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Comparison of Acarbose and Voglibose in Diabetes Patients Who Are Inadequately Controlled with Basal Insulin Treatment: Randomized, Parallel, Open-Label, Active-Controlled Study

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We studied the efficacy and safety of acarbose in comparison with voglibose in type 2 diabetes patients whose blood glucose levels were inadequately controlled with basal insulin alone or in combination with metformin (or a sulfonylurea). This study was a 24-week prospective, open-label, randomized, active-controlled multi-center study. Participants were randomized to receive either acarbose (n = 59, 300 mg/day) or voglibose (n = 62, 0.9 mg/day). The mean HbA_{1c} at week 24 was significantly decreased approximately 0.7% from baseline in both acarbose (from 8.43% ± 0.71% to 7.71% ± 0.93%) and voglibose groups (from 8.38% ± 0.73% to 7.68% ± 0.94%). The mean fasting plasma glucose level and self-monitoring of blood glucose data from 1 hr before and after each meal were significantly decreased at week 24 in comparison to baseline in both groups. The levels 1 hr after dinner at week 24 were significantly decreased in the acarbose group (from 233.54 ± 69.38 to 176.80 ± 46.63 mg/dL) compared with the voglibose group (from 224.18 ± 70.07 to 193.01 ± 55.39 mg/dL). In conclusion, both acarbose and voglibose are efficacious and safe in patients with type 2 diabetes who are inadequately controlled with basal insulin. (ClinicalTrials.gov number, NCT00970528)

Keywords: Diabetes Mellitus, Type 2; Acarbose; Voglibose

INTRODUCTION

Given the progressive nature of diabetes and the substantial evidence supporting the beneficial effects of insulin regimens, it is imperative that patients utilize insulin therapy to maintain glycemic control as well as reduce morbidity and mortality rates associated with diabetes and its related complications (1-3). The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend that an $HbA_{1c} \geq 7.0\%$ should serve as a call to action, using insulin therapy to reverse the inevitable deterioration in glycemic control. Initial treatment targeting fasting blood glucose is expected to facilitate reaching treatment goals and is the recommended approach for early insulin initiation (4, 5). A once-daily injection of basal insulin, with once-daily monitoring of blood glucose, provides a simple-to-manage cornerstone of therapy.

However, basal insulin treatment, such as insulin glargine and detemir, has less effect on postprandial glucose level management compared with fasting glucose levels (6). Furthermore, a recent study suggests that a gradual loss in daytime postprandial glycemic control precedes a stepwise deterioration in nocturnal fasting periods in worsening diabetes, whereas nocturnal fasting glycemic control remains essentially unchanged as long as HbA_{1c} levels remain $< 8\%$ (7). Once fasting glucose is tightly controlled with basal insulin, adding oral hypoglycemic agents or short-acting insulin can help achieve the target goal of HbA_{1c} through improving postprandial blood glucose excursion (8, 9).

Acarbose and voglibose are α-glucosidase inhibitors that typically reduce postpran-

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dial glucose concentrations by delaying carbohydrate digestion and therefore absorption in the gut, and can be a useful first-line treatment in the patients who have a combination of slightly raised basal glucose concentrations and marked postprandial hyperglycemia (10-14). α-glucosidase inhibitors have been used in Asian patients with type 2 diabetes as first-line and second-line therapies targeting the postprandial glucose level, and often used with a basal insulin regimen when basal insulin treatment alone did not result in glycemic control because they had eaten a high carbohydrate containing meal. However, there are no direct comparison data between acarbose and voglibose regarding glycemic control and side effects when added to basal insulin treatment in patients with type 2 diabetes.

In this study, we evaluated the efficacy and safety of acarbose and voglibose in type 2 diabetes patients whose blood glucose levels were inadequately controlled with insulin glargine (or insulin detemir) alone or in combination with metformin (or a sulfonylurea).

