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ORIGINAL ARTICLE

Efficacy and safety of combination therapy with an α-glucosidase inhibitor and a dipeptidyl peptidase-4 inhibitor in patients with type 2 diabetes mellitus: A systematic review with meta-analysis

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ABSTRACT

Aims/Introduction: The combination of dipeptidyl peptidase-4 (DPP4) inhibitors and α-glucosidase inhibitors (AGIs) might provide an additive or synergistic glucose-lowering effect, as they have a complementary mode of action. In the present study, we examined the efficacy and safety of the addition of a DPP4 inhibitor to patients with type 2 diabetes inadequately controlled with an AGI.

Materials and Methods: We carried out an electronic search of MEDLINE, EMBASE, the Cochrane Library and Clinicaltrials.gov through October 2016. Randomized controlled trials written in English that compared DPP4 inhibitors plus AGI (DPP4i/AGI) and placebo plus AGI (PCB/AGI) in patients with type 2 diabetes were selected. Data on the study characteristics, efficacy and safety outcomes were extracted, and the risk of potential biases was assessed. The efficacy and safety of DPP4i/AGI and PCB/AGI were compared.

Results: Of 756 potentially relevant published articles and 40 registered trials, five studies including 845 patients randomized to DPP4i/AGI and 832 patients randomized to PCB/AGI were included for meta-analysis. Compared with PCB/AGI, DPP4i/AGI showed a greater reduction in glycated hemoglobin (weighted mean difference −1.2%, 95% confidence interval −1.6 to −0.8), fasting plasma glucose and 2-h postprandial plasma glucose levels, with no increase in bodyweight. The risks of hypoglycemia and gastrointestinal adverse events were similar between DPP4i/AGI and PCB/AGI.

Conclusions: The addition of a DPP4 inhibitor to patients with type 2 diabetes inadequately controlled with an AGI achieved better glycemic control without further increasing the risk of weight gain and hypoglycemia.

INTRODUCTION

Recent research findings over the past two decades have challenged the traditional 'insulinocentric' understanding of the pathophysiology of type 2 diabetes mellitus as characterized by impaired insulin secretion and action. Presently, the pathophysiology of type 2 diabetes mellitus is recognized as a more complex one, encompassing defective β-cell responses to incretin hormones, increased glucagon secretion from α-cells, increased lipolysis and dysregulated adipokine secretion, increased renal glucose reabsorption, and insulin resistance in the brain[1]. Fortunately, various pharmacological treatments are available that enable the customization of antidiabetes treatment for an individual patient.

Dipeptidyl peptidase-4 (DPP4) inhibitors enhance the plasma concentration of active glucagon-like peptide-1

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(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which leads to the net result of increased insulin secretion and decreased glucagon secretion[2–5]. However, DPP4 inhibitors alone cannot achieve a plasma concentration of GLP-1 that is enough to decelerate gastric emptying or decrease appetite. Furthermore, DPP4 inhibitors decrease total GLP-1 secretion[6,7], which could be a result of feedback inhibition by increased active GLP-1 concentrations. In this regard, incretin secretagogues might be useful to further increase the therapeutic efficacy of DPP4 inhibitors. The α-glucosidase inhibitors (AGIs), acarbose, miglitol and voglibose, delay carbohydrate absorption from the small intestine by inhibiting the hydrolysis of oligosaccharides and disaccharides into monosaccharides[8]. As such, AGIs are used to reduce postprandial glucose (PPG) levels in patients with type 2 diabetes mellitus[8]. Interestingly, AGIs decrease carbohydrate absorption in the proximal gut and result in the delivery of a relatively large amount of undigested carbohydrate to the distal gut; thus, AGIs might result in decreased GIP secretion from the K-cells and increased GLP-1 secretion from the L-cells[9,10]. Indeed, in non-diabetic healthy individuals, acarbose increased GLP-1 secretion when given with sucrose[11] and voglibose increased GLP-1 secretion when given with a standardized meal[12]. In patients with type 2 diabetes mellitus, simultaneous administration of acarbose and sucrose resulted in increased GLP-1 release[13], and a 2-day administration of miglitol increased GLP-1 secretion and decreased GIP secretion after a meal[9]. In addition, a 24-week acarbose treatment in patients with newly diagnosed type 2 diabetes mellitus increased postprandial GLP-1 levels[14]. However, in another study[15], ingestion of acarbose with a mixed test meal failed to enhance GLP-1 release in patients with type 2 diabetes mellitus. Furthermore, in elderly type 2 diabetes patients treated with acarbose, just 20% of the patients showed increased GLP-1 secretion, and no significant correlations between serum GLP-1 levels and serum glucose or insulin levels were observed[16]. Intriguingly, miglitol, but not acarbose, increased active postprandial GLP-1 levels in individuals with visceral obesity (50% of the participants had impaired glucose tolerance or diabetes)[17]. These inconsistent results might be explained by the different clinical characteristics of the study participants and varying pharmacokinetics of drugs. Despite the controversy over incretin hormone secretion with AGI, the combination of these two drugs might provide an additive (or perhaps synergistic) effect on glucose control with complementary mechanism of action in patients with type 2 diabetes mellitus. In an animal study with prediabetic *db*/*db* mice, combined treatment with voglibose and a DPP4 inhibitor (alogliptin) prevented the development of diabetes and preserved the pancreatic β-cell mass, which was accompanied by synergistically increased active GLP-1 levels[18]. In the present systematic review and meta-analysis, we examined the efficacy and safety of the combination of DPP4 inhibitor and AGI in patients with inadequately controlled type 2 diabetes mellitus.

