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Meta-analysis and critical review on the efficacy and safety of alpha-glucosidase inhibitors in Asian and non-Asian populations

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ABSTRACT

Aims/Introduction: To evaluate the efficacy and safety of alpha-glucosidase inhibitors (AGI) in Asian and non-Asian type 2 diabetes patients.

Materials and Methods: Studies were identified through a literature search of MEDLINE, EMBASE and other databases until December 2016. All statistical analyses were carried out in Review Manager statistical software by computing the weighted mean difference or odds ratio and 95% confidence interval.

Results: A total of 67 studies were included. AGI vs placebo: compared with the placebo, AGI treatment led to a greater decrease in hemoglobin A1c (HbA1c), fasting plasma glucose and postprandial plasma glucose. No significant difference was observed in HbA1c change, fasting plasma glucose change, postprandial plasma glucose change or incidence of hypoglycemia between Asian and non-Asian patients. AGI vs active controls: in Asian patients, AGI treatment showed a lower reduction in HbA1c compared with dipeptidyl peptidase-4 inhibitors and sulfonylurea. In non-Asian patients, AGI treatment showed a lower reduction in HbA1c compared with thiazolidinedione. No significant difference was observed in HbA1c change and bodyweight change when comparing AGI with other oral hypoglycemic agents between Asian and non-Asian patients.

Conclusions: The effects of AGI treatment on glycemic control and bodyweight reduction were superior to the placebo without an increased incidence of hypoglycemia, but with an increased incidence of gastrointestinal discomforts. The hypoglycemic effects of AGI were comparable between Asian and non-Asian patients.

INTRODUCTION

Diabetes mellitus is a group of chronic disorders characterized by elevated plasma glucose levels, and a series of macrovascular and microvascular disorders. Type 2 diabetes mellitus, which accounts for at least 90% of diabetes mellitus, is characterized by insulin resistance and the progressive loss of pancreatic β-cell function. The prevalence of type 2 diabetes mellitus has increased rapidly in Asian countries in recent years. Currently, China has the largest diabetic population in the world. In adults of aged ≥20 years, the age-standardized prevalence of total diabetes and prediabetes was 9.7% and 15.5%, respectively, according to the China National Diabetes and Metabolic Disorders Study from June 2007 to May 2008 by Yang *et al.*[1]

Alpha-glucosidase inhibitors (AGI), which could delay the absorption of dietary carbohydrates in the gastrointestinal tract by inhibiting the alpha-glucosidase enzymes, are widely used in the treatment of patients with type 2 diabetes mellitus[2]. AGI is one of the second-line oral hypoglycemic agents (OHAs), and is usually used as monotherapy for mild diabetes, and in combination with other oral drugs or insulin for severe diabetes[3].

Many randomized controlled trials (RCTs) have assessed the efficacy of AGI in lowering plasma glucose levels, as well as bodyweight, with a low risk of hypoglycemia compared with a placebo or other OHAs in both Asian and non-Asian patients[4–7]. Similarly, literature reviews and meta-analyses have also reported the beneficial effects of AGI on glycemic control and pancreatic β-cell function[8–10]. A study by Hara *et al.*[11] in 1996 showed that the efficacy of α-glucosidase inhibitors treatment was more continuous and significant in the high

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carbohydrate group than in the low carbohydrate group in the 6-month follow-up study. Thus, the present meta-analysis was designed to evaluate the clinical efficacy and safety of AGI in Asian and non-Asian patients, and to compare the effects of AGI therapy between Asian and non-Asian diabetes patients. It was hypothesized that because of the different percentage of carbohydrates in the diets of Asian type 2 diabetes mellitus patients and non-Asian type 2 diabetes mellitus patients, and according to the previous study published, there might be different efficacy in α-glucosidase inhibitors treatment.

METHODS

Search strategy

Studies were identified through a literature search of MEDLINE, EMBASE and other databases. The electronic search was first carried out in December 2015, and was repeated in December 2016. References were collected until December 2016. The search was carried out using the following terms: type 2 diabetes, AGI, acarbose, voglibose, miglitol, RCTs and clinical trials.

Study selection and data extraction

Studies selected from the databases were assessed for eligibility by two investigators independently, based on the inclusion criteria below. When discrepancies occurred, a third investigator was invited to carry out additional assessment of the study. To evaluate the hypoglycemic efficacy and safety of AGI, and to compare the differences between Asian and non-Asian patients, the reduction of hemoglobin A1c (HbA1c) from the baseline of both AGI and a placebo or other OHAs treatment should be reported in a study. Therefore, the inclusion criteria were: (i) type 2 diabetes patients aged ≥18 years; (ii) placebo-controlled or active-controlled trials of AGI treatment; (iii) study duration >12 weeks; (iv) the efficacy of glucose control was the primary outcome of the study; and (v) trials were double-blind RCTs. Exclusion criteria were: (i) non-RCTs carried out in type 2 diabetes mellitus patients; (ii) trials in type 1 diabetes patients; and (iii) study duration <12 weeks. A study was categorized as being carried out in Asian patients if ≥50% of participants were Asian, and as non-Asian if ≥50% of participants were non-Asian.

