Diabetologia (2002) 45: 188–194

Diabetologia
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Articles

A phosphodiesterase inhibitor, cilostazol, