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Efficacy and safety of alogliptin versus acarbose in Chinese type 2 diabetes patients with high cardiovascular risk or coronary heart disease treated with aspirin and inadequately controlled with metformin monotherapy or drug-naive: A multicentre, randomized, open-label, prospective study (ACADEMIC)

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Abstract

Aims: To demonstrate the noninferiority of alogliptin to acarbose, in terms of antidiabetic efficacy, in Chinese people with uncontrolled type 2 diabetes (T2D) and high cardiovascular risk.

Materials and Methods: ACADEMIC (NCT03794336) was a randomized, open-label, phase IV study conducted at 46 sites in China. Antidiabetic treatment-naive or metformin-treated adults with uncontrolled T2D (glycated haemoglobin [HbA1c] 58.0–97.0 mmol/mol) were randomized 2:1 to alogliptin 25 mg once daily or acarbose 100 mg three times daily for 16 weeks. All participants had a documented history of coronary heart disease or high cardiovascular risk at screening and received aspirin (acetylsalicylic acid) 100 mg daily throughout the trial. The primary endpoints were change in HbA1c versus baseline, and the incidence of gastrointestinal adverse events (AEs). Safety and tolerability were also assessed.

Results: A total of 1088 participants were randomized. Alogliptin was noninferior to acarbose for the change in Week-16 HbA1c (least-squares mean change [standard error] −11.9 [0.4] vs. −11.4 [0.5] mmol/mol, respectively; difference between arms −0.5 [0.7] mmol/mol; 95% confidence interval −1.9 to 0.8 mmol/mol), and was associated with a lower incidence of gastrointestinal AEs (8.9% vs. 33.6%, respectively; $P < 0.0001$). More alogliptin than acarbose recipients achieved HbA1c <53.0 mmol/mol without gastrointestinal AEs (48.0% vs. 32.7%; $P < 0.0001$). Discontinuations due to treatment-related AEs were less frequent with alogliptin than acarbose (0.3% vs. 2.5%).

Conclusions: Glycaemic control was comparable between alogliptin and acarbose, but the gastrointestinal tolerability of alogliptin was better. More patients achieved

target HbA1c without gastrointestinal AEs with alogliptin, suggesting that this agent may be preferred in clinical practice.

KEYWORDS
cardiovascular disease, DPP-IV inhibitor, glycaemic control, phase IV study, randomised trial, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes (T2D) is a progressive metabolic disease that causes significant morbidity and mortality worldwide.[1] In China, the prevalence of diabetes has increased from 1.3% in 1980 to 12.8% in 2018.[2,3] An estimated 130 million people in China have diabetes,[2] making it the country with the largest population of people with diabetes in the world.[4]

Studies have demonstrated that T2D is an independent predictor of cardiovascular disease (CVD).[5,6] People with T2D not only have a significantly increased risk of all-cause death and death from cardiovascular causes,[5] but the risk is further increased in individuals with T2D and other cardiovascular risk factors, such as hypertension.[7] Therefore, cardiovascular risk reduction is now a central pillar of T2D management.[8,9]

Chinese guidelines for T2D management recommend low-dose aspirin, unless contraindicated, for secondary prevention in all individuals with T2D and pre-existing CVD and for primary prevention in those at high cardiovascular risk.[10] Although the clinical utility of aspirin for CVD prevention is well established, it is associated with an increased risk of gastrointestinal adverse events (AEs), even at low doses, with a 3-month incidence of endoscopic ulcers of 7%.[11] In one randomized controlled study in patients at risk of aspirin-associated gastric ulcer, the 6-month incidence of endoscopic gastric ulcers was 8.6% in individuals receiving enteric-coated aspirin 325 mg/d, and 8.2% of aspirin recipients had to discontinue treatment because of gastrointestinal AEs.[12]

Gastrointestinal tolerability may be problematic in patients with T2D receiving oral antidiabetic agents (OADs) together with aspirin. In the placebo-controlled ACE study, which enrolled people with T2D and high cardiovascular risk, 94% of whom were taking aspirin, 7% of those randomized to the alpha-glucosidase inhibitor (AGI) acarbose withdrew from the study due to gastrointestinal AEs (vs. 5% of those randomized to placebo).[13] As T2D progresses, additional antidiabetic agents may be required to maintain (or regain) glycaemic control, and these may have adverse gastrointestinal effects of their own. Thus, the additive gastrointestinal toxicity of antidiabetic therapy may be an important consideration in individuals who require aspirin.

