Combination therapy of metformin plus dipeptidyl peptidase-4 inhibitor versus metformin plus sulfonylurea and their association with a decreased risk of cardiovascular disease in type 2 diabetes mellitus patients

Fei Wang, MD[a], Yuan He, MD[b], Rong Zhang, MD[a], Qiang Zeng, MD[a,*], Xiaolan Zhao, MD[c,*]

Abstract

Background: Clinical trials assessing the combination therapy of metformin plus dipeptidyl peptidase-4 inhibitors versus metformin plus Sulfonylureas on risk of cardiovascular disease, cardiovascular mortality and/or all-cause mortality in type 2 diabetes have shown conflicting results. We therefore evaluated the combination therapy on the risk of cardiovascular disease, cardiovascular mortality and/or all-cause mortality in type 2 diabetes.

Methods: A systematic search of Medline/PubMed (from 2000 to September 2015), EMBASE (from 2000 to September 2015), and Web of Knowledge (from 2000 to September 2015) for research articles published in English was carried out to examine how combination therapy affects the risk of CVD mortality and/or all-cause mortality in T2DM patients. In addition, the risks of cardiovascular events, CVD mortality, and/or all-cause mortality as well as the adjusted relative risk (RR) or equivalent (hazard ratio or odds ratio) and the corresponding variance or equivalent are reported.

Results: The accumulative RRs (95% confidence intervals) for T2DM patients treated with the combination therapy of metformin plus DPP-4 inhibitor versus metformin plus sulfonylurea were 0.71 (0.56–0.90) for nonfatal cardiovascular events, 1.001 (0.85–1.18) for fatal cardiovascular events, 0.58 (0.41–0.82) for CVD mortality, and 0.72 (0.59–0.87) for all-cause mortality.

Conclusions: The combination therapy of metformin plus DPP-4 inhibitor significantly decreased the RR of nonfatal cardiovascular events, CVD mortality, and all-cause mortality, compared with the combination therapy of metformin plus sulfonylurea. However, the number fatal cardiovascular events (e.g., heart failure) was not significantly different between the 2 groups.

Abbreviations: CI = confidence interval, CVD = cardiovascular disease, DPP-4 = dipeptidyl peptidase-4, MET = metformin, NICE = National Institute for Health and Care Excellence, RCT = randomised controlled trial, RR = relative risk, SU = sulfonylureas, T2DM = type 2 diabetes mellitus.

Keywords: adjusted relative risk, hazard ratio, type 2 diabetes mellitus

1. Introduction

As a global public health issue, type 2 diabetes mellitus (T2DM) affected approximately 347 million individuals worldwide in 2008, among whom 10% are adults.[1] With some association with microvascular and macrovascular morbidity and mortality, hyperglycemia has been targeted in the management of T2DM.[2] Moreover, patients with T2DM have a 2- to 4-fold higher risk of cardiovascular disease (CVD) and CVD mortality compared with patients without T2DM.[3] However, it has not been demonstrated by clinical trials that those with T2DM who have achieved normal glucose levels can lower their risk for cardiovascular events.

In 2012, the American Diabetes Association and the European Association for the Study of Diabetes proposed that metformin monotherapy was the first-line glucose-lowering drug treatment, without contraindications.[4] Unfortunately, many patients on metformin monotherapy failed to meet or keep glycemic control for a long period. Based on the 2009 guidelines of the National Institute for Health and Care Excellence (NICE), it is necessary to add a sulfonylurea to metformin therapy as long as this is not contraindicated by factors such as obesity or risk of hypoglycemia; otherwise, a dipeptidyl peptidase-4 (DPP-4) inhibitor or

thiazolidinedione can be added. After the release of these guidelines, however, a greater understanding of alternative agents has been observed. Nonetheless, the choice of an additional therapeutic agent remains complex because the agents have to be compared with regard to their efficacy and safety.

Sulfonylureas have been the most widely used add-on to metformin therapy for several years, but they may increase cardiovascular risks.[5,6] In recent years, as a class of agents, DPP-4 inhibitors have been permitted to treat T2DM and to improve the control of glycemia by increasing incretin levels. In several clinical studies, metformin plus DPP-4 inhibitor achieved similar glucose control with a lower risk for CVD, CVD mortality, and all-cause mortality than metformin plus sulfonylurea.[7–9] However, Scirica et al have reported that adding a DPP-4 inhibitor to standard metformin therapy in T2DM patients ran a high risk for cardiovascular events.[10]

Given these inconsistencies in the literature, we performed a meta-analysis on the relationships of metformin plus DPP-4 inhibitor versus metformin plus sulfonylurea on CVD, CVD morbidity, and all-cause mortality in T2DM patients.

2. Methods

2.1. Literature search

A systematic search of Medline/PubMed (from 2000 to September 2015), EMBASE (from 2000 to September 2015), and Web of Knowledge (from 2000 to September 2015) for research articles published in English was carried out to examine how combination therapy affects the risk of CVD mortality and/or all-cause mortality in T2DM patients. The search was designed using the following key words or phrases: "dipeptidyl peptidase-4 inhibitors," "DPP-4 inhibitors," the names of individual available DPP-4 inhibitors ("alogliptin," "dutogliptin," "linagliptin," "saxagliptin," "sitagliptin," and "vildagliptin"), "sulfonylurea," sulfonylurea compounds ("glimepiride," "acetohexamide," "tolbutamide," "tolazamide," "glyburide," "glipizide," "biguanides," and "chlorpropamide"), and the combination of "metformin" and "cardiovascular," "stroke," "myocardial infarction," or "heart failure." In the search, only studies of human subjects were selected. Two researchers assessed the relevance of the cited article abstracts. When at least one of the reviewers judged the abstracts to be pertinent, the studies were retrieved for further consideration. If there was a discrepancy, it was resolved by consensus. Sometimes, a third investigator was needed to be involved to reach a consensus. In the case of multiple reports from the same trial, the reviewers chose the most complete and/or more recently reported data.

2.2. Study selection

The inclusion criteria used were as follows: randomized clinical trials, case reports, or cohort studies that investigated the relationship of therapy with metformin plus DPP-4 inhibitor versus metformin plus sulfonylurea on the risk of CVD and/or mortality; the relative risk (RR) or equivalent (e.g., hazard ratio, odds ratio) and the corresponding variance or equivalent reported; and diagnosis of T2DM applying the standard criteria.

2.3. Data extraction

Two observers abstracted the data independently, and a senior investigator was required in the case of potential discrepancies. It was necessary to take the following events into account:

cardiovascular events (e.g., nonfatal myocardial infarction, stroke); fatal heart failure; and death from any cause.

2.4. Study quality

To assess the quality of each study, the following criteria were followed: in the assessment of randomized controlled trials, both the quality of reporting of meta-analyses guidelines and the Jadad scale were used; cohort and case-control studies were assessed using the Newcastle–Ottawa scale; and it was necessary for the studies selected to have well-defined inclusion criteria for patients and clear definitions of treatment responses. To evaluate potential publication bias, Begg rank correlation test and Egger linear regression test were used.

2.5. Statistical analysis

All the analyses were based on previous published studies, thus no ethical approval and patient consent are required. To account for the possibility of events occurring in the treatment group versus the control group, the metan routine (STATA Stata Corp, version 12.0) was applied to calculate the RRs of the effect of randomized treatments.[11] It was necessary to make a separate calculation of the RR and 95% confidence interval (CI) for each outcome for each trial, with data grouped based on the intention-to-treat principle.[12] Pooled RRs underwent logarithmic transformation and were weighted for the inverse of variance. When heterogeneity failed to be explained, it was necessary to make an overall estimation of effect based on a fixed-effects model or a random-effects model. The Q statistic was applied to test the assumption of homogeneity between the treatment effects in different trials, and the I^2 statistic was applied for further quantification. Significance was set as $P < .1$ or $I^2 \geq 50\%$.

3. Results

3.1. Search results and characteristics of the study

Through electronic searches, 203 citations were identified based on the inclusion criteria, and 195 were excluded. A total of 139 studies were duplicates, 20 studies were reviews, 6 studies did not include a combination with metformin, 9 studies involved multiple drug combinations, and 21 studies did not report CVD or mortality to be an outcome (Fig. 1).

