Objective: Recent studies have raised concern about the cardiovascular safety of dipeptidyl peptidase-4 (DPP4) inhibitors. We performed a systematic review through meta-analysis to compare cardiovascular outcomes of sulfonylurea (SU) versus DPP4 inhibitors when used in combination with metformin.

Methods: After searching for trials using combination therapy of metformin with DPP4 inhibitor or SU in PubMed, Cochrane Library, and Embase, one prospective observation study and 15 randomized controlled studies were selected.

Results: Regarding the primary analysis endpoint, there were no significant differences in the risk of all-cause mortality between SU and DPP4 inhibitors as an add-on therapy to metformin (random-effect relative risk [RR], 1.14; 95% confidence interval [CI], 0.98–1.33; \(p=0.811; \text{I}^2=0\%\)). Cardiovascular death was also similar between the two drug classes in the five studies which reported outcomes (random-effect RR, 1.03; 95% CI, 0.83–1.27; \(p=0.517; \text{I}^2=0\%\)). Furthermore, there were no significant differences in major adverse cardiac events (MACE), coronary heart disease, myocardial infarction, ischemic stroke and heart failure. However, there were less hypoglycemic events and weight gain in the DPP4 inhibitor group as compared with the SU group (random-effect RR, 3.79; 95% CI, 1.53–9.39; \(p<0.001; \text{I}^2=98.2\) and weighted mean difference, 1.68; 95% CI, 1.07–2.29; \(p<0.001; \text{I}^2=94.7\), respectively).

Conclusion: As add-on therapy to metformin, there were no significant differences in all-cause mortality and cardiovascular mortality between DPP4 inhibitors and SUs.

Keywords: Diabetes mellitus; Sulfonylurea compounds; DPP4 inhibitor; Cardiovascular risk
In cases where the maximal dose of a single agent cannot maintain HbA1c below 6.5%, combination therapy is recommended. Although the recommended specific agent differs according to baseline risk stratification, DPP4 inhibitors, SUs, thiazolidinediones, α-glucosidase inhibitors, and sodium-glucose cotransport-2 (SGLT-2) inhibitors can be used as a combination therapy with metformin. When there is a compelling need to minimize hypoglycemia, DPP4 inhibitor 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 combination therapy should be preferred according to individual status. In Korea, DPP4 inhibitor and SU are the most commonly used drugs for add-on therapy with metformin.

DPP4 inhibitor acts by decreasing degradation of GLP1 and glucose-dependent insulinotropic peptide. It has been shown to effectively control blood glucose levels and lower level of HbA1C with minimal risk of hypoglycemia and good tolerability. However, previous studies have shown concerns of increased risk of heart failure. On the other hand, SU, a secretagogue of insulin, can effectively decrease blood glucose with neutral effects on the cardiovascular system, but hypoglycemia and weight gain are common side effects. In this current study, we conducted a systematic review through meta-analysis to compare the cardiovascular risk of DPP4 inhibitors with that of SUs during combination therapy with metformin.

**MATERIALS AND METHODS**

1. **Data sources and searches**
   We performed systemic electronic search of MEDLINE, Cochrane Library, and Embase, with no language limits, using search terms as following: “Diabetes mellitus,” “Sulfonylurea,” “glimepiride,” “Glipizide,” “gliclazide,” “glibenclamide,” “glyburide,” “glibuidone,” “Dipeptidyl peptidase-4 inhibitor,” “DPP4 inhibitor,” “Sitagliptin,” “Vildagliptin,” “Linagliptin,” “Saxagliptin,” “Alogliptin,” and “Dutaglitiptin.”

2. **Study selection**
   Two reviewers (W.K. Jeon and J. Kang) independently searched the articles with the following inclusion criteria: 1) Both randomized control trials (RCTs) and non-randomized trials examining efficacy of combination therapy of metformin with DPP4 inhibitor compared to SU were searched, except case-control studies; 2) The study should analyze cardiovascular risks of combination therapy, including cardiovascular death, myocardial ischemia, and heart failure; and 3) Each study should propose incidence rate of mortality or morbidities. Disagreed articles were resolved by discussion (**Supplementary Table 1**).