MATERIALS AND METHODS

Study population and design

This study was a prospective, parallel group, open-label, randomized, active-controlled clinical trial that was conducted at 11 study centers in Korea. Patients with type 2 diabetes aged 18-79 yr who were already taking insulin glargine (or insulin detemir) alone or in combination with metformin (or a sulfonylurea) for at least 3 months prior to screening, and had an HbA_{1C} > 7.0% and ≤ 10.0%, were eligible to be randomized.

Eligible patients gave informed consent and were randomized in a ratio of 1:1 to receive acarbose (up to 100 mg three times daily) or voglibose (up to 0.3 mg three times daily). All subjects were instructed to keep their metformin and sulfonylurea dose throughout the study.

Of the 156 subjects screened for this study, 124 subjects were randomized to either the acarbose or voglibose group. A total of 32 subjects was screened but not randomized. Of these 32 subjects, 29 were excluded for unmet eligibility criteria (24 for inclusion and 5 for exclusion criteria). The other 3 subjects were excluded for the following reasons: one subject was recommended to be hospitalized for blood glucose control by the investigator, another was not able to be contacted and was withdrawn from the study due to problems related to patient's diary, and the final subject was withdrawn with consent.

Among 124 randomized subjects, 2 subjects in the acarbose group whose medication compliance was not reported were regarded as non-treated with the study drug. A total of 122 subjects (60 in the acarbose group and 62 in the voglibose group) who were treated with study medications were included in the safety set. Of those subjects who were included in the safety set, one subject in the treatment group was excluded from the modified intent-to-treat (mITT) set due to no HbA_{1c} values after treatment. A total of 121 subjects (59 in the acarbose group and 62 in the voglibose group) were included in the mITT set. A total of 102 subjects (47 in the acarbose group and 55 in the voglibose group) who complied with all study protocol criteria and the study medication regimen was included in the per-protocol (PP) set.

Efficacy and safety evaluation

The primary endpoint was mean HbA_{1c} change from baseline to week 24. Secondary endpoints were diurnal glucose concentration checked by self-monitoring of blood glucose (SMBG), fasting plasma glucose level, lipid parameters including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), apolipoprotein A (Apo A), apolipoprotein B (Apo B), as well as body weight, body mass index (BMI), and high sensitivity C reactive protein (hs-CRP) level. The HbA_{1c} level was evaluated at 0, 8, 24 weeks, and fasting glucose and SMBG information were collected from patient diary at every visit. The other parameters were checked at baseline and week 24. To determine efficacy parameters, all laboratory determinations were performed by a central laboratory, Seoul Clinical Laboratories (SCL) in Korea. HbA_{1C} was determined by turbidimetric inhibition immunoassay (NGSP, Roche Diagnostics, Indianapolis, IN, USA). Lipid profiles were done by enzymatic colorimetic assays (HITACHI, Tokyo, Japan) and hs-CRP level was determined by immunoturbidimetric assays (HITACHI).

Subjects tested six-point SMBG profiles (pre-meal and 1 hr post-meal) using the same type of blood-glucose meter (provided by investigators) on any 2 days within a week and recorded it in a patient diary prior to every visit (CareSens, i-sens, Seoul, Korea). Subjects checked preprandial glucose levels 1 hr before each meal and postprandial glucose levels 1 hr after the beginning of each meal. At every visit, we performed physical examinations and checked whether patients experienced hypoglycemic events. Hypoglycemia was defined as blood glucose concentrations less than 50 mg/dL with or without symptoms of hypoglycemia. Hypoglycemia symptoms included fatigue, sweating, palpitation, tremor, confusion, seizure, and loss of consciousness. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia which the subject required assistance from another person and was associated with prompt recovery after oral carbohydrates, or intravenous glucose or glucagon administration. Subjects were asked to self-monitor glucose values whenever they experienced symptoms that might have resulted from hypoglycemia.

To evaluate adverse events, blood pressure, electrocardiography, hematologic parameters, blood chemistry, and urine analyses were also monitored.