Similar to study selection, data extraction was also completed by two independent investigators. Using a standardized form, the following data were collected: author, publication year, treatment group, study duration, baseline characteristics of patients (sample size, age, diabetic duration, HbA1c, fasting plasma glucose [FPG], postprandial plasma glucose [PPG], body mass index [BMI], bodyweight, total cholesterol [TC], triglycerides [TG], low-density lipoprotein cholesterol [LDL], high-density lipoprotein cholesterol [HDL]) and outcome measures (change from baseline to study end-points for HbA1c, FPG, PPG, bodyweight, TC, TG, LDL, HDL, incidence of hypoglycemia, flatulence, diarrhea, abdominal pain, constipation).

Statistical analysis

All statistical analyses were carried out in Review Manager statistical software (version 5.3; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). I^2 statistics were provided to quantify the between-study heterogeneity. A value of $P \geq 0.10$ or $I^2 < 50\%$ was considered to show homogeneity, then treatment effects were analyzed using a fixed-effect model. Otherwise, a random effects model was used.

Descriptive analysis of the baseline age, sex, diabetes duration, baseline HbA1c, BMI, and bodyweight was used for the demographics and baseline characteristics of patients before treatment. The weighted mean difference (WMD) and 95% confidence intervals (CI) were used to evaluate the changes of HbA1c, FPG, PPG and bodyweight from baseline to study end-point. The odds ratio (OR) and 95% CI were provided to evaluate the rate of adverse effects. Results are expressed as *P*-values, and $P < 0.05$ represented a statistically significant difference. We assessed publication bias by visual inspection of the funnel plot. The quality and the risk of bias of included studies were assessed according to the Cochrane Handbook guidelines.

RESULTS

Search results and study characteristics

The study selection process is summarized in Figure 1. After a literature search and review in detail, 67 articles were judged to be appropriate for inclusion in the meta-analysis in the end. Among the 67 studies, 29 were carried out in Asian patients, and 38 were carried out in non-Asian patients. Among the 29 studies in Asian patients, nine compared AGI with placebo therapy[4,7,12–18], and 21 compared AGI with other OHAs, such as dipeptidyl peptidase-4 (DPP-4) inhibitors[7,19–26], metformin (MET)[27,28], sulfonylureas (SU)[29–32], glinides[33–35] and thiazolidinedione (TZD)[30,36]. Among the 38 studies in non-Asian patients, 33 compared AGI with placebo therapy[5,6,37–67], and 12 compared AGI with other OHAs, such as MET[37,42,66,68], SU[38,41,59,64,69,70] and TZD[68,71,72]. Baseline characteristics of patients are shown in Table 1. Age, percentage of males, baseline HbA1c, and diabetes duration were comparable between Asian and non-Asian patients. However, baseline BMI and bodyweight were significantly higher in non-Asian patients compared with that of Asian patients (details of included studies are given in Table S1.)

Methodological quality

All the studies comprised an AGI treatment group and a placebo or other OHA treatment group as a control group in a RCT. Eligibility criteria were clearly reported in all studies. All these studies stated whether they tested for balanced baseline characteristics between the comparison groups. Funnel plots assessing the precision of the data suggested a low risk of publication bias (data not shown). The quality and the risk of bias of included studies were assessed according to the Cochrane Handbook guidelines. Overall, the risk of bias was low (results are shown in Figure S1).

