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SHORT COMMUNICATION

Differential effect of concomitant antidiabetic agents on carotid atherosclerosis: a subgroup analysis of the PROLOGUE study

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Abstract

Accumulated evidence shows that some antidiabetic agents attenuate the progression of carotid atherosclerosis assessed as intima-media thickness (IMT). Although some studies have demonstrated an inhibitory effect of dipeptidyl peptidase-4 inhibitors on carotid IMT progression, in the PROLOGUE study sitagliptin failed to slow progression relative to conventional therapy for 24 months. We hypothesized that differences in the concomitant antidiabetic agents between the groups have influenced the progression of carotid IMT. We performed a post hoc analysis of the PROLOGUE study using subgroups stratified by concomitant antidiabetic agents. Although no subgroup with any combination of agents in the overall patients showed a significant difference between sitagliptin group and conventional therapy group in the changes from baseline in mean common carotid artery (CCA)-IMT at 24 months, a significant attenuation of mean CCA-IMT progression was observed in the sitagliptin group relative to conventional therapy group only in three combination subgroups aged < 70 years, namely no thiazolidinedione; no thiazolidinedione or biguanide; and no thiazolidinedione, biguanide or α-glucosidase inhibitor, even after adjustment for multiple confounding factors. In the three subgroups, no significant difference between sitagliptin group and conventional therapy group in the changes from baseline in HbA1c at 24 months was detected. Our data suggest that some concomitant agents, whose prescription frequencies were increased in the conventional therapy group, may have masked the inhibitory effect of sitagliptin on carotid IMT progression in the PROLOGUE study.

Keywords Antidiabetic agent · Combination therapy · Intima-media thickness · Sitagliptin · Type 2 diabetes mellitus

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Introduction

Since carotid atherosclerosis as assessed by intima-media thickness (IMT) is known to be an independent and strong surrogate marker for the prediction of future cardiovascular (CV) events in a wide range of populations, including subjects with type 2 diabetes mellitus (T2DM) [1–3], measurement of carotid IMT may be of value when evaluating the effects of antidiabetic agents on atherosclerosis, possibly leading to improved management of T2DM and more favorable CV outcomes [4]. Indeed, previous randomized clinical trials (RCTs) have demonstrated the effectiveness of the metformin [5], pioglitazone [6,7], and α-glucosidase inhibitor (α-GI) [8] in delaying carotid IMT progression. However, whether dipeptidyl peptidase-4 (DPP-4) inhibitors have long-term inhibitory effects on carotid IMT is controversial.

Recently, we reported a multicenter prospective RCT, the PROLOGUE study, in which the inhibitory effect of sitagliptin on carotid atherosclerosis was compared with that of conventional therapy during 24 months [9]. No significant differences in the annual changes in carotid IMT were found between the treatment groups. In the study, antidiabetic agents were added during study interval to achieve the target level of HbA1c, especially in the conventional therapy group. In addition to the aforementioned clinical studies, some antidiabetic agents, such as DPP-4 inhibitors [10–13], metformin [14–16], and pioglitazone [17–19], are known to demonstrate the antiatherosclerotic effects in pre-clinical studies. Therefore, we hypothesized that this difference in concomitant antidiabetic agents between the groups may have influenced the progression rates of carotid IMT. To test this hypothesis, we have performed an exploratory post hoc analysis of the PROLOGUE study using subgroups stratified by use of concomitant antidiabetic agents.

Methods

Study design and participants

The rationale and design of the PROLOGUE study have been described elsewhere [9,20]. In brief, it was a multicenter, 24-month prospective, randomized, open-label, blinded endpoint study that compared the inhibitory effect on carotid IMT progression of the addition of sitagliptin to conventional therapy in Japanese people with T2DM (6.2% ≤ HbA1c < 9.4%). The primary endpoint of the PROLOGUE study was the change in mean common carotid artery (CCA)-IMT at 24 months after randomization. A total of 442 participants were randomly assigned to two groups according to the allocation factors age (< 65 or ≥ 65 years), sex, use of statins, use of antidiabetic agents, HbA1c (< 7.0% or ≥ 7.0%), office systolic blood pressure (< 135 or ≥ 135 mmHg), and maximum IMT (< 1.0 or ≥ 1.0 mm). Subjects who had received a DPP-4 inhibitor, a glucagon-like peptide-1 analog, or insulin treatment prior to randomization were excluded. The study was performed before the launch of sodium glucose cotransporter 2 inhibitors on the market in Japan. A therapeutic target HbA1c level (< 6.2%) was set originally in the study [9,20]. In addition, whenever further glycemic control was needed, clinical investigators were permitted to increase the dose of sitagliptin or add/increase the conventional antidiabetic agents in compliance with the Japanese Treatment Guide for Diabetes. The ethical committees of the participating institutions approved the study protocol. Written informed consent for participation in the study was obtained from all subjects.