METHODS

We carried out a systematic review and meta-analysis following the predeveloped protocol by authors that defined study eligibility, data sources, search terms, outcome variables, and data extraction and analysis strategy (Appendix S1). The study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA statement)[19].

Eligibility Criteria

Randomized controlled trials that compared the addition of DPP4 inhibitor to AGI (DPP4i/AGI) and the addition of a placebo to AGI (PCB/AGI) in patients with type 2 diabetes mellitus were regarded as eligible for inclusion. Among the initially retrieved studies, we included only studies written in English with treatment durations of at least 12 weeks that contained information of glycated hemoglobin (HbA1c) changes from baseline. Concurrent use of other antihyperglycemic agents was allowed. Studies that were duplicates or extensions of another study were excluded. Two independent authors (SHM and J-HY) thoroughly evaluated the study titles, abstracts and full texts to assess the eligibility of the studies, and any disagreements were resolved by a third investigator (YMC).

Data Sources and Search Strategies

We systematically searched to identify potentially relevant trials from inception to November 2016 from the following electronic bibliographic databases: MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL). To identify unpublished studies, we also searched for trials registered in ClinicalTrials.gov. The keywords of search terms were as follows: 'DPP4 inhibitor,' 'vildagliptin,' 'sitagliptin,' 'linagliptin,' 'alogliptin,' 'saxagliptin,' 'gemigliptin,' 'dutogliptin,' 'gosogliptin,' 'anagliptin,' 'teneligliptin,' 'evogliptin,' 'omarigliptin,' 'trelagliptin,' 'alpha-glucosidase inhibitor,' 'acarbose,' 'miglitol' and 'voglibose.' The detailed search terms used in this study are provided in Appendix S1.

Data Extraction

Data were independently extracted by two authors (SHM and J-HY) from the selected eligible studies according to the protocol. Any discrepancies were subsequently referred to the third author (YMC) and resolved through discussion. The primary efficacy outcome was the change in HbA1c levels from baseline, and the secondary efficacy outcomes were the change from baseline in fasting plasma glucose (FPG) levels, 2-h PPG levels and bodyweight. The safety outcomes were the risk of hypoglycemia and gastrointestinal (GI) adverse events. The following information was additionally extracted from each study: name of first author; publication year; drug name and doses of AGI and DPP4 inhibitor; duration of treatment; concomitant oral antidiabetic agents; number of patients initially randomized; and baseline characteristics, such as mean age, percentage of men, duration of diabetes, body mass index and the HbA1c level at baseline.

For continuous outcome data, we extracted mean differences between the DPP4i/AGI and PCB/AGI groups, and their standard errors from the articles as the summary measures. Least squares mean differences from analysis of covariance adjusted for covariates between groups were used if they were available. In some studies, simple arithmetic mean differences between baseline and final measurements were calculated for summary statistics where no adjustments were applied. For studies that did not reported standard deviations for the changes in means, we imputed missing standard deviations using correlation coefficients between baseline and post-treatment measurements calculated from other included studies that reported standard deviations for changes and for baseline and post-treatment measurements[20]. The following formula was used for calculating the correlation coefficients: $r = (SD\ [B]^2 + SD\ [F]^2 - SD\ [C]^2) / (2 \times SD\ [B] \times SD\ [F])$, where r is the correlation coefficient, SD is the standard deviation, B is the baseline measurement, F is the final measurement and C is the change in mean measurement. For dichotomous outcomes, the number of patients reporting adverse events per randomized patient in each group was extracted.

Assessment of the Study Quality and Risk of Bias

Two independent reviewers (SHM and J-HY) evaluated the quality and risk of bias in each collected study according to the Cochrane Collaboration's tool, and any differences were resolved by mutual agreement. We considered six aspects of risk of bias: randomization implementation, proper allocation concealment, double blinding of participants and personnel, missing or incomplete data, selective outcome reporting, and other bias.