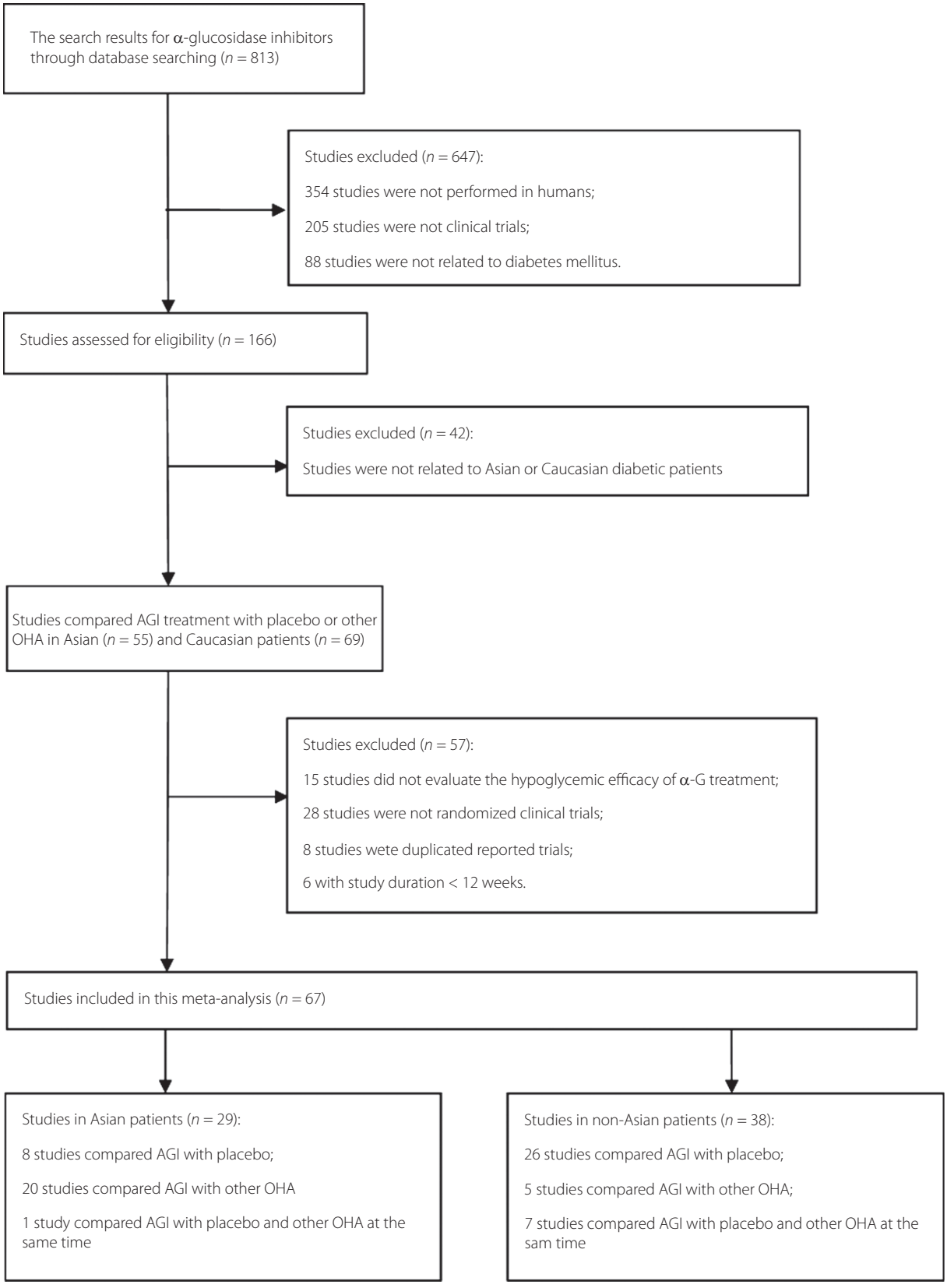

Figure 1 | The flowchart of studies included in this meta-analysis. AGI, alpha-glucosidase inhibitors.

Table 1 | Baseline characteristics of patients receiving alpha-glucosidase inhibitors treatment compared with the placebo or other oral hypoglycemic agents

	Asian				Non-Asian			
	AGI	Placebo	AGI	Other OHA	AGI	Placebo	AGI	Other OHA
No. studies	9	9	21	21	33	33	12	12
No. patients	634	555	2050	2388	2348	2225	636	624
Age (years)	58 ± 4.26	57.75 ± 5.18	59.12 ± 5.26	59.64 ± 4.94	58.80 ± 3.63	58.92 ± 4.19	58.29 ± 3.85	56.04 ± 3.11
Male (%)	54.99 ± 14.39	50.74 ± 14.06	63.26 ± 9.06	61.89 ± 12.04	55.12 ± 14.56	55.54 ± 12.39	54.28 ± 20.67	52.93 ± 14.28
Baseline BMI (kg/m^2)	24.96 ± 0.53	24.63 ± 0.86	25.70 ± 0.99	25.52 ± 1.28	29.72 ± 2.54	29.79 ± 2.72	28.83 ± 1.97	28.87 ± 2.15
DM duration (years)	7.76 ± 5.93	7.25 ± 5.68	5.91 ± 4.14	6.11 ± 4.24	6.68 ± 3.16	6.14 ± 2.91	7.56 ± 4.32	7.16 ± 3.84
Baseline HbA1c (%)	8.48 ± 1.33	8.41 ± 1.18	7.65 ± 0.59	7.81 ± 0.67	8.14 ± 1.23	8.17 ± 1.20	8.60 ± 0.76	8.78 ± 0.78
Baseline bodyweight (kg)	63.88 ± 1.85	63.57 ± 3.14	68.68 ± 4.59	67.77 ± 4.18	83.14 ± 9.47	83.26 ± 8.38	81.06 ± 5.97	81.41 ± 5.31

Data are presented as mean ± standard deviation. AGI, alpha-glucosidase inhibitor; BMI, body mass index; DM, diabetes mellitus; HbA1c, hemoglobin A1c; OHA, oral hypoglycemic agents.