In this post hoc analysis, we compared the changes in mean CCA-IMT from baseline at 24 months in subgroups of the original arms stratified according to the usage of concomitant antidiabetic agents at 24 months (Fig. 1). In detail, the participants were stratified into *Group A*, *B*, and *C*. The *Group A* means subgroups who did not take at least one antidiabetic agent among sulfonylurea (SU), biguanide (BG), α-GI, thiazolidinedione (TZD), and glinide (GL). Similarly, the Group B (or C) means subgroups who did not take at least two (or three) antidiabetic agents among them. As in the PROLOGUE study [9] we also analyzed the outcomes in the overall participants and those under 70 years of age.

Measurement of carotid IMT

The protocol and method for measuring carotid IMT have been described in detail previously [9]. In brief, the primary parameter of the carotid IMT in the PROLOGUE study was the mean far wall CCA-IMT in the right and left CCAs 10 mm from the bulb. The carotid ultrasonography was performed at each local institute by expert sonographers who were unaware of the clinical details of the participants, and the images were stored as JPEG files and shipped to a central laboratory, where carotid IMT parameters were measured by a skilled analyst in a blinded manner.

Statistical analysis

Summary statistics are shown as frequencies for categorical data and as the mean ± standard deviation for continuous variables. Differences between the groups were assessed by the two-tailed unpaired Student's *t* test or Chi square test. The baseline-adjusted means of mean

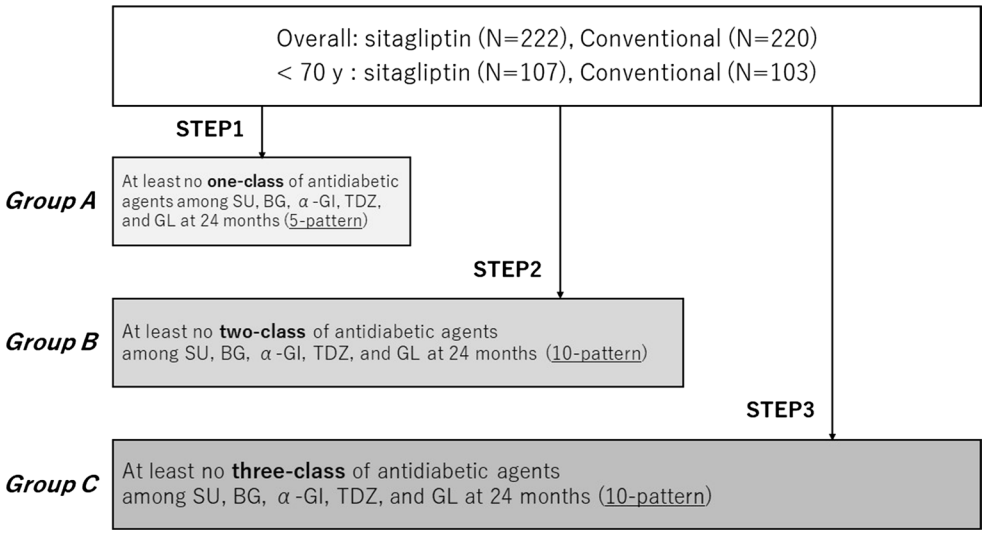

Fig. 1 Flow chart of participants' stratification according to the combination of antidiabetic agents at 24 months. SU, sulfonylurea; BG, biguanide; α-GI, α-glucosidase inhibitor; TZD, thiazolidinedione; GL, glinide

CCA-IMT were estimated by analysis of covariance with treatment effect and the baseline values as covariate. We also performed multivariable regression analyses to confirm differences between the treatment groups in the specific subgroups. A p value <0.05 was considered statistically significant. We did not consider adjustment for multiple testing in the present post hoc analysis. All statistical analyses were performed using R Statistical Software (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Participants' characteristics and concomitant antidiabetic agents

The overall participants' characteristics are described elsewhere [9]. The mean age was 69.2 ± 9.3 in the sitagliptin group; 69.5 ± 9.2 in the conventional therapy group, and the baseline characteristics of participants aged <70 years are listed in Table 1, showing that there were no significant differences between the treatment groups, in common with the overall participants [9].