3. **Data extraction and quality assessment**
   Two reviewers independently extracted data from the included articles using a standardized form. By comparing data from each reviewer, internal consistency was examined and inconsistent data was corrected by discussion. Extracted data was all-cause mortality, cardiovascular death, ischemic stroke or transient ischemic attack, serious cardiovascular or cerebrovascular adverse event reported in the study which was regarded as major adverse cardiac events (MACE), coronary heart disease, myocardial infarction, heart failure, hypoglycemic event and weight change.
In case of RCTs, quality was assessed by using the Cochrane Collaboration’s tool for assessing the risk of bias 2.0 for RCTs. Random sequence generation, allocation concealment, blinding of participants, blinded outcome assessment, complete follow-up, and selective reporting were assessed. In case of non-randomized trials, the Strengthening The Reporting of Observational studies in Epidemiology (STROBE) checklist was used.

4. Data synthesis and analysis
Meta-analysis was performed based on the random-effect model. To qualitatively assess for small study bias, funnel plots were constructed. To quantitatively assess, Egger’s linear regression method was used. If small study bias was found, the trim and fill method was used. Cochran’s Q via a $\chi^2$ test and $I^2$ statistics 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 LP, College Station, TX, USA) were used in statistical analysis.

RESULTS

1. Identification and selection of studies
Our first search yielded 4753 studies from PubMed, Cochrane Library, and Embase (641, 388, and 3,724 studies respectively). After removal of duplicated, irrelevant, or retrospective studies, and short follow-up duration under 1 year, 15 studies were included in our current analysis. Among the studies, one was a prospective observational study and 14 were RCTs. The study selection process is summarized in Fig. 1.

2. Description of included trials
The characteristics of 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...
### Table 1. Characteristics of included studies

| Study                  | Type       | SU dose        | DPP4 inhibitor dose | Duration | Inclusion criteria                                                                 | Primary outcome                               | Quality of evidence |
|------------------------|------------|----------------|--------------------|----------|-----------------------------------------------------------------------------------|-----------------------------------------------|---------------------|
| 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        | Glimepiride 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 et al.\(^{21}\)  | 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 et al.\(^{22}\)   | 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                |
| Baptist Galhwitz 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                |
| Burkhard Goke et al.\(^{24}\) | RCT        | Glipizide 20 mg qd | Saxagliptin 5 mg qd | 52 weeks | Aged ≥18 years T2DM HbA1c 6.5%–10.0% Metformin ≥1,500 mg                          | Change in HbA1c from baseline                | High                |
| Markku 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                                          | Change in HbA1c from baseline                | 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.
alogliptin or saxagliptin, respectively. The only non-randomized study permitted various SUs and DPP4 inhibitors. Duration of patient follow-up ranged from 52 weeks to over 312 weeks. All patients were diagnosed as T2DM and seven studies required a minimum dose of metformin to be 1,500 mg before considering combination therapy.

The result of Cochrane collaboration’s risk assessment is shown in Table 2. One prospective cohort study 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 was achieved from 13 studies while Rosenstock et al. reported no mortality events during follow-up and thus was excluded in the analysis. There was no significant difference in all-cause mortality among 12 studies comparing SU and DPP4 inhibitor as an add-on therapy to metformin (random-effect relative risk [RR], 1.14; 95% confidence interval [CI], 0.98–1.33; \( p=0.811; I^2=0\% \)) (Fig. 2). Cardiovascular death also showed no significant difference in an analysis of 5 studies which reported cardiovascular death as one of the outcomes (random-effect RR, 1.03; 95% CI, 0.83–1.27; \( p=0.517; I^2=0\% \)) (Fig. 2).

