6 mg qd	Vildagliptin 50 mg bid	52 weeks	· Aged 18–73 years · T2DM · HbA1c 6.5%–8.5% · Metformin ≥1,500 mg	Change in HbA1c from baseline	High
Filozof and Gautier[21]	RCT	Gliclazide 320 mg qd	Vildagliptin 50 mg bid	52 weeks	· Aged 18–78 years · T2DM · HbA1c 7.5%–11.0% · Metformin ≥1,500 mg	Change in HbA1c from baseline	High
Foley and Sreenan[22]	RCT	Gliclazide 320 mg qd	Vildagliptin 50 mg bid	104 weeks	· Aged ≥18 years T2DM · HbA1c 7.5%–11.0% · Drug naïve	Change in HbA1c from baseline	High
Gallwitz et al.[23]	RCT	Glimepiride 4 mg qd	Linagliptin 5 mg qd	104 weeks	· Aged 18–80 years · T2DM · HbA1c 6.5%–10.0% · Metformin ≥1,500 mg	Change in HbA1c from baseline	High
Göke et al.[24]	RCT	Glipizide 20 mg qd	Saxagliptin 5 mg qd	52 weeks	· Aged ≥18 years · T2DM · HbA1c 6.5%–10% · Metformin ≥1,500 mg	Change in HbA1c from baseline	High
Laakso et al.[25]	RCT	Glimepiride 4 mg qd	Linagliptin 5 mg qd	52 weeks	· Aged ≥18 years · T2DM · HbA1c 7.0%–10.0% · CKD	Change in HbA1c from baseline	High
Matthews et al.[26]	RCT	Glimepiride 6 mg qd	Vildagliptin 50 mg bid	104 weeks	· Aged 18–73 years · T2DM · HbA1c 6.5%–8.5% · Metformin ≥1,500 mg	Change in HbA1c from baseline	High
Rosenstock et al.[27]	RCT	Glipizide 10 mg qd	Alogliptin 25 mg qd	52 weeks	· Aged 65–90 years · T2DM · HbA1c 6.5%–9.0% without medication or HbA1c 6.5%–8.0% with monotherapy	Change in HbA1c from baseline	High
Schernthaner et al.[28]	RCT	Glimepiride 6 mg qd	Saxagliptin 5 mg qd	52 weeks	· Aged ≥65 years · T2DM · HbA1c 7.0%–9.0% · Metformin any dose	Change in HbA1c from baseline	High
Seck et al.[29]	RCT	Glipizide 20 mg qd	Sitagliptin 100 mg qd	104 weeks	· Aged 18–78 years · T2DM · HbA1c 6.5%–10.0% · Metformin ≥1,500 mg	Change in HbA1c from baseline	High
Arjona Ferreira et al.[30]	RCT	Glipizide 2.5–20 mg	Sitagliptin 25–50 mg qd	54 weeks	· Aged ≥30 years · T2DM · CKD · HbA1c 6.5%–9.0%	Change in HbA1c from baseline	Moderate
Rosenstock et al.[31]	RCT	Glimepiride 1–4 mg	Linagliptin 5 mg qd	Median 6.2 years	· Adults · T2DM · HbA1c 6.5%–8.5% · High CV risk	CV death Nonfatal MI and stroke	High

SU, sulfonylurea; DPP4, dipeptidyl peptidase-4; T2DM, type 2 diabetes mellitus; RCT, randomized controlled trial; bid, twice a day; qd, once a day; ESRD, end-stage renal disease; HbA1c, hemoglobin A1C; CKD, chronic kidney disease; CV, cardiovascular; MI, myocardial infarction.

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Table 2. Outcomes of the Cochrane risk of bias 2.0 tool

Study	1	2	3	4	5	Overall risk of bias
Arjona Ferreira et al.[18]	Low	Low	Low	Low	Low	Low
Del Prato et al.[19]	Low	Low	Some concerns	Low	Low	Some concerns
Ferrannini et al.[20]	Low	Low	Low	Low	Low	Low
Filozof and Gautier[21]	Low	Low	Low	Low	Low	Low
Foley and Sreenan[22]	Low	Low	Low	Low	Low	Low
Gallwitz et al.[23]	Low	Low	Low	Low	Low	Low
Göke et al.[24]	Low	Low	Some concerns	Low	Low	Some concerns
Laakso et al.[25]	Low	Low	Low	Low	Low	Low
Matthews et al.[26]	Low	Low	Low	Low	Low	Low
Rosenstock et al.[27]	Low	Low	Low	Low	Low	Low
Schernthaner et al.[28]	Low	Low	Low	Low	Low	Low
Seck et al.[29]	Low	Low	Some concerns	Low	Low	Some concerns
Arjona Ferreira et al.[30]	Low	Low	Low	Low	Low	Low
Rosenstock et al.[31]	Low	Low	Low	Low	Low	Low

1, bias due to randomization process; 2, bias due to deviations from the intended interventions; 3, bias due to missing outcome data; 4, bias in measurement of the outcome; 5, bias in selection of the reported result.

