Alogliptin, a Dipeptidyl Peptidase 4 Inhibitor, Prevents the Progression of Carotid Atherosclerosis in Patients With Type 2 Diabetes: The Study of Preventive Effects of Alogliptin on Diabetic Atherosclerosis (SPEAD-A)

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OBJECTIVE

Recent experimental studies have shown that dipeptidyl peptidase 4 (DPP-4) inhibitors have antiatherosclerotic benefits in glucagon-like peptide 1–dependent and –independent manners. The current study investigated the effects of alogliptin, a DPP-4 inhibitor, on the progression of carotid atherosclerosis in patients with type 2 diabetes mellitus (T2DM).

RESEARCH DESIGN AND METHODS

This prospective, randomized, open-label, blinded-end point, multicenter, parallel-group, comparative study included 341 patients with T2DM free of a history of apparent cardiovascular diseases recruited at 11 clinical units and randomly allocated to treatment with alogliptin (*n* = 172) or conventional treatment (*n* = 169). Primary outcomes were changes in mean common and maximum intima-media thickness (IMT) of the carotid artery measured by carotid arterial echography during a 24-month treatment period.

RESULTS

Alogliptin treatment had a more potent glucose-lowering effect than the conventional treatment (−0.3 ± 0.7% vs. −0.1 ± 0.8%, *P* = 0.004) without an increase of hypoglycemia. Changes in the mean common and the right and left maximum IMT of the carotid arteries were significantly greater after alogliptin treatment than after conventional treatment (−0.026 mm [SE 0.009] vs. 0.005 mm [SE 0.009], *P* = 0.022; −0.045 mm [SE 0.018] vs. 0.011 mm [SE 0.017], *P* = 0.025, and −0.079 mm [SE 0.018] vs. −0.015 mm [SE 0.018], *P* = 0.013, respectively).

CONCLUSIONS

Alogliptin treatment attenuated the progression of carotid IMT in patients with T2DM free of apparent cardiovascular disease compared with the conventional treatment.

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Patients with type 2 diabetes mellitus (T2DM) are at high risk for cardiovascular (CV) diseases (CVD), which is one of the major causes of morbidity and mortality in these patients (1). Thus, one of the main goals of T2DM management is to reduce the incidence of CVD. In this regard, although clinical studies have shown that HbA_{1c} is a risk factor for CVD in patients with T2DM (2), there is little evidence that glycemic control and/or treatment with any particular oral hypoglycemic agents actually reduces the incidence of CVD (3,4).

Dipeptidyl peptidase 4 (DPP-4) inhibitors, a new class of oral hypoglycemic agents, inhibit the degradation of active glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide and increase their biological effects (e.g., augmentation of glucose-dependent insulin secretion and suppression of glucagon release) (5). In addition, these agents have potential antiatherosclerotic properties. In a rodent model of atherosclerosis, GLP-1 and GLP-1 receptor agonists were reported to inhibit atherosclerosis and inflammation (6–9), and DPP-4 inhibitors, including alogliptin, inhibit these pathological processes in GLP-1–dependent and –independent manners (10–12).

These studies are promising and suggest that DPP-4 inhibitors could also reduce CV risk in T2DM. However, three recent randomized clinical trials reported that DPP-4 inhibitors did not reduce CV risk, but they also did not increase the risk compared with placebo in patients with T2DM with history of CVD or at high-risk for CVD (13–15). Subjects in these studies had already received a multitude of therapies for other pathologies. Thus, these factors may possibly have influenced the results of the above three trials. On the other hand, early and effective intervention before the development of advanced atherosclerosis in patients without history of CVD may increase the chance of significant reduction not only of microvascular disease but also CVD (16). However, assessing the long-term effects of a single drug on primary CVD in a clinical setting is no doubt difficult.

Progressive thickening of the carotid artery intima-media is considered a surrogate marker for CVD in patients with T2DM (17–19) and has been used in the evaluation of the effects of various interventions on the progression of atherosclerosis. To our knowledge, no published studies have reported the long-term antiatherosclerotic effects of DPP-4 inhibitors in patients with T2DM free of CVD. The current study investigated the effects of alogliptin on the intima-media thickness (IMT) in apparent CVD-free patients with T2DM.

RESEARCH DESIGN AND METHODS

Study Design

The Study of Preventive Effects of Alogliptin on Diabetic Atherosclerosis (SPEAD-A) trial was a multicenter prospective, randomized, open-label, blinded-end point (PROBE) study, as described previously (20). This study was registered on the University Hospital Medical Information Network Clinical Trials Registry (UMIN000005311), a nonprofit organization in Japan that meets the requirements of the International Committee of Medical Journal Editors (ICMJE).