Regarding morbidity events, DPP4 inhibitors were associated with a higher risk of ischemic stroke or transient ischemic attack from an analysis of six studies which reported such outcomes (random-effect RR, 2.78; 95% CI, 1.06–7.30; \( p=0.065; I^2=51.9\% \)) (Fig. 3). However, there was no significant difference in MACE (random-effect RR, 1.05; 95% CI, 0.91–1.23; \( p=0.568; I^2=0\% \)), coronary heart disease (random-effect RR, 0.96; 95% CI, 0.79–1.17; \( p=0.742; I^2=0\% \)), myocardial infarction (random-effect RR, 1.04; 95% CI, 0.83–1.29; \( p=0.640; I^2=0\% \)) and heart failure (random-effect RR, 0.90; 95% CI, 0.73–1.12; \( p=0.839; I^2=0\% \)) in analysis of studies which reported outcomes (Fig. 3).

Regarding the representative side effects of specific agents, DPP4 inhibitors showed significantly lower risk of hypoglycemic events in analysis of twelve studies which reported such outcomes (random-effect RR, 3.79; 95% CI, 1.53–9.39; \( p=0.001; I^2=98.2\% \)) (Fig. 4) and weight gain in analysis of eight studies which reported such outcomes (weight mean difference, 1.68; 95% CI, 1.07–2.29; \( p<0.001; I^2=94.7\% \)) (Fig. 4).

Table 2. Cochrane risk of bias tools 2.0

| 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 et al.21           | Low| Low| Low          | Low| Low          | Low                  |
| Foley et al.22             | Low| Low| Low          | Low| Low          | Low                  |
| Baptist Galhwitz et al.23  | Low| Low| Low          | Low| Low          | Low                  |
| Burkhard Goke et al.24     | Low| Low| Some concerns| Low| Low          | Some concerns        |
| Markku Laakso et al.25     | Low| Low| Low          | Low| Low          | Low                  |
| Matthews et al.24          | 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.
4. Analysis of small study bias

The presence of small study bias was assessed and confirmed by funnel plot asymmetry and Egger’s linear regression method. The funnel plot test of primary analysis end point was presented in Supplementary Fig. 1. The only found small study bias in the analysis was ischemic stroke (bias coefficient=1.387; SE=0.444; t=3.12; p=0.036; 95% CI, 0.153–2.621).

After adjustment through the trim and fill method, there was no significant difference in ischemic stroke between SU and DPP4 inhibitor (random-effect RR, 1.28; 95% CI, 0.50–3.29; p=0.612) (Fig. 3).

**DISCUSSION**

We conducted systematic review of one prospective study and 14 RCTs including the CAROLINA trial, one of the most recent and largest studies with long-term follow-up. All of the studies compared the efficacy and safety of add-on therapy on top of metformin between DPP4 inhibitors and SUs for adults diagnosed with T2DM. In our analysis, we found no significant differences in all-cause mortality and cardiovascular mortality between DPP4 inhibitor and SU. Morbidities like MACE, coronary heart disease, myocardial infarction, ischemic stroke and heart failure also showed no significant differences. There was a slight difference in ischemic stroke, but after correction for small study bias, the difference was not significant. There were some endpoints that did show differences between the two drug classes. One was the rate of hypoglycemic event, which was significantly lower with DPP4 inhibitors, and the other was weight gain, which was significantly lower with DPP4 inhibitors. Such favorable results regarding hypoglycemia and weight gain are consistent with
DPP4 Inhibitors vs. Sulfonylurea: a Meta-Analysis

### Stroke/TIA

| Author               | Year | Events/total SU | DPP4 inhibitor | Weight (%) | RR (95% CI) |
|----------------------|------|-----------------|----------------|------------|-------------|
| Gitt et al.          | 2013 | 3/153           | 1/463          | 12.27      | 9.24 (0.95–89.50) |
| Del Prato et al.     | 2014 | 3/869           | 5/1,753        | 20.67      | 1.21 (0.29–5.07)  |
| Ferrannini et al.    | 2009 | 7/1,393         | 0/1,389        | 8.77       | 15.03 (0.86–263.46) |
| Baptist Galhwitz et al. | 2012 | 10/755         | 1/764          | 13.95      | 10.13 (1.29–79.33) |
| Burkhard Goke et al. | 2013 | 1/430           | 0/428          | 7.35       | 2.99 (0.12–73.68)  |
| Rosenstock et al.    | 2019 | 153/3,010       | 129/3,023      | 37.01      | 1.20 (0.95–1.53)   |