Table 1 presents the characteristics of the studies.[7–9,12–16] Of the 8 included studies, 6 were retrospective cohort studies and 2 were randomized clinical trials. Of the 8 studies, 1 of them was executed in the United States, 1 in Denmark, 1 in the United Kingdom, 1 in Korea, 1 in Taiwan, 2 in Germany, and 1 in Canada. The number of participants ranged from 616 in the study by Gitt et al[13] to 328,283 in the study by Seong et al.[7] The average
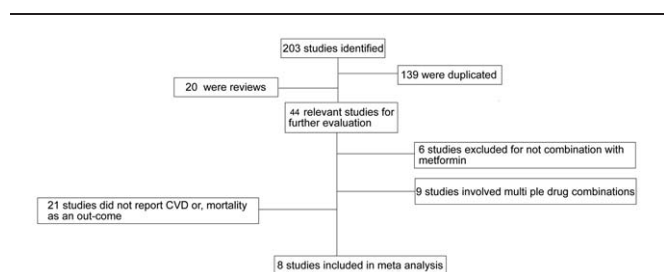

Figure 1. Flow chart summarizing the selection process.

Table 1

Characteristics of observational studies of metformin plus dipeptidyl peptidase-4 inhibitor versus metformin plus sulfonylurea and their association with a decreased risk of cardiovascular disease, cardiovascular mortality, and/or all-cause mortality.

Author, publication year (ref.)	Country, period of study	Study design	Sample size	Male/female	Age (y)	Diabetes duration	A1C, %	Variables controlled for	Duration of follow-up (y)	Outcome
Mogensen 2014	Denmark, 2007–2011	Retrospective study	SU+MET: 25,092	14,915/10,177	62.3±12.7	NR	NR	Age, sex, duration of GLT, calendar year, Charlson score, concomitant CV pharmacotherapy and income	2.3 (0.5–4.8)	All-cause mortality, CVD mortality, CVD
			DPP-4+MET: 11,138	6657/4581	59.7±11.8	NR	NR	Age, sex, duration of GLT, calendar year, Charlson score, concomitant CV pharmacotherapy and income	2.3 (0.7–4.6)	All-cause mortality, CVD mortality, CVD
Morgan 2014	UK, 2007–2012	Retrospective study	SU+MET: 33,983	20,944/13,039	62.3±12.8	5.1±4.8	9.1±1.8	Age at index date, gender, diabetes duration, HbA1c, systolic blood pressure (SBP), total cholesterol, BMI, smoking status	NR	All-cause mortality, CVD, Cardiac vascular disease
			DPP-4+MET: 7864	4612/3252	59.6±11.5	5.5±4.5	8.5±1.5	Age at index date, gender, diabetes duration, HbA1c, systolic blood pressure (SBP), total cholesterol, BMI, smoking status	NR	All-cause mortality, CVD
Seong, 2015	Korea, 2006–2010	Retrospective study	SU+MET: 253,563	139,497/114,066	58.7±12.5	NR	NR	Age at index date, gender, duration of diabetes, presence of comorbidities, and use of the medications specified below	Each patient started on the index date and ended at the earliest occurrence of a study outcome, therapy discontinuation (therapy stop or switch), death (in-hospital death), or the end of the study period (December 31, 2010)	CVD
			DPP-4+MET: 74,720	39,865/348,55	57.0±12.0	NR	NR	Age at index date, gender, duration of diabetes, presence of comorbidities, and use of the medications specified below	Each patient started on the index date and ended at the earliest occurrence of a study outcome, therapy discontinuation (therapy stop or switch), death (in-hospital death), or the end of the study period (December 31, 2010)	CVD
Ou, 2015	Taiwan, 2009–2012	Retrospective study	SU+MET: 10,089	5449/4640	57.8±12.3	50.8±40.8	NR	NR	Patients were followed until death or 31 December 2013	
			DPP-4+MET: 10,089	5433/4656	57.9±12.3	50.8±39.0	NR	NR	Patients were followed until death or 31 December 2013	
Gallwitz, 2012	Germany	RCT	SU+MET: 775	471/304	59.8±9.4		7.7±0.9	NR	2	CVD mortality, CVD
			DPP-4+MET: 776	462/314	59.8±9.4		7.7±0.9	NR	2	CVD mortality, CVD
Gitt, 2013	Germany	RCT	SU+MET: 153	69/84	67.7±1.60	NR	7.3±0.41	NR	1	CVD
			DPP-4+MET: 463	238/225	65.2±1.6	NR	7.3±0.36	NR	1	CVD

(continued)

Table 1

(continued).

