# Sitagliptin Attenuates the Progression of Carotid Intima-Media Thickening in Insulin-Treated Patients With Type 2 Diabetes: The Sitagliptin Preventive Study of Intima-Media Thickness Evaluation (SPIKE)

## A Randomized Controlled Trial

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**Collaborators on the Sitagliptin Preventive Study of Intima-Media Thickness Evaluation (SPIKE) trial can be found in the Supplementary Data online.*



### OBJECTIVE

**The effect of additional treatment with oral hypoglycemic agents on the progression of atherosclerosis remains unknown in insulin-treated patients with type 2 diabetes mellitus (T2DM). We assessed the effects of sitagliptin, a dipeptidyl peptidase 4 inhibitor, on carotid intima-media thickness (IMT) in T2DM.**

### RESEARCH DESIGN AND METHODS

**This prospective, randomized, open-label, blinded end point, multicenter, parallel-group, comparative study included 282 insulin-treated patients with T2DM free of a history of apparent cardiovascular diseases who were recruited at 12 clinical units and randomly allocated to either the sitagliptin group (*n* = 142) or the control group (*n* = 140). The primary outcomes were changes in mean and maximum IMT of the common carotid artery measured by echography at the end of a 104-week treatment period.**

### RESULTS

**Sitagliptin had a more potent glucose-lowering effect compared with the conventional treatment (−0.5 ± 1.0% vs. −0.2 ± 0.9%; *P* = 0.004), without increasing hypoglycemic episodes or body weight. Changes in the mean and left maximum IMT, but not right maximum IMT, of the common carotid arteries were significantly greater after sitagliptin treatment compared with conventional treatment (−0.029 [SE 0.013] vs. 0.024 [0.013] mm [*P* = 0.005]; −0.065 [0.027] vs. 0.022 [0.026] mm [*P* = 0.021]; −0.007 [0.031] vs. 0.027 [0.031] mm [*P* = 0.45], respectively). Over 104 weeks, sitagliptin, but not conventional treatment, significantly reduced the mean IMT and left maximum IMT of common carotid arteries relative to the baseline.**

### CONCLUSIONS

**Sitagliptin attenuated the progression of carotid IMT in insulin-treated patients with T2DM free of apparent cardiovascular disease compared with conventional treatment.**

Type 2 diabetes mellitus (T2DM) increases the likelihood of developing cardiovascular disease (CVD), which is one of the major causes of mortality and morbidity in these patients (1). Recent studies have cast doubt on the benefits of strict glycemic control, especially using insulin, on CVD in patients with established atherosclerosis or long-standing T2DM (2–4) for two main reasons: *1*) It is assumed that frequent episodes of severe hypoglycemia might reduce their beneficial effects (5), and *2*) weight gain may adversely affect the prognosis. Therefore, reducing insulin dose by stimulating endogenous insulin secretion and increasing insulin sensitivity using oral hypoglycemic agents (OHAs) (6,7) may reduce these adverse effects of insulin therapy. However, the effects of treatment with insulin plus other traditional OHAs on the progression of atherosclerosis remain largely unknown. New OHAs with the least risk of undeliverable effects and multiple beneficial effects on cardiovascular (CV) profiles when used with insulin are essential for the treatment of T2DM.

Sitagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, increases insulin secretion and suppresses glucagon release by protecting the degradation of incretins without increased risk of hypoglycemia and clinically relevant weight gain (8,9). Furthermore, the addition of DPP-4 inhibitors to ongoing insulin therapy was reported to have specific advantages in reducing the frequency of hypoglycemia and weight gain, in addition to the expected benefits associated with glycemic control and limiting insulin dose (10–12). In addition, evidence from preclinical studies suggests that DPP-4 inhibitors could have beneficial effects on atherosclerosis in both GLP-1-dependent and -independent manners (13–15). Thus the addition of DPP-4 inhibitors to insulin therapy is expected to have beneficial effects on CVD in patients with T2DM.

This study is a multicenter, prospective, randomized, open-label, blinded end point (PROBE) study designed to determine the effect of adding sitagliptin to insulin treatment (sitagliptin group) compared with conventional treatment (non-sitagliptin group) on carotid artery intima-media thickness (IMT) in CVD-free patients with T2DM. IMT, a marker of progression of atherosclerosis, was evaluated by a simple and noninvasive procedure.

## RESEARCH DESIGN AND METHODS

### Study Population

Japanese patients with T2DM who regularly attended the outpatient diabetes clinics at 12 institutions in Japan were asked to participate in this study, as previously described in detail (16). Patients with T2DM in whom the target of blood glucose control specified in the *Treatment Guide for Diabetes* in 2010 (edited by the Japan Diabetes Society) (17) was not achieved despite insulin therapy, in addition to dietary/exercise therapy or concomitant therapeutic drugs for T2DM (other than DPP-4 inhibitors) over a period of ≥3 months, were included in the study. Patients who withdrew from previous treatment with DPP-4 inhibitor for more than 12 weeks were also included; additional inclusion criteria included ≥30 but <80 years of age (regardless of sex) and signing the consent form for participation in the study. The following exclusion criteria also were applied: *1*) type 1 or secondary diabetes; *2*) presence of severe infectious disease, before or after surgery, or severe trauma; *3*) history of myocardial infarction, angina pectoris, cerebral stroke, or cerebral infarction; *4*) retinopathy requiring laser photocoagulation and/or vitrectomy or history of these treatments within 1 year; *5*) moderate or severe renal dysfunction (serum creatinine: males, >1.4 mg/dL; females, >1.2 mg/dL); *6*) severe liver dysfunction (aspartate aminotransferase ≥100 IU/L); *7*) moderate or severe heart failure (New York Heart Association stage III severity or higher); *8*) treatment with an incretin preparation, such as other DPP-4 inhibitors, at the start of the study; *9*) treatment with drugs that are not concomitantly administrable with incretin preparations with regard to the national health insurance, such as DPP-4 inhibitors, at the start of the study; *10*) pregnant, lactating, or possibly pregnant women or those planning to become pregnant during the study period; *11*) medical history of hypersensitivity to investigational drugs; and *12*) those patients judged as ineligible by the clinical investigators.

The subjects were screened consecutively, and patients who met the above eligibility criteria were asked to participate. All patients who agreed to participate were entered into the study. The protocol was approved by the institutional review board of each participating institution, in compliance with the Declaration of Helsinki and current legal regulations in Japan. Written informed consent was obtained from all participants after a full explanation of the study. This study is registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000007396), which is a nonprofit organization in Japan, and meets the requirements of the International Committee of Medical Journal Editors.

### Randomization and Study Intervention

Patients were registered at the administration office of this trial via the Internet; once enrolled, they were randomly assigned to either the sitagliptin group or the control group receiving conventional treatment consisting of drugs other than DPP-4 inhibitors. Randomization was performed using a dynamic allocation method based on the number of insulin injections, with/without concomitant pioglitazone, age, and sex.

Patients in the sitagliptin group were started on sitagliptin (25 mg once daily) in addition to ongoing insulin therapy. The dose of sulfonylurea was tapered when considered clinically appropriate to avoid hypoglycemia when starting sitagliptin. Initiation of treatment with sitagliptin 50 mg once daily was permitted in patients who were not treated with a sulfonylurea. In patients treated with sitagliptin 25 or 50 mg once daily for 12 weeks, the dose of sitagliptin was increased to a maximum of 100 mg once daily when $HbA_{1c}$ was ≥7.0% (8.6 mmol/mol) (17). The participating physicians were allowed to reduce sitagliptin to 25 or 50 mg/day if treatment with 50 or 100 mg/day was considered poorly tolerated. The insulin dose could also be adjusted, with priority given to achieve fasting blood glucose or 2-h postprandial blood glucose as recommended in the *Treatment Guide for Diabetes* (17). In the control group, either increasing the dose of current therapy (e.g., insulin) or adding a sulfonylurea, glinide, or α-glucosidase inhibitor was allowed, with the goal of achieving the target value specified in the *Treatment Guide for Diabetes* (usually $HbA_{1c}$ <6.9% [8.44 mmol/mol]) (17). The addition of other DPP-4 inhibitors or GLP-1 analogs was banned in the control group. Dose adjustment and addition of metformin and

pioglitazone during the study were banned in both groups. In cases of hypoglycemia, the dose of insulin and/or OHA was titrated. The use of antihyperlipidemic and antihypertensive drugs was allowed during the study.

### Observation Variables and Schedule

The study period was 104 weeks after the patients were registered. All randomized participants were followed for 104 weeks until the end of the study, regardless of adherence to or discontinuation of study medication for any reason. Clinical outcome, adherence, and adverse events (AEs) were confirmed, and clinical and biochemical data were collected at 0, 26, 52, 78, and 104 weeks after randomization.

### Primary Outcomes

The primary study outcomes were changes in mean IMT of the common carotid artery (mean-IMT-CCA) and maximum IMT of the common carotid artery (max-IMT-CCA) after the 104-week treatment period. Investigations were carried out at the start of the study, after 52 weeks, and after 104 weeks.

### Safety Evaluation

AEs were recorded during study as described in the Supplementary Data online.

### Measurement of Carotid IMT

Ultrasonographic scans of the carotid artery were performed by expert sonographers who were specifically trained to perform the prescribed study examination, as reported previously (16). To avoid intersonographer variability, each participant was examined by the same sonographer with 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. The mean intrainvestigator coefficient of variation for measurement of mean-IMT-CCA and max-IMT-CCA (± SD) in each institution was 1.6 ± 1.2% and 2.4 ± 2.3%, respectively. The extracranial common carotid artery, the carotid bulb, and the internal carotid artery in the neck were scanned bilaterally in at least three different longitudinal projections (anterior, lateral, and posterior, which approximately corresponded to 60, 90, 150 degrees for the right carotid artery, and 210, 270, and 300 degrees for the left carotid artery marked on the Meijer arc) as well as transverse projections, and the site of greatest thickness, including plaque lesions, was identified along the arterial walls. IMT represents the distance between two parallel echogenic lines corresponding to the vascular lumen and the adventitia. To avoid interreader variability, all scans were electronically stored and e-mailed to the central office (IMT Evaluation Committee, Osaka, Japan) to be read, in a random order, by a single experienced reader blinded to the clinical characteristics of the patients using automated, digital edge-detection software (IntimaScope; Media Cross, Tokyo, Japan) (16). The software system averages 60 points of IMT values in the segment 2 cm proximal to the dilation of the carotid bulb (mean-IMT-CCA). In addition, the largest IMTs, including plaque lesions in the common carotid arteries (max-IMT-CCA), were also measured separately. Reproducibility analysis of replicate measurements in 20 subjects yielded absolute mean differences of 0.02 ± 0.01 and 0.01 ± 0.01 for mean-IMT-CCA and max-IMT-CCA, respectively. The intraobserver coefficient of variation for the measurement was 1.1% and 0.7%, respectively.