Statistical Analysis

For continuous variables, such as the change from baseline in HbA1c, FPG, 2-h PPG levels and bodyweight, weighted mean difference (WMD) with 95% confidence intervals (CIs) between

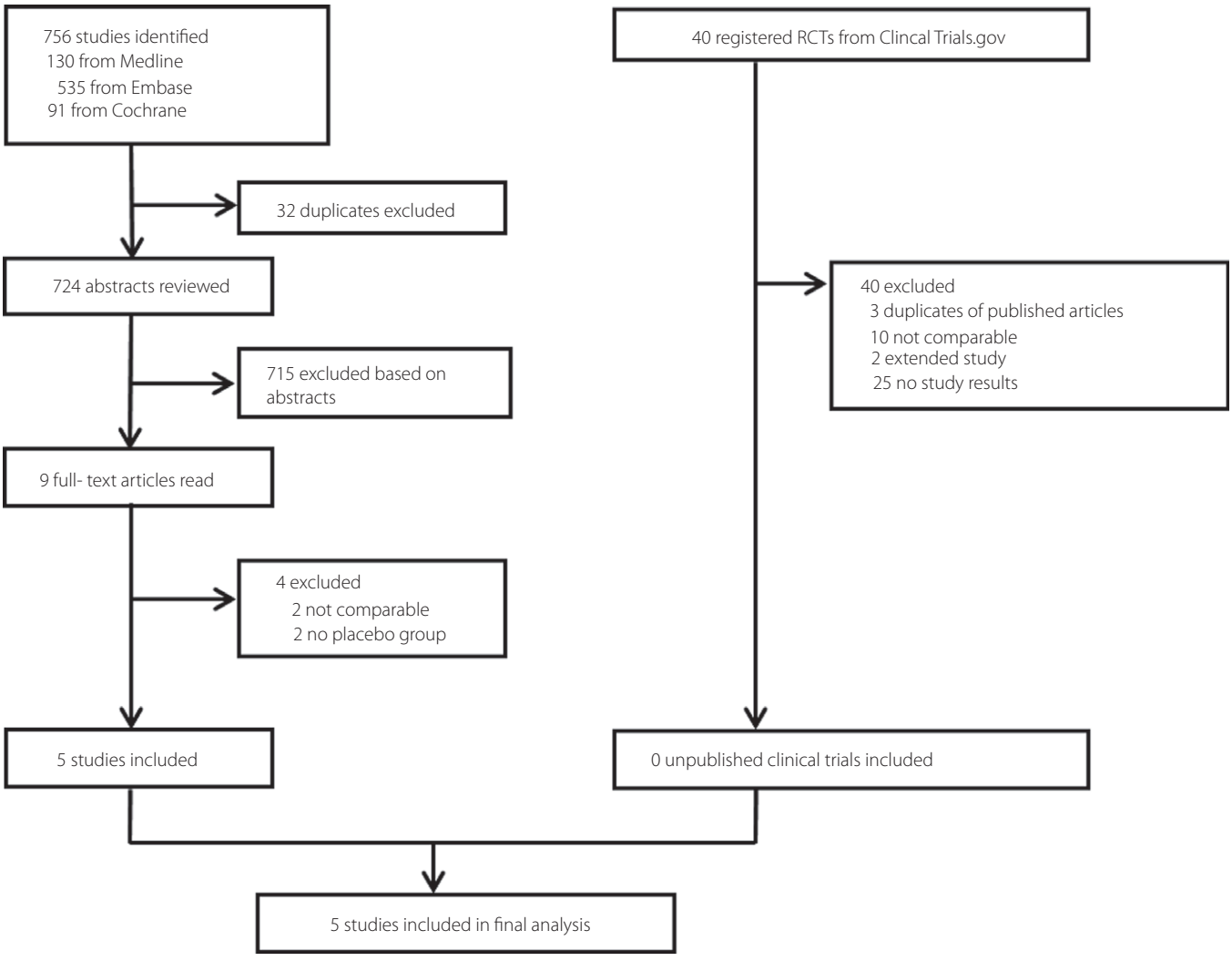


Figure 1 | Study selection process. RCT, randomized controlled trial.