As in the total participants, the prevalence of each class of antidiabetic agents, such as SU, BG, α-GI, TZD, and GL, in participants aged <70 years had increased in the conventional therapy group by 24 months and was significantly greater at 24 months than those in the sitagliptin groups (Table 2). The proportions of patients receiving statin treatment at baseline and 24 months were comparable between the groups in the overall and participants aged <70 years.

Changes in CCA-IMT for 24 months

Based on their use of combinations of concomitant antidiabetic agents at 24 months, participants were stratified into subgroups (Fig. 1). In the overall participants, no combination of antidiabetic agents had any impact on the difference between the two treatment groups in the change in CCA-IMT at 24 months (Table 3, left side). In patients aged <70 years, only three types of combination, namely no TZD in *Group A* (sitagliptin group 0.008 ± 0.069, conventional therapy group 0.017 ± 0.068, $p=0.049$), no TZD or BG in *Group B* (sitagliptin group 0.009 ± 0.069, conventional therapy 0.026 ± 0.072, $p=0.042$), and no TZD, BG, or α-GI in *Group C* (sitagliptin group 0.009 ± 0.072, conventional therapy 0.037 ± 0.077, $p=0.045$), showed a significant difference in the change of CCA-IMT between the treatment groups (Table 3, Right side), although no significant differences between the treatment groups in such subgroups were found in the overall participants (Fig. 2). When adjusted by baseline values in the mean CCA-IMT, sitagliptin treatment tended to attenuate the CCA-IMT progression in the three subgroups, although the group differences were all of borderline significance (Table 4), while no significant difference in changes of HbA1c was shown in the three subgroups (Table 5). Finally, the differences between the treatment groups in the three subgroups remained significant, even after adjustment for multiple confounding factors, such as age, sex, baseline mean CCA-IMT, systolic blood pressure, and HbA1c (Table 6).

Table 1 Baseline demographics and clinical characteristics in participants with aged <70 years

Characteristic	Sitagliptin group ($n=107$)	Conventional therapy group ($n=103$)	p value
Age, years	61.6 ± 6.7	61.8 ± 6.6	0.863
Male	77 (72.0)	73 (70.9)	0.863
Body mass index, kg/m^2	26.1 ± 4.2	25.3 ± 4.1	0.154
Hypertension	83 (77.6)	79 (76.7)	1.000
Dyslipidemia	80 (74.8)	75 (72.8)	0.869
Myocardial infarction	25 (23.4)	27 (26.2)	0.750
Percutaneous coronary intervention	25 (23.4)	31 (30.1)	0.344
Coronary artery bypass grafting	6 (5.6)	7 (6.8)	0.943
Chronic heart failure	6 (5.6)	14 (13.6)	0.083
Arrhythmia	16 (15.0)	12 (11.7)	0.616
Stroke	10 (9.3)	11 (10.7)	0.927
Systolic blood pressure, mmHg	127.6 ± 17.1	127.9 ± 15.1	0.912
Diastolic blood pressure, mmHg	74.1 ± 11.0	73.3 ± 12.0	0.644
HbA1c, %	7.00 ± 0.69	6.97 ± 0.56	0.688
Fasting plasma glucose, mmol/L	7.65 ± 2.58	7.66 ± 1.98	0.971
Low-density lipoprotein cholesterol, mmol/L	2.45 ± 0.69	2.49 ± 0.76	0.737
Serum creatinine, μmol/L	70.5 ± 17.7	71.5 ± 19.1	0.676
Estimated glomerular filtration rate, mL/min/1.73 m^2	74.5 ± 17.3	73.4 ± 17.7	0.662
Mean common carotid artery IMT, mm	0.800 ± 0.180	0.787 ± 0.146	0.565
Mean bulb IMT, mm	1.032 ± 0.442	1.057 ± 0.384	0.691
Mean internal carotid artery IMT, mm	0.762 ± 0.301	0.764 ± 0.256	0.958
Max common carotid artery IMT, mm	1.165 ± 0.261	1.139 ± 0.189	0.422
Max bulb IMT, mm	1.728 ± 0.804	1.789 ± 0.811	0.626
Max internal carotid artery IMT, mm	1.254 ± 0.484	1.291 ± 0.504	0.642
Plaque area, mm^2	9.298 ± 5.254	10.450 ± 5.358	0.272
Plaque gray scale median	49.8 ± 15.6	49.6 ± 19.1	0.954

Data are presented as number (%) or means (SD)

IMT intima-media thickness

Table 2 Prevalence of each class of antidiabetic agents at baseline and 24 months

Class of antidiabetic agents	Baseline			24 months		
	Sitagliptin group	Conventional therapy group	p value	Sitagliptin group	Conventional therapy group	p value
	Upper: overall ($n=222$)	Upper: overall ($n=220$)		Upper: overall ($n=192$)	Upper: overall ($n=193$)	
	Lower: <70 years ($n=107$)	Lower: <70 years ($n=103$)		Lower: <70 years ($n=95$)	Lower: <70 years ($n=94$)	
Sulfonylurea	56 (25.2)	52 (23.6)	0.740	36 (18.8)	61 (31.6)	0.005
	29 (27.1)	24 (23.3)	0.635	18 (18.9)	31 (33.0)	0.042
Biguanide	34 (15.3)	32 (14.5)	0.894	45 (23.4)	68 (35.2)	0.014
	21 (19.6)	13 (12.6)	0.234	27 (28.4)	43 (45.7)	0.021
α-glucosidase inhibitor	72 (32.4)	66 (30.0)	0.609	46 (24.0)	81 (42.0)	<0.001
	33 (30.8)	30 (29.1)	0.904	20 (21.1)	36 (38.3)	0.015
Thiazolidinedione	53 (23.9)	53 (24.1)	1.000	37 (19.3)	62 (32.1)	0.005
	29 (27.1)	27 (26.2)	1.000	21 (22.1)	34 (36.2)	0.049
Glinide	7 (3.2)	19 (8.6)	0.015	3 (1.6)	21 (10.9)	<0.001
	2 (1.9)	7 (6.8)	0.155	1 (1.1)	14 (14.9)	0.001

Data are presented as the number of participants (%)

Table 3 Stratified comparison of changes in the mean CCA-IMT

Antidiabetic-agent combination	Overall			< 70 years		
	Sitagliptin group	Conventional therapy group	*p* value	Sitagliptin group	Conventional therapy group	*p* value
Group A						
No SU	0.006 (0.088) ($n=156$)	0.005 (0.085) ($n=132$)	0.925	0.001 (0.072) ($n=77$)	0.010 (0.065) ($n=63$)	0.463
No BG	−0.004 (0.088) ($n=147$)	0.014 (0.086) ($n=125$)	0.107	−0.005 (0.074) ($n=68$)	0.019 (0.067) ($n=51$)	0.086
No α-GI	−0.003 (0.083) ($n=146$)	0.002 (0.073) ($n=112$)	0.605	−0.003 (0.076) ($n=75$)	0.015 (0.067) ($n=58$)	0.170
No TZD	−0.001 (0.089) ($n=155$)	0.006 (0.086) ($n=131$)	0.494	−0.008 (0.069) ($n=74$)	0.017 (0.068) ($n=60$)	0.049
No GL	0.002 (0.087) ($n=189$)	0.004 (0.083) ($n=172$)	0.807	−0.004 (0.072) ($n=94$)	0.014 (0.065) ($n=80$)	0.099
Group B						
No SU or BG	−0.000 (0.089) ($n=126$)	0.012 (0.088) ($n=96$)	0.324	0.000 (0.073) ($n=59$)	0.011 (0.064) ($n=41$)	0.457
No SU or α-GI	0.002 (0.085) ($n=123$)	−0.008 (0.078) ($n=70$)	0.480	0.006 (0.075) ($n=61$)	0.006 (0.069) ($n=36$)	0.974
No SU or TZD	0.003 (0.090) ($n=125$)	0.004 (0.091) ($n=90$)	0.947	−0.003 (0.066) ($n=59$)	0.006 (0.070) ($n=41$)	0.518
No SU or GL	0.006 (0.088) ($n=153$)	0.002 (0.089) ($n=111$)	0.714	0.002 (0.072) ($n=76$)	0.007 (0.066) ($n=49$)	0.681
No BG or α-GI	−0.006 (0.085) ($n=117$)	0.011 (0.079) ($n=64$)	0.224	−0.002 (0.078) ($n=54$)	0.023 (0.074) ($n=28$)	0.196
No BG or TZD	−0.008 (0.090) ($n=123$)	0.016 (0.093) ($n=85$)	0.081	−0.009 (0.069) ($n=56$)	0.026 (0.072) ($n=30$)	0.042
No BG or GL	−0.005 (0.088) ($n=145$)	0.012 (0.089) ($n=108$)	0.147	−0.005 (0.074) ($n=68$)	0.019 (0.067) ($n=40$)	0.121
No α-GI or TZD	−0.008 (0.084) ($n=117$)	0.004 (0.070) ($n=74$)	0.332	−0.008 (0.072) ($n=60$)	0.020 (0.070) ($n=38$)	0.077
No α-GI or GL	−0.004 (0.083) ($n=144$)	0.003 (0.073) ($n=105$)	0.539	−0.003 (0.076) ($n=75$)	0.017 (0.065) ($n=54$)	0.146
No TZD or GL	−0.002 (0.089) ($n=153$)	0.003 (0.088) ($n=115$)	0.653	−0.007 (0.069) ($n=73$)	0.016 (0.067) ($n=51$)	0.079
Group C						
No SU, BG, or α-Gl	−0.002 (0.086) ($n=102$)	−0.002 (0.079) ($n=40$)	0.997	0.007 (0.076) ($n=48$)	0.007 (0.070) ($n=21$)	0.995
No SU, BG, or TZD	−0.003 (0.092) ($n=105$)	0.014 (0.096) ($n=64$)	0.303	−0.004 (0.066) ($n=48$)	0.010 (0.067) ($n=24$)	0.434
No SU, BG, or GL	−0.001 (0.089) ($n=124$)	0.010 (0.093) ($n=79$)	0.427	0.000 (0.073) ($n=59$)	0.008 (0.063) ($n=30$)	0.651
No SU, α-Gl, or TZD	0.003 (0.086) ($n=98$)	−0.013 (0.071) ($n=45$)	0.540	0.000 (0.070) ($n=48$)	0.003 (0.070) ($n=23$)	0.899
No SU, α-Gl, or GL	0.001 (0.085) ($n=121$)	−0.007 (0.079) ($n=63$)	0.528	0.006 (0.075) ($n=61$)	0.008 (0.067) ($n=32$)	0.917
No SU, TZD, or GL	0.003 (0.091) ($n=123$)	−0.000 (0.095) ($n=74$)	0.817	−0.002 (0.067) ($n=48$)	0.002 (0.068) ($n=24$)	0.806
No BG, α-Gl, or TZD	−0.012 (0.087) ($n=97$)	0.015 (0.072) ($n=40$)	0.113	−0.009 (0.072) ($n=46$)	0.037 (0.077) ($n=15$)	0.045