Study Population

Japanese patients with T2DM who periodically attended the diabetes outpatient clinics at 11 institutions in Japan (listed in the Supplementary Data) were approached to participate in this study. The inclusion criteria were as follows: *1*) patients with T2DM in whom the target blood glucose control specified in the *Treatment Guide for Diabetes* (edited by the Japan Diabetes Society) (21) could not be achieved despite dietary/exercise therapy or concomitant treatment for T2DM other than DPP-4 inhibitors administered for 3 months or longer and whose HbA_{1c} was below 9.4% (patients were also included after a 12-week or longer withdrawal of previous treatment with DPP-4 inhibitors); *2*) age $\geq$30 years, irrespective of sex; and *3*) signed consent for participation in the study after a full explanation of the study. The exclusion criteria were as follows: *1*) type 1 or secondary diabetes; *2*) severe infections before or after surgery or severe trauma; *3*) myocardial infarction, angina pectoris, cerebral stroke, or cerebral infarction; *4*) moderate or severe renal dysfunction (serum creatinine: male, $>$1.4 mg/dL; female, $>$1.2 mg/dL); *5*) severe liver dysfunction (aspartate aminotransferase $\geq$100 IU/L); *6*) moderate or severe heart failure (New York Heart Association stage III or higher); *7*) under treatment with an incretin preparation, such as other DPP-4 inhibitors, at the start of the study; *8*) under insulin treatment; *9*) under treatment with therapeutic drugs not concomitantly administrable with incretin preparations with regard to the National Health Insurance program, such as DPP-4 inhibitors, at the start of the study; *10*) pregnancy, lactation, possible or planned pregnancy; *11*) medical history of hypersensitivity to investigational drugs; or *12*) judged as ineligible by clinical investigators.

The study subjects were screened consecutively, and those who met the above criteria were invited to participate in the current study. All patients who agreed to participate were registered. The protocol was approved by the institutional review board at each participating institution, and the study was conducted in compliance with the Declaration of Helsinki and current legal regulations in Japan.

Randomization and Study Intervention

Patients were registered at the administration office of the SPEAD-A trial via the Internet, and once enrolled, were randomly assigned in equal numbers into the alogliptin treatment group or the conventional treatment group (on drugs other than DPP-4 inhibitors). Randomization was performed using a dynamic allocation method based on the with/without administration of pioglitazone, age, and sex.

Treatment was continued until the target value of HbA_{1c} specified in the *Treatment Guide for Diabetes* (21) was achieved (usually HbA_{1c} level $<$7.0%) in all patients. In the conventional treatment group, the dosage of current therapy was increased or a concomitant oral glucose-lowering drug (excluding other DPP-4 inhibitors, GLP-1 analogs, and insulin) was added. In the alogliptin treatment group, alogliptin was administered orally at 25 mg, once daily. However, the addition of an alternative glucose-lowering agent (excluding other DPP-4 inhibitors, GLP-1 analogs, and insulin) was permitted. In the case of hypoglycemia, the dose of any concomitantly used oral glucose-lowering drug was titrated. The use of antihyperlipidemic and antihypertensive drugs was permitted during the study.

Observation Items and Schedule

The study period was 2 years after registration (registration period: March 2011 to June 2013). All patients were

monitored for 2 years, regardless of adherence to or discontinuation of study medications for any reason. Clinical outcomes, adherence, and adverse events (AEs) were ascertained and adjudicated by each investigator in an open fashion. Clinical and biochemical data were collected at 0, 26, 52, 78, and 104 weeks after randomization.

Study Outcomes

The primary study outcomes were changes in right and left maximum IMT of the common carotid artery (max-IMT-CCA) and mean IMT of the CCA (mean-IMT-CCA) during the 104-week treatment period measured by carotid arterial echography. These measurements were performed at the start of the study and repeated after 52 and 104 weeks and at the time of any discontinuations or changes in medication and/or dose.

The secondary outcomes were *1*) changes in parameters related to glycemic control (HbA_{1c}, fasting plasma glucose, and immunoreactive insulin); *2*) changes in parameters related to diabetic nephropathy, including urinary albumin excretion and estimated glomerular filtration rate (eGFR); *3*) changes in lipid parameters (total cholesterol, HDL cholesterol, triglyceride, and LDL cholesterol); *4*) changes in biochemical parameters, including serum intercellular adhesion molecule 1, vascular cell adhesion molecule 1 (VCAM-1), interleukin-6, and hs-CRP; *5*) occurrence of CV events, including sudden death, coronary heart disease, and stroke; and *6*) appearance of any AE.

Safety and CV Events Evaluation

For the sake of patient safety, all AEs were recorded during the treatment and follow-up. AEs were defined as any untoward medical occurrence in a clinical trial subject administered a medicinal product and that did not necessarily have a causal relationship with this treatment. The association between AEs and the study medication was classified as related or not related to the study drug by one of the investigators. All related AEs that resulted in a withdrawal of the subject from the study were monitored until resolution. Serious AEs were defined as death or life-threatening events that required inpatient hospitalization, caused prolongation of existing hospitalization, or even resulted in persistent or significant disability/incapacity and needed intervention to prevent permanent impairment or damage. If participants suffered any AEs/serious AEs, all details were documented and reported. Serious AEs were reported to the principal investigator and the ethics committee. Both of them judged whether the diagnosis was appropriate or made a decision on whether the patient should be withdrawn from the trial. CV events were diagnosed and fully assessed by members of the cardiovascular end point committee (including two cardiologists and a neurologist).

Measurement of Carotid IMT

Ultrasonographic scanning of the carotid arteries was performed by expert sonographers who were specifically trained to perform the prescribed study examination. The mean intrainvestigator coefficient of variation for measurement of mean-IMT-CCA and max-IMT-CCA ($\pm$ SD) in each institution was 1.9 $\pm$ 1.1% and 2.8 $\pm$ 2.2%, respectively. To avoid intersonographer variability, each participant was examined by the same sonographer using the same equipment (high-resolution B-mode ultrasound scanner equipped with a high-frequency [$>$7.5-MHz] linear transducer, with a limit of detection of $<$0.1 mm) throughout all the visits. Scanning of extracranial CCAs, the carotid bulb, and the internal carotid arteries (ICA) in the neck was performed in at least three different longitudinal projections (anterior, lateral, and posterior, which approximately corresponded to 60°, 90°, and 150° for the right carotid artery and 210°, 270°, and 300° for the left carotid artery marked on the Meijer arc) as well as transverse projections. The site of greatest thickness, including plaque lesions, was sought along the arterial walls. The IMT was measured as the distance between two parallel echogenic lines corresponding to the vascular lumen and the adventitial layer.

To avoid interreader variability, all scans were electronically stored and sent to the central office (IMT Evaluation Committee, Osaka, Japan) and read by a single experienced reader blinded to the clinical characteristics of the subjects and type of treatment, in a random order, using automated digital edge-detection software (Intimascope; Media Cross, Tokyo, Japan) (22). The software system averaged 60 points of IMT values in the segment 2 cm proximal to the dilation of the carotid bulb (mean-IMT-CCA). In addition, the greatest thicknesses of IMT, including plaque lesions in the CCA (max-IMT-CCA), the carotid bulb (max-IMT-Bulb), and the ICA (max-IMT-ICA), were also measured separately. Reproducibility analysis of replicate measurements in 20 subjects yielded absolute mean $\pm$ SD differences of 0.02 $\pm$ 0.01, 0.01 $\pm$ 0.01, 0.02 $\pm$ 0.01, and 0.01 $\pm$ 0.01 mm for mean-IMT-CCA, max-IMT-CCA, max-IMT-Bulb, and max-IMT-ICA, respectively. The intrareader coefficient of variation for measurement was 1.1%, 0.7%, 0.7%, and 0.8%, respectively.

Biochemical Tests

Blood samples were obtained after overnight fast. Serum lipids (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides), HbA_{1c} (NGSP), glucose, insulin, and creatinine were measured with standard techniques. Measurements of hs-CRP, interleukin-6, intercellular adhesion molecule 1, and VCAM-1 were outsourced to a private laboratory (SRL Laboratory, Tokyo, Japan). Urinary albumin excretion was measured by the improved bromocresol purple method using a spot urine sample. The eGFR was calculated by the formula: eGFR (mL/min per 1.73 m^2) = $194 \times age^{-0.287} \times serum\ creatinine^{-0.1094}$ ($\times$0.739 for females) (23).

Sample Size

The progression of carotid IMT in patients with T2DM is considered to be 0.034 $\pm$ 0.054 mm/year, and a 1% improvement in the HbA_{1c} value is associated with 0.02 mm/year improvement in IMT (24). Therefore, in the 2-year observation period, registration of at least 324 patients was required to obtain 90% power to detect a difference of 0.04 mm in IMT between the two treatment groups, assuming a SD of 0.108, 5% dropout, and 0.05 level of significance. According to this calculation, the target number of enrolled patients was set at 324 for the 2-year registration period.

Statistical Analysis

Efficacy, regardless of adherence, was analyzed using an intent-to-treat approach. Results are presented as mean $\pm$ SD or median (interquartile range) for continuous variables or number (proportion) of patients for

categorical variables. The primary end point was a change in IMT from baseline to week 104. Primary analysis was performed using the mixed-effects model for repeated measures with treatment group, time (week), interactions between treatment group and time (week), and baseline IMT as fixed effects; an unstructured covariate was used to model the covariance of within-subject variability. For the occurrence of CV events, one of the secondary end points—time to onset—was analyzed using a log-rank test and Cox proportional hazards model.

Baseline and follow-up group comparisons were assessed with the Student *t* test or Wilcoxon rank sum test for continuous variables and the Fisher exact test for categorical variables. Changes from baseline to treatment visits were assessed with one-sample *t* test and the Wilcoxon signed rank test within the group. The number and percentage of patients reporting AEs was presented by treatment group and compared between the two treatment groups using the Fisher exact test. All statistical tests were two-sided with 5% significance level. Analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC). The administrative office of the SPEAD-A trial analyzed the data based on instructions from an independent biostatistician.