Efficacy and adverse effects of AGI treatment vs placebo in Asian type 2 diabetes mellitus patients

Pooled analysis of the data from Asian patients showed that treatment with AGI was associated with a significantly greater decrease in HbA1c levels from baseline (WMD −0.55%, 95% CI −0.64 to −0.45%, $P < 0.00001$) than that with placebo therapy. Separately, AGI treatment led to greater decreases in HbA1c both in monotherapy (WMD −0.44%, 95% CI −0.46 to −0.42%, $P < 0.00001$) and in add-on therapy (WMD −0.59%, 95% CI −0.66 to −0.52%, $P < 0.00001$) compared with placebo. Compared with the placebo, AGI treatment also resulted in significantly greater reductions in FPG levels (WMD −0.61 mmol/L, 95% CI −0.89 to −0.33 mmol/L, $P < 0.0001$), 1-h PPG levels (WMD −2.16 mmol/L, 95% CI −3.37 to −0.95 mmol/L, $P < 0.0005$) and 2-h PPG levels (WMD −3.00 mmol/L, 95% CI −3.58 to −2.42 mmol/L, $P < 0.00001$) than placebo therapy.

In Asian patients, AGI treatment was associated with a slightly greater reduction in bodyweight than placebo therapy (WMD −0.63 kg, 95% CI −1.23 to −0.03 kg, $P = 0.04$). No statistically significant difference was found in the change of TC, TG, LDL or HDL levels between AGI and placebo therapy (details are shown in Table 2).

Compared with placebo therapy, treatment with AGI did not show an increased incidence of hypoglycemia (OR 1.25, 95% CI 0.82–1.91, $P = 0.30$) in Asian patients. AGI also did not increase the incidence of hypoglycemia when used as an add-on therapy. Compared with the placebo, treatment with AGI led to a significantly increased incidence of flatulence (OR 3.24, 95% CI 2.29–4.58, $P < 0.00001$) and diarrhea (OR 3.25, 95% CI 1.78–5.94, $P = 0.0001$).

Efficacy and adverse effects of AGI treatment vs placebo in Non-Asian type 2 diabetes mellitus patients

Analysis of the data from non-Asian patients showed that treatment with AGI was associated with a significantly greater decrease in HbA1c levels from baseline (WMD −0.71%, 95% CI −0.79 to −0.64%, $P < 0.00001$) than treatment with the placebo. Compared with the placebo, AGI treatment resulted in a significantly greater reduction in FPG levels (WMD −0.98 mmol/L, 95% CI −1.17 to −0.78 mmol/L, $P < 0.00001$), 1-h PPG levels (WMD −2.49 mmol/L, 95% CI −3.31 to −1.67 mmol/L, $P < 0.00001$) and 2-h PPG levels (WMD −2.33 mmol/L, 95% CI −3.29 to −1.37 mmol/L, $P < 0.00001$) than placebo therapy.

In non-Asian patients, treatment with AGI showed a significantly greater decrease in bodyweight (WMD −0.48 kg, 95% CI −0.92 to −0.05 kg, $P = 0.03$) than placebo therapy. The TG level also significantly decreased (WMD −0.21 mmol/L, 95% CI −0.34 to −0.09 mmol/L, $P = 0.0010$) in AGI treatment compared with placebo therapy. However, no statistically significant difference was found in the change of TC, LDL or HDL levels between AGI and placebo therapy (details are shown in Table 2).

Compared with placebo therapy, treatment with AGI showed an increased incidence of hypoglycemia (OR 1.75, 95% CI 1.19–2.55, $P = 0.004$) in terms of all included patients. When used as an add-on therapy, AGI also showed an increased incidence of hypoglycemia (OR 1.96, 95% CI 1.27–3.03, $P = 0.002$). However, when used as a monotherapy, AGI showed a comparable incidence of hypoglycemia with the placebo. Compared with placebo therapy, AGI treatment showed an increased incidence of flatulence (OR 6.93, 95% CI 5.81–8.27, $P < 0.00001$), diarrhea (OR 4.53, 95% CI 3.70–5.55, $P < 0.00001$) and abdominal pain (OR 2.83, 95% CI 1.91–4.20, $P < 0.00001$).