When glycaemic control is inadequate despite lifestyle modification, Chinese T2D guidelines recommend metformin as the first-line OAD of choice.[10] If metformin monotherapy is suboptimally effective, the addition of a second OAD is recommended, with the main options being AGIs, insulin secretagogues, thiazolidinediones, and dipeptidyl peptidase-4 (DPP-4) inhibitors. However, in clinical practice in China (and other East Asian countries), acarbose is commonly used as monotherapy for patients with mild T2D, and in combination with metformin for those with more advanced diabetes. Both metformin and acarbose are associated with gastrointestinal AEs,[14] the risk of which is increased further when these two agents are used in combination.[15,16]

Clinical practice guidelines in the United States differ from the guidelines in China in that they specify DPP-4 inhibitors and AGIs as acceptable alternatives to metformin for first-line pharmacotherapy.[17] DPP-4 inhibitors have similar glucose-lowering efficacy to acarbose, but have better gastrointestinal tolerability.[18,19] We wanted to test the hypothesis that a DPP-4 inhibitor might be a better choice of OAD than an AGI in Chinese patients with T2D who were also receiving aspirin. Accordingly, we designed a randomized controlled trial to compare the efficacy, safety and tolerability of alogliptin versus acarbose in this setting.

2 | MATERIALS AND METHODS

The ACADEMIC study (NCT03794336) was a randomized, active-controlled, parallel-group, open-label, multicentre, phase IV trial conducted at 46 centres in China between June 2019 and December 2020. The study was conducted in accordance with the Declaration of Helsinki,[20] the International Conference for Harmonization Good Clinical Practice guidelines,[21] and local regulations. The institutional review board/ethics committee at each study site approved the protocol and trial documentation prior to the start of the study, and all participants provided written informed consent before any study procedures were undertaken.

2.1 | Eligibility

Adults aged ≥18 years were eligible for inclusion if they had T2D, a glycated haemoglobin (HbA1c) concentration of 58.0–97.0 mmol/mol, and a fasting plasma glucose (FPG) level ≤13.3 mmol/L (240 mg/dL) at screening, and were either treatment-naive or had received metformin monotherapy (≥1500 mg/d, or titrated to the maximum tolerated dose) for ≥12 weeks. The definition of 'treatment-naive' permitted the inclusion of people who had stopped OAD therapy >3 months previously. Additionally, participants had to have either established coronary heart disease (CHD; defined as previous myocardial infarction [MI] or angina [unstable or stable]) or high cardiovascular risk, which was defined as age >50 years plus ≥1

additional cardiovascular risk factor (ie, a family history of CVD, hypertension, smoking, dyslipidaemia or proteinuria). Thus, all participants in the ACADEMIC study had an indication for low-dose aspirin, but were enrolled regardless of whether they were actually taking aspirin at screening.

Individuals who had received DPP-4 inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1RAs) within the previous year were excluded, as were people with contraindications to DPP-4 inhibitors or AGIs, and those with an unstable cardiovascular disorder (except unstable angina), renal impairment, liver disease or an acute coronary syndrome event within the previous 6 months.

2.2 | Treatment

The study consisted of a 1-week screening period followed by a 16-week treatment period. Eligible participants were randomized 2:1 to receive either alogliptin (Nesina; Takeda, Osaka, Japan) or acarbose (Glucobay; Bayer, Leverkusen, Germany) in addition to metformin, if applicable. Alogliptin was taken at a dose of 25 mg (given as a single tablet) once daily throughout the trial. Acarbose was taken at a dose of 50 mg (given as a single 50-mg tablet) three times daily for 7 days, then 100 mg (given as two 50-mg tablets) three times daily thereafter. Participants were instructed to take acarbose with meals.

Modification of randomized treatment in response to hypoglycaemia (defined as any blood glucose level <3.9 mmol/L) was individualized according to OAD treatment status at screening and treatment allocation and was at the investigator's discretion. Treatment intensification (ie, the addition of a new OAD, insulin or GLP-1RA to study treatment) was not permitted. Participants receiving metformin at screening were instructed to continue taking it at the same dosage and dose frequency as before; investigators could subsequently stop or change the dose of metformin if clinically indicated.

All participants received open-label aspirin (Bayaspirin; Bayer) 100 mg once daily for the duration of the trial, unless discontinuation was clinically indicated.

Randomization was performed using a centralized interactive response service. Patients were stratified according to their cardiovascular history (with/without CHD), and their aspirin treatment status (taking/not taking aspirin), OAD treatment status (treatment-naive vs. metformin) and HbA1c (<75.0 vs. ≥75.0 mmol/mol) at screening.

2.3 | Investigations and endpoints

Randomization occurred at Week 0, which was considered the baseline visit. Patients returned at Weeks 1, 2, 4, 8, 12 and 16 for assessment. Participants were asked to keep a diary and record any changes in OAD or concomitant drug treatment, and any AEs experienced, between study visits. Data from participants' diaries were extracted and recorded at each study visit. Additionally, adherence to study medication was assessed at each visit by comparing the number of dosage units returned with the number corresponding to full (100%) adherence.