Author, publication year (ref.)	Country, period of study	Study design	Sample size	Male/female	Age (y)	Diabetes duration	A1C, %	Variables controlled for	Duration of follow-up (y)	Outcome
Kannan, 2015	USA	Retrospective study	SU+MET: 9419 DPP-4+MET: 1487	5173/4252 800/688	60.6+12.6 60.6+12.6	NR NR	NR NR	Age, sex, race (Caucasian vs non-Caucasian), body mass index (BMI), number of encounters, median household income, smoking status, systolic and diastolic blood pressure, hypertension, dyslipidemia, cerebral vascular event, presence of neuropathy, retinopathy, dementia, chronic obstructive pulmonary disease, cancer, atrial fibrillation, antihypertensive medications, lipid-lowering agents, antiplatelet agents, and propensity for being on MF+SU at baseline	4 4	All-cause mortality, CVD All-cause mortality, CVD
MD, 2015	Canada	Retrospective study	SU+MET: 9521	6008/3513	60.6+10	NR	NR	Age, sex, year of cohort entry, duration of treated diabetes, body mass index (BMI), excessive alcohol use, smoking, glycated hemoglobin (A1C) levels (last measure prior to cohort entry), and history of MI or stroke	NR	All-cause mortality, CVD
			DPP-4+MET: 2286	1353/933	62.9+11.2	NR	NR	Age, sex, year of cohort entry, duration of treated diabetes, body mass index (BMI), excessive alcohol use, smoking, glycated hemoglobin (A1C) levels (last measure prior to cohort entry), and history of MI or stroke	NR	All-cause mortality, CVD

CVD = cardiac vascular disease, DPP-4 = dipeptidyl peptidase-4 inhibitors, MET = metformin, RCT = randomised controlled trial, SU = sulfonylureas.
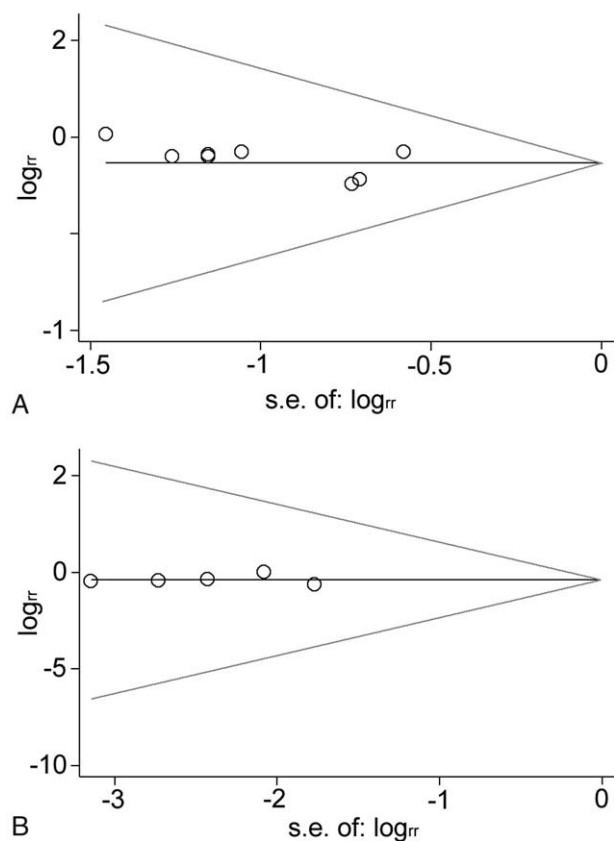
Figure 2. Funnel pool: comparison of metformin plus dipeptidyl peptidase-4 inhibitor versus metformin plus sulfonylurea treatment outcome of a risk of no fatal CVD (A) and all-cause mortality (B) in Type 2 diabetes mellitus patients. CVD = cardiovascular disease.

patient age ranged between 57.0 and 67.7 years. The average time of follow-up was 1.0 to 4.0 years. Among the studies, 8 stated nonfatal cardiovascular events, 5 reported fatal cardiovascular events, 2 reported cardiovascular mortalities, and 5 reported all-cause mortality. Of the 451,418 participants included in these studies, 342,595 participants received metformin plus sulfonylurea combination therapy, and 108,823 participants received metformin plus DPP-4 inhibitor combination therapy.

3.2. Study quality

According to the quality assessment of the respective studies, randomized controlled trials had Jadad scores that ranged between 1 and 5. Of the randomized controlled trials that were withdrawn from this study, 2 full studies[12,13] failed to describe the method of randomization in detail, and 3 studies received Jadad scores of 2. All trials had pointed out inclusion criteria for patients as well as definitions of the diagnosis and treatment responses. Moreover, there were comparable baseline characteristics of all study populations between the metformin plus DPP-4 inhibitor and metformin plus sulfonylurea groups. There was no evidence of publication bias by rank correlation or regression testing (Fig. 2).

3.3. Cardiovascular events

Figure 3 depicts the nonfatal cardiovascular events and fatal cardiovascular events based on the random-effects models,

pooling the adjusted RRs for association with combination therapy of metformin and DPP-4 inhibitor versus metformin and sulfonylurea. By sensitivity analysis, the pooled RR estimates (95% CI) for the nonfatal cardiovascular events and fatal cardiovascular events were 0.71 (0.56–0.90), $I^2 = 88.1\%$, $P = .004$ and 1.001 (0.85–1.18), $I^2 = 24.9\%$, $P = .99$, respectively. Statistically, the pooled RR estimates were not significant for fatal cardiovascular events, while the use of combination therapy of metformin plus DPP-4 inhibitor was significantly related to a decreased risk of nonfatal cardiovascular events.

By excluding the study by Ou et al,[14] a further sensitivity analysis was carried out in which the outcome was inferior. The heterogeneity of nonfatal cardiovascular events and fatal cardiovascular events all became small ($I^2 = 0\%$). The combination therapy of metformin plus DPP-4 inhibitor had a significantly lower risk of nonfatal cardiovascular events, with a pooled estimate of 0.68 (0.62–0.75), $P < .01$, compared with metformin plus sulfonylurea combination therapy (Fig. 4). However, fatal cardiovascular events were not statistically significant, with a pooled estimate of 0.84 (0.66–1.06), $P = .15$. The outcome seemed to be relatively stable.

3.4. Cardiovascular mortality and all-cause mortality

Figure 5 clearly shows the study-specific and pooled RRs of CVD mortality and all-cause mortality for association with metformin plus DPP-4 inhibitor versus metformin plus sulfonylurea combination therapy. The pooled RR estimates (95% CI) were 0.58 (0.41–0.82), $I^2 = 0$, $P = .002$ and .72 (0.59–0.87), $I^2 = 70.7\%$, $P = .001$, respectively. The RRs of CVD mortality and all-cause mortality were statistically significant for association with the combination therapy of metformin plus DPP-4 inhibitor versus metformin plus sulfonylurea. These findings indicated that DPP-4 inhibitor versus sulfonylurea can lower the risk of CVD mortality and all-cause mortality in patients with T2DM. By excluding the study by Kannan et al,[16] sensitivity analysis of all-cause mortality was performed in which the outcome was inferior to the others. With the heterogeneity becoming small ($I^2 = 0\%$), the pooled estimate was 0.65 (0.59–0.72), $P < .01$ (Fig. 6). Statistically, there were significant differences between metformin plus DPP-4 inhibitor combination therapy and metformin plus sulfonylurea combination therapy. The outcome was relatively stable.

4. Discussion

T2DM affects a substantial and increasing number of people around the world.[15–17] As it is a progressive pathological process, many patients choose oral antihyperglycemic agents to obtain normal glycemic levels. For example, combination therapy of metformin plus sulfonylurea is the second step for T2DM patients in the recommended treatment process.[18] Nevertheless, based on the evidence, it is easy to see the beneficial effect of good glycemic control on the progression of microvascular complications in T2DM.[19–21] In addition, there has been an increasing incidence of cardiovascular events, and the majority of T2DM patients die from cardiovascular-related disease.[22] In previous retrospective cohort studies and meta-analyses, sulfonylurea monotherapy relative to metformin or metformin plus sulfonylurea combination therapy increased the overall mortality risk and CVD in patients suffering from T2DM.[23–25]

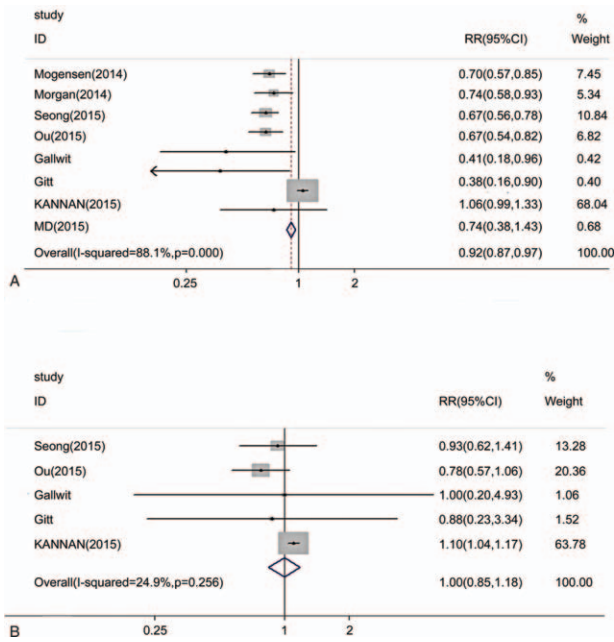As hormones are released in response to changing glucose levels, endogenous glucagonlike peptide-1 and glucose-depen-