DISCUSSION

We conducted a systematic review and meta-analysis of 1 prospective study and 14 RCTs, including the CAROLINA trial, one of the most recent and largest studies with long-term follow-up.[31] These studies all compared the efficacy and safety of SUs and DPP4 inhibitors as add-on therapies to metformin in adults diagnosed with T2DM. In our analysis, we found no significant differences in all-cause mortality and cardiovascular mortality between SUs and DPP4 inhibitors. Morbidities like MACE, coronary heart disease, myocardial infarction, and heart failure also showed no significant differences. Only ischemic stroke or transient ischemic attack showed a significantly higher risk with SUs than with DPP4 inhibitors. Side effects also showed differences between the two drug classes. Specifically, SUs showed a significantly higher rate of hypoglycemic events and greater weight gain. These favorable results of DPP4 inhibitors regarding hypoglycemia and weight gain are consistent with previous reports.[32] Collectively, our data showed no differences between SUs and DPP4 inhibitors regarding most of the hard clinical endpoints—except for ischemic stroke, which favored DPP4 inhibitors—but regarding side effects, DPP4 inhibitors showed beneficial effects, suggesting the safety and good feasibility of DPP4 inhibitors when add-on therapy is needed on top of metformin.

Several placebo-controlled randomized studies have been reported using DPP4 inhibitors as add-on therapy to metformin.[14,33-37] Although the risk of hospitalization for heart failure was increased in the SAVOR-TIMI 53 trial,[14] most studies showed non-inferior cardiovascular outcomes of DPP4 inhibitors compared to placebo. There was no difference in hospitalization for heart failure in the CARMELINA[34] and TECOS trials[37].

Some researchers had concerns about the harmful effect of SUs on cardiovascular risk and mortality.[38,39] Because this concern was not always supported,[40] this controversial finding has been debated for a long time. Neuroprotective effects of DPP4 inhibitors were also seen in many preclinical and clinical studies. These studies proposed neuroprotective mechanisms of DPP4 inhibitors that included not only mediating factors such as glucagon-like peptide 1, brain-derived neurotrophic factor, stromal-derived factor 1, and vascular endothelial growth factor, but also direct neurogenesis.[41]

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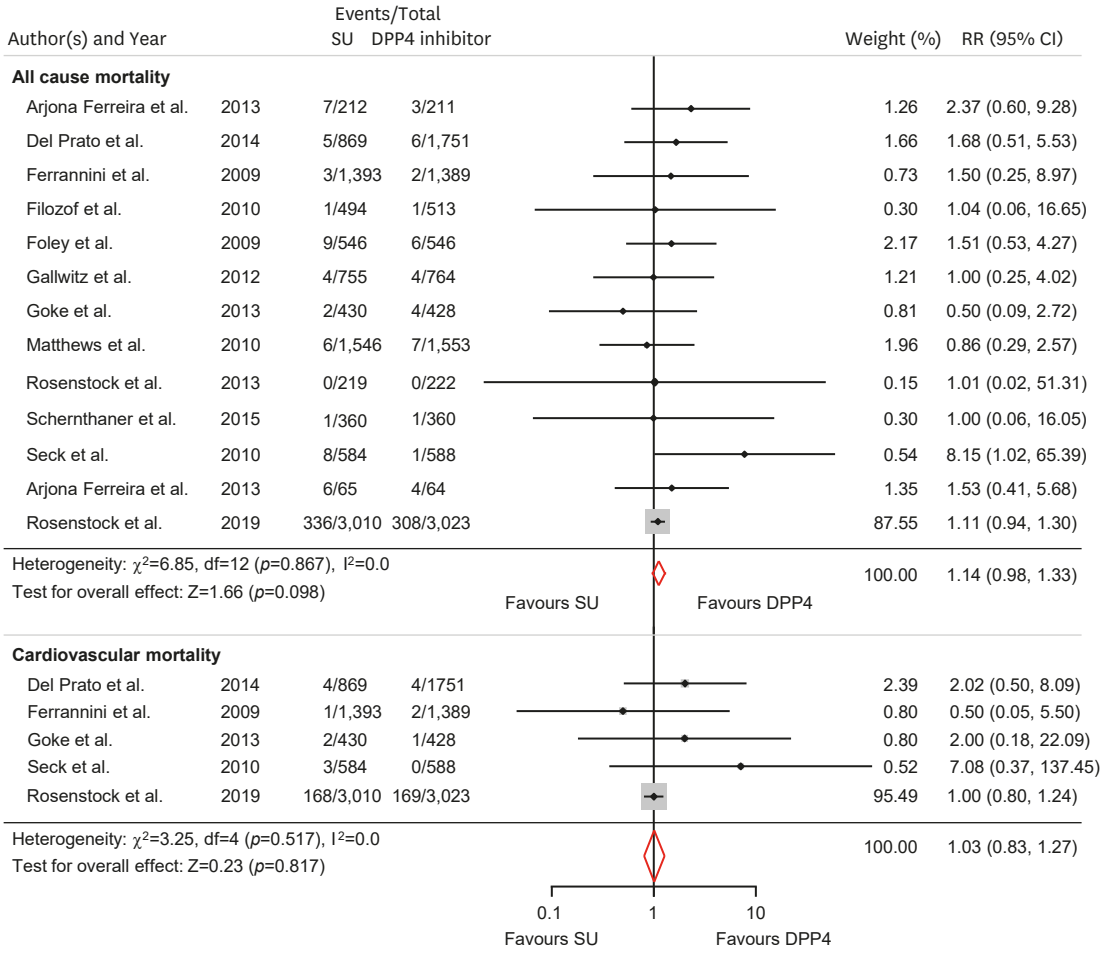