### Sample Size

Yokoyama et al. (18) reported previously that the mean ± SD rate of increase in carotid IMT in Japanese patients with diabetes was 0.034 ± 0.054 mm/year and that 1% improvement in $HbA_{1c}$ was associated with a 0.02-mm/year improvement in IMT. Given these results, it was assumed that during a 2-year observation period, registration of at least 232 patients was required to obtain 80% power to detect a difference of 0.04 mm in IMT between the two treatment groups, assuming an SD of 0.108, 15% dropout, and a 0.05 level of significance. On the basis of this calculation, the target number of enrolled patients was set at 274 for the 2-year registration period.

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

| | Sitagliptin group | Conventional group | *P* value |
|---|---|---|---|
| Male sex | 83 (61) | 82 (60) | 1.00 |
| Age (years) | 63.8 ± 9.7 | 63.6 ± 1.0 | 0.90 |
| Current smoking | 30 (22) | 29 (21) | 0.22 |
| Hypertension | 75 (55) | 86 (63) | 0.22 |
| Dyslipidemia | 91 (66) | 84 (61) | 0.45 |
| Duration of diabetes (years) | 17.2 ± 8.5 | 17.3 ± 8.7 | 0.94 |
| Insulin injections (time/day) | 2.9 ± 1.2 | 2.9 ± 1.2 | 0.88 |
| Use of oral glucose-lowering agents | | | |
| Metformin | 49 (36) | 48 (35) | 1.00 |
| Sulfonylurea | 17 (12) | 15 (11) | 0.85 |
| Glinides | 2 (1) | 19 (14) | <0.001 |
| Thiazolidinediones | 13 (9) | 11 (8) | 0.83 |
| α-Glucosidase inhibitor | 41 (30) | 42 (31) | 1.00 |
| Use of antihypertensive drugs | | | |
| ACE inhibitors | 8 (6) | 4 (3) | 0.59 |
| Angiotensin II receptor blockers | 53 (39) | 69 (50) | 0.07 |
| Direct renin inhibitor | 1 (1) | 1 (1) | 1.00 |
| Calcium channel blocker | 39 (28) | 45 (33) | 0.51 |
| Diuretic drugs | 12 (9) | 13 (9) | 1.00 |
| α-Adrenergic receptor antagonist | 2 (1) | 2 (1) | 1.00 |
| β-Adrenergic receptor antagonist | 1 (1) | 2 (1) | 1.00 |
| Others | 1 (1) | 2 (1) | 1.00 |
| Use of lipid-lowering agents | | | |
| Statins | 66 (48) | 63 (46) | 0.81 |
| Ezetimibe | 5 (4) | 9 (7) | 0.41 |
| Resins | 0 (0) | 0 (0) | — |
| Fibrates | 4 (3) | 3 (2) | 1.00 |
| Use of antithrombotic agents | | | |
| Antiplatelet agents | 29 (21) | 30 (22) | 1.00 |
| Anticoagulants | 5 (4) | 1 (1) | 0.21 |
| Others | 0 (0) | 0 (0) | — |

Data are *n* (%) of patients or mean ± SD values, unless otherwise indicated.

### Statistical Analysis

Efficacy was analyzed using mainly the full analysis set based on the intent-to-treat principle and secondarily using the protocol set. Primary analysis was performed using a mixed-effects model for repeated measures, with treatment group, time (weeks), interactions between treatment group and time (weeks), 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, time to onset (one of the secondary end points) 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 the one-sample *t* test and Wilcoxon signed rank test within the group. The number and percentage of patients reporting AEs were presented by treatment group and compared between the two treatment groups using Fisher exact test. All statistical tests were two-sided with a 5% significance level. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

## RESULTS

### Participants

A total of 282 participants were randomly allocated to either the sitagliptin group ($n$ = 142) or the conventional treatment group ($n$ = 140). After excluding 8 patients from analyses (they withdrew from the study and/or objected to the inclusion of their data in the analysis), 137 in the sitagliptin group and 137 in the conventional treatment group were included in the full analysis set (Supplementary Fig. 1). As shown in Tables 1, 2, and 3, baseline clinical characteristics, including potential risk factors for carotid atherosclerosis, were comparable between the groups.

### IMT of the Common Carotid Artery

In the mixed-effects model for repeated measures in the full-set analysis, sitagliptin significantly slowed the worsening of the mean-IMT-CCA and left max-IMT-CCA, but not right max-IMT-CCA, at 104 weeks (i.e., primary end points of the study) compared with conventional treatment (Table 2). Similar findings were noted even in the adjusted mixed-effect models, including model 1 (age and sex); model 2 (model 1 plus BMI, $HbA_{1c}$, total cholesterol, HDL cholesterol, triglycerides, and systolic blood pressure); model 3 (model 2 plus smoking, ACE/angiotensin II receptor blocker, statin, and antiplatelets); and model 4 (model 3 plus OHA) (Supplementary Table 1). Also, ANCOVA models that included treatment group, age, sex, baseline IMT, systolic blood pressure, and administration of statins produced findings similar to those of the mixed-effects models (Supplementary Table 2). Over 104 weeks, sitagliptin treatment, but not conventional treatment, significantly reduced the mean-IMT-CCA and left max-IMT-CCA, but not right max-IMT-CCA, relative to baseline values (Table 2).

**Table 2—Effects of sitagliptin on IMT**

| | | | Treatment effect (sitagliptin-conventional treatment) | | *P* value |
|---|---|---|---|---|---|
| | Sitagliptin group | Conventional group | Mean change (95% CI) | *P* value | between groups |
| Common mean IMT (mm) | | | | | |
| Baseline | 0.84 ± 0.19 ($n$ = 136) | 0.84 ± 0.21 ($n$ = 137) | | | 0.81 |
| 52 weeks | 0.88 ± 0.19 ($n$ = 127) | 0.87 ± 0.24 ($n$ = 124) | | | 0.82 |
| 104 weeks | 0.81 ± 0.19 ($n$ = 121) | 0.86 ± 0.24 ($n$ = 122) | | | 0.07 |
| Mean change (SE) | | | | | |
| 52 weeks | 0.027 (0.013)* | 0.028 (0.014)* | −0.001 (−0.039 to 0.036) | 0.94 | |
| 104 weeks | −0.029 (0.013)* | 0.024 (0.013) | −0.053 (−0.090 to −0.016) | 0.005 | |
| Right maximum IMT (mm) | | | | | |
| Baseline | 1.04 ± 0.29 ($n$ = 136) | 1.06 ± 0.40 ($n$ = 137) | | | 0.69 |
| 52 weeks | 1.09 ± 0.42 ($n$ = 127) | 1.08 ± 0.42 ($n$ = 123) | | | 0.78 |
| 104 weeks | 1.03 ± 0.34 ($n$ = 121) | 1.09 ± 0.49 ($n$ = 122) | | | 0.29 |
| Mean change (SE) | | | | | |
| 52 weeks | 0.049 (0.031) | 0.013 (0.032) | 0.036 (−0.052 to 0.123) | 0.42 | |
| 104 weeks | −0.007 (0.031) | 0.027 (0.031) | −0.033 (−0.121 to 0.054) | 0.45 | |
| Left maximum IMT (mm) | | | | | |
| Baseline | 1.10 ± 0.32 ($n$ = 137) | 1.11 ± 0.41 ($n$ = 137) | | | 0.87 |
| 52 weeks | 1.15 ± 0.42 ($n$ = 127) | 1.12 ± 0.45 ($n$ = 124) | | | 0.67 |
| 104 weeks | 1.03 ± 0.30 ($n$ = 121) | 1.12 ± 0.42 ($n$ = 122) | | | 0.07 |
| Mean change (SE) | | | | | |
| 52 weeks | 0.038 (0.026) | 0.021 (0.026) | 0.016 (−0.057 to 0.089) | 0.66 | |
| 104 weeks | −0.065 (0.027)* | 0.022 (0.026) | −0.087 (−0.161 to −0.014) | 0.021 | |