The primary efficacy endpoint was difference between the treatment arms in mean change from baseline in HbA1c at Week 16. The primary safety endpoint was difference between treatment groups in the incidence of gastrointestinal AEs. Secondary efficacy endpoints were differences between the treatment arms, at Week 16, in (a) the proportion of participants with HbA1c <53.0 mmol/mol, (b) the proportion of participants with HbA1c <53.0 mmol/mol and no gastrointestinal AEs, (c) the change from baseline in FPG, (d) the change from baseline in 2-hour postprandial glucose (PPG), and (e) the change from baseline in β-cell function, using homeostatic model assessment (HOMA-β). Secondary safety endpoints were differences between the treatment arms, at Week 16, in the occurrence of hypoglycaemic events and all other AEs, change from baseline in lipid levels, and change from baseline in body weight.

Hypoglycaemic events were defined either as symptomatic episodes that resolved promptly with food intake, or as any blood glucose measurement ≤3.9 mmol/L regardless of symptoms. Severe hypoglycaemia was defined as any hypoglycaemic event requiring the assistance of another person.

The variables HbA1c, FPG, 2-hour PPG, HOMA-β, fasting lipid levels and body weight were measured at baseline and Week 16. AEs and adherence were assessed using participant diaries and returned study medication, respectively, at each study visit. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA; www.meddra.org).

2.4 | Statistical analyses

We estimated that a study population of 842 participants would have 90% power, at a two-sided alpha of 0.05, to show noninferiority between groups in terms of HbA1c change from baseline to Week 16, assuming a dropout rate of 10%, a margin of 3.3 mmol/mol and a standard deviation (SD) of 13.1 mmol/mol. A population of 1082 participants would have 90% power to detect an 8% between-group difference in the incidence of gastrointestinal AEs, assuming that the incidence of gastrointestinal AEs with acarbose was approximately 20%. As the study had co-primary endpoints, the larger sample size of 1082 was chosen to ensure 90% power for both endpoints.

All efficacy data were analysed according to the intention-to-treat (ITT) principle (ie, including all randomized participants who received at least one dose of study medication, and who had paired data [baseline and post-baseline] for at least one efficacy variable). The safety population was defined as all participants who received at least one dose of study medication.

Standard descriptive statistics (n, mean and SD) were calculated for continuous variables (including demographic and baseline characteristics), while number and percentage of participants were calculated for categorical variables. Missing data for continuous efficacy variables at Week 16 were imputed using last observation carried forward (LOCF) methodology, where possible, or were left as missing if no post-baseline data were available. For categorical variables, participants with missing data were generally not included when calculating percentages.

An analysis of covariance model was used to assess changes in HbA1c, FPG, 2-hour PPG and HOMA-β, with treatment and alogliptin/acarbose use as fixed effects and baseline HbA1c as a covariate. For each endpoint, the model was used to estimate the difference between treatment groups as well as the 95% confidence interval (CI). For the primary efficacy endpoint, noninferiority was confirmed if the upper limit of the 95% CI was <0.3% (noninferiority margin).

Within each treatment arm, the proportion of participants with HbA1c <53 mmol/mol at Week 16 was calculated for subgroups of participants defined by T2D duration (<3 years vs. ≥3 years), age (<65 years vs. ≥65 years), sex (male vs. female), body mass index (BMI; <24 vs. 24–28 vs. ≥28 kg/m^2), HbA1c at screening (<75 vs. ≥75.0 mmol/mol), cardiovascular risk profile (CHD vs. high cardiovascular risk), metformin or aspirin use (yes vs. no), and FPG and 2-h PPG at baseline (<median vs. ≥median). Logistic regression models were used to identify predictors of HbA1c response.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