After adjustment for small study bias

- Heterogeneity: $\chi^2=10.39$, df=5 ($p=0.065$); $I^2=51.9$
- Test for overall effect: $Z=2.07$ ($p=0.039$)

### MACE

| Author               | Year | Events/total SU | DPP4 inhibitor | Weight (%) | RR (95% CI) |
|----------------------|------|-----------------|----------------|------------|-------------|
| Filozof et al.       | 2010 | 12/494          | 7/513          | 2.58       | 1.80 (0.70–4.61) |
| Markku Laakso et al. | 2015 | 8/122           | 3/113          | 1.25       | 2.57 (0.67–9.95)  |
| Rosenstock et al.    | 2013 | 2/219           | 1/222          | 0.39       | 2.04 (0.18–22.63) |
| Schernthaner et al.  | 2015 | 0/360           | 1/360          | 0.22       | 0.33 (0.01–8.19)  |
| Arjona Ferreira et al. | 2013 | 6/65            | 5/64           | 1.49       | 1.20 (0.35–4.15)  |
| Rosenstock et al.    | 2019 | 362/3,010       | 356/3,023      | 94.07      | 1.02 (0.88–1.20)  |

Heterogeneity: $\chi^2=3.87$, df=5 ($p=0.568$); $I^2=0.0$
- Test for overall effect: $Z=0.68$ ($p=0.496$)

### Coronary heart disease

| Author               | Year | Events/total SU | DPP4 inhibitor | Weight (%) | RR (95% CI) |
|----------------------|------|-----------------|----------------|------------|-------------|
| Gitt et al.          | 2013 | 1/153           | 2/463          | 0.66       | 1.52 (0.14–16.84) |
| Baptist Galhwitz et al. | 2012 | 20/755         | 16/764         | 8.60       | 1.26 (0.65–2.45)  |
| Rosenstock et al.    | 2013 | 0/219           | 1/222          | 0.37       | 0.34 (0.01–8.30)  |
| Rosenstock et al.    | 2019 | 189/3,010       | 202/3,023      | 90.38      | 0.94 (0.76–1.15)  |

Heterogeneity: $\chi^2=1.25$, df=3 ($p=0.742$); $I^2=0.0$
- Test for overall effect: $Z=0.42$ ($p=0.675$)

### Myocardial infarction

| Author               | Year | Events/total SU | DPP4 inhibitor | Weight (%) | RR (95% CI) |
|----------------------|------|-----------------|----------------|------------|-------------|
| Gitt et al.          | 2013 | 0/153           | 2/463          | 0.51       | 0.60 (0.03–12.59) |
| Del Prato et al.     | 2014 | 4/869           | 5/1,753        | 2.27       | 1.63 (0.43–6.03)  |
| Ferrannini et al.    | 2009 | 7/1,393         | 5/1,389        | 3.56       | 1.40 (0.44–4.42)  |
| Baptist Galhwitz et al. | 2012 | 10/755         | 5/764          | 4.05       | 2.02 (0.69–5.92)  |
| Burkhard Goke et al. | 2013 | 1/430           | 0/428          | 0.46       | 2.99 (0.12–73.68) |
| Schernthaner et al.  | 2015 | 0/360           | 1/360          | 0.46       | 0.33 (0.01–8.19)  |
| Seck et al.          | 2010 | 3/584           | 0/588          | 0.54       | 7.08 (0.37–137.45) |
| Rosenstock et al.    | 2011 | 148/3,010       | 153/3,023      | 87.70      | 0.97 (0.77–1.22)  |

Heterogeneity: $\chi^2=5.12$, df=7 ($p=0.640$); $I^2=0.0$
- Test for overall effect: $Z=0.51$ ($p=0.755$)