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

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

| | Sitagliptin group | Conventional group | *P* value |
|---|---|---|---|
| BMI (kg/m$^2$) | | | |
| At baseline | 25.0 ± 4.3 (*n* = 137) | 25.0 ± 3.8 (*n* = 137) | 0.88 |
| Change from baseline | | | |
| 26 weeks | 0.1 ± 1.4 (*n* = 135) | 0.1 ± 0.9 (*n* = 136) | 0.66 |
| 52 weeks | 0.2 ± 1.1 (*n* = 128) | 0.1 ± 1.2 (*n* = 127) | 0.75 |
| 78 weeks | 0.2 ± 1.3 (*n* = 121)* | 0.1 ± 1.1 (*n* = 122) | 0.23 |
| 104 weeks | 0.1 ± 1.5 (*n* = 119) | 0.1 ± 1.8 (*n* = 117) | 0.81 |
| $HbA_{1c}$ | | | |
| At baseline (%) | 8.1 ± 1.1 (*n* = 137) | 8.0 ± 1.0 (*n* = 137) | 0.45 |
| At baseline (mmol/mol) | 64.9 ± 11.9 (*n* = 137) | 63.9 ± 10.6 (*n* = 137) | 0.45 |
| Change from baseline ($HbA_{1c}$ %) | | | |
| 26 weeks | −0.5 ± 0.9 (*n* = 136)§ | −0.3 ± 1.0 (*n* = 136)# | 0.02 |
| 52 weeks | −0.5 ± 1.0 (*n* = 130)§ | −0.4 ± 1.0 (*n* = 129)§ | 0.28 |
| 78 weeks | −0.5 ± 1.0 (*n* = 123)§ | −0.3 ± 0.9 (*n* = 126)# | 0.09 |
| 104 weeks | −0.5 ± 1.0 (*n* = 121)§ | −0.2 ± 0.9 (*n* = 122)* | 0.004 |
| Fasting blood glucose (mmol/L) | | | |
| At baseline | 8.64 ± 2.85 (*n* = 136) | 8.42 ± 2.55 (*n* = 137) | 0.51 |
| Change from baseline | | | |
| 26 weeks | −0.21 ± 3.19 (*n* = 134) | −0.18 ± 2.80 (*n* = 134) | 0.95 |
| 52 weeks | −0.67 ± 3.54 (*n* = 129)* | −0.26 ± 2.36 (*n* = 129) | 0.28 |
| 78 weeks | −0.54 ± 3.69 (*n* = 122) | 0.00 ± 3.12 (*n* = 126) | 0.21 |
| 104 weeks | −0.50 ± 3.35 (*n* = 120) | −0.40 ± 2.64 (*n* = 122) | 0.79 |
| C-peptide (ng/mL) | | | |
| At baseline | 1.2 ± 0.8 (*n* = 137) | 1.2 ± 0.7 (*n* = 136) | 0.61 |
| Change from baseline | | | |
| 52 weeks | 0.1 ± 0.8 (*n* = 126) | 0.1 ± 0.7 (*n* = 123)* | 0.82 |
| 104 weeks | 0.3 ± 0.8 (*n* = 122)§ | 0.0 ± 0.6 (*n* = 121) | 0.02 |
| Total cholesterol (mmol/L) | | | |
| At baseline | 5.02 ± 0.91 (*n* = 136) | 4.94 ± 0.86 (*n* = 137) | 0.50 |
| Change from baseline (%) | | | |
| 26 weeks | −2.0 ± 14.1 (*n* = 131) | −1.0 ± 14.3 (*n* = 127) | 0.57 |
| 52 weeks | −2.7 ± 13.4 (*n* = 129)* | −0.9 ± 12.4 (*n* = 129) | 0.26 |
| 78 weeks | −1.2 ± 14.9 (*n* = 122) | 0.3 ± 13.3 (*n* = 123) | 0.43 |
| 104 weeks | −2.7 ± 15.6 (*n* = 121) | −1.8 ± 14.6 (*n* = 122) | 0.63 |
| LDL cholesterol (mmol/L) | | | |
| At baseline | 2.85 ± 0.78 (*n* = 137) | 2.78 ± 0.70 (*n* = 136) | 0.44 |
| Change from baseline (%) | | | |
| 52 weeks | 1.4 ± 21.4 (*n* = 126) | 4.9 ± 21.6 (*n* = 121)* | 0.21 |
| 104 weeks | 0.9 ± 23.4 (*n* = 122) | 5.2 ± 23.9 (*n* = 121)* | 0.16 |
| HDL cholesterol (mmol/L) | | | |
| At baseline | 1.46 ± 0.37 (*n* = 136) | 1.39 ± 0.38 (*n* = 137) | 0.14 |
| Change from baseline (%) | | | |
| 26 weeks | 1.8 ± 13.5 (*n* = 136) | 4.3 ± 16.9 (*n* = 134) | 0.18 |
| 52 weeks | −2.4 ± 13.4 (*n* = 130)* | 0.2 ± 15.4 (*n* = 128) | 0.14 |
| 78 weeks | 2.9 ± 15.3 (*n* = 123)* | 5.5 ± 16.3 (*n* = 125)§ | 0.21 |
| 104 weeks | 0.2 ± 15.2 (*n* = 121) | −0.5 ± 14.7 (*n* = 121) | 0.74 |

*Continued on p. 460*

### Secondary Outcomes

Although both types of treatment significantly reduced $HbA_{1c}$ levels from baseline, the improvement in $HbA_{1c}$ (value at end of study − value at baseline) was significantly greater in the sitagliptin group (−0.5 ± 1.0%) than the conventional group (−0.2 ± 0.9%; *P* = 0.004) (Table 3). Similarly, there was a significant difference in the change in serum C-peptide concentrations (value at end of study − value at baseline); serum C-peptide concentration was significantly increased in the sitagliptin group but not in the conventional group (Table 3). There were no differences in the value and changes in fasting blood glucose concentrations at each visit during the observation period. Notably, the use of glinides was significantly higher during the study, and the use of α-glucosidase inhibitors tended to be higher among the conventional group than among the sitagliptin group at the end of the study (Supplementary Table 3).