Comparisons between Asian and Non-Asian patients in AGI vs placebo treatment

When AGI was compared with the placebo, no significant difference was observed in HbA1c change, FPG change, 1-h PPG

Table 2 | Glycemic control, bodyweight change and lipid profile changes of alpha-glucosidase inhibitor treatment compared with the placebo in Asian and non-Asian patients with type 2 diabetes

Variables	Asian				Non-Asian				Difference	95% CI	*P*-value
	No. studies	No. participants	WMD from baseline	95% CI	No. studies	No. participants	WMD from baseline	95% CI			
HbA1c (%)											
Acarbose	5	214/212	−0.58*	−0.74, −0.42	26	1,417/1,461	−0.73*	−0.81, −0.65	−0.10	−0.76, 0.55	0.751
Miglitol	2	159/153	−0.55*	−0.79, −0.31	7	824/636	−0.66*	−0.82, −0.50	−0.01	−1.04, 1.02	0.983
Voglibose	2	211/135	−0.50*	−0.62, −0.38	–	–	–	–	–	–	–
Total	9	584/500	−0.55*	−0.64, −0.45	33	2,241/2,097	−0.71*	−0.79, −0.64	0.097	−0.42, 0.62	0.709
FPG (mmol/L)											
Acarbose	4	194/192	−0.73*	−0.85, −0.61	25	1,362/1,408	−0.99*	−1.26, −0.73	0.19	−0.83, 1.21	0.702
Total	6	408/325	−0.61*	−0.89, −0.33	32	2,186/2,044	−0.98*	−1.17, −0.78	0.39	−0.40, 1.19	0.318
PPG-1h (mmol/l)	3	140/139	−2.16*	−3.37, −0.95	7	350/350	−2.49*	−3.31, −1.67	0.90	−0.45, 2.24	0.164
PPG-2 h (mmol/L)	4	233/226	−3.00*	−3.58, −2.42	20	1475/1310	−2.33*	−3.29, −1.37	−0.29	−1.80, 1.22	0.692
Bodyweight (kg)	4	211/215	−0.63	−1.23, −0.03	21	1,048/1,054	−0.48*	−0.92, −0.05	0.45	−1.28, 2.18	0.599
TC (mmol/L)	4	214/213	0.07	−0.10, 0.24	15	876/681	0.00	−0.27, 0.27	−0.032	−0.71, 0.64	0.923
TG (mmol/L)	4	214/213	−0.03	−0.39, 0.33	19	1,105/926	−0.21*	−0.34, −0.09	−0.068	−0.58, 0.44	0.788
LDL-C (mmol/L)	4	214/213	0.12	−0.05, 0.29	9	680/485	−0.02	−0.19, 0.15	−0.026	−0.73, 0.67	0.936
HDL-C (mmol/L)	3	169/169	0.02	−0.04, 0.08	13	791/596	0.01	−0.02, 0.04	−0.081	−0.17, 0.010	0.076

**P*-value <0.05. FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PPG, postprandial plasma glucose; TC, total cholesterol; TG, triglycerides.

change or 2-h PPG change between Asian and non-Asian patients. Similarly, both Asian and non-Asian patients showed comparable changes in bodyweight, TC, TG, LDL and HDL when AGI was compared with the placebo (details are shown in Table 2).

When compared with the placebo, AGI treatment in non-Asian patients showed a significantly increased incidence of diarrhea (−0.19, 95% CI −0.33–0.045, $P = 0.013$) compared with AGI treatment in Asian patients. However, no significant difference was observed in the incidence of flatulence and abdominal pain. Compared with the placebo, the incidence of hypoglycemia in AGI treatment was comparable between Asian and non-Asian patients (details are shown in Table 3).

Efficacy of AGI treatment vs active controls in Asian and Non-Asian Patients

In Asian patients, AGI treatment was associated with a significantly lower reduction in HbA1c levels than DPP-4 inhibitors (WMD 0.36%, 95% CI 0.20–0.52%, $P < 0.00001$), and a slightly lower reduction in HbA1c levels compared with SU (WMD 0.46%, 95% CI 0.03–0.88%, $P = 0.04$). No statistically significant difference was observed in HbA1c reduction between AGI and MET, AGI and TZD or AGI and glinides in Asian patients. In non-Asian patients, AGI treatment was associated with a significantly lower reduction in HbA1c levels (WMD 0.71%, 95% CI 0.27–1.16%, $P = 0.002$) than TZD. No statistically significant difference was observed in HbA1c reduction between AGI and MET or AGI and SU in non-Asian patients. Between Asian and non-Asian patients, no significant difference was observed in HbA1c change when comparing AGI with MET, AGI with SU or AGI with TZD (details are shown in Table 4).

In Asian patients, AGI treatment led to a significantly lower reduction in FPG levels than MET (WMD 0.23 mmol/L, 95% CI 0.21 to 0.26 mmol/L, $P < 0.00001$) and DPP-4 inhibitors (WMD 0.41 mmol/L, 95% CI 0.05 to 0.78 mmol/L, $P = 0.03$). No statistically significant difference was observed in FPG reduction between AGI and SU or AGI and glinide. In non-Asian patients, AGI treatment was associated with a significantly lower reduction in FPG levels than SU (WMD 1.45 mmol/L, 95% CI 0.50 to 2.40 mmol/L, $P = 0.003$), a significantly lower decrease in 2-h PPG levels than MET (WMD 0.83 mmol/L, 95% CI 0.69 to 0.97 mmol/L, $P < 0.00001$). When compared with MET, AGI treatment in Asian patients was associated with a significantly greater decrease in 2-h PPG levels (−1.77 mmol/L, 95% CI −1.98 to −1.55 mmol/L, $P = 0.001$) than in non-Asian patients. Between Asian and non-Asian patients, no significant difference was observed in FPG change when comparing AGI with MET or AGI with SU (details are shown in Table 4).