TABLE 1 Demographic and baseline characteristics of all randomized participants

Characteristic	Alogliptin (n = 725)	Acarbose (n = 363)	Total (n = 1088)
Age, years	59.3 ± 7.5	60.5 ± 7.2	59.7 ± 7.4
Age <65 years, n (%)	546 (75.3)	251 (69.1)	797 (73.3)
Male sex, n (%)	386 (53.2)	188 (51.8)	574 (52.8)
Body weight, kg	69.6 ± 11.4	69.8 ± 10.4	69.7 ± 11.1
BMI, kg/m^2	25.7 ± 3.4	25.8 ± 3.0	25.7 ± 3.3
HbA1c, mmol/mol	66.0 ± 11.6	65.5 ± 12.0	65.9 ± 11.8
≥75.0 mmol/mol, n (%)	209 (28.8)	107 (29.5)	316 (29.0)
Duration of diabetes, years	3.45 ± 4.76	3.66 ± 4.63	3.52 ± 4.72
Diabetes duration <3 years, n (%)	451 (62.2)	212 (58.7)	663 (61.0)
Diabetes complications			
Any complication	142 (19.6)	59 (16.3)	201 (18.5)
Distal neuropathy	83 (11.4)	27 (7.4)	110 (10.1)
Nephropathy	49 (6.8)	25 (6.9)	74 (6.8)
Peripheral artery disease	51 (7.0)	21 (5.8)	72 (6.6)
Retinopathy	13 (1.8)	6 (1.7)	19 (1.7)
Atherosclerotic disease[a]	9 (1.2)	7 (1.9)	16 (1.5)
Autonomic neuropathy	9 (1.2)	2 (0.6)	11 (1.0)
Duration of diabetes complications, years[b]	1.49 ± 2.08	2.32 ± 2.97	1.73 ± 2.40
CHD, n (%)	126 (17.4)	64 (17.6)	190 (17.5)
High cardiovascular risk, n (%)	599 (82.6)	299 (82.4)	898 (82.5)
Aspirin use, n (%)	155 (21.4)	78 (21.5)	233 (21.4)
Diabetes treatment-naive, n (%)	439 (60.6)	219 (60.3)	658 (60.5)
Receiving metformin, n (%)	286 (39.4)	144 (39.7)	430 (39.5)
FPG, mmol/L	8.69 ± 1.85	8.76 ± 1.3	8.71 ± 1.87
2-hour PPG, mmol/L	11.04 ± 2.87	10.06 ± 2.40	10.71 ± 2.76
HOMA-β, %	35.30 ± 53.33	34.40 ± 46.32	35.00 ± 51.06
Lipids, mmol/L			
Total cholesterol	4.78 ± 1.04	4.89 ± 1.09	4.82 ± 1.06
Triglycerides	1.72 ± 0.99	1.69 ± 0.94	1.71 ± 0.98
LDL cholesterol	2.85 ± 0.84	2.92 ± 0.86	2.87 ± 0.85
HDL cholesterol	1.22 ± 0.28	1.22 ± 0.27	1.22 ± 0.28

Note: Continuous variables are expressed as mean ± standard deviation.

Abbreviations: BMI, body mass index; CHD, coronary heart disease; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HOMA-β, homeostatic model assessment of β-cell function; LDL, low-density lipoprotein; PPG, postprandial glucose.

[a]Suspected or confirmed atherosclerotic lesions in the early stage of the disease (ie, where organ-specific ischaemia, necrosis or fibrosis is not obvious, and there are no clinical manifestations such as transient ischaemic attacks). Also included were less obvious dizziness or chest tightness, and cases where simple physical examination revealed fundus arteriosclerosis.

[b]Among the 201 participants with diabetes complications at baseline.

TABLE 2 Primary and continuous secondary efficacy endpoints (ITT population [alogliptin, n = 715; acarbose, n = 357]). Results for categorical secondary efficacy endpoints are shown in Figure 1

Outcome	Treatment arm	Baseline[a]	Week 16 (LOCF)[a]	ANCOVA analysis			
				Change[b,c]	Difference between arms[b]	95% CI	*P* value
Primary efficacy endpoint							
HbA1c, mmol/mol	Alogliptin	66.0 ± 11.7	53.9 ± 10.7	−11.9 (0.4)	−0.5 (0.7)	−1.9, 0.8	0.4418
	Acarbose	65.5 ± 12.0	54.2 ± 11.9	−11.4 (0.5)			
Secondary efficacy endpoints							
FPG, mmol/L	Alogliptin	8.70 ± 1.85	7.95 ± 1.89	−0.76 (0.06)	−0.05 (0.11)	−0.26, 0.17	0.6746
	Acarbose	8.73 ± 1.93	8.01 ± 1.97	−0.71 (0.09)			
2-hour PPG, mmol/L	Alogliptin	11.05 ± 2.87	9.91 ± 2.72	−0.91 (0.09)	0.52 (0.16)	0.20, 0.84	**0.0016**
	Acarbose	10.02 ± 2.39	9.01 ± 2.52	−1.42 (0.13)			
HOMA-β, %	Alogliptin	35.31 ± 53.61	41.42 ± 35.27	6.29 (1.28)	2.58 (2.21)	−1.75, 6.92	0.2429
	Acarbose	34.55 ± 46.73	38.66 ± 36.57	3.70 (1.80)			

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HOMA-β, homeostatic model assessment of β-cell function; ITT, intention-to-treat; LOCF, last observation carried forward; PPG, postprandial glucose.
[a]Mean ± standard deviation.
[b]Least-squares mean (standard error).
[c]Difference between baseline and Week 16.

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

Of the 1293 participants screened, 1088 were randomized and 1086 received at least one dose of study medication (Figure S1). Two participants, both of whom were randomized to receive alogliptin, withdrew before the first dose of study medication. The ITT population included 1072 participants, of whom 715 received alogliptin and 357 received acarbose.

The demographic and baseline characteristics of the randomized population are shown in Table 1. The groups were comparable at baseline with respect to mean age, body weight, duration of diabetes, cardiovascular risk, aspirin use, HOMA-β and lipid levels; the ratio of treatment-naive to metformin-treated participants was approximately 60:40 in both arms. Baseline mean HbA1c was 66.0 mmol/mol in the alogliptin arm and 65.5 mmol/mol in the acarbose arm. A higher proportion of participants in the alogliptin arm had diabetic complications compared with those in the acarbose arm (19.6% vs. 16.3%, respectively), driven primarily by higher rates of distal neuropathy in the alogliptin group (11.4% vs. 7.4%).