Statistical methods

The primary efficacy variable was mean HbA_{1c} change from baseline to week 24 in the modified intent to treat (mITT) population with last observation carried forward for the patients who discontinued prematurely, comparing acarbose group with voglibose group. Subjects included in the mITT analysis received at least one dose of study medication, had efficacy data at baseline, and had at least one post-baseline measurement of the respective variable. Sample size calculation was based on a margin of non-inferiority, the value of 0.5, in adjusted mean change from baseline to HbA_{1c} and standard deviation of difference between groups of 1.0. We calculated that 51 patients per group were needed to demonstrate non-inferiority of acarbose group (alpha 0.05, one-sided, 80% power).

Statistics were performed using the SAS 9.1 package. Data were presented as mean ± SD for continuous variables and as frequency and percentage for categorical variables, unless otherwise specified. Baseline characteristics and safety evaluation were compared using two sample t-test and Pearson's chi-square test, as appropriate. Primary and secondary variables were analyzed using an ANCOVA model with treatment and pooled center as the classification variables and baseline value as the covariate. Except for efficacy analysis, all statistical analysis for the baseline character and safety evaluation was performed by using two-sided test and at 5% level of significance. Efficacy analysis was performed by using one-sided test and at 5% level of significance. And all *P* value were considered statistically significant when $P < 0.05$. Safety analyses were performed in the all treated patients, which included randomized patients who received at least one dose of study medication. Safety parameters included any adverse events, hypoglycemia, laboratory safety findings, vital signs and physical examination.

Table 1. Demographics and other baseline characteristics

Characteristics	Acarbose (n = 59)	Voglibose (n = 62)	*P* value
Men	29 (49.15)	33 (53.23)	0.654†
Age (yr)	58.36 ± 8.59	58.73 ± 10.09	0.829*
SBP (mmHg)	124.83 ± 15.51	126.79 ± 13.84	0.464*
DBP (mmHg)	75.10 ± 10.00	75.26 ± 9.59	0.930*
Body weights (kg)	64.30 ± 9.94	65.64 ± 9.18	0.444*
BMI (kg/m^2)	24.70 ± 3.29	24.99 ± 3.09	0.614*
Fasting glucose (mg/dL)	128.03 ± 46.54	132.37 ± 40.58	0.587*
Total cholesterol (mg/dL)	159.71 ± 35.43	163.08 ± 29.94	0.573*
LDL-C (mg/dL)	89.54 ± 28.57	91.21 ± 26.61	0.740*
HDL-C (mg/dL)	46.64 ± 10.48	49.69 ± 13.34	0.166*
Triglyceride (mg/dL)	132.81 ± 75.80	131.87 ± 82.91	0.850‡
Apolipoprotein A (mg/dL)	140.97 ± 21.85	146.77 ± 24.41	0.171*
Apolipoprotein B (mg/dL)	69.98 ± 19.42	70.08 ± 19.64	0.978*
Duration of diabetes (yr)	14.23 ± 7.27	15.67 ± 8.79	0.329*
Diabetic complication	39 (66.10)	42 (67.74)	0.848†
Diabetic retinopathy	23 (38.98)	27 (43.55)	
Diabetic neuropathy	24 (40.68)	23 (37.10)	
Diabetic nephropathy	9 (15.25)	5 (8.06)	
Macroangiopathy	3 (5.08)	1 (1.61)	
Other	4 (6.78)	0 (0.00)	

Data are presented as the means ± SD, or No. (%). *Unpaired t-test; †Pearson's chi-square test; ‡Wilcoxon rank sum test. SBP, systolic blood pressure; DBP, diastolic blood pressure, BMI, body mass index; LDL-C, low dense lipoprotein cholesterol, HDL-C, high dense lipoprotein cholesterol. Missing [Subject]: Acarbose-(Fasting glucose[1]), Voglibose-(BMI [1]).

Ethics statement

This study protocol was reviewed and approved by the institutional review board of Korea University Anam Hospital (AN09158) and other involved centers. The study protocol was registered at the ClinicalTrials.gov (NCT00970528). Informed consent form explaining the procedures of the study and potential hazards was reviewed and approved by the board. All participants submitted the informed consent.