Similarly, there were no differences between the two groups in other risk factors for atherosclerosis, such as BMI, blood pressure, and lipid parameters, at baseline or in their changes during the observation period (Table 3). Blood pressure and lipid metabolism were well controlled in both groups throughout the study. There were also no significant differences in the use of antihypertensive drugs and lipid-lowering agents (Supplementary Table 4). Also, no significant changes were observed in the levels of various markers of inflammation and endothelial damage (Table 4).

During the study, 123 patients (65 in the sitagliptin group and 58 in the conventional group) developed AEs, and 17 patients (8 and 9, respectively) developed serious AEs. There were no significant differences in the incidence of any AEs and serious AEs between the two groups. We recorded 104 hypoglycemic events (in 52 patients in the sitagliptin group and 52 patients in the conventional treatment group) (Supplementary Table 5). There was no significant difference in the average number of hypoglycemic events between the two groups (0.34 ± 0.85 times/month/person in the sitagliptin group vs. 0.36 ± 0.80 times/month/person in the conventional treatment group). One severe hypoglycemic event occurred in each group. Five patients

**Table 3—Continued**

| | Sitagliptin group | Conventional group | *P* value |
|---|---|---|---|
| Triglyceride (mmol/L) | | | |
| At baseline | 1.13 (0.83–1.55) (*n* = 136) | 1.17 (0.90–1.72) (*n* = 137) | 0.22 |
| Change from baseline (%) | | | |
| 26 weeks | 8.6 (−23.4 to 49.0) (*n* = 134)§ | −4.3 (−24.2 to 25.3) (*n* = 133) | 0.07 |
| 52 weeks | 0.7 (−30.0 to 34.1) (*n* = 129) | −1.9 (−21.0 to 29.8) (*n* = 129) | 0.69 |
| 78 weeks | −6.5 (−25.0 to 23.8) (*n* = 122) | −6.7 (−27.4 to 33.3) (*n* = 125) | 0.94 |
| 104 weeks | 0.0 (−25.1 to 44.6) (*n* = 120) | −1.6 (−24.6 to 16.7) (*n* = 122) | 0.35 |
| Systolic blood pressure (mmHg) | | | |
| At baseline | 130 ± 16 (*n* = 137) | 132 ± 14 (*n* = 137) | 0.88 |
| Change from baseline | | | |
| 26 weeks | 2 ± 16 (*n* = 131) | 3 ± 16 (*n* = 120) | 0.55 |
| 52 weeks | −1 ± 17 (*n* = 129) | 1 ± 16 (*n* = 126) | 0.39 |
| 78 weeks | 2 ± 15 (*n* = 123) | 3 ± 17 (*n* = 125)* | 0.61 |
| 104 weeks | 0 ± 19 (*n* = 119) | 3 ± 17 (*n* = 122) | 0.20 |
| Diastolic blood pressure (mmHg) | | | |
| At baseline | 75 ± 11 (*n* = 137) | 75 ± 12 (*n* = 137) | 0.79 |
| Change from baseline | | | |
| 26 weeks | −2 ± 10 (*n* = 131)* | 0 ± 12 (*n* = 120) | 0.11 |
| 52 weeks | −1 ± 11 (*n* = 129) | −1 ± 12 (*n* = 126) | 0.58 |
| 78 weeks | −1 ± 12 (*n* = 123) | 0 ± 14 (*n* = 125) | 0.51 |
| 104 weeks | 0 ± 11 (*n* = 119) | 2 ± 13 (*n* = 122) | 0.16 |

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

developed CV events, and 6 patients were diagnosed with cancer. There was no significant difference in the incidence of CVD and cancer between the two groups.

## CONCLUSIONS

This is the first PROBE trial to demonstrate that the addition of sitagliptin to insulin treatment significantly diminished the progression of mean-IMT-CCA and left max-IMT-CCA, but not right max-IMT-CCA, compared with conventional treatment. Because of these discrepant results, it might be viewed as an exaggeration if we were to conclude that sitagliptin attenuates the progression of carotid IMT. However, the mean-IMT-CCA is the most reliable parameter among these three prespecified primary outcomes of this study: It is generally believed that the mean-IMT-CCA is more reproducible compared with max-IMT-CCA and that max-IMT-CCA is more accurately measured on the left side than the right side since the left wall of the common carotid artery is thicker and more elastic than the right (19). Therefore, the positive results for the mean-IMT-CCA and left max-IMT-CCA are more reliable than the negative result on the right max-IMT-CCA, which could be a result of the underpowered sample. Accordingly, it is feasible to conclude with confidence that sitagliptin has a beneficial effect on carotid IMT in this population. It should be noted that mean-IMT-CCA and left max-IMT-CCA were significantly regressed in the sitagliptin group during the 104-week observation period.