Table 3 (continued)

Antidiabetic-agent combination	Overall			< 70 years		
	Sitagliptin group	Conventional therapy group	*p* value	Sitagliptin group	Conventional therapy group	*p* value
No BG, α-Gl, or GL	−0.006 (0.085) (*n* = 115)	0.013 (0.080) (*n* = 57)	0.172	−0.002 (0.078) (*n* = 54)	0.027 (0.072) (*n* = 24)	0.147
No BG, TZD, or GL	−0.008 (0.090) (*n* = 122)	0.014 (0.096) (*n* = 71)	0.126	−0.009 (0.069) (*n* = 56)	0.025 (0.071) (*n* = 22)	0.074
No α-Gl, TZD, or GL	−0.009 (0.084) (*n* = 116)	0.005 (0.069) (*n* = 68)	0.271	−0.008 (0.072) (*n* = 60)	0.022 (0.067) (*n* = 35)	0.059

Data are presented as means (SD), mm

α-GI α-glucosidase inhibitor, *BG* biguanide, *CCA* common carotid artery, *GL* glinide, *IMT* intima-media thickness, *SU* sulfonylurea, *TZD* thiazolidinedione

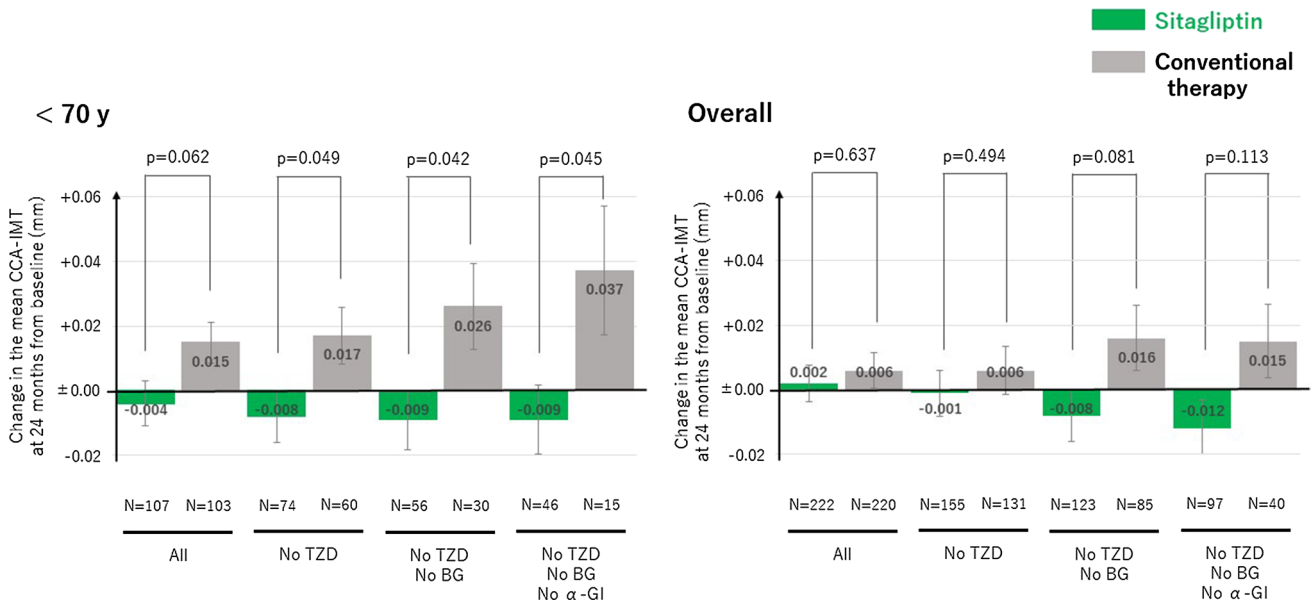

Fig. 2 Influence of differences in the specified combinations of antidiabetic agents on CCA-IMT progression (left panel: < 70 years, right panel: overall participants). The CCA-IMT progression in the conventional therapy group was significantly accelerated compared to the sitagliptin group only in three subgroups aged <70 years who received treatment without specified combinations of antidiabetic agents. Bars indicate mean ±SE. CCA, common carotid artery; IMT, intima-media thickness; TZD, thiazolidinedione; BG, biguanide; α-GI, α-glucosidase inhibitor

Table 4 Group difference in baseline-adjusted change of mean CCA-IMT in the subgroups aged < 70 years

Subgroups	Group difference in baseline-adjusted mean (95% CI)	*p* value
No TZD	−0.039 (−0.103 to 0.025)	0.070
No TZD or BG	−0.019 (−0.099 to 0.061)	0.052
No TZD, BG, or α-GI	−0.018 (−0.115 to 0.080)	0.064

Abbreviations see Table 3