Table 1—Clinical characteristics of the patients in the two groups

	Alogliptin treatment group *n* = 172	Conventional treatment group *n* = 169	*P* value
Male sex	101 (63)	98 (61)	0.72
Age (years)	64.4 ± 9.8	64.8 ± 9.1	0.82
Current smoking	43 (27)	33 (21)	0.24
Hypertension	90 (56)	91 (57)	1.00
Dyslipidemia	86 (53)	94 (58)	0.43
Duration of T2DM (years)	9 (5.0, 15.0)	8.2 (4.0, 15.0)	0.94
Use of oral glucose-lowering agents			
Metformin	84 (52)	75 (47)	0.37
Sulfonylurea	80 (50)	90 (56)	0.32
Glinides	9 (6)	16 (10)	0.21
Thiazolidinediones	35 (22)	38 (24)	0.79
α-Glucosidase inhibitor	56 (35)	51 (32)	0.64
Use of antihypertensive drugs			
ACE inhibitors	7 (4)	4 (2)	0.54
Angiotensin II receptor blockers	72 (45)	68 (42)	0.74
Direct renin inhibitor	0 (0)	1 (1)	1.00
Calcium channel blocker	47 (29)	58 (36)	0.23
Diuretic drugs	7 (4)	8 (5)	1.00
α-Adrenergic receptor antagonist	3 (2)	0 (0)	0.25
β-Adrenergic receptor antagonist	3 (2)	8 (5)	0.22
Others	1 (0)	4 (2)	0.37
Use of lipid-lowering agents			
Statins	61 (38)	74 (46)	0.18
Ezetimibe	5 (3)	2 (1)	0.45
Resins	0 (0)	1 (1)	1.00
Fibrates	6 (4)	9 (6)	0.60
Use of antithrombotic agents			
Antiplatelet agents	19 (12)	23 (14)	0.62
Anticoagulants	1 (1)	3 (2)	0.62
Others	0 (0)	1 (1)	1.00

Data are *n* (%), mean ± SD, or median (interquartile range).

RESULTS

A total of 341 participants were randomly allocated into the alogliptin group (*n* = 172) or the conventional treatment group (*n* = 169). After excluding from the analyses 19 patients who withdrew from the study and/or objected to the inclusion of their data in any analysis, 161 in the alogliptin treatment group and 161 in the conventional treatment group were included in the full analysis set (Supplementary Fig. 1). The baseline demographic and clinical characteristics of the 322 study participants are reported in Tables 1–4. Most subjects had previously attended educational programs about diet and exercise therapy and received appropriate medical treatments. Blood glucose, lipids, and blood pressure (BP) levels were well controlled in all subjects.

All patients of both groups met the criteria for inclusion in IMT analysis based on the criteria of the intention-to-treat population. Over 104 weeks, alogliptin treatment, but not conventional treatment, significantly reduced the mean-IMT-CCA and the right and left max-IMT-CCA relative to the baseline (Table 2). In a mixed-effects model for repeated measures, alogliptin significantly prevented the progression in mean-IMT-CCA and right and left max-IMT-CCA (i.e., primary end points of the study) compared with conventional treatment (Table 2). Similar findings were noted even in the mixed-effects models adjusted for age and sex (data not shown). ANCOVA models that included treatment group, age, sex, baseline IMT, systolic BP, and administration of statins also produced findings similar to those in the mixed-effects models (model 1, Supplementary Table 1).

The mean change in BMI was 0.3 ± 1.9 kg/m^2 in the alogliptin group versus −0.3 ± 1.7 kg/m^2 in the conventional treatment group at 104 weeks (P = 0.003, Table 3). The Δchange in HbA_{1c} (value at end of study − value at baseline) improved significantly in the alogliptin group (−0.3 ± 0.7%) but not in the conventional treatment group (−0.1 ± 0.8%, P = 0.004; Table 3). The effect of alogliptin on the reduction in HbA_{1c} may be underestimated because the use of α-glucosidase inhibitors and glinides was significantly higher in the conventional treatment group than in the alogliptin group at the end of study (Supplementary Table 2). On the one hand, ANCOVA models that included changes in HbA_{1c} from baseline in addition to the factors in model 1 showed that alogliptin significantly prevented the progression in carotid IMT compared with conventional treatment (model 2, Supplementary Table 1). On the other hand, fasting blood glucose and plasma insulin levels were not different between the two groups. BP and lipid metabolism