In Asian patients, AGI treatment resulted in a significantly greater decrease in bodyweight than MET (WMD −0.63 kg, 95% CI −0.77 to −0.49 kg, $P < 0.00001$) and DPP-4 inhibitors (WMD −0.83 kg, 95% CI −1.15 to −0.50 kg, $P < 0.00001$). In

Table 3 | Safety and adverse effects of alpha-glucosidase inhibitor treatment compared with the placebo in Asian and non-Asian patients with type 2 diabetes

Variables	Asian					Non-Asian					*P*-value of difference
	No. studies	No. participants	No. adverse effects	OR	95% CI	No. studies	No. participants	No. adverse effects	OR	95% CI	
Hypoglycemia											
Mono	–	–	–	–	–	5	293/296	14/12	1.15	0.52, 2.58	–
Add-on	4	245/238	69/58	1.23	0.80, 1.89	7	657/674	69/41	1.96*	1.27, 3.03	0.407
Total	5	407/318	71/58	1.25	0.82, 1.91	12	950/970	83/53	1.75*	1.19, 2.55	0.278
Gastrointestinal events											
Flatulence	8	472/420	164/74	3.24*	2.29, 4.58	19	1,656/1,393	1,047/313	6.93*	5.81, 8.27	0.083
Diarrhea	6	355/304	46/15	3.25*	1.78, 5.94	17	1,572/1,309	595/155	4.53*	3.70, 5.55	0.013*
Abdominal pain	2	77/76	5/1	3.87	0.61, 24.36	11	849/778	107/36	2.83*	1.91, 4.20	0.453
Constipation	2	99/55	7/0	9.00	0.50, 160.65	4	291/308	29/22	1.45	0.81, 2.59	0.819

*P-value <0.05.

non-Asian patients, AGI treatment led to a significantly greater decrease in bodyweight compared with SU (WMD −2.80 kg, 95% CI −3.24 to −2.35 kg, $P < 0.00001$) and TZD (WMD −3.09 kg, 95% CI −4.01 to −2.17 kg, $P < 0.00001$). Between Asian and non-Asian patients, no significant difference was observed in bodyweight change when comparing AGI with MET or comparing AGI with SU (details are shown in Table 4).

Meta-regression analysis between baseline BMI and glycemic control or bodyweight change

Results from meta-regression analysis showed that adjusted by the baseline age, percentage of males, duration of diabetes and baseline HbA1c, HbA1c change from baseline corrected by the placebo was not associated with baseline BMI, and bodyweight change from baseline corrected by the placebo was not associated with baseline BMI either ($P < 0.05$).

DISCUSSION

According to the results of the present meta-analysis, the placebo-corrected HbA1c, FPG, and PPG changes between Asian and non-Asian populations did not show any significant difference. Bodyweight change and lipid profile changes between Asian and non-Asian patients were also comparable. In addition, the incidence of hypoglycemia, flatulence, diarrhea, and constipation were comparable between Asian and non-Asian populations. However, the incidence of diarrhea (difference −0.19, 95% CI −0.33 to 0.045, $P = 0.013$) was significantly higher in non-Asian populations. The results of hypoglycemic effects were not consistent with those of Hara *et al.*[11] The possible reasons might be as follows. First, the study of Hara *et al.* was a prospective, real-world study, whereas the studies included in our meta-analysis were all randomized controlled trials. The results from the real world were sometimes different from those from clinical registered studies. Second, the risk of bias might be another possible reason. No randomization was used in the real-world studies, which might be associated with selection bias, as the baseline characteristics might influence the results. Whereas in the meta-analysis, the high heterogeneity might be associated with some risk of bias, though we did not carry out sensitivity analysis and meta-regression analysis.

The placebo-corrected efficacy in AGI treatment of our meta-analysis is in accordance with the results from previous meta-analyses. One meta-analysis reported by Van de Laar *et al.*[73] showed that in clinical trials (36 trials in Caucasians and 5 trials in Asians), acarbose decreased HbA1c by 0.77%, miglitol by 0.68% and voglibose yielded a difference of 0.47%. For FPG, acarbose was associated with a mean FPG reduction of 1.09 mmol/L, miglitol 0.52 mmol/L and voglibose 0.60 mmol/L. Van de Laar *et al.*[73] also found that bodyweight change, and TC, LDL, and HDL change were comparable between AGI treatment and the placebo. However, they found a small effect of −0.09 mmol/L for acarbose on TG that was borderline statistically significant (95% CI 0.18 to 0.00, $P = 0.06$), which was nearly consistent with the TG change in non-Asian patients in our meta-analysis. The results of another meta-analysis by Hanefeld *et al.*[74] also showed that TG levels significantly decreased during acarbose treatment compared with the placebo ($P < 0.001$). AGI acts by delaying the enzymatic breakdown of carbohydrates in the small intestine[2], and thus directly reduces postprandial blood glucose. Evidence that other AGI mechanisms are involved in glycemic control is yet to be found. The same applies to its effect on blood lipids, which might be secondary owing to improved PPG. However, the exact mechanism remains unclear.