RESULTS

Baseline characteristics of the study subjects

The demographics and clinical characteristics of the randomized subjects are summarized in Table 1. For the acarbose group, 49.2% of the subjects were male, the mean age was 58.4 yr, and 66.1% of subjects had diabetic complications. For voglibose group, 53.2% of subjects were male, the mean age was 58.7 yr, and 67.7% of subjects had diabetic complications. The demographics and baseline characteristics of acarbose group were comparable to voglibose group, and there were no significant differences between groups. Most subjects (91.7% of the acarbose group and 98.4% of the voglibose group) had comorbidities such as hypertension, dyslipidemia, hepatic steatosis, and gastritis (data not shown).

Change of HbA_{1c}

Table 2 presents the change in HbA_{1c} from baseline to week 24 by group as well as the difference between the groups. At week 24, the mean HbA_{1c} decreased from 8.43% ± 0.71% to 7.71% ± 0.93% in acarbose group and from 8.38% ± 0.73% to 7.68% ± 0.94% in voglibose group, respectively. The difference in least square means (LSM) between groups was -0.01% without significance (90% confidence interval [CI] -0.27, 0.24; $P = 0.467$). The upper limit of the 90% CI is 0.24 did not exceed 0.5, there-

Table 2. Change of HbA_{1c} from baseline data

Parameters	Acarbose (n = 59)	Voglibose (n = 62)	*P* value
Baseline (%)	8.43 ± 0.71	8.38 ± 0.73	
Week 24 (%)	7.71 ± 0.93	7.68 ± 0.94	
Change	-0.72 ± 0.98	-0.70 ± 0.82	
P value (within group)	< 0.001*	< 0.001*	
Difference of LSM (90% CI) (between group)	-0.01 (-0.27-0.24)		0.467†

Data are presented as the means ± SD. Change = week 24-baseline. *Paired t-test; †ANCOVA model with treatment, baseline value as covariate and pooled center as factors (one-side test). LSM, Least squares mean.

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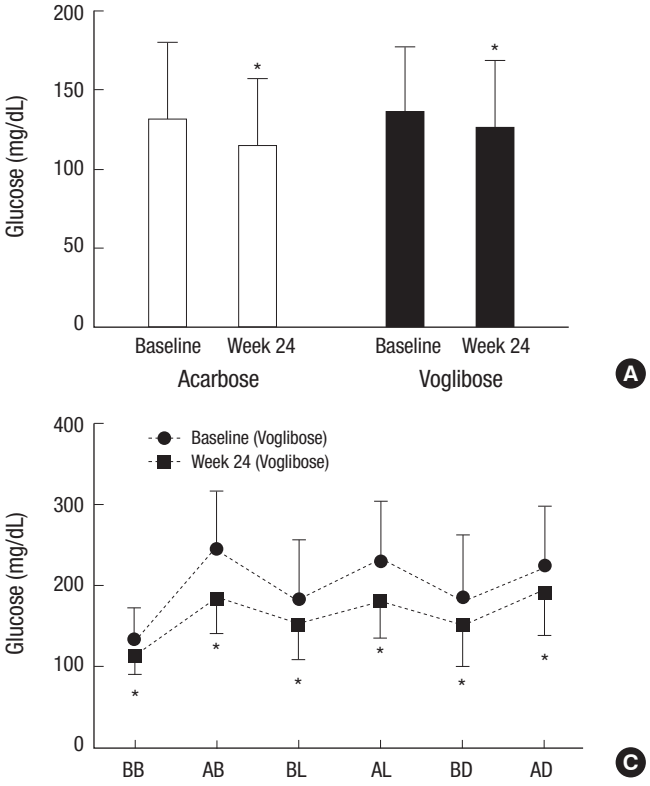
fore the non-inferiority of acarbose group declared.

Glycemic measurements

The fasting glucose level and the change in self-monitored diurnal blood glucose levels from baseline to week 24 by group, as well as the differences between groups, are shown in Fig. 1. The mean fasting plasma glucose level at week 24 decreased by 16.27 ± 59.63 mg/dL in acarbose group and 10.44 ± 42.30 mg/dL in voglibose group (Fig. 1A). The difference in LSM between groups was -9.11 mg/dL but without significance (90% CI, -21.47-3.25; P = 0.112). At all time-points in SMBG measurement, the changes in blood glucose level from baseline to week 24 were significant in both treatment groups (Table 3, Fig. 1B). There were no significant differences between treatment groups, except 1 hr after dinner time-point. At week 24, the SMBG values 1 hr after dinner decreased by 55.99 ± 68.93 (Median, -52.25; Range, -295.00-113.50) mg/dL in acarbose group and 33.52 ± 73.24 (Median, -19.50; Range, -267.00-100.00) mg/dL in voglibose group compared to baseline. The difference of LSM between groups was -15.88 mg/dL (90% CI, -30.81-0.95) and was statisti-



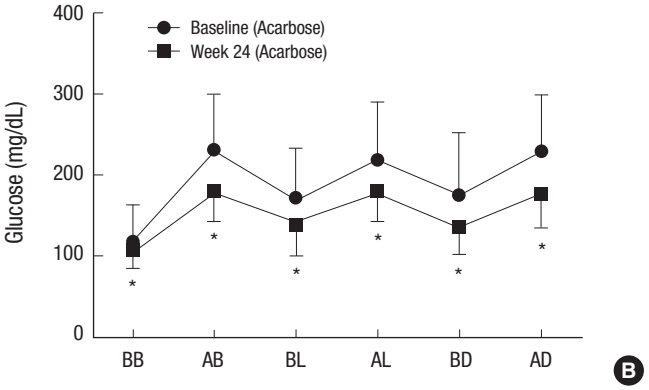


Fig. 1. Fasting plasma glucose and mean glucose levels checked by 6 points during a day. (**A**) The mean fasting plasma glucose level at week 24 decreased by 16.27 ± 59.63 mg/dL in acarbose group and 10.44 ± 42.30 mg/dL in voglibose group. There were no statistically significant differences between the groups in changes in fasting glucose levels from baseline to week 24. (**B**) The glucose levels of 6 points at week 24 in acarbose group. (**C**) The glucose levels of 6 points at week 24 in voglibose group. The glucose levels of all time points significantly decreased compared with baseline within each acarbose and voglibose groups. Only those of 1 hr after dinner at week 24 significantly decreased in acarbose group compared with voglibose group. BB, before breakfast; AB, after breakfast; BL, before lunch; AL, after lunch; BD, before dinner; AD, after dinner. *P < 0.05; Change from baseline.

Table 3. Fasting plasma glucose and diurnal glucose concentration (mITT analysis)

Glucose level at		Acarbose (n = 59)		Voglibose (n = 62)		P value (between group)
		No.	Mean ± SD	No.	Mean ± SD	
Fasting (mg/dL)	Baseline	59	131.63 ± 48.55	62	136.16 ± 41.33	
	Week 24	59	115.36 ± 41.88	62	125.73 ± 43.10	
	Change	59	-16.27 ± 59.63	62	-10.44 ± 42.30	
	P value (within group)		0.041*		0.057*	
	Difference of LSM (90% CI) (between group)		-9.11 (-23.88-5.65)			0.112†
1 hr before dinner (mg/dL)	Baseline	54	170.57 ± 75.32	57	177.19 ± 78.80	
	Week 24	58	139.64 ± 36.23	61	151.24 ± 49.94	
	Change	53	-31.80 ± 67.66	56	-25.02 ± 78.92	
	P value (within group)		0.001*		0.086†	
	Difference of LSM (90% CI) (between group)		-10.66 (-26.03-4.70)			0.021*
1 hr after dinner (mg/dL)	Baseline	57	233.54 ± 69.38	56	224.18 ± 70.07	
	Week 24	58	176.80 ± 46.63	61	193.01 ± 55.39	
	Change	56	-55.99 ± 68.93	55	-33.52 ± 73.24	
	P value (within group)		< 0.001*		0.040†	
	Difference of LSM (90% CI) (between group)		-15.88 (-33.72-1.96)			0.001*

Data are presented as the number of subjects, means and SD. Change = week 24-Baseline. *Paired t-test; †ANCOVA model with treatment, baseline value as covariate and pooled center as factors (one-side test). LSM, Least squares mean.