Discussion

The major finding of this post hoc subgroup analysis of the PROLOGUE study was that sitagliptin significantly attenuated CCA-IMT progression in comparison with conventional therapy in subgroups aged < 70 years who were not concurrently taking specified combinations of antidiabetic agents, such as TZD, BG, and α-GI.

Table 5 Changes in clinical variables from baseline to 24 months in the subgroups aged < 70 years

Variables	No TZD			No BG or TZD			No BG, α-Gl, or TZD		
	Sitagliptin group ($n=74$)	Conventional therapy group ($n=60$)	p value	Sitagliptin group ($n=56$)	Conventional therapy group ($n=30$)	p value	Sitagliptin group ($n=46$)	Conventional therapy group ($n=15$)	p value
HbA1c, %	−0.261 (0.583)	−0.110 (0.787)	0.215	−0.233 (0.553)	−0.138 (0.727)	0.512	−0.198 (0.578)	0.050 (0.901)	0.234
Body mass index, kg/m^2	−0.314 (1.414)	0.009 (1.425)	0.218	−0.106 (1.119)	−0.216 (1.608)	0.727	−0.147 (1.158)	−0.292 (1.795)	0.738
Systolic blood pressure, mmHg	0.250 (17.849)	−2.500 (16.562)	0.364	1.852 (18.881)	−4.800 (15.372)	0.103	1.000 (16.537)	−9.333 (14.744)	0.036
Diastolic blood pressure, mmHg	1.875 (11.825)	−1.667 (10.708)	0.076	3.222 (11.270)	−3.500 (9.602)	0.007	3.068 (10.810)	−3.800 (11.085)	0.039
Low-density lipoprotein cholesterol, mmol/L	−0.994 (22.865)	−4.606 (21.771)	0.384	−0.436 (24.987)	−5.182 (20.435)	0.394	−2.618 (23.403)	−6.038 (17.747)	0.631
High-density lipoprotein cholesterol, mmol/L	−0.539 (7.637)	−0.093 (11.941)	0.799	0.272 (7.362)	0.307 (9.477)	0.985	−0.239 (7.083)	1.879 (9.657)	0.378
Estimated glomerular filtration rate, mL/min/1.73m^2	−2.375 (9.227)	−3.764 (10.362)	0.417	−3.313 (8.280)	−4.142 (10.899)	0.695	−3.849 (8.632)	−4.433 (12.743)	0.842