Previous studies demonstrated that thiazolidinedione drugs had only partial effects on the prevention of carotid IMT progression in insulin-treated patients with T2DM (20,21), whereas they reduced carotid IMT in non-insulin-treated patients with T2DM (22,23). Thus it may be more difficult to slow carotid IMT progression in insulin-treated patients with T2DM than in others. In this regard, the higher rate of increase in carotid IMT among insulin-treated compared with non-insulin-treated patients with T2DM is probably related to the longer duration of T2DM, poor glycemic control, higher frequency of hypoglycemic episodes, increased chance of weight gain, and/or more advanced atherosclerosis. The higher rate of worsening of carotid IMT seems to correlate with the less-than-ideal effect of sitagliptin on carotid IMT progression at 52 weeks. In turn, treatment with sitagliptin resulted in regression of the mean-IMT-CCA and left max-IMT-CCA at the end of the sitagliptin treatment protocol. Thus long-term treatment may be required to lessen the worsening of carotid IMT in insulin-treated patients with T2DM.

In this study, the addition of sitagliptin to insulin therapy had a sustained glucose-lowering effect amounting to about 0.5% over 2 years from baseline, which is almost similar to previous reports (10–12,24). On the other hand, conventional treatment reduced $HbA_{1c}$ level by only 0.2%, despite our effort to achieve an optimal glycemic target by adjusting the OHA dosage. In this regard, the dose of insulin was not increased during the study because of concerns about the potential AEs of insulin, such as hypoglycemia and weight gain. Accordingly, sitagliptin treatment was superior to conventional treatment in terms of $HbA_{1c}$ reduction without increasing the incidence of hypoglycemic episodes and weight gain in insulin-treated patients, consistent with previous studies (10–12). However, the difference in $HbA_{1c}$ between the two treatment groups does not seem to correlate with the reduction in carotid IMT, since changes in $HbA_{1c}$ did not correlate with changes in mean-IMT-CCA and right and left max-IMT-CCA in both groups (data not shown). In addition, sitagliptin treatment still attenuated the progression of mean-IMT-CCA and left max-IMT-CCA compared with conventional treatment, even after adjusting for changes in $HbA_{1c}$ from baseline (Supplementary Table 2). Thus the differences in carotid IMT progression could not be explained by the difference in $HbA_{1c}$, suggesting that these changes in the carotid artery could be independent of the glucose-lowering effects. In addition, it is possible that the frequent use of glinides

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

| | Sitagliptin group | Conventional group | *P* value |
|---|---|---|---|
| eGFR (mL/min/1.73 $m^2$) | | | |
| At baseline | 77.7 ± 21.2 (*n* = 137) | 79.7 ± 24.2 (*n* = 137) | 0.47 |
| Change from baseline | | | |
| 52 weeks | −2.9 ± 9.7 (*n* = 130)§ | −2.6 ± 10.2 (*n* = 129)# | 0.81 |
| 104 weeks | −4.0 ± 10.3 (*n* = 120)§ | −2.7 ± 11.8 (*n* = 122)* | 0.36 |
| UAE (mg/g creatinine) | | | |
| At baseline | 20.3 (8.4–82.2) (*n* = 136) | 19.0 (8.1–83.6) (*n* = 134) | 0.64 |
| Change from baseline | | | |
| 52 weeks | −0.5 (−12.7 to 9.1) (*n* = 118) | −0.2 (−8.7 to 9.2) (*n* = 121) | 0.59 |
| 104 weeks | 0.7 (−9.4 to 17.2) (*n* = 114) | −0.1 (–11.3 to 8.7) (*n* = 114) | 0.37 |
| hs-CRP (ng/dL) | | | |
| At baseline | 506 (210–1,310) (*n* = 137) | 487 (277–1,004) (*n* = 136) | 0.75 |
| Change from baseline | | | |
| 52 weeks | −17 (−154 to 216) (*n* = 126) | 5 (−189 to 298) (*n* = 123) | 0.70 |
| 104 weeks | 15 (−142 to 196) (*n* = 122) | −9 (−198 to 206) (*n* = 121) | 0.71 |
| IL-6 (ng/dL) | | | |
| At baseline | 1.7 (1.2–2.6) (*n* = 137) | 2.0 (1.2–3.0) (*n* = 136) | 0.34 |
| Change from baseline | | | |
| 52 weeks | −0.1 (−0.5 to 0.5) (*n* = 126) | 0.0 (−0.5 to 0.5) (*n* = 123) | 0.63 |
| 104 weeks | 0.6 (−0.2 to 1.2) (*n* = 122)§ | 0.4 (−0.2 to 1.0) (*n* = 121)§ | 0.53 |
| ICAM-1 (ng/mL) | | | |
| At baseline | 224 (180–267) (*n* = 137) | 234 (196–270) (*n* = 136) | 0.40 |
| Change from baseline | | | |
| 52 weeks | −2 (−21 to 19) (*n* = 126) | −6 (−29 to 13) (*n* = 123) | 0.06 |
| 104 weeks | −5 (−23 to 15) (*n* = 122) | −7 (−34 to 21) (*n* = 121) | 0.45 |
| VCAM-1 (ng/mL) | | | |
| At baseline | 728 (636–912) (*n* = 137) | 784 (651–971) (*n* = 160) | 0.25 |
| Change from baseline | | | |
| 52 weeks | −58 (−101 to 32) (*n* = 126)§ | −57 (−113 to 20) (*n* = 123)§ | 0.53 |
| 104 weeks | −12 (−75 to 73) (*n* = 122) | 1 (−84 to 107) (*n* = 121) | 0.50 |

Data are mean ± SD or median (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 groups were analyzed by the one-sample *t* test or Wilcoxon signed rank test. Differences in parameters from baseline to 52 and 104 weeks between groups were analyzed by the Student *t* test or Wilcoxon rank sum test. eGFR, estimated glomerular filtration rate; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; IL-6, interleukin 6; UAE, urinary albumin excretion. *$P < 0.05$. #$P < 0.01$. §$P < 0.001$.

and α-glucosidase inhibitors in the conventional treatment group over time affected the results. In this regard, the effect of sitagliptin on the reduction in carotid IMT may not be overestimated; previous reports demonstrated beneficial effects of those medications on carotid IMT (25,26). Indeed, almost similar findings were observed in ANCOVA models after adjusting for the use of glinides and α-glucosidase inhibitors (data not shown).

Previous reports demonstrated that short-term treatment with DPP-4 inhibitors decreased the levels of various markers of inflammation and endothelial injury in patients with T2DM (27,28). However, in this study of longer duration, no such beneficial effects of sitagliptin on these markers were found. Although the exact reason for these inconsistent findings is not clear, several factors could have affected the proinflammatory conditions, such as both transient and chronic nonatherosclerotic diseases and additional treatment within a relatively short time. In addition, a subanalysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) demonstrated that the relationships between serum biomarkers of chronic inflammation and endothelial injury at multiple time points and the progression of carotid IMT remain unclear in patients with type 1 diabetes (29). Interestingly, a recent report suggested that evaluation of local inflammation and oxidative stress in the vascular wall, not in serum, was helpful in the full assessment of "non-glycaemic-dependent" antiatherosclerotic effects of DPP-4 inhibitors (30).

Although the exact mechanism by which DPP-4 inhibitors induce regression of carotid IMT remains uncertain at present, previous studies postulated a few scenarios. Inhibition of macrophage accumulation and inflammation by enhancing GLP-1 signaling with sitagliptin or GLP-1 receptor agonists reduced atherosclerotic lesion formation in a mouse model of atherosclerosis (13,31). Our group also demonstrated that another DPP-4 inhibitor suppressed macrophage-related inflammation and DPP-4-induced smooth muscle proliferation in vitro (14). Furthermore, Nagashima et al. (32) demonstrated that GLP-1 suppressed foam cell formation from murine macrophages. These mechanisms could potentially contribute to reduced atherosclerosis. In the future, measurement of local inflammation and the ability to form foam cells in human monocytes isolated from peripheral blood may be helpful in investigating the mechanism behind the beneficial effects of sitagliptin on carotid IMT.

Three recent randomized clinical studies showed that the use of DPP-4 inhibitors did not increase nor decrease the CVD event rate among patients with T2DM compared with placebo (33–35). Since these safety outcome studies were originally designed as noninferiority clinical trials, they probably lacked sufficient power to evaluate the beneficial effects of DPP-4 inhibitors on CVD. In general, the number of CV events required in a superiority trial is larger than that in a noninferiority trial (36). Therefore a larger-scale prospective clinical trial with a longer observation period is required to assess the CV efficacy of DPP-4 inhibitors. On the other hand, we focused on the effects of sitagliptin on the progression of carotid atherosclerosis, not CVD, as a first step because of practical constraints, including trial costs and concern about feasibility in relation to long-term intervention; progression or regression of carotid atherosclerosis remains a controversial surrogate for CV effects (37,38). In addition, the

subjects of the above-mentioned three trials (29–31) were patients with T2DM with a history of CVD or at high risk for CVD. In comparison, our study enrolled insulin-treated subjects with T2DM who were free from apparent CVD. Considering the results of this study, we believe that early and effective intervention with DPP-4 inhibitors before the development of advanced atherosclerosis in patients without a history of apparent CVD is likely to be beneficial in the prevention of carotid IMT progression.

### Study Limitations

In addition to the limitations described above, we used a PROBE design, which may bias the assessment of outcomes. The reason for using an open-label study 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. Further, all statistical methods and data handling were prespecified under the blinded condition before the database was locked. Second, there may have been measurement errors in IMT as a result of intersonographer differences among institutions, which were not evaluated in this study. However, high reproducibility of the measurement of IMT by each sonographer may reduce these errors. Third, the chance of false-positive findings may increase because the multiplicity of testing for the primary end points was not specifically adjusted in our analysis. Finally, it is likely that other yet unknown factors and known factors such as change in lifestyle, duration and/or severity of CV risk factors, and family history of CVD that we did not evaluate in this study can explain the differences in changes in carotid IMT between the two treatment groups. Patients lost to follow-up are unlikely to have a major influence on the results because there were no significant differences in baseline characteristics and AEs between the two groups.

### Summary

Compared with the conventional treatment, sitagliptin treatment attenuated the progression of carotid IMT in insulin-treated patients with T2DM who were free of a history of apparent CVD. Although our data suggest a promising effect of sitagliptin on carotid IMT progression, a large-scale prospective trial is required to establish the usefulness of DPP-4 inhibitors in the primary prevention of CVD in patients with T2DM.

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