Table 4. Changes in efficacy variables from baseline to week 24

Variables	Acarbose (n = 59)			Voglibose (n = 62)			*P* value†
	No.	Mean ± SD	Median (Range)	No.	Mean ± SD	Median (Range)	
Body weight (kg)	59	-0.67 ± 1.89*	-0.70 (-7.20-2.90)	62	-0.87 ± 1.81*	-0.80 (-5.10-3.50)	0.291
BMI (kg/m^2)	59	-0.26 ± 0.71*	-0.26 (-2.68-0.98)	61	-0.32 ± 0.68*	-0.31 (-1.92-1.51)	0.332
Total cholesterol (mg/dL)	56	5.63 ± 29.66	4.50 (-69.00-104.00)	62	-1.29 ± 27.02	-3.00 (-97.00-46.00)	0.119
LDL-C (mg/dL)	56	5.20 ± 25.01	3.00 (-62.00-101.00)	62	-0.29 ± 23.58	-2.00 (-87.00-42.00)	0.111
HDL-C (mg/dL)	56	1.84 ± 8.54	1.00 (-19.00-38.00)	62	0.19 ± 6.91	1.50 (-26.00-16.00)	0.118
Non-HDL-C (mg/dL)	56	3.79 ± 27.58	1.00 (-59.00-107.00)	62	-1.48 ± 25.50	-2.00 (-87.00-59.00)	0.267
TG (mg/dL)	56	-5.43 ± 64.13	-7.00 (-182.00-194.00)	62	-8.48 ± 58.54	-5.00 (-218.00-156.00)	0.341
ApoA (mg/dL)	56	-2.68 ± 17.76	-4.00 (-51.00-37.00)	62	-4.00 ± 16.99	-4.50 (-48.00-32.00)	0.493
ApoB (mg/dL)	56	8.32 ± 17.46*	6.00 (-18.00-64.00)	62	4.21 ± 16.43*	4.00 (-45.00-41.00)	0.073
CRP (mg/L)	56	0.34 ± 7.27	0.10 (-28.30-34.60)	62	0.03 ± 5.90	-0.10 (-29.50-30.60)	0.183

Data are presented as the number of subjects, means ± SD, Median and Range (min-max). *$P < 0.05$; Change from baseline in group; †ANCOVA model with treatment, baseline value as covariate and site as factors (one-side test). BMI, body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low dense lipoprotein cholesterol; HDL-C, high dense lipoprotein cholesterol; non-HDL-C, non-high dense lipoprotein cholesterol; ApoA, apolipoprotein A; ApoB, apolipoprotein B; CRP, C-reactive protein.

cally significant ($P = 0.040$).

Anthropometric measurements, lipid parameters, and hs-CRP

Table 4 presents the changes in body weight, BMI, lipid profiles and hs-CRP levels from baseline to week 24 by group as well as the difference between groups in mITT set. The mean body weight at week 24 significantly decreased by 0.67 ± 1.89 kg in acarbose group and 0.87 ± 1.81 kg in the voglibose group compared to baseline, respectively. The mean BMI also significantly decreased by 0.26 ± 0.71 kg/m^2 in the acarbose group and 0.32 ± 0.68 kg/m^2 in voglibose group, respectively. Both body weight and BMI differences between two groups were not statistically significant.

The change in lipid parameter levels (total cholesterol, LDL-C, HDL-C, non-HDL-C, triglycerides, and Apo- A, B) from baseline to week 24 by group, as well as the differences between groups, is shown in Table 4. The changes of total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, and non-HDL cholesterol levels between baseline and week 24 in both acarbose and voglibose groups could not show the significant differences. The mean Apo B level increased by 8.32 ± 17.46 (Median, 6.00; Range, -18.00-64.00) mg/dL and 4.21 ± 16.43 (Median, 4.00; Range, -45.00-41.00) mg/dL in acarbose and voglibose groups, respectively. The differences of LSM between groups in all lipid parameters were not statistically significant. The change of hs-CRP level from baseline to week 24 did not show any differences within and between the two groups.

Table 5. Adverse events (safety set) by acarbose and voglibose

Adverse events	Acarbose (n = 59)	Voglibose (n = 62)	*P* value
	No. (%)	No. (%)	
Serious adverse events (SAE)	2 (3.3)	4 (6.5)	0.680‡
Gastrointestinal adverse events	20 (33.3)	16 (25.8)	0.362†
Any hypoglycemia	7 (11.7)	6 (9.7)	0.722†
Discontinued due to adverse events	1 (1.7)	1 (1.6)	1.000‡
Adverse drug reaction*	10 (16.7)	6 (9.7)	0.253†
Gastrointestinal disorders	9 (15.0)	2 (3.2)	
Abdominal discomfort	2 (3.3)	1 (1.6)	
Dyspepsia	2 (3.3)	0 (0.0)	
Flatulence	2 (3.3)	0 (0.0)	
Gastrointestinal disorder	1 (1.7)	0 (0.0)	
Abdominal distension	1 (1.7)	1 (1.6)	
Diarrhea	1 (1.7)	0 (0.0)	
Nausea	1 (1.7)	0 (0.0)	
Abdominal pain	0 (0.0)	1 (1.6)	
General disorders	1 (1.7)	3 (4.8)	
Chills	1 (1.7)	0 (0.0)	
Asthenia	0 (0.0)	1 (1.6)	
Fatigue	0 (0.0)	1 (1.6)	
Hunger	0 (0.0)	1 (1.6)	
Metabolic disorders	3 (5.0)	0 (0.0)	
Hypoglycemia	3 (5.0)	0 (0.0)	
Eye disorders	1 (1.7)	0 (0.0)	
Retinopathy	1 (1.7)	0 (0.0)	
Nervous system disorders	1 (1.7)	0 (0.0)	
Dizziness	1 (1.7)	0 (0.0)	
Tremor	1 (1.7)	0 (0.0)	
Respiratory disorders	0 (0.0)	1 (1.6)	
Dyspnea	0 (0.0)	1 (1.6)	
Skin disorders	0 (0.0)	1 (1.6)	
Hyperhidrosis	0 (0.0)	1 (1.6)	

*Causal relationship-Related; †Pearson's chi-square test; ‡Fisher's exact test.

Adverse events

The adverse events reported during study are summarized in Table 5. A total of 137 adverse events in 44/60 (73.3%) subjects in acarbose group and 143 adverse events in 42/62 (67.7%) subjects in voglibose group were reported during the study. Of those, 125 events in 43/60 (71.7%) subjects in the acarbose group and 132 events in 41/62 (66.1%) subjects in voglibose group were reported after treatment with the study medications. Among them, 22 events reported in 10/60 (16.7%) subjects in the acarbose group and 8 events reported in 6/62 (9.8%) subjects in voglibose group were judged to be related to the study drugs. Gastrointestinal side effects were reported in 20/60 (33.3%) subjects and 16/62 (25.8%) subjects in acarbose and voglibose group, respectively.

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No deaths occurred during the study. Serious adverse events (SAEs) were reported in 2/60 (3.3%) subjects in acarbose group and 4/62 (6.5%) subjects in voglibose group. In acarbose group, 2/60 (3.3%) subjects experienced two SAEs (pancreatic carcinoma in one subject and *Escherichia* sepsis in another subject). In voglibose group, 4/62 (6.5%) subjects experienced four SAEs (one subject with each cartilage injury, radius fracture, malignant lung neoplasm, and varicose veins). None of the SAEs was assessed by the investigator as related to the study drug.

DISCUSSION

Alpha-glucosidase inhibitors (AGIs) may be used for patients with type 2 diabetes to target postprandial hyperglycemia by delaying absorption of carbohydrates (10, 11). Currently, four AGIs (acarbose, miglitol, voglibose, and emiglitate) have been used. Of these, acarbose is the most commonly prescribed. AGIs are much cheaper than many other newly developed medications and therefore these drugs can be continued for long periods of time (15). In particular, because AGIs lower the postprandial elevation of glucose and insulin levels (16), they may be used as an additional therapy to basal insulin, which targets control of fasting blood glucose but not postprandial glucose excursion. AGIs have been widely used in Asian patients with type 2 diabetes who consume high carbohydrate diets (17-20).