Figure 3. Forest plot: relative risk (RR) estimates and 95% confidence intervals (CIs) for the nonfatal cardiovascular events (A) and fatal cardiovascular events (B) associated with the combination therapy of metformin plus DPP-4 inhibitor versus metformin plus sulfonylurea by study and pooled along with the proportion of events for each outcome. DPP-4 = dipeptidyl peptidase-4 inhibitors.

dent insulinotropic polypeptide levels are enhanced, which is how DPP-4 inhibitors work. Evidence has shown that the use of DPP-4 inhibitors decreases the risk of cardiovascular events.[26,27] In addition, a recent meta-analysis has indicated that the combination therapy of metformin plus DPP-4 inhibitor significantly
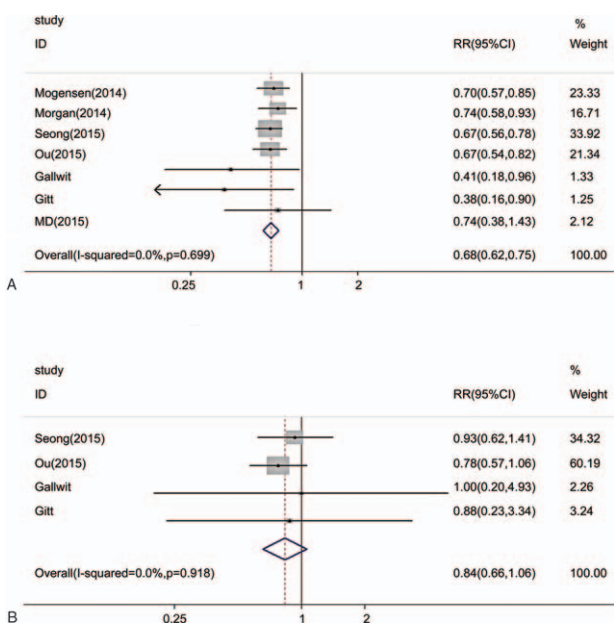

Figure 4. Forest plot: relative risk (RR) estimates and 95% confidence intervals (CIs) for the nonfatal cardiovascular events (A) and fatal cardiovascular events (B) associated with the combination therapy of metformin plus DPP-4 inhibitor versus metformin plus sulfonylurea, excluding the study by Ou et al and pooled along with proportion of events for each outcome. DPP-4 = dipeptidyl peptidase-4 inhibitors.
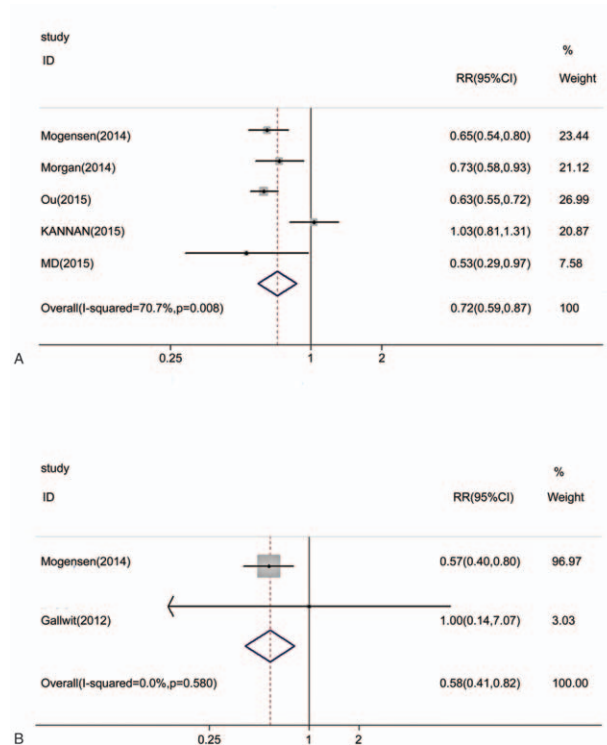

Figure 5. Forest plot: relative risk (RR) estimates and 95% confidence intervals (CIs) for cardiovascular mortality (A) and all-cause mortality (B) associated with the combination therapy of metformin plus DPP-4 inhibitor versus metformin plus sulfonylurea by study and pooled along with proportion of events for each outcome.

decreases the risks of CVD, cardiovascular mortality, and all-cause mortality in T2DM patients.