Table 1 | Characteristics of the studies included in the meta-analysis

Study source	Study duration (weeks)	Study arms	Randomized participants (*n*)	Mean age (years)	Men (%)	Fasting plasma glucose (mg/dL)	Baseline BMI (kg/m^2)	Baseline HbA1c (%)	Mean duration of diabetes (years)
Seino *et al.* (2011)[21]	12	Alogliptin 25 mg + voglibose 0.2 mg t.i.d.	79	62.9	63.3	NR	23.3	7.9	8.44
		Placebo + voglibose 0.2 mg t.i.d.	75	62.3	64.0	NR	24.4	8.1	7.52
Su *et al.* (2014)[22]	12	Vildagliptin 50 mg bid + AGI + metformin	260	48.65	NR	167.9	NR	9.0	NR
		Placebo + AGI + metformin	260	49.67	NR	159.6	NR	8.7	NR
Tajima *et al.* (2013)[23]	12	Sitagliptin 50 mg + voglibose 0.2–0.3 mg t.i.d.	70	62.3	60.0	152.7	23.9	7.9	8.2
		Placebo + voglibose 0.2–0.3 mg t.i.d.	63	58.6	71.4	151.5	24.3	7.9	6.1
Wang *et al.* (2015)[24]	12	Vildagliptin 50 mg bid + acarbose + metformin	245	46.61	57.9	160.4	24.1	8.9	8.09
		Placebo + acarbose + metformin	245	45.67	54.6	168.7	24.3	8.6	8.17
Wang *et al.* (2017)[25]	24	Sitagliptin 100 mg q.d. + acarbose 50 or 100 mg t.i.d.	191	56.5	50.8	178.4	25.9	8.1	7.4
		Placebo + acarbose 50 or 100 mg t.i.d.	189	57.8	51.3	176.6	26.0	8.1	8.2

BMI, body mass index; HbA1c, glycated hemoglobin; NR, not recorded.

treatment groups were calculated. For the analysis of dichotomous outcomes, such as the risk of hypoglycemia, relative risks (RR) and their corresponding 95% CIs were calculated. The random effects model of meta-analysis was used to calculate pooled WMDs or RRs, 95% CIs and *P*-values, with $P < 0.05$ considered statistically significant. We also calculated the I^2 statistic, which is an indicator of heterogeneity across the included studies in percentages. The presence of publication bias for the primary outcome was investigated graphically using a funnel plot along with Egger's test for funnel plot asymmetry. We used the Stata statistical package for all analyses (version 12; StataCorp, College Station, Texas, USA).

RESULTS

Search Results and Study Characteristics

We retrieved 756 potentially relevant studies by searching MEDLINE, EMBASE and CENTRAL, of which five articles were included for the meta-analysis. From the 40 clinical trials identified from ClinicalTrials.gov (www.clinicaltrials.gov, accessed 10 November 2016), no clinical trial was included in the analysis. Therefore, five studies with a total of 1,799 study participants (845 randomized to treatment group and 832 randomized to control group) and a mean trial duration of 14 weeks were included in the present study[21–25]. The process of study selection is outlined in Figure 1, and the characteristics of included studies are summarized in Table 1.

Quality of Included Studies and Publication Bias Assessment

Just two studies stated the process of random sequence generation[21,23], and three studies described the method of allocation concealment[21,24,25]. Four out of five randomized controlled trials adequately described double-blinding for the participants and the personnel, and were thus considered as low risk[21,23–25]. Three studies addressed details of incomplete outcome data and others did not[21,23,25]. All five studies were considered to be free of selective outcome reporting or other biases. The risk of bias assessment is summarized in Figure S1.

Efficacy Outcomes

All five studies reported the changes in HbA1c levels from baseline. In pooled analysis of all included studies, DPP4i/AGI showed greater HbA1c level reduction than PCB/AGI (WMD −1.2%, 95% CI: −1.6 to −0.8%; Figure 2). The test for heterogeneity showed the possibility of significant heterogeneity across the included studies ($I^2 = 95.7\%$, $P < 0.001$). When we assessed the potential risk of publication bias by funnel plot and Egger's regression test, a small study effect was not apparent (Figure S2), but this does not clearly show the absence of publication bias because of the small number of studies and the large heterogeneity.

The change in FPG levels was assessed in all included studies (Figure 3a). The DPP4i/AGI group showed greater reduction in FPG levels than the PCB/AGI group in the pooled analysis (WMD −26.8 mg/dL, 95% CI: −39.9 to −13.8 mg/dL). The test