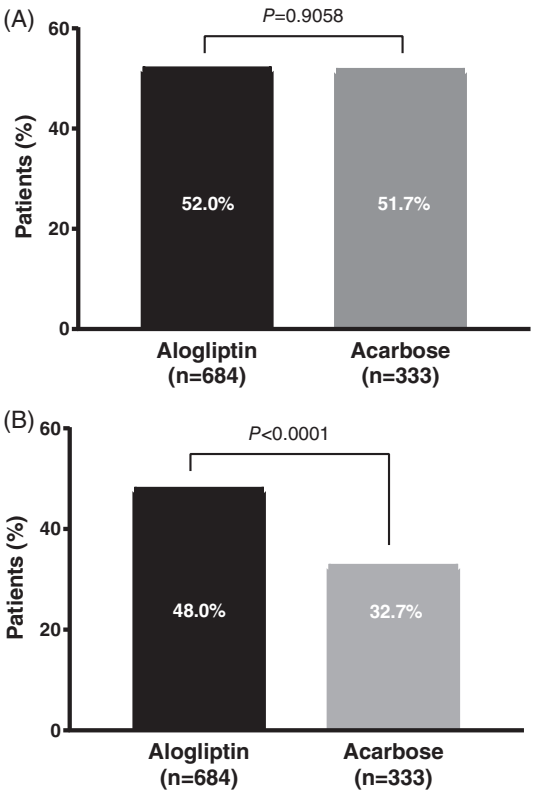

FIGURE 1 Percentage of participants achieving A, a glycated haemoglobin (HbA1c) level <53 mmol/mol at week 16 and B, an HbA1c level <53 mmol/mol without gastrointestinal adverse events at Week 16 (intention-to-treat population)

3.2 | Adherence

Among those who were randomized and received at least one dose of medication (n = 1086), adherence could be assessed for 699/723 participants (96.7%) in the alogliptin arm and 353/363 participants (97.2%) in the acarbose arm. Mean (SD) adherence was 99.2 (6.1)% in the alogliptin arm, and 97.9 (8.8)% in the acarbose arm. Four participants in the alogliptin arm (0.6%) had <80% adherence to study treatment, compared with 10 participants (2.8%) in the acarbose arm.

Variable	Subgroup	Alogliptin (N=715) n (%)	Acarbose (N=357) n (%)	Risk difference†	95% CI	*P*-value	*P*-value (interaction)
No. of patients with HbA1c <7%		356 (52.0)	172 (51.7)				
Duration of diabetes	≥3 years	123 (46.9)	56 (40.3)	6.7	−3.5, 16.8	0.2018	0.0941
	<3 years	233 (55.2)	115 (59.9)	−4.7	−13.1, 3.7	0.2777	
Age	≥65 years	259 (50.1)	122 (53.5)	−3.4	−11.2, 4.4	0.3906	0.0601
	<65 years	97 (58.1)	50 (47.6)	10.5	−1.7, 22.6	0.0918	
Sex	Male	193 (53.2)	95 (55.2)	−2.1	−11.1, 7.0	0.6546	0.4528
	Female	163 (50.8)	77 (47.8)	3.0	−6.5, 12.4	0.5409	
Body mass index	<24 kg/m²	121 (53.3)	51 (53.1)	0.2	−11.7, 12.1	0.9765	0.6101
	24–28 kg/m²	151 (51.2)	90 (53.6)	−2.4	−11.8, 7.1	0.6214	
	≥28 kg/m²	84 (51.9)	31 (45.6)	6.3	−7.9, 20.4	0.3860	
HbA1c at screening	≥9%	77 (40.1)	37 (38.5)	1.6	−10.4, 13.5	0.7983	0.8016
	<9%	279 (56.7)	135 (57.0)	−0.3	−7.9, 7.4	0.9482	
CV risk profile	CHD	61 (51.3)	31 (52.5)	−1.3	−16.9, 14.3	0.8720	0.8165
	High CV risk	295 (52.2)	141 (51.5)	0.8	−6.5, 8.0	0.8379	
Aspirin	Yes	78 (52.7)	39 (54.2)	−1.5	−15.5, 12.6	0.8382	0.7703
	No	278 (51.9)	133 (51.0)	0.9	−6.5, 8.3	0.8098	
Metformin	Yes	129 (47.4)	62 (45.6)	1.8	−8.4, 12.1	0.7258	0.7041
	No	227 (55.1)	110 (55.8)	−0.7	−9.2, 7.7	0.8635	
FPG at baseline	>8.41 mmol/L	135 (40.1)	53 (32.5)	7.5	−1.3, 16.4	0.1026	0.0311
	≤8.41 mmol/L	221 (63.7)	119 (70.0)	−6.3	−14.9, 2.2	0.1554	
PPG at baseline	>10.47 mmol/L	168 (44.1)	33 (27.5)	16.6	7.2, 26.0	0.0012	0.0033
	≤10.47 mmol/L	187 (62.1)	139 (65.3)	−3.1	−11.6, 5.3	0.4677	