Table 2—Effects of alogliptin on IMT

		Alogliptin treatment		Conventional treatment	Treatment effect (alogliptin-conventional treatment)		*P* value between
	n	group	*n*	group	Mean change (95% CI)	*P* value	groups
Common mean IMT							
Baseline (mm)	161	0.83 ± 0.15	161	0.83 ± 0.17			0.87
52 weeks (mm)	152	0.79 ± 0.14	157	0.82 ± 0.16			0.18
104 weeks (mm)	151	0.80 ± 0.16	153	0.84 ± 0.18			0.052
Mean change (SEM)							
52 weeks		−0.029 (0.009)#		−0.012 (0.009)	−0.017 (−0.042, 0.007)	0.17	
104 weeks		−0.026 (0.009)#		0.005 (0.009)	−0.030 (−0.057, −0.004)	0.022	
Right maximum IMT							
Baseline (mm)	161	1.04 ± 0.32	161	1.03 ± 0.26			0.77
52 weeks (mm)	152	0.97 ± 0.23	157	1.02 ± 0.30			0.099
104 weeks (mm)	151	0.99 ± 0.27	153	1.04 ± 0.30			0.10
Mean change (SEM)							
52 weeks		−0.062 (0.019)#		−0.008 (0.018)	−0.053 (−0.105, −0.002)	0.041	
104 weeks		−0.045 (0.018)*		0.011 (0.017)	−0.056 (−0.105, −0.007)	0.025	
Left maximum IMT							
Baseline (mm)	161	1.09 ± 0.33	161	1.10 ± 0.42			0.72
52 weeks (mm)	153	1.05 ± 0.37	157	1.08 ± 0.36			0.50
104 weeks (mm)	151	1.01 ± 0.28	153	1.10 ± 0.40			0.032
Mean change (SEM)							
52 weeks		−0.040 (0.019)*		−0.031 (0.019)	−0.009 (−0.062, 0.043)	0.72	
104 weeks		−0.079 (0.018)§		−0.015 (0.018)	−0.064 (−0.114, −0.014)	0.013	

Data are mean ± SD unless otherwise stated. Comparisons of IMTs during treatment with those at baseline were performed by one-sample *t* test based on a mixed-effects model for repeated measures. Differences in IMT between groups at each point were analyzed by the Student *t* test. Differences in Δchange in IMT from baseline at 52 and 104 weeks between groups at each point (treatment effect) were analyzed with mixed-effects model for repeated measures. Treatment group, week, interactions between treatment group and week, and baseline IMT were included as fixed effects. *$P < 0.05$; #$P < 0.01$; §$P < 0.001$.

were well controlled in both groups throughout the study, but there were no significant differences in other risk factors for atherosclerosis at the end of the study (Table 3). A modest difference in VCAM-1 was noted, but no changes were observed in other markers of inflammation and endothelial damage (Table 4).

During the study, 37 patients developed any AEs and 19 developed serious AEs. There were no significant differences in the incidences of any AEs and serious AEs between the alogliptin group and the conventional treatment group. The most frequent AE was hypoglycemia, followed by gastrointestinal disorders (Supplementary Table 3). Overall, AEs in 8 patients resulted in discontinuation of alogliptin. Hypoglycemic events were recorded in 11 patients (5 patients of the alogliptin group and 6 patients of the control group). However, none of the patients experienced severe hypoglycemia. Only a few patients developed CV events ($n = 5$) or were diagnosed with cancer ($n = 5$); therefore, there was no significant difference in the incidence of CVD between the two groups.

CONCLUSIONS

In this study, the rate of mean-IMT-CCA and right and left max-IMT-CCA diminished significantly in the alogliptin treatment group compared with the conventional-treatment group. Interestingly, there was substantial regression of the mean-IMT-CCA and of the right and left max-IMT-CCA at the end of the alogliptin treatment protocol. These results suggest that alogliptin treatment prevents the progression of atherosclerosis in patients with T2DM free of past history of apparent CVD.

In the current study, we confirmed that alogliptin had a sustainable glucose-lowering effect by ~0.3% over 2 years, a finding almost identical to that of a recent randomized clinical study with alogliptin (13) and other DPP-4 inhibitors (14,15). The glucose-lowering effect of alogliptin is not subtle, considering that most patients had already achieved relatively good glycemic control at baseline. This glucose-lowering effect was probably achieved at least by lessening fluctuations in blood glucose levels (25), which was not evaluated in this study because alogliptin produced only a modest reduction in the fasting blood glucose level. Importantly, the reduction was achieved without increasing the risk of hypoglycemia.

However, the difference in HbA_{1c} between the two groups is probably not closely related to the reduction in carotid IMT, because changes in HbA_{1c} were only very modestly associated with changes in mean-IMT-CCA and right max-IMT-CCA and were not associated with changes in left max-IMT-CCA (mean-IMT-CCA: $r = -0.18$, $P < 0.05$; right max-IMT-CCA: $r = -0.18$, $P < 0.05$; left max-IMT-CCA: $r = -0.12$, P = NS) in the alogliptin treatment group. In addition, alogliptin treatment still attenuated the progression of carotid IMT compared with the conventional treatment even after adjustment for changes in HbA_{1c} from baseline (Supplementary Table 1). Furthermore, significant differences in mean-IMT-CCA and right max-IMT-CCA were still observed in the post hoc matched-pair set ($n = 103$, each group) for changes in HbA_{1c} from baseline (data not shown). These data suggest that the glucose-lowering effect of alogliptin alone could not explain carotid IMT regression.