AGI improves postprandial glycemic control by delaying the absorption of carbohydrates in the small intestine without promoting the secretion of insulin. Therefore, AGI treatment did not increase the risk of hypoglycemia when used as a monotherapy according to the results of many previous

Table 4 | Glycemic control and body weight change of alpha-glucosidase inhibitor treatment compared with active controls in Asian and non-Asian patients with type 2 diabetes

Variables	Asian				Non-Asian				Difference	95% CI	*P*-value
	No. studies	No. participants	WMD from baseline	95% CI	No. studies	No. participants	WMD from baseline	95% CI			
HbA1c (%)											
AGI vs MET	2	273/404	0.05	−0.07, 0.17	4	159/158	0.47	−0.06, 1.01	−0.49	−2.63, 1.65	0.560
AGI vs SU	4	75/67	0.46*	0.03, 0.88	6	151/147	0.50	−0.22, 1.22	−0.33	−1.25, 0.60	0.486
AGI vs glinide	3	72/69	0.07	−0.09, 0.23	–	–	–	–	–	–	–
AGI vs TZD	2	30/32	0.16	−0.40, 0.72	3	326/319	0.71*	0.27, 1.16	−0.04	−0.61, 0.53	0.836
AGI vs DPP-4i	11	1,189/1,414	0.36*	0.20, 0.52	–	–	–	–	–	–	–
FPG (mmol/L)											
AGI vs MET	2	273/404	0.23*	0.21, 0.26	3	128/131	0.23	−0.82, 1.28	−0.47	−2.43, 1.50	0.504
AGI vs SU	2	32/39	0.57	−0.56, 1.70	6	151/147	1.45*	0.50, 2.40	−1.3	−2.66, 0.058	0.058
AGI vs glinide	3	72/69	0.10	−0.49, 0.69	–	–	–	–	–	–	–
AGI vs TZD	–	–	–	–	3	326/319	0.56	−0.43, 1.56	–	–	–
AGI vs DPP-4i	10	1,158/1,390	0.41*	0.05, 0.78	–	–	–	–	–	–	–
PPG-1 h (mmol/L)											
AGI vs MET	–	–	–	–	3	144/144	0.13	−0.40, 0.65	–	–	–
AGI vs SU	–	–	–	–	5	131/129	−0.09	−0.91, 0.72	–	–	–
AGI vs glinide	–	–	–	–	–	–	–	–	–	–	–
AGI vs TZD	–	–	–	–	–	–	–	–	–	–	–
AGI vs DPP-4i	–	–	–	–	–	–	–	–	–	–	–
PPG-2 h (mmol/L)											
AGI vs MET	2	273/404	−0.34	−1.42, 0.73	2	97/100	0.83*	0.69, 0.97	−1.77	−1.98, −1.55	0.001*
AGI vs SU	–	–	–	–	–	–	–	–	–	–	–
AGI vs glinide	–	–	–	–	–	–	–	–	–	–	–
AGI vs TZD	–	–	–	–	2	190/190	0.67	−2.30, 3.63	–	–	–
AGI vs DPP-4i	3	526/539	0.91	−0.42, 2.24	–	–	–	–	–	–	–
Bodyweight (kg)											
AGI vs MET	2	273/404	−0.63*	−0.77, −0.49	4	159/159	−0.40	−1.92, 1.12	−2.56	−7.41, 2.30	0.218
AGI vs SU	3	60/52	−1.59	−6.66, 3.49	3	92/94	−2.80*	−3.24, −2.35	−0.47	−1.50, 0.56	0.277
AGI vs glinide	–	–	–	–	–	–	–	–	–	–	–
AGI vs TZD	–	–	–	–	3	326/319	−3.09*	−4.01, −2.17	–	–	–
AGI vs DPP-4i	9	996/1,231	−0.83*	−1.15, −0.50	–	–	–	–	–	–	–

**P*-value <0.05. AGI, alpha-glucosidase inhibitors; DPP-4 inhibitors, dipeptidyl peptidase-4; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; MET, metformin; PPG, postprandial plasma glucose; SU, sulfonylureas; TZD, thiazolidinedione.

studies[20,27,44], which were consistent with the present results. However, our meta-analysis also found that AGI as add-on therapy was associated with an increased risk of hypoglycemia in non-Asian populations. This phenomenon could be attributed to the use of combined agents, such an SU, glinides and DPP-4 inhibitors, which could promote insulin secretion and increase the risk of hypoglycemia accordingly.