Combination therapy of metformin plus DPP-4 inhibitor significantly lowered the RR of nonfatal cardiovascular events, cardiovascular mortality, and all-cause mortality, compared with the combination of metformin plus sulfonylurea. However, there was no significant difference for fatal cardiovascular events between the 2 groups.[6,8] Based on these results, it is easy to understand the inconclusive outcomes of many large clinical studies comparing the studies of DPP-4 inhibitors and sulfonylureas on nonfatal cardiovascular events, CVD fatality, and all-
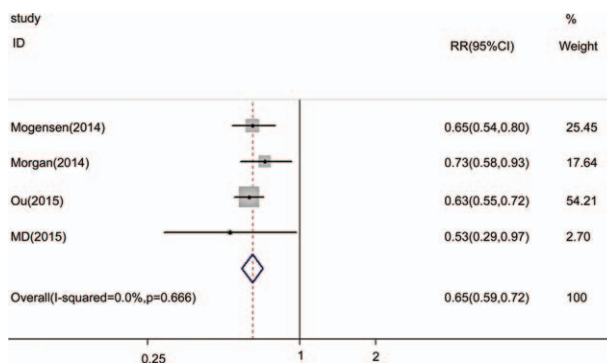

Figure 6. Forest plot: relative risk (RR) estimates and 95% confidence intervals (CIs) for cardiovascular mortality associated with the combination therapy of metformin plus DPP-4 inhibitor versus metformin plus sulfonylurea, excluding the study by Kannan et al and pooled along with proportion of events for each outcome. DPP-4 = dipeptidyl peptidase-4 inhibitors.

cause mortality in T2DM patients, while the fatal cardiovascular events remain obscure.

In our analysis, from a statistical perspective, heterogeneity was significant across outcomes. After ruling out the study by Kannan et al,[16] with an outcome that was inferior, the result, with a small heterogeneity ($I^2 = 0\%$), becomes stable. According to the study by Kannan et al,[16] there is a great risk of congestive heart failure among users of metformin plus DPP-4 inhibitor, compared with metformin plus sulfonylurea. Moreover, regarding cardiovascular risk reduction, the combination therapy of metformin plus DPP-4 inhibitor was not better than metformin plus sulfonylurea. A potential explanation may be that the study had many limitations. If it was not accurately written down in the electronic health record by the healthcare providers in the USA, no events or prescriptions that occurred beyond the health system in the USA were included in the study. In addition, the study included patients such as those who had the greatest risk for heart failure hospitalization, those who suffered from an existing diagnosis of heart failure, those who had elevated levels of N-terminal prohormone brain natriuretic peptide at baseline, and those with an estimated glomerular filtration rate < 60 mL/min.

There are some limitations confronting the meta-analysis conducted in this report. First, some studies were not randomized controlled trials. Second, there were not ample studies presented in the meta-analysis. Third, we failed to mention the data of studies published only in abstract form (and some additional studies) because it was impossible to conduct a thorough analysis. Finally, some studies did not describe the duration of T2DM in patients or the monitoring index of blood glucose (A1C). These reasons are likely a source of prejudice. It is obvious that we need to carry out more trials that are highly qualified, well-designed, randomized, controlled, multicentered, and adequately powered to command the standards of therapy for T2DM with metformin plus DPP-4 inhibitor or metformin plus sulfonylurea to decrease the risk of cardiovascular events, CVD mortality, and all-cause fatality.

In conclusion, our meta-analysis showed that the combination therapy of metformin plus DPP-4 inhibitor significantly lowered the RR of nonfatal cardiovascular events, CVD fatality, as well as all-cause mortality, compared with the use of metformin plus sulfonylurea. However, there were no significant differences in terms of fatal cardiovascular events (e.g., heart failure) between the 2 groups, indicating that T2DM patients who are at high risk of cardiovascular events may use metformin plus DPP-4 inhibitor instead of metformin plus sulfonylurea to decrease the risk of cardiovascular events as well as CVD mortality. Obviously, more studies should be carried out to evaluate how combination therapy of metformin plus DPP-4 inhibitor versus metformin plus sulfonylurea is associated with cardiovascular events, cardiovascular mortality, and/or all-cause mortality.