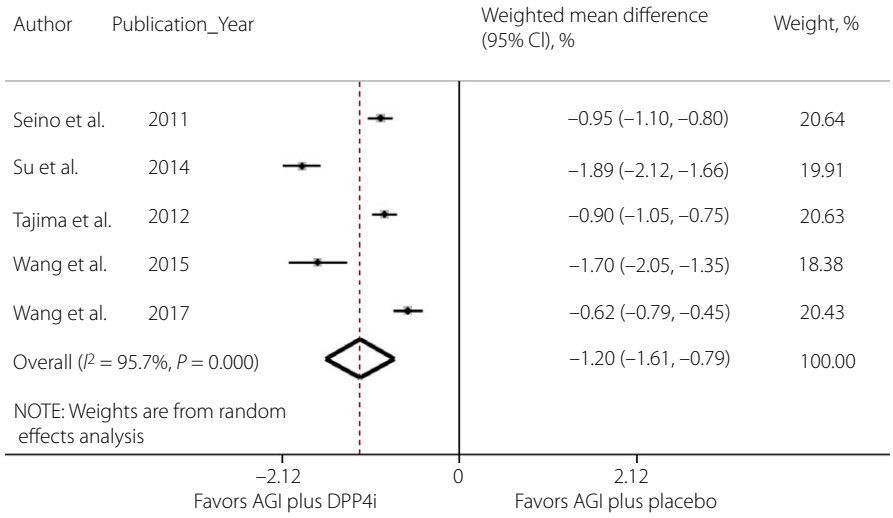


Figure 2 | Weighted mean difference in change in glycated hemoglobin levels from baseline. The change in glycated hemoglobin levels (%) from baseline with dipeptidyl peptidase-4 inhibitor plus α-glucosidase inhibitor (DPP4i/AGI) vs placebo plus α-glucosidase inhibitor (PCB/AGI) analyzed using the random effects model. The squares indicate an individual study's effects, and the size of the squares corresponds to the study's weight in the meta-analysis, with the horizontal lines extending from the symbols representing 95% confidence intervals (CI). The diamonds indicate pooled estimates.

for heterogeneity showed the result to be heterogeneous across the studies (I^2 = 95.1%, P < 0.001).

Four out of five studies reported changes in 2-h PPG levels from baseline (Figure 3b).[21–24] The reduction in 2-h PPG levels was greater in the DPP4i/AGI group than in the PCB/AGI group (WMD −34.5 mg/dL, 95% CI: −52.9 to −16.1 mg/dL). I^2 was significant and showed that a large proportion of heterogeneity was present among the trials (I^2 = 96.3%, P < 0.001).

Four studies reported the results of bodyweight change (Figure 3c).[21,22,24,25] The DPP4i/AGI group did not show any significant increase or decrease in bodyweight compared with the PCB/AGI group in the pooled analysis (WMD 0.1 kg, 95% CI: −0.3 to −0.4 kg). The I^2 test showed no significant heterogeneity between the study outcomes (P = 0.440).

Safety Outcomes

Four out of five studies were included for the meta-analysis for the risk of hypoglycemia (Figure 4a).[21,23–25] Pooled analysis of the four studies did not show a significant increase or decrease in the risk of hypoglycemia in the DPP4i/AGI group compared with the PCB/AGI group (RR 1.4, 95% CI: 0.4 to 4.6). The test for heterogeneity was not significant (P = 0.891).

Three studies reported GI adverse events, which were predefined as nausea, vomiting and diarrhea (Figure 4b).[23–25] The risk for GI adverse events was not significant between the DPP4i/AGI group and the PCB/AGI group (RR 1.2, 95% CI: 0.3 to 4.4). There was no significant heterogeneity (P = 0.659).