Fig. 2. Meta-analyses of all-cause mortality and cardiovascular mortality.
SU, sulfonylurea; DPP4, dipeptidyl peptidase-4; RR, relative risk; CI, confidence interval; df, degrees of freedom.

The results of head-to-head comparisons with SUs and DPP4 inhibitors in previous meta-analyses have not been consistent. Some studies have shown lower cardiovascular mortality with DPP4 inhibitors,[38,42] while others have shown no significant differences.[43,44] DPP4 inhibitors showed favorable trends regarding myocardial infarction in two previous meta-analyses,[38,45] but others reported negative findings.[43,44] Regarding MACE, 2 studies showed a lower risk with DPP4 inhibitors,[32,43] while another study showed no significant difference.[46] These inconsistent results could be explained by the different characteristics of included studies. In particular, meta-analyses of observational studies have a higher risk for potential bias than meta-analyses of only randomized trials. Some studies included in previous meta-analyses showed overly wide CIs, indicating lower reliability of the results.

There are several limitations of this study. First, this was a study-level meta-analysis, not a patient-level analysis, and thus we did not have individual patient data. Therefore, although we identified 15 studies, not all studies could be included in each analysis. Certain studies reported different combinations of the outcomes that we analyzed in the present study. Second, there were significant differences in the weight of the studies included. For example, our analysis heavily depended on the CAROLINA trial because it was the largest trial with the longest follow-up among the 15 studies. However, we performed a sensitivity