In human studies, short-term treatment with DPP-4 inhibitors reduced

Table 3—Effects of alogliptin on BMI, glucose metabolism, lipid metabolism, and blood pressure

	n	Alogliptin treatment group	*n*	Conventional treatment group	*P* value
BMI at baseline (kg/m^2)	161	24.6 ± 4.3	161	24.9 ± 3.7	0.49
Change from baseline					
26 weeks	153	0.2 ± 1.3	158	0.0 ± 1.8	0.18
52 weeks	154	0.1 ± 1.3	156	−0.2 ± 1.6	0.037
78 weeks	150	0.2 ± 1.5	153	−0.2 ± 1.6	0.045
104 weeks	147	0.3 ± 1.9	150	−0.3 ± 1.7	0.003
HbA_{1c} at baseline (%)	158	7.3 ± 0.8	160	7.2 ± 0.8	0.54
HbA_{1c} at baseline (mmol/mol)	158	56.3 ± 8.5	160	55.7 ± 9.3	0.54
Change from baseline (HbA_{1c} %)					
26 weeks	158	−0.4 ± 0.7§	160	0.0 ± 0.9	<0.001
52 weeks	153	−0.4 ± 0.6§	157	−0.1 ± 0.8	<0.001
78 weeks	152	−0.4 ± 0.8§	154	0.0 ± 1.1	<0.001
104 weeks	150	−0.3 ± 0.7§	153	−0.1 ± 0.8	0.004
Fasting blood glucose at baseline (mmol/L)	160	7.81 ± 1.5	161	7.85 ± 1.93	0.85
Change from baseline					
26 weeks	158	−0.55 ± 1.64§	159	−0.06 ± 2.19	0.026
52 weeks	150	−0.59 ± 1.48§	157	−0.32 ± 1.81	0.15
78 weeks	147	−0.54 ± 1.84§	152	−0.13 ± 2.52	0.11
104 weeks	149	−0.45 ± 1.56§	153	−0.28 ± 2.03	0.41
Insulin at baseline (pmol/L)	158	57.2 ± 68.0	161	58.3 ± 43.9	0.86
Change from baseline					
52 weeks	145	−2.0 ± 47.3	154	−5.0 ± 37.0	0.54
104 weeks	147	2.7 ± 72.8	152	0.0 ± 43.5	0.70
Total cholesterol at baseline (mmol/L)	160	5.00 ± 0.77	159	5.01 ± 0.75	0.86
Change from baseline (%)					
26 weeks	122	0.0 ± 11.7	138	−1.7 ± 11.7	0.25
52 weeks	153	−2.1 ± 11.4*	154	−3.0 ± 11.6#	0.50
78 weeks	152	−3.8 ± 12.4§	150	−3.0 ± 13.5#	0.59
104 weeks	150	−2.2 ± 13.9	151	−3.5 ± 14.4#	0.43
LDL cholesterol at baseline (mmol/L)	158	2.89 ± 0.68	160	2.93 ± 0.64	0.62
Change from baseline (%)					
52 weeks	145	0.0 ± 17.1	153	−0.9 ± 17.3	0.25
104 weeks	146	−0.4 ± 22.0	150	−2.6 ± 20.2	0.37
HDL cholesterol at baseline (mmol/L)	160	1.47 ± 0.38	161	1.41 ± 0.36	0.16
Change from baseline (%)					
26 weeks	156	−1.6 ± 12.9	160	−1.5 ± 15.8	0.95
52 weeks	153	−2.2 ± 19.3	157	−1.4 ± 14.7	0.70
78 weeks	151	−3.9 ± 12.3§	153	0.2 ± 16.5	0.015
104 weeks	149	−2.0 ± 12.5	153	1.1 ± 15.7	0.065
Triglyceride at baseline (mmol/L)	160	1.19 (0.82, 1.76)	161	1.25 (090, 1.68)	0.31
Change from baseline (%)					
26 weeks	151	0.0 (−14.7, 28.6)	159	−0.5 (−17.2, 23.8)	0.55
52 weeks	150	−7.3 (−24.4, 27.9)	157	−3.7 (−22.7, 23.1)	0.57
78 weeks	147	−6.3 (−23.5, 16.9)	153	−5.5 (−24.7, 19.8)	0.62
104 weeks	149	−1.3 (−24.3, 24.3)	152	−5.5 (−24.2, 19.8)	0.35
Systolic BP (mmHg)	161	130 ± 16	161	132 ± 15	0.34
Change from baseline					
26 weeks	156	−1 ± 16	159	−4 ± 15§	0.10
52 weeks	154	0 ± 16	156	−1 ± 16	0.70
78 weeks	147	−1 ± 19	152	−4 ± 14#	0.19
104 weeks	150	2 ± 19	152	0 ± 15	0.35
Diastolic BP (mmHg)	161	75 ± 12	161	75 ± 11	1.00
Change from baseline					
26 weeks	156	−2 ± 10	159	−2 ± 11*	0.62
52 weeks	154	−1 ± 11	156	−1 ± 16*	0.48
78 weeks	147	−3 ± 13#	152	−4 ± 14§	0.75
104 weeks	150	0 ± 12	152	0 ± 15	0.35

Data are mean ± SD or median (interquartile range). Differences in parameters between groups at baseline were analyzed by the Student *t* test or Wilcoxon rank sum test. Differences in parameters from baseline to 52 and 104 weeks within group were analyzed by one-sample *t* test or the Wilcoxon signed rank test. Differences in parameters from baseline to 52 and 104 weeks between groups were analyzed by the Student *t* test or the Wilcoxon rank sum test. *$P < 0.05$; #$P < 0.01$; §$P < 0.001$.