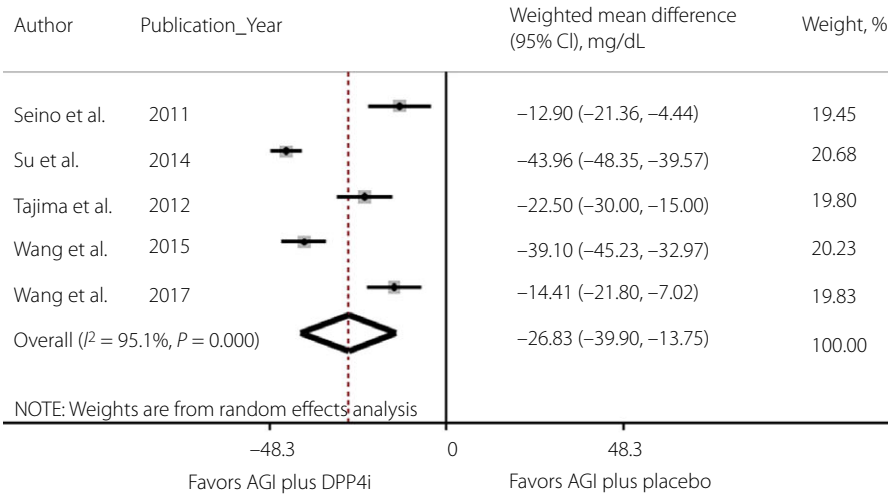
DISCUSSION

Addition of a DPP4 inhibitor resulted in significant reductions in HbA1c levels relative to the placebo in patients with type 2 diabetes mellitus who received an AGI therapy. However, substantial heterogeneity (I^2 = 95.7%) was found in the magnitude of HbA1c level reduction, which might be due to different baseline HbA1c levels because the glucose-lowering efficacy of an antidiabetic agent depends on baseline HbA1c levels[26]. As such, HbA1c levels in the studies by Su *et al.*[22] and Wang *et al.*[24], with higher baseline HbA1c levels, showed a greater reduction than that in other studies. In addition, concurrent use of metformin, which is known to augment GLP-1 secretion from L-cells[27], might be ascribed to the observed greater glucose-lowering effect by addition of DPP4 inhibitors in these studies[22,24]. It is of note that these two studies[22,24] used vildagliptin. It was reported that vildagliptin tightly binds to DPP4 with a very slow rate of dissociation[28], although its effect on HbA1c-lowering efficacy might be negligible[29].

AGI increases GLP-1 secretion, but might decrease GIP secretion[9,10]. Because DPP4 inhibitor protects GLP-1 and GIP from enzymatic degradation, a combination of DPP4 inhibitor and AGI might synergistically increase active GLP-1 levels, but might be neutral for active GIP levels. Considering that insulinotrophic effect of GIP is reduced, but glucagonotrophic effect is preserved in patients with type 2 diabetes mellitus[30], the opposite actions of both agents on GIP levels might not adversely affect glycemic control.

Both FPG and 2-h PPG levels showed greater reduction in patients treated with DPP4i/AGI than those treated with PCB/AGI, which explains the improved HbA1c levels. Previous studies have shown that DPP4 inhibitors as monotherapy are effective in lowering both FPG and 2 h PPG, of which 2-h PPG reduction is predominant[31–33]. In our current study, two studies showed a predominant PPG-lowering effect[21,23], whereas two

(a)



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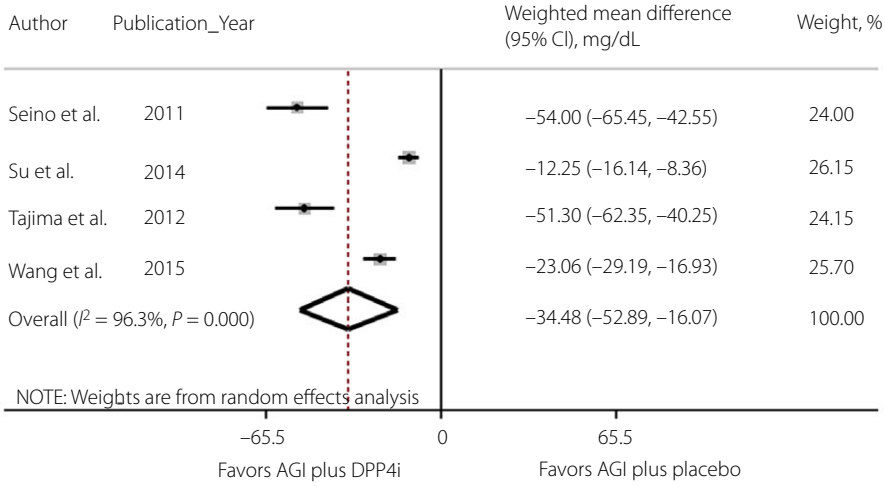

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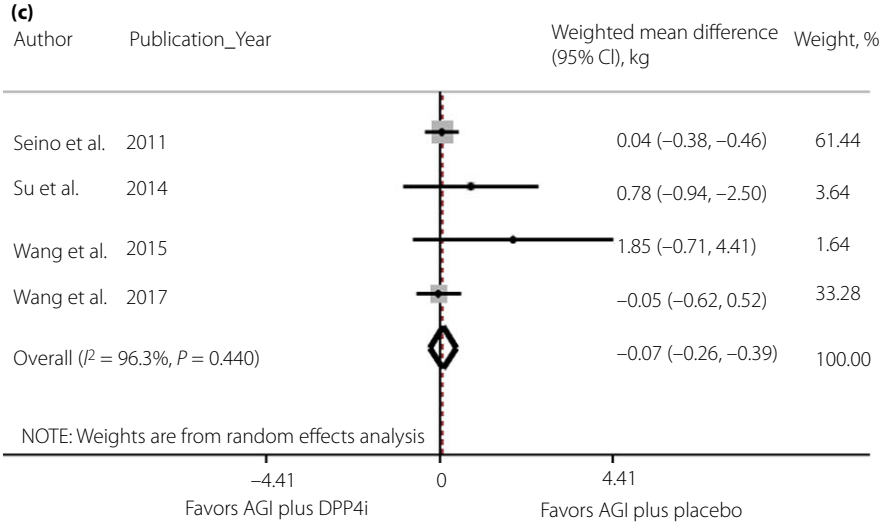