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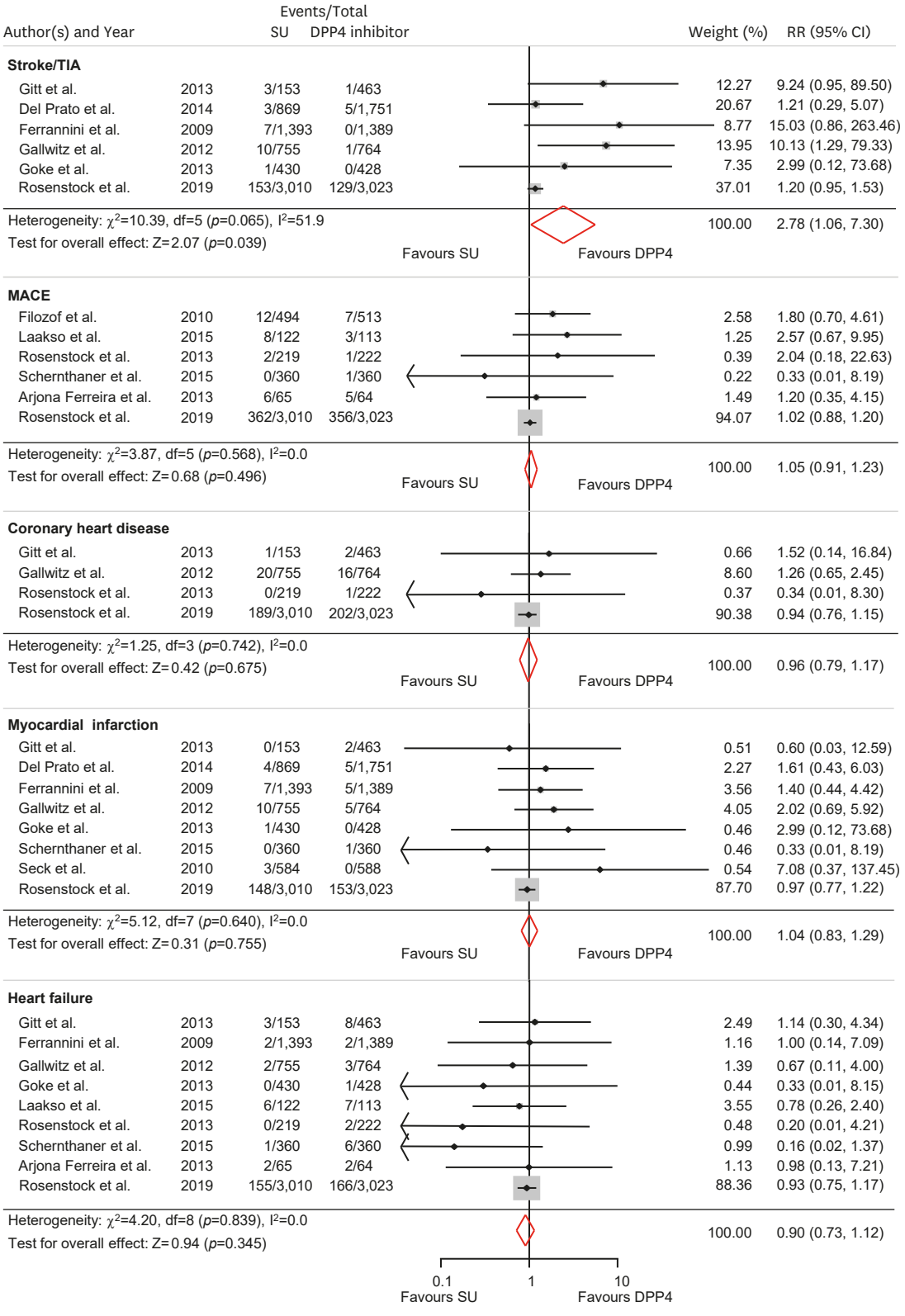

Fig. 3. Meta-analyses of various morbidities; ischemic stroke, MACE, coronary heart disease, myocardial infarction, and heart failure.
MACE, major adverse cardiac events; SU, sulfonylurea; DPP4, dipeptidyl peptidase-4; RR, relative risk; CI, confidence interval; df, degrees of freedom.