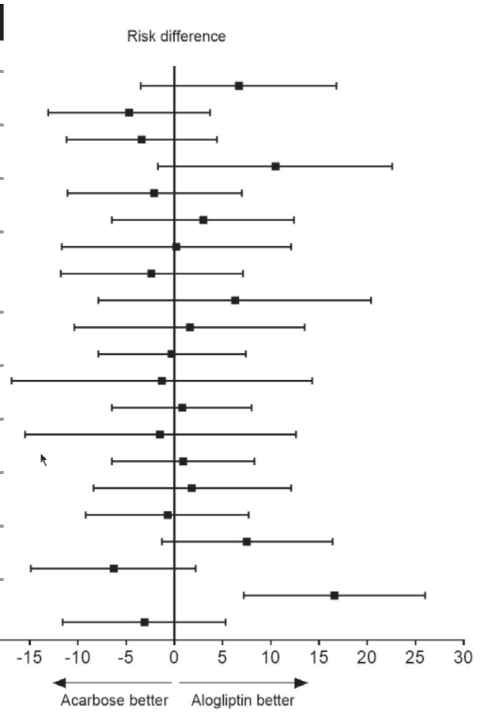

FIGURE 2 Percentage of participants achieving a glycated haemoglobin (HbA1c) level <53 mmol/mol at Week 16: Subgroup analysis of the intention-to-treat population. † Risk difference was calculated as the percentage for alogliptin minus the percentage for acarbose. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; FPG, fasting plasma glucose; PPG, postprandial glucose

3.3 | Efficacy

In the ITT analysis (LOCF), the least-squares mean (LSM) change in HbA1c between baseline and Week 16 was −11.9 mmol/mol (standard error [SE] 0.4; 95% CI −12.7 to −11.1) with alogliptin and −11.4 mmol/mol (SE 0.5; 95% CI −12.5 to −10.3) with acarbose (Table 2). The between-group difference for change in HbA1c from baseline was −0.5 mmol/mol (SE 0.7; 95% CI −1.9 to 0.8; $P = 0.4418$). The upper limit of the 95% CI was below the predefined noninferiority threshold of 3.3 mmol/mol; therefore, alogliptin was noninferior to acarbose on the primary efficacy endpoint of change in HbA1c at Week 16.

There was no significant difference between the two treatments in the percentage of participants with HbA1c <53.0 mmol/mol at Week 16, either in the overall study population (52.0% with alogliptin vs. 51.7% with acarbose; $P = 0.9058$ [Figure 1]) or in the subgroup analyses (Figure 2), except in participants with above-median 2-hour PPG values at baseline. In the latter subgroup, 44.1% of those randomized to alogliptin had HbA1c <53.0 mmol/mol at Week 16, compared with 27.5% of those who received acarbose ($P = 0.0012$). However, significantly more participants in the alogliptin arm achieved an HbA1c <53.0 mmol/mol without gastrointestinal AEs compared with the acarbose arm (48.0% vs. 32.7%, respectively; $P < 0.0001$ [Figure 1]). Whether or not patients were metformin-naive at baseline did not change this finding (Table S1). This was due to the higher frequency of gastrointestinal AEs with acarbose (see Safety, below).

In the logistic regression analysis, T2D duration of <3 years, HbA1c level <75.0 mmol/mol at screening and FPG level below the median value at baseline were potential predictors of achieving HbA1c <53.0 mmol/mol at Week 16 (Table S2).

Alogliptin and acarbose were equally efficacious in reducing FPG and improving β-cell function over 16 weeks (Table 2). However, acarbose was significantly more efficacious than alogliptin in reducing 2-hour PPG (LSM [SE] change from baseline: −0.91 [0.09] mmol/L with alogliptin vs. −1.42 [0.13] mmol/L with acarbose; difference 0.52 [0.16] mmol/L; 95% CI 0.20–0.84; $P = 0.0016$).