Figure 3 | Meta-analysis for secondary efficacy outcomes. (a) Change in fasting plasma glucose (mg/dL) from baseline with dipeptidyl peptidase-4 inhibitor plus α-glucosidase inhibitor (DPP4i/AGI) vs placebo plus α-glucosidase inhibitor (PCB/AGI) analyzed using the random effects model. (b) Change in 2-h postprandial glucose (mg/dL) from baseline with DPP4i/AGI vs PCB/AGI analyzed using the random effects model. (c) Change in bodyweight (kg) from baseline with DPP4i/AGI vs PCB/AGI analyzed using the random effects model. The squares indicate an individual study's effects, and the size of the squares corresponds to the study's weight in the meta-analysis, with the horizontal lines extending from the symbols representing 95% confidence intervals (CI). The diamonds indicate pooled estimates.

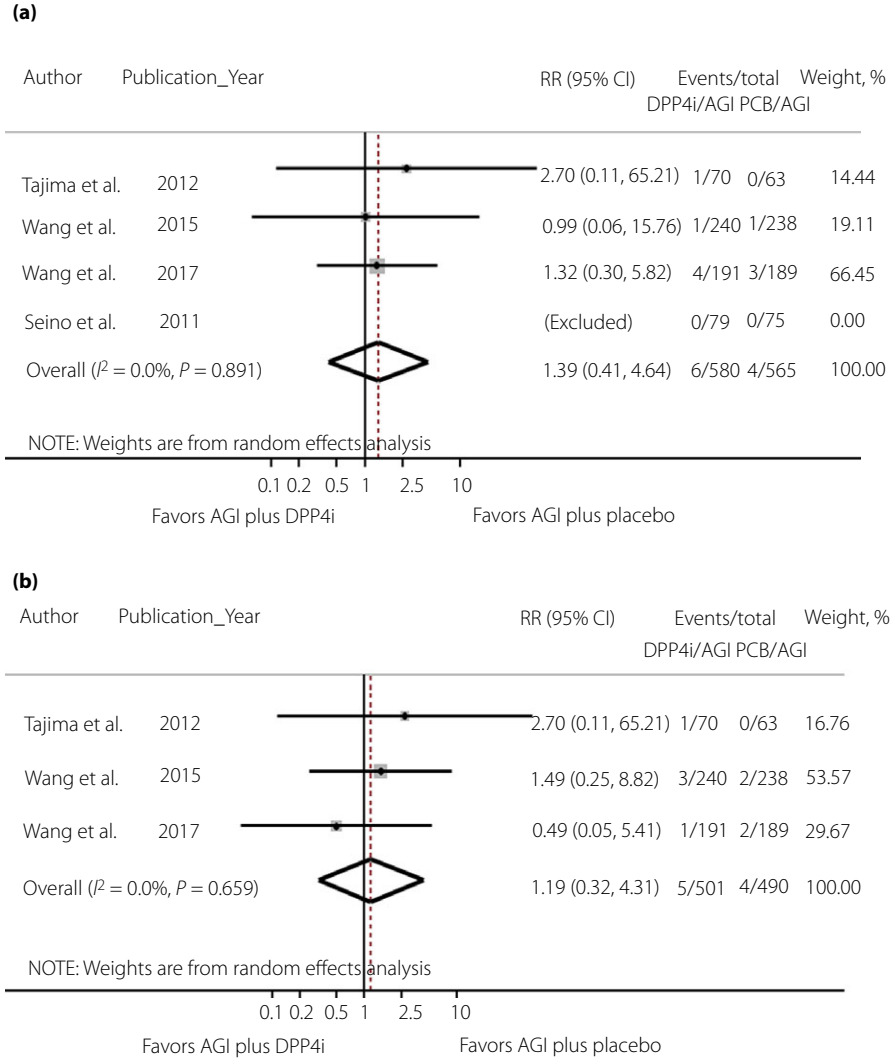

Figure 4 | Meta-analysis for safety outcomes. (a) Relative risk of hypoglycemia with dipeptidyl peptidase-4 inhibitor plus α-glucosidase inhibitor (DPP4i/AGI) vs placebo plus α-glucosidase inhibitor (PCB/AGI) analyzed using the random effects model. (b) Relative risk (RR) of gastrointestinal adverse events with DPP4i/AGI vs PCB/AGI analyzed using the random effects model. The squares indicate an individual study's effects, and the size of the squares corresponds to the study's weight in the meta-analysis, with the horizontal lines extending from the symbols representing 95% confidence intervals (CI). The diamonds indicate pooled estimates.

other studies showed a predominant FPG-lowering effect[22,24]. In contrast to the former two studies, the latter two studies recruited patients with concomitant metformin therapy. However, the discrepancy might not be explained by background metformin therapy, because, even if a DPP4 inhibitor was added on to pre-existing metformin therapy, the PPG-lowering effect was much greater than the FPG-lowering effect[34–38].