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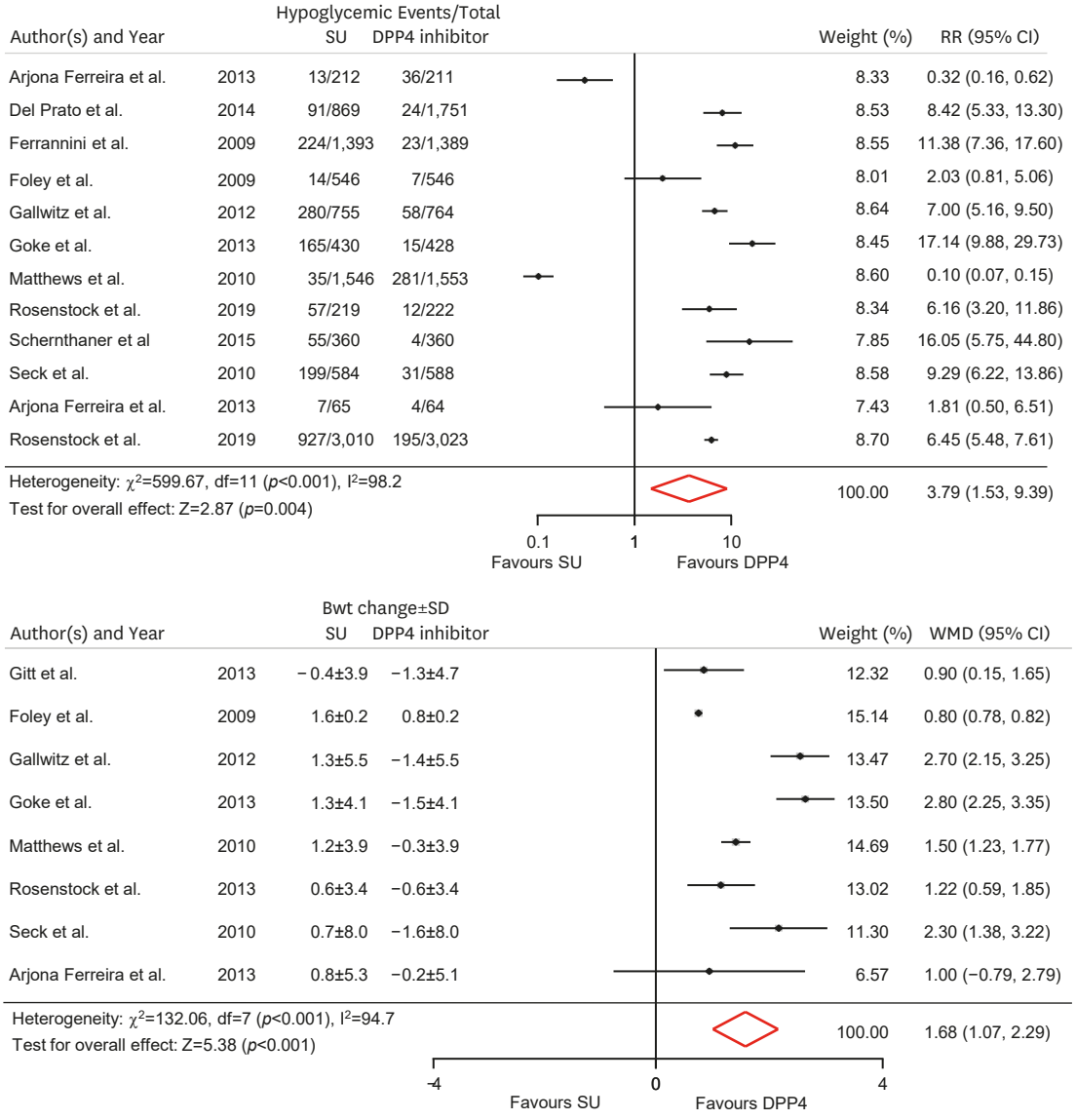

Fig. 4. Meta-analyses of hypoglycemia and weight gain.
SU, sulfonylurea; DPP4, dipeptidyl peptidase-4; RR, relative risk; CI, confidence interval; df, degrees of freedom; SD, standard deviation; WMD, weighted mean difference.

analysis excluding the CAROLINA study, and found consistent results across all studies' outcomes (**Supplementary Figs. 2-4**). Third, most of the RCTs were sponsored or funded by pharmaceutical companies. Fourth, we did not distinguish individual drugs within the same class or different drug doses. Therefore, we could not differentiate whether our findings reflected a class effect or the effect of a certain individual drug. Efficacy and safety can be different in individual drugs of the same class or between different doses of the same drug. Although linagliptin, alogliptin, and sitagliptin showed no significant differences in cardiovascular events or hospitalization for heart failure,[33-36] saxagliptin showed a higher risk of hospitalization for heart failure.[14] Finally, we did not consider other medications that might affect patients' cardiovascular status, such as antihypertensive drugs or statins.

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In conclusion, there were no significant differences in major cardiovascular outcomes except ischemic stroke between SUs and DPP4 inhibitors when used on top of metformin. DPP4 inhibitors showed slightly beneficial effects, such as a lower risk of ischemic stroke, lower rates of hypoglycemia, and less weight gain, suggesting good safety and feasibility of these drugs. DPP4 inhibitors can be a good option for add-on therapy to metformin in patients with T2DM. Nonetheless, regarding cardiovascular risk and cost-effectiveness, SUs can be a reasonable alternative.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
List of excluded studies

Click here to view

Supplementary Fig. 1
Funnel plots of all-cause mortality and hypoglycemia.

Click here to view

Supplementary Fig. 2
Meta-analyses of all-cause mortality and cardiovascular mortality after removal of the CAROLINA study.

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Supplementary Fig. 3
Meta-analyses of various morbidities after removal of the CAROLINA study; ischemic stroke, MACE, coronary heart disease, myocardial infarction, and heart failure.

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Supplementary Fig. 4
Meta-analyses of hypoglycemia after removal of the CAROLINA study.

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