Data are presented as means (SD). Abbreviations see Table 3

A definite relationship between DPP-4 inhibitors treatment and improvement of CV outcomes in patients with T2DM remains to be determined, being still in debate [21]. It is also controversial whether DPP-4 inhibitors can delay the progression of carotid atherosclerosis in people with T2DM. Although some studies have found that DPP-4 inhibitors attenuated carotid IMT progression relative to conventional therapy [22,23], the PROLOGUE study failed to show a significant difference between the treatment groups, although the decrease in HbA1c was significantly greater in the sitagliptin group without hypoglycemic episode [9]. Possible reasons for this apparent discrepancy, such as differences in medical history, insulin use, and concomitant medications including antidiabetic agents, have been discussed previously [9]. However, actual clinical factors that had an influence on the results of the PROLUGE study were yet to be fully investigated.

In the present sub-study, we focused on differences between the groups in the concomitant use of antidiabetic agents. Although such differences in the overall patients were not found to influence the changes in the CCA-IMT, our results suggested that certain combinations of antidiabetic agents in patients aged < 70 years inhibited CCA-IMT progression in the conventional therapy group. In fact, the participants in previous studies were younger (approximately 65 y) than those in the PROLOGUE study [22,23]. Thus, attenuation of carotid IMT progression by antidiabetic agents may depend partly on age, being more difficult to achieve in older patients. This may enhance a clinical importance of earlier medical intervention to suppress carotid atherosclerosis progression in patients with T2DM, although precise reason for such effect in younger population remains uncertain. Furthermore, previous studies included diabetes patients without history of CV disease [22,23], while in the PROLOGUE study approximately two-thirds of patients had history of CV disease and had been treated for secondary prevention [9]. We have recently demonstrated that sitagliptin could partly attenuate carotid atherosclerosis in a subgroup receiving primary prevention of cardiovascular event (mean age 67 or 68 years), but not in that receiving secondary prevention (mean age 70 or 71 years), in another subanalysis of the PROLOGUE study [24]. Given these results, it may be, at least in part, hard that DPP-4 inhibitor therapy can attenuate carotid atherosclerosis in older T2DM patients with advanced vascular damages. Furthermore, given the fact that some concomitant agents, such as statin [25,26] and some antiplatelet [27], which could potentially prevent carotid atherosclerotic progression often administered in population treated for secondary prevention of CV disease, it might be in part hard to detect the inhibitory effect of sitagliptin itself in the PROLOGUE study. Especially, when other classes of antidiabetic agents with potency to reduce atherosclerosis, such as TZD and BG, were added in the control group, it is just conceivable that beneficial effect on carotid CCA-IMT progression was further masked in the sitagliptin group.

Table 6 Multivariable regression analyses showing differences in the mean CCA-IMT between the treatment groups (sitagliptin group minus conventional therapy group) in the subgroups aged < 70 years

	Estimate	SE	t-ratio	*p* value
No TZD subgroup (*N* = 127, excluded 7 patients due to missing data)				
Model 1	−0.030	0.012	−2.404	0.018
Model 2	−0.030	0.013	−2.407	0.018
Model 3	−0.028	0.012	−2.251	0.026
Model 4	−0.027	0.012	−2.177	0.032
Model 5	−0.028	0.013	−2.185	0.031
No TZD or BG subgroup (*N* = 80, excluded 6 patients due to missing data)				
Model 1	−0.041	0.017	−2.481	0.016
Model 2	−0.041	0.017	−2.479	0.016
Model 3	−0.040	0.017	−2.432	0.018
Model 4	−0.038	0.017	−2.301	0.025
Model 5	−0.040	0.017	−2.324	0.023
No TZD, BG, or α-GI subgroup (*N* = 56, excluded 5 patients due to missing data)				
Model 1	−0.052	0.023	−2.305	0.026
Model 2	−0.054	0.023	−2.396	0.021
Model 3	−0.051	0.023	−2.265	0.028
Model 4	−0.050	0.023	−2.187	0.034
Model 5	−0.056	0.025	−2.226	0.031

Model 1 were adjusted for age. Model 2 were adjusted for Model 1 and sex. Model 3 were adjusted for Model 2 and baseline mean CCA-IMT. Model 4 were adjusted for Model 3 and baseline systolic blood pressure. Model 5 were adjusted for Model 4 and baseline HbA1c. Abbreviations see Table 3

Previous clinical studies have demonstrated that some antidiabetic agents, such as metformin [5], pioglitazone [6,7], and α-GI [8], can attenuate carotid IMT progression compared with SUs or a placebo. In the PROLOGUE study, the prevalence rates of these antidiabetic agents had increased by 24 months in the conventional therapy group and exceeded those in the sitagliptin group. In the three subgroups aged < 70 years who did not receive treatment with specific combinations of antidiabetic agents, CCA-IMT progression was significantly greater in the conventional therapy group than in the sitagliptin group. Hence, sitagliptin may attenuate CCA-IMT progression during 24 months in these subgroups, in part independent of any improvement of glycemic control. These results raise the possibility that certain agents masked the difference between the treatment groups in the change in CCA-IMT. On the other hand, no significant differences in the change in CCA-IMT were evident between the treatment groups when stratified by the other combinations of antidiabetic agents. Actually, there was no increase at least in the usages of metformin and pioglitazone in previous studies [22,23].

Combination treatment with antidiabetic agents is aimed primarily at achieving better glycemic control. In fact, combination therapy of DPP-4 inhibitors with other types of antidiabetic agents, such as BG or TZD, has been shown to improve glycemic control and is well tolerated [28,29]. In addition, recent large-scale cohort studies have shown that different combinations of antidiabetic agents resulted in different CV outcomes in patients with T2DM [30,31]. Among them, second-line treatment with DPP-4 inhibitors and TZD besides first-line BG was significantly associated with a decreased risk of CV events, heart failure, and mortality relative to non-use of these agents and conventional treatment. In the present subgroup analysis, increased CCA-IMT progression was also demonstrated in the subgroup that was not using these agents. Thus, these agents may have a possible ability to improve CV outcomes, accompanied in part by slowing the rate of progression of atherosclerosis, although a meta-analysis of 41 RCTs showed that regression or delayed progression of carotid IMT induced by CV drug treatment, such as lipid lowering, antihypertensive, or antidiabetic agents, did not improve clinical outcome during mean 2.4 years follow-up [32]. Furthermore, recent meta-analyses in patients with T2DM suggested that carotid IMT measurement did not add CV risk predictive value to the Framingham risk score and was not associated with subsequent CV events [33,34]. Because measurements of carotid IMT were prone to generate variability in follow-up studies and less reproducibility [32], there may be a technical fragility in the carotid IMT as a surrogate marker in clinical trials [35]. However, appropriate CV drug treatment itself should be important to control relevant risk factors. Therefore, resultant attenuation of carotid IMT progression and reduction of atherosclerosis may lead to improvement of CV outcomes in the long term, although further studies are required to evaluate its clinical significance [36,37]. Therefore, our results have important implications for clinical decision making when electing and prescribing antidiabetic agents, especially in patients with T2DM who have high-risk of CV disease and need to decrease the risk of atherosclerotic CV events.

This sub-study of the PROLOGUE study has limitations that merit attention. A major limitation was the fact that we did not consider adjustment for multiple testing in the present sub-study, suggesting that our results might be potentially caused by chance. Because the present study was an exploratory and post hoc analysis, the sample size was limited and might be underpowered to detect differences in the outcome between the treatment groups. Second, the analyses did not take into account the dosage of the antidiabetic agents or the patients' adherence to them. In addition, no information both on the other concomitant agents and the other clinical relevant covariates was considered in each stratified subgroup. Hence, it may be difficult to determine which antidiabetic agent specifically influenced the carotid atherosclerosis. Furthermore, the goal of this substudy was to investigate the masking effect of other types of

antidiabetic agents over effect of sitagliptin on carotid IMT; therefore, our present sub-study was not aimed at determining the antidiabetic drugs or combination of them that can best inhibit the progression of carotid IMT.

In conclusion, we have obtained evidence that differences in combinations of antidiabetic agents between the treatment groups may have influenced CCA-IMT progression, a primary endpoint in the PROLOGUE study [9]. Additionally, sitagliptin slowed CCA-IMT progression relative to conventional therapy in those subgroups aged < 70 years who received treatment without specific combinations of antidiabetic agents, such as TZD, BG, and α-GI, that have clear evidence for the benefit of carotid atherosclerosis.

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Author Contributions All authors were PROLOGUE Study Investigators, contributed to the planning and conduct of the study, and critically reviewed the manuscript. A.T. prepared the first draft of the manuscript. A.K. was responsible for the statistical analyses. K.N. critically supervised the study. All authors read and approved the final version of manuscript.

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Compliance with ethical standards

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