Table 4—Effects of alogliptin on markers of renal function, inflammation, and endothelial injury

	n	Alogliptin treatment group	*n*	Conventional treatment group	*P* value
eGFR (mL/min/1.73 m^2)	161	78 ± 20	161	77 ± 18	0.59
Change from baseline					
26 weeks	156	−1 ± 10	160	1 ± 9	0.025
52 weeks	154	−1 ± 9	157	1 ± 11	0.18
78 weeks	152	−1 ± 10	157	0 ± 11	0.44
104 weeks	150	−1 ± 10	153	0 ± 10	0.27
UAE at baseline (mg/g creatinine)	158	14.0 (7.8, 54.2)	160	15.8 (7.4, 46.5)	0.96
Change from baseline					
26 weeks	103	0.6 (−5.0, 8.6)	111	0.8 (−3.5, 18.5)	0.14
52 weeks	144	−0.3 (−9.2, 5.2)	141	0.7 (−4.4, 7.5)	0.067
78 weeks	128	−1.0 (−9.2, 5.1)	119	1.0 (−4.1, 13.8)	0.014
104 weeks	145	0.3 (−5.3, 8.8)	144	0.4 (−5.1, 14.0)	0.48
hs-CRP (ng/dL)	158	443 (209, 924)	161	545 (244, 868)	0.42
Change from baseline					
52 weeks	145	69 (−65, 245)	153	23 (−189, 280)	0.28
104 weeks	146	56 (−103, 250)	153	13 (−205, 200)	0.18
Interleukin-6 at baseline (ng/dL)	158	2.1 (1.4, 2.7)	160	2.2 (1.5, 2.9)	0.26
Change from baseline					
52 weeks	145	0.0 (−0.7, 0.6)	153	−0.3 (−0.9, 0.4)§	0.041
104 weeks	145	0.1 (−0.3, 0.7)*	147	0.0 (−0.6, 0.6)	0.12
ICAM-1 at baseline (ng/mL)	158	230 (187, 286)	160	218 (185, 297)	0.35
Change from baseline					
52 weeks	145	−2 (−28, 31)	153	−6 (−26, 20)	0.62
104 weeks	144	−6 (−37, 22)*	147	−9 (−39, 10)	0.42
VCAM-1 at baseline (ng/mL)	148	664 (551, 821)	160	718 (580, 879)	0.065
Change from baseline					
52 weeks	145	32 (−78, 101)	153	9 (−68, 89)	0.45
104 weeks	145	20 (−57, 90)*	147	−8 (−102, 81)	0.030

Data are mean ± SD or median (interquartile range). Differences in parameters between the groups at baseline were analyzed by the Student *t* test or the Wilcoxon rank sum test. Differences in parameters from baseline to 52 and 104 weeks within the group were analyzed by the one-sample *t* test or the Wilcoxon signed rank test. Differences in parameters from baseline to 52 and 104 weeks between the groups were analyzed by the Student *t* test or the Wilcoxon rank sum test. ICAM-1, intercellular adhesion molecule 1; UAE, urinary albumin excretion. *$P < 0.05$; §$P < 0.001$.

the levels of various markers of chronic inflammation and endothelial injury (26,27). In contrast, in the present longer study, no such beneficial effects for alogliptin were noted as judged by these markers. Although the exact reason for these inconsistent findings is still unclear, we propose the following possible scenarios: First, both transient and chronic nonatherosclerotic diseases could have coincidentally affected the proinflammatory conditions.

Second, the levels of these markers could have been altered by the additional treatment within a relatively short time. In this study, the use of α-glucosidase inhibitors and glinides was significantly higher (Supplementary Table 2), and the use of statins and calcium channel blockers tended to be higher in the control group than in the alogliptin group at the end of study (Supplementary Table 4). Indeed, one previous study showed that 3-week treatment with α-glucosidase inhibitors reduced the levels of inflammatory and cell adhesion markers in patients with T2DM (28). Furthermore, short-term statin treatment is reported to improve inflammation (29). In addition, our results showed a significant reduction of BMI in the conventional treatment group. Thus, these factors may have had beneficial effects on the markers in the conventional treatment group and may have canceled the difference between the two groups. Furthermore, in this study, we evaluated only a few inflammatory cytokines, including hs-CRP, which is mainly produced by hepatocytes. Thus, measurement of other cytokines, including tumor necrosis factor-α, is probably needed in future studies. In addition, Balestrieri et al. (30) used immunohistochemistry to determine the expression levels of various inflammatory cytokines and markers of oxidative stress in tissue samples obtained by carotid endarterectomy. They showed that the expression levels of such markers were lower in the atherosclerotic lesions of patients who received incretin-based therapy compared with patients never treated by such therapy, although the same treatments did not have any effect on serum inflammatory cytokine levels in both groups (30). Thus, evaluations of local inflammation and oxidative stress in the vascular wall are probably helpful in the assessment of "non–glycemic-dependent" antiatherosclerotic effects of DPP-4 inhibitors.

In this study, alogliptin seemed to have already resulted in carotid IMT regression at 52 weeks. A similar rapid reduction (within 24 weeks) in mean carotid IMT was reported in patients with T2DM treated with pioglitazone (31,32); however, other studies could not confirm this effect (33). Although the direct action of pioglitazone on atherosclerosis has been reported (34), several reports showed the direct effects of DPP-4 inhibitors on atherosclerosis. We recently demonstrated that another DPP-4 inhibitor suppressed DPP-4–induced smooth muscle proliferation and macrophage inflammation in vitro (11). In addition, Nagashima et al. (35) demonstrated

that GLP-1 suppressed foam cell formation from murine macrophages. These mechanisms may potentially contribute to the reduced atherosclerosis. However, the exact mechanism by which DPP-4 inhibitors reverse carotid IMT remains unknown at present. DPP-4 inhibitors block the cleavage and inactivation of stromal cell-derived factor-1, which is known to modulate the mobilization of endothelial progenitor cells from the bone marrow. A study of patients with T2DM demonstrated that DPP-4 inhibitors increased the number of circulating endothelial progenitor cells with concomitant upregulation of stromal cell-derived factor-1 (36). These effects of DPP-4 inhibitors may contribute to slowing the progression of atherosclerosis. Further studies are needed to investigate these issues.

Our results showed a low rate of progression of IMT, even in the conventional group (0.005 mm). Generally, the rate of carotid IMT progression is high in untreated patients with T2DM (24). However, few studies reported that progression of carotid IMT could almost be prevented in patients with T2DM, even in the control/placebo group of intervention trials (24), although the reports were not always consistent (24,37). The exact reason for differences among these studies was not investigated, but we believe that several factors, such as differences in T2DM status (e.g., HbA_{1c}, type of medications), control of several CV risk factors (e.g., stage of atherosclerosis), prevalence of complications (e.g., nephropathy), duration of the follow-up period, and race, can affect carotid IMT progression. In this study, BP and total cholesterol levels were significantly lower at 52 weeks relative to the baseline in the conventional treatment group. These changes were probably due to the use of statins and calcium channel blockers and probably at least partly explain the low rate of carotid IMT progression at 52 weeks. It is possible that this effect on carotid IMT progression was attenuated in the second half of the study by a weaker BP control.

Three recent randomized clinical studies showed that DPP-4 inhibitors neither reduce nor increase the risk for CVD in patients with T2DM compared with placebo (13–15). The subjects of these three trials were patients with T2DM with a history of CVD or at high-risk for CVD. In comparison, our study enrolled subjects with T2DM who were free from apparent CVD and had not received insulin treatment. Thus, not surprisingly, given the earlier stage of disease, our subjects had lower HbA_{1c} levels and a lower prevalence of hypertension and dyslipidemia, reflecting lower uses of therapies for other pathologies, than did subjects in the above-cited studies. In the present clinical trial, we used surrogate end points due to practical constraints, including trial costs and concern about feasibility in relation to long-term intervention. We demonstrated the efficacy and benefits of alogliptin used at the early stage of disease in preventing the progression of IMT.

Consistent with our results, a few recent studies reported possible beneficial effects for DPP-4 inhibitors on the progression of carotid IMT (38,39). Short-term treatment with both sitagliptin and vildagliptin reduced the progression of IMT in a subanalysis of a small number of patients with T2DM, although with no control group (38). Another study involving a small group of subjects showed that sitagliptin treatment attenuated the progression of IMT compared with the control groups in patients with coronary artery disease and impaired glucose tolerance or mild T2DM (39). However, the current study was different from previous studies with respect to study design, sample size, length of the observation period, and the clinical characteristics of the participants. This is the first PROBE trial that investigated the long-term effects of alogliptin on the progression of carotid IMT in patients with T2DM free of CVD that included a relatively large sample size.

The current study has certain limitations. First, we used the PROBE design, which may cause bias in the assessment of outcomes. The reason for the open label was practical constraints, including trial costs, in an investigator-initiated trial. In an effort to overcome possible bias, a single experienced reader, who was blinded to the clinical characteristics of the subjects and type of treatment, measured carotid IMT using automated digital edge-detection technology.

Second, we used surrogate markers as primary end point and our study lacked sufficient power to detect differences in onset of CVD. In addition, progression or regression of carotid atherosclerosis remains a controversial surrogate for CV effects (19,40).

Third, there may have been measurement errors in IMT due to intersonographer differences, which were not evaluated in this study. However, this parameter was measured by the same expert sonographer in each institution throughout all of the visits based on the study protocol. In addition, we did not find significant heterogeneity in changes in IMT among institutions (data not shown).

Fourth, multiple testing in primary and secondary end points increases the chance of false-positive findings, and thus, our results should be interpreted with caution.

Finally, it is likely that other yet unknown factors can explain the difference in Δchange in IMT between the two treatment groups.

In conclusion, alogliptin treatment attenuated the progression of carotid IMT in patients with T2DM free of a history of apparent CVD compared with the conventional treatment. A large-scale prospective trial is required to establish the usefulness of DPP-4 inhibitors for primary prevention of CVD in patients with T2DM.

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