3.4 | Safety

3.4.1 | Primary and secondary safety endpoints

The proportion of participants with ≥1 gastrointestinal AE was significantly lower with alogliptin (64/723; 8.9%) than with acarbose (122/363; 33.6%; $P < 0.0001$). Hypoglycaemia was infrequent with both treatments, with three participants in the alogliptin arm (0.4%) and four in the acarbose arm (1.1%) reporting at least one hypoglycaemic episode. The between-group difference was not statistically significant ($P = 0.1820$), and there were no cases of severe hypoglycaemia in either arm. Changes from baseline in total cholesterol, triglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol were minimal, and were not clinically relevant in either

TABLE 3 Treatment-emergent adverse events

	Alogliptin (n = 723)	Acarbose (n = 363)
Any TEAE	241 (33.3)	184 (50.7)
Any serious TEAE	18 (2.5)	18 (5.0)
Any treatment-related TEAE	45 (6.2)	118 (32.5)
Any serious treatment-related TEAE	2 (0.3)	1 (0.3)
Any treatment-related TEAE leading to study discontinuation	2 (0.3)	9 (2.5)
System organ class		
Preferred term		
Gastrointestinal	62 (8.6)	124 (34.2)
Constipation	21 (2.9)	7 (1.9)
Flatulence	10 (1.4)	81 (22.3)
Abdominal distension	10 (1.4)	39 (10.7)
Diarrhoea	9 (1.2)	12 (3.3)
Upper abdominal pain	3 (0.4)	8 (2.2)
Abdominal pain	3 (0.4)	4 (1.1)
Nausea	3 (0.4)	4 (1.1)
Injury, poisoning and procedural complications	76 (10.5)	57 (15.7)
Overdose	69 (9.5)	55 (15.2)
Metabolism and nutrition disorders	60 (8.3)	30 (8.3)
Hyperlipidaemia	28 (3.9)	10 (2.8)
Hyperuricaemia	20 (2.8)	8 (2.2)
Infections and infestations	38 (5.3)	27 (7.4)
Urinary tract infection	16 (2.2)	16 (4.4)
Upper respiratory tract infection	8 (1.1)	9 (2.5)
Investigations	21 (2.9)	13 (3.6)
Weight decreased	6 (0.8)	8 (2.2)
Skin and subcutaneous tissue disorders	11 (1.5)	3 (0.8)
Nervous system disorders	9 (1.2)	11 (3.0)
Dizziness	2 (0.3)	5 (1.4)
Respiratory, thoracic and mediastinal disorders	9 (1.2)	5 (1.4)
Musculoskeletal and connective tissue disorders	8 (1.1)	7 (1.9)
Renal and urinary disorders	8 (1.1)	7 (1.9)
General disorders and administration site conditions	6 (0.8)	7 (1.9)

Abbreviation: TEAE, treatment-emergent adverse event.

treatment group (Table S3). Acarbose was associated with a mean reduction in body weight of 0.85 kg, whereas there was a smaller decrease (0.10 kg) with alogliptin.

3.4.2 | Treatment-emergent AEs

Treatment-emergent AEs (TEAEs) are summarized in Table 3. The proportion of participants with any TEAE was 50.7% with acarbose versus 33.3% with alogliptin, and the proportions of those with treatment-related TEAEs were 32.5% and 6.2%, respectively. Thus, most TEAEs in participants receiving alogliptin were not treatment-related. The most commonly reported TEAEs were overdose (9.5%), hyperlipidaemia (3.9%) and constipation (2.9%) with alogliptin, and flatulence (22.3%), overdose (15.5%) and abdominal distension (10.7%) with acarbose. With the exception of constipation, which occurred more commonly with alogliptin (2.9% vs. 1.9%), individual gastrointestinal TEAEs were at least twice as common with acarbose versus alogliptin. In both treatment groups, the incidence of gastrointestinal TEAEs peaked in the first week of the study, and subsequently decreased (Table S4); however, these effects occurred more frequently with acarbose than with alogliptin in most study weeks, and a difference was still apparent at Week 16.

Significantly more participants discontinued treatment due to a treatment-related TEAE with acarbose compared with alogliptin (2.5% vs. 0.3%; $P = 0.0006$). No new safety signals were identified during the study, and there were no deaths from treatment-related TEAEs in either treatment arm.

4 | DISCUSSION

In our study of Chinese individuals with T2D and established CHD or high cardiovascular risk, alogliptin was noninferior to acarbose with regard to HbA1c reductions over 16 weeks. Additionally, both treatments showed similar efficacy in reducing HbA1c level to <53.0 mmol/mol (from mean baseline values of >64.0 mmol/mol), lowering FPG level and improving β-cell function. Moreover, the efficacy of these treatments (based on achievement of HbA1c <53.0 mmol/mol) remained similar in subgroups defined by baseline age (above vs. below 65 years), sex, duration of T2D (above vs. below 3 years), HbA1c (≥75.0 vs. <75.0 mmol/mol), cardiovascular risk profile (established CHD vs. high cardiovascular risk), aspirin use (yes vs. no), metformin use (yes vs. no) and BMI (<24 vs. 24–28 vs. >28 kg/m^2).

Although the glycaemic efficacy of the two drugs was comparable, participants receiving acarbose experienced higher rates of TEAEs, particularly gastrointestinal effects, such as flatulence and abdominal distension, than those receiving alogliptin. Consequently, the proportion of participants achieving HbA1c <53.0 mmol/mol without gastrointestinal AEs was significantly higher with alogliptin than with acarbose. Furthermore, there were fewer discontinuations due to treatment-related TEAEs with alogliptin versus acarbose.

It is important to recognize that acarbose and aspirin produce gastrointestinal AEs via different mechanisms. Acarbose exerts its effects in the intestine, whereas aspirin directly stimulates the gastric mucosa. It could therefore be hypothesized that the simultaneous use of the two drugs may have additive or even synergistic effects in terms of gastrointestinal burden. We believe that it is important to

consider both gastrointestinal tolerability and glycaemic efficacy, particularly because AEs can reduce adherence in patients with T2D.[22-24]

Adherence to treatment was slightly lower with acarbose than with alogliptin, but was very high (>95%) in both treatment arms. However, adherence rates obtained in clinical trials are usually higher than those observed in clinical practice,[25] and this can result in gaps between the expected and actual clinical effects of drug treatments.[26] Changes in HbA1c have been found to be smaller in real-world studies than in clinical trials of OADs,[27,28] and much of the difference has been attributed to poor adherence or persistence with therapy.[27] Additionally, an inverse relationship has been found between adherence to OADs and dosing frequency.[29]

Because of the difference in dose frequency between alogliptin and acarbose, it might be expected that the gap between expectation (based on clinical trial data) and reality, in terms of the change in HbA1c, would be greater for acarbose than for alogliptin, even if the two treatments were equally well tolerated. However, our data also suggest that treatment persistence may be lower for acarbose than alogliptin because of differences in tolerability. At present, the relative real-world performance of AGIs and DPP-4 inhibitors, in terms of glycaemic outcomes, adherence and persistence, has not been adequately studied in a Chinese population. In two large observational studies that included large numbers of East Asian participants with T2D, acarbose was associated with changes in HbA1c of 9.8 to 12.0 mmol/mol (from mean baseline levels of 66.0 mmol/mol) after 3 months.[30,31] Moreover, rates of discontinuation due to AEs have been <1% in observational studies of acarbose.[30-33] Although these findings tend to challenge the hypothesis that acarbose may be less effective in the real world than suggested by clinical trials, observational research is inherently difficult to interpret due to confounding factors and sources of potential bias. A prescription refill study from Israel has suggested that up to one-third of participants prescribed acarbose may discontinue treatment during the first year.[34]

Our study confirms that alogliptin is efficacious and well tolerated in Chinese people with T2D receiving aspirin for primary or secondary CVD prevention. These results are consistent with those of EXAMINE, a cardiovascular outcomes trial in which predominantly White individuals with T2D and a recent history of acute coronary syndrome received alogliptin (6.25–25 mg daily, depending on glomerular filtration rate; n = 2701) or placebo (n = 2679). Over 90% of participants were taking aspirin at baseline. Compared with placebo, alogliptin produced a significantly greater mean change in HbA1c (LSM between-group difference −3.9 mmol/mol, 95% CI −4.7 to −3.1; $P < 0.001$) and had a similar safety and tolerability profile. However, no effect of alogliptin on the incidence of cardiovascular events was seen.

Our trial has a number of important limitations that must be taken into account. Its short duration (16 weeks) means that conclusions cannot be made about the longer-term efficacy, safety or tolerability of either alogliptin or acarbose in individuals with T2D receiving aspirin. As noted previously, the trial does not provide any insights into the ability of either treatment to modify cardiovascular risk in this population, but is useful mainly in showing that alogliptin and acarbose have similar glycaemic efficacy but different tolerability profiles during short-term use in a Chinese population. Rates of medication adherence were very high, and this may not be reproducible in clinical practice. Lastly, as our study was conducted exclusively in a Chinese population, the results cannot necessarily be generalized to other populations.

In conclusion, we found that alogliptin had comparable glycaemic efficacy to acarbose in Chinese people with T2D taking low-dose aspirin for primary or secondary CVD prevention, and had better gastrointestinal tolerability.

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CONFLICT OF INTEREST

B.G. has attended advisory boards for Novo Nordisk, Eli Lilly and AstraZeneca, and has been a speaker for Novo Nordisk, Eli Lilly, AstraZeneca, Sanofi and Bayer. W.G. and F.X. have received speaker fees from Novo Nordisk and Sanofi. H.W. has participated in clinical trials sponsored by Novo Nordisk, Eli Lilly and Sanofi, and has been a speaker for these companies. Q.J. has been a speaker for Eli Lilly, Bayer, Novo Nordisk and Sanofi, and has attended advisory boards for Novo Nordisk, Eli Lilly and AstraZeneca. R.Z. and X.Z. are employees of Sanofi China and hold shares and/or stock options in the company.

AUTHOR CONTRIBUTIONS

Q.J. led the study design, trial operation, data analysis and manuscript preparation. All authors were involved in the study design, trial operation, and data collection, and in the preparation, review and final approval of the manuscript for publication.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14661.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient-level data and related documents [including, e.g., the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications]. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://www.clinicalstudydatarequest.com.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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