### Heart failure

| Author               | Year | Events/total SU | DPP4 inhibitor | Weight (%) | RR (95% CI) |
|----------------------|------|-----------------|----------------|------------|-------------|
| Gitt et al.          | 2013 | 3/153           | 8/463          | 2.49       | 1.14 (0.30–4.34) |
| Ferrannini et al.    | 2009 | 2/1,393         | 2/1,389        | 1.16       | 1.00 (0.14–7.09) |
| Baptist Galhwitz et al. | 2012 | 2/755          | 3/764          | 1.39       | 0.67 (0.11–4.00) |
| Burkhard Goke et al. | 2013 | 0/430           | 1/428          | 0.44       | 0.33 (0.01–8.15)  |
| Markku Laakso et al. | 2015 | 6/122           | 7/113          | 3.55       | 0.78 (0.26–2.40)  |
| Rosenstock et al.    | 2013 | 0/219           | 2/222          | 0.48       | 0.20 (0.07–4.21)  |
| Schernthaner et al.  | 2015 | 1/360           | 0/360          | 0.99       | 0.16 (0.02–1.37)  |
| Arjona Ferreira et al. | 2013 | 2/65            | 2/64           | 1.13       | 0.98 (0.13–7.21)  |
| Rosenstock et al.    | 2019 | 155/3,010       | 166/3,023      | 88.36      | 0.93 (0.75–1.17)  |

Heterogeneity: $\chi^2=4.20$, df=8 ($p=0.639$); $I^2=0.0$
- Test for overall effect: $Z=0.94$ ($p=0.345$)

#### Heart failure

Fig. 3. Meta-analyses for 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.
Collectively, our data showed no differences between DPP4 inhibitors and SUs regarding hard clinical endpoints, but regarding side effects, DPP4 inhibitors showed beneficial effect, suggesting the safety and good feasibility of DPP4 inhibitors when add-on therapy is needed on top of metformin.

Several previous placebo-controlled randomized studies have been reported using DPP4 inhibitors as add-on therapy to metformin. Although the risk of hospitalization for heart failure was increased in the SAVOR-TIMI 53 trial, 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 and TECOS trials.

Some researchers had concern about the harmful effect of SU on cardiovascular risk and mortality. Because this concern was not supported always, this controversial finding had been debated for a long time.

The results of head-to-head comparisons with DPP4 inhibitor and SU in previous meta-analyses have not been consistent. Some studies showed lower cardiovascular mortality with DPP4 inhibitors, while others showed no significant differences. DPP4 inhibitors
showed favorable trend regarding myocardial infarction in two previous meta-analyses,\textsuperscript{38,44} but others reported negative findings.\textsuperscript{42,43} Regarding MACE, 2 studies showed lower risk with DPP4 inhibitors,\textsuperscript{32,42} while one other study showed no significant difference.\textsuperscript{45} These inconsistent results could be explained by different character of included studies. There is more possibility that studies which are including observational studies have potential bias, than the studies which analyzed only randomized trials. Some studies analyzed in previous meta-analysis showed too much wide CI, which lower reliability of the results. Moreover, most of the studies included in previous meta-analyses were designed to analyze the effect of treatment, not mortality or MACE.

There are several limitations in this study. First, our meta-analysis was not a patient-level but rather a study-level meta-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 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 study among the 15 studies. However, we performed a sensitivity analysis excluding the CAROLINA study, and found consistent results across all studies outcomes except for ischemic stroke (Supplementary Figs. 2-4). Third, Most of RCTs were sponsored or funded by pharmaceutical company. Fourth, we did not distinguish each individual drugs within the same class or the different drug doses. Therefore, we could not differentiate whether our findings are a class effect or an effect of a certain individual drug. Efficacy and safety can be different in each individual drugs of same class or by doses of same drugs. Although linagliptin, alogliptin, and sitagliptin showed no significant difference in cardiovascular event or hospitalization for heart failure,\textsuperscript{31-36} saxagliptin showed increased hospitalization for heart failure.\textsuperscript{14} Finally, we did not consider other medications which might affect patient’s cardiovascular status, like antihypertensive drugs or statins.

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

**SUPPLEMENTARY MATERIALS**

**Supplementary Table 1**
List of excluded studies

Click here to view

**Supplementary Fig. 1**
The Funnel plot test of all-cause mortality.

Click here to view
Supplementary Fig. 2
Meta-analyses for all-cause mortality and cardiovascular mortality after removal of CAROLINA study.

Click here to view

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

Click here to view

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

Click here to view

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