In this study, the mean HbA_{1c} level at week 24 decreased significantly by approximately 0.7% from baseline in both acarbose and voglibose groups. There was no statistically significant difference between two groups in the change of HbA_{1c} level. We consider the reduction in HbA_{1c} level after the addition of acarbose or voglibose might be derived not only from decreased postprandial glucose levels but also from decreased fasting glucose level, although the mean changes in SMBG levels 1 hr after the meal were larger than 1 hr before the meal. In many studies (16, 21-23), AGIs reduce both fasting and postprandial glucose levels, a phenomenon that the authors suggest was due to a greater reduction in postprandial hyperglycemia that secondarily leads to a decreased fasting plasma glucose concentration. In our study, the mean changes in SMBG levels were not significantly different between the groups, except the SMBG level 1 hr after dinner. The mean change in SMBG levels 1 hr after dinner in acarbose group was larger than in voglibose group. Based on these results, both drugs were regarded to have similar effects on glycemic control. However, the effects of acarbose on postprandial glucose were slightly superior to those of voglibose.

In this study, both acarbose and voglibose reduced body weight, which is thought to result from improving the postprandial hyperinsulinemia that causes weight gain (16, 23, 24). Although several studies have reported that AGIs have neutral effects on body weight (25), many other studies and latest meta-analyses showed that AGIs positively affect body weight change due to decreased caloric absorption and less food intake as a result of gastrointestinal adverse effects (26-28).

Upon examining the lipid profiles, ApoA showed a tendency to decrease in both groups. Total cholesterol, HDL-C, non-HDL-C, and LDL-C did not change significantly in both group. However, both acarbose and voglibose significantly elevated the ApoB level, which is associated with LDL-cholesterol. Hegele et al. (29) also reported ApoB elevation after acarbose treatment, which is thought to be caused by chronically increased acetate production due to fermentation of non-absorbed carbohydrates, similar to lactulose ingestion (30, 31). However, the exact mechanism has not yet been studied and requires further investigation. Currently available studies on cardiovascular disease (CVD) contain no evidence of an increased CVD risk associated with AGI use, despite the elevation in ApoB (29, 32-34). In addition, CRP, which is a marker of CVD, was not elevated after using these medications. These results suggest that the drugs exert greater influence on secondary changes due to reduced blood glucose rather than directly influencing dyslipidemia.

The most common reported side effect of AGIs is abdominal flatulence, and other gastrointestinal side effects are frequently found (12, 35). Gastrointestinal adverse effects (flatulence, diarrhea, etc.) were the most frequent side effect in this study as well, but there was only a single case in each study group resulting in discontinuation of the medication because of an adverse event. Therefore, there were no major problems using the drugs. Hypoglycemia was reported in 11.7% of subjects in the acarbose group and 9.7% of subjects in the voglibose group. Hypoglycemic events in this study do not appear to have been caused by AGIs because the frequencies are similar to or lower than that reported in studies on glargine or detemir (36-38). Furthermore, there is a report that acarbose usage may reduce necessary insulin dose, therefore minimizing the risk of hypoglycemia and weight gain (39). Thus, both drugs seem to have no serious side effects and may be safely used.

Taken together, these data showed that the addition of α-glucosidase inhibitors could help lower the levels of HbA_{1c} and blood glucose in patients with type 2 diabetes who were inadequately controlled with insulin glargine (or insulin detemir) alone or in combination with metformin (or a sulfonylurea). In conclusion, both acarbose and voglibose are comparably effective on glycemic control of HbA_{1c} and blood glucose levels.

DISCLOSURE

The authors have no conflicts of interest to disclose. The co-authors, Seung Hun Lee and Hee Kang Shin, are employee of the funding pharmaceutical the Bayer Korea Ltd, but did not involve data production or writing. They have assisted only the study procedure. Both Seung Hun Lee and Hee Kang Shin do not hold

stock in the Bayer group.

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