References

[1] Farzadfar F, Finucane MM, Danaei G, et al. Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Cholesterol) National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. Lancet 2011;377:578–86.

[2] Anonymous . Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998;317:703–13.

[3] Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215–22.

[4] Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55:1577–96.

[5] Roumie CL, Greevy RA, Grijalva CG, et al. Association between intensification of metformin treatment with insulin vs sulfonylureas and cardiovascular events and all-cause mortality among patients with diabetes. JAMA 2014;311:2288–96.

[6] Rao AD, Kuhadiya N, Reynolds K, et al. Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality?: a meta-analysis of observational studies. Diabetes Care 2008;31:1672–8.

[7] Seong JM, Choi NK, Shin JY, et al. Differential cardiovascular outcomes after dipeptidyl peptidase-4 inhibitor, sulfonylurea, and pioglitazone therapy, all in combination with metformin, for type 2 diabetes: a population-based cohort study. PLoS One 2015;10:e0124287.

[8] Mogensen UM, Andersson C, Fosbol EL, et al. Cardiovascular safety of combination therapies with incretin-based drugs and metformin compared with a combination of metformin and sulphonylurea in type 2 diabetes mellitus—a retrospective nationwide study. Diabetes Obes Metab 2014;16:1001–8.

[9] Morgan CL, Mukherjee J, Jenkins-Jones S, et al. Combination therapy with metformin plus sulphonylureas versus metformin plus DPP-4 inhibitors: association with major adverse cardiovascular events and all-cause mortality. Diabetes Obes Metab 2014;16:977–83.

[10] Udell JA, Bhatt DL, Braunwald E, et al. InvestigatorsSaxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe renal impairment: observations from the SAVOR-TIMI 53 Trial. Diabetes Care 2015;38:696–705.

[11] Field AP. Meta-analysis of correlation coefficients: a Monte Carlo comparison of fixed- and random-effects methods. Psychol Methods 2001;6:161–80.

[12] Gallwitz B, Rosenstock J, Rauch T, et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. Lancet 2012;380:475–83.

[13] Gitt AK, Bramlage P, Binz C, et al. Prognostic implications of DPP-4 inhibitor vs. sulfonylurea use on top of metformin in a real world setting—results of the 1 year follow-up of the prospective DiaRegis registry. Int J Clin Pract 2013;67:1005–14.

[14] Ou SM, Shih CJ, Chao PW, et al. Effects on clinical outcomes of adding dipeptidyl peptidase-4 inhibitors versus sulfonylureas to metformin therapy in patients with type 2 diabetes mellitus. Ann Intern Med 2015;163:663–72.

[15] Yu OH, Yin H, Azoulay L. The combination of DPP-4 inhibitors versus sulfonylureas with metformin after failure of first-line treatment in the risk for major cardiovascular events and death. Can J Diabetes 2015;39:383–9.

[16] Kannan S, Pantalone KM, Matsuda S, et al. Risk of overall mortality and cardiovascular events in patients with type 2 diabetes on dual drug therapy including metformin: a large database study from the Cleveland Clinic. J Diabetes 2016;8:279–85.

[17] Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat Rev Endocrinol 2012;8:228–36.

[18] Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2006;29:1963–72.

[19] Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–12.

[20] Group AC, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–72.

[21] Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–39.

[22] King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 1998;21:1414–31.

[23] Tzoulaki I, Molokhia M, Curcin V, et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ 2009;339:b4731.

[24] Pantalone KM, Kattan MW, Yu C, et al. Increase in overall mortality risk in patients with type 2 diabetes receiving glipizide, glyburide or glimepiride monotherapy versus metformin: a retrospective analysis. Diabetes Obes Metab 2012;14:803–9.

[25] Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2013;15:938–53.

[26] Aschner P, Katzeff HL, Guo H, et al. Sitagliptin Study GEfficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes. Diabetes Obes Metab 2010;12: 252–61.

[27] Patil HR, Al Badarin FJ, Al Shami HA, et al. Meta-analysis of effect of dipeptidyl peptidase-4 inhibitors on cardiovascular risk in type 2 diabetes mellitus. Am J Cardiol 2012;110:826–33.