Weight gain is one of the most unwanted side-effects when increasing the dose or adding another class of antidiabetic drugs in patients with inadequately controlled type 2 diabetes mellitus. The current meta-analysis found no increase in bodyweight after the addition of a DPP4 inhibitor to an AGI. A meta-analysis that compared acarbose and placebo in patients with type 2 diabetes mellitus showed reduced body mass index

in favor of acarbose[8]. Some AGIs have been reported to reduce appetite and change the gut hormone levels in postprandial status[9,39]. DPP4 inhibitors have neutral effects on bodyweight[40,41]. Whereas GLP-1 decreases bodyweight by acting on the appetite center[42], GIP can increase bodyweight by increasing adipogenesis based on animal experiments[43,44]. Given that the combination of the two agents increases active GLP-1 levels, but might not affect active GIP levels, as discussed above, it might decrease bodyweight or body fat mass. In a 24-week, open-label, parallel, three-arm study on overweight Japanese patients with type 2 diabetes mellitus, miglitol alone or miglitol/sitagliptin combination, but not sitagliptin alone, reduced the total body fat mass and miglitol/sitagliptin reduced visceral fat mass[45]. Therefore, DPP4i/AGI combination therapy might be one of the favorable therapeutic options for overweight/obese type 2 diabetes patients.

The risk of hypoglycemia was not increased when adding DPP4 inhibitors to AGI therapy. In general, AGI monotherapy does not cause hypoglycemia[46]. However, when AGI is combined with sulfonylureas or insulin, it might increase the risk of hypoglycemia[47]. DPP4 inhibitors, when used alone or in combination with metformin, are unlikely to cause hypoglycemia because of the glucose-dependent mode of action with regard to the regulation of insulin and glucagon secretion[48]. Furthermore, DPP4 inhibitors improve α-cell sensitivity to glucose, with a consequent stimulation of α-cell under low glucose levels[49,50]. Therefore, theoretically, the addition of DPP4 inhibitors to AGI should not increase the risk of hypoglycemia, which was in accordance with the present results.

Flatulence, diarrhea and abdominal pain are frequent side-effects of AGIs, with a dose-dependent increase in incidence[51]. In contrast, GI side-effects, such as nausea, vomiting and diarrhea, have been far less reported with DPP4 inhibitors than with GLP-1 receptor agonists, another incretin-based therapy, whose GI side-effects are common and sometimes result in discontinuation of therapy[40,52]. The discrepancy in the incidence of GI side-effects between DPP4 inhibitors and GLP-1 receptor agonists can be explained by different levels of GLP-1 receptor agonism achieved by DPP4 inhibitors and exogenous GLP-1 receptor agonists[53]. In this regard, it was a concern that the combination of AGI and DPP4 inhibitor might increase the incidence of GI side-effects by increasing active GLP-1 levels, but it was not the case observed in the present meta-analysis.

There were some limitations to the present study. First, the number of included studies was small. However, because the results among the included studies were consistent and favored DPP4i/AGI over PCB/AGI, the conclusion of this study seems reliable and robust enough to show the efficacy and safety of the addition of a DPP4 inhibitor to an AGI in patients with type 2 diabetes mellitus. Second, because we could not compare the outcomes among DPP4 inhibitor plus AGI, placebo plus AGI, placebo plus DPP4 inhibitor and placebo alone in patients with type 2 diabetes mellitus who were naïve to DPP4 inhibitors or AGIs, we could not determine whether the glucose-lowering effect of the combination of DPP4 inhibitor and AGI is additive or synergistic. However, considering that DPP4i/AGI did not result in weight loss or GI side-effects more commonly than PCB/AGI, we could infer that this combination therapy seems far less potent in elevating plasma active GLP-1 levels than GLP-1 receptor agonist therapy. Finally, all of the included studies were carried out in Asians, whose glucose-lowering responses to incretin-based therapy are known to be greater than in other ethnic groups[54–56]. To generalize the present results, clinical trials are necessary in other ethnic groups.

In conclusion, the addition of a DPP4 inhibitor to patients with inadequately controlled type 2 diabetes mellitus with AGI therapy achieved a clinically significant improvement in glycemic control without increasing the risk of weight gain and hypoglycemia. Therefore, this combination should be a viable option in the pharmacological therapy for type 2 diabetes mellitus.

ACKNOWLEDGMENTS

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DISCLOSURE

YMC received research grants from AstraZeneca and LG Chemical. The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1 | Study protocol.
Figure S1 | Risk of bias assessment.
Figure S2 | Funnel plot and Egger's test for the primary outcome.