The incidence of flatulence, abdominal pain, and constipation were comparable between Asian and non-Asian populations. However, the incidence of diarrhea was significantly higher in non-Asian populations. Because of the specific mechanism, the adverse effects of AGI were mostly gastrointestinal. Results from other meta-analyses also found an increased incidence of gastrointestinal discomforts related to AGI, such as flatulence, diarrhea, abdominal pain and constipation. Van de Laar *et al.*[73] found that patients treated with acarbose had significantly more gastrointestinal adverse effects, and these adverse effects were dose-dependent. The frequency of adverse effects might vary among different districts. Hanefeld *et al.*[74] found that the most common complaints in AGI treatment were gastrointestinal side-effects, and the frequency of any adverse effects varied from country to country.

According to the present results, HbA1c change, FPG change, and bodyweight change were comparable between Asian and non-Asian patients in AGI treatment, compared with MET, SU and TZD. However, compared with MET, AGI treatment in Asian patients was associated with a greater decrease in 2-h PPG than in non-Asian patients. Compared

with DPP-4 inhibitors, AGI treatment showed a lower decrease in HbA1c and FPG, a greater decrease in bodyweight, and a comparable change in PPG. Consistent with the present results, another meta-analysis in 2013 by Zhu *et al.*[75] showed that acarbose monotherapy generally had a similar ability to MET, SU and glinides to reduce HbA1c levels. However, different from the present results, Zhu *et al.*[75] found that acarbose achieved a greater absolute reduction of HbA1c levels with Eastern diets (East and Southeast Asian countries) than with the Western diet (European and North American countries) in type 2 diabetes patients. On the basis of this phenomenon, the author suggested that AGI was more efficacious in type 2 diabetes mellitus patients with the Eastern diet, which was attributed to the specific mechanism of AGI. However, we did not achieve a similar conclusion from our meta-analysis. The possible reason for this might be that the inclusion criteria for these two meta-analyses were different, which led to different included studies. Second, the quality of some studies involving the Eastern diet group was low in the article by Zhu *et al.*, and should not be included in the meta-analysis because of the potential for publication and performance biases. Additionally, the number of studies and patients included in MET treatment, SU treatment, TZD treatment and glinides treatment was limited in the present meta-analysis, and this limited sample size might also have influenced our results. Therefore, more high-quality RCTs are required in the future to obtain more valuable and reliable conclusions. The glycemic results of DPP-4 inhibitors were consistent with a previous meta-analysis from Cai *et al.*[10] As stated by Iwamoto[20], different mechanisms of the two types of drugs might explain this result. The mechanism of AGI involves delaying the absorption of carbohydrates in the small intestine, whereas the mechanism of DPP-4 inhibitors involves improving insulin secretion and reducing glucagon secretion, promoting both fasting and postprandial glycemic control.

The present meta-analysis systematically evaluated the efficacy and safety of AGI treatment in Asian and non-Asian type 2 diabetes patients, and compared the differences between Asian and non-Asian patients. However, the meta-analysis had several potential limitations. First, data from different studies were synthesized to assess the treatment efficacy and safety of AGI. The inclusion criteria, baseline characteristics and titration of the study drugs might have been different among all studies, which could lead to bias of the results. Second, we discussed the effects of AGI treatment compared with different control groups; however, the number of included trials in some groups were low, such as AGI vs MET in Asian patients, and AGI vs DPP-4 inhibitors in Caucasian patients, which might influence the results of the meta-analysis. Finally, the problem of publication bias cannot be ignored, because publication bias might have negatively influenced the results observed to some extent, though assessment of publication bias using the funnel plot was carried out to minimize the risk. In addition, the meta-analysis had its limitation in analyzing the percentage of carbohydrates in Asian and Caucasian type 2 diabetes mellitus patients due to the absence of data in the included studies. This might be a new point in our future analysis.

According to our meta-analysis, the effects of AGI treatment on glycemic control and bodyweight reduction were superior to the placebo, without an increased incidence of hypoglycemia, whereas with an increased incidence of gastrointestinal discomforts. The hypoglycemic effect of AGI treatment was not superior to other OHAs, such as MET, SU, TZD and DPP-4 inhibitors. Additionally, the hypoglycemic effects and hypoglycemia risk of AGI treatment were comparable between Asian and non-Asian type 2 diabetes patients.

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DISCLOSURE

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:

Table S1 | Characteristics of randomized controlled trials in alpha-glucosidase inhibitors treatment of Asian and non-Asian patients with type 2 diabetes

Figure S1 | Evaluation of risk of bias of included studies. (a) Summary of risk of bias of studies in Asian patients. (b) Summary of risk of bias of studies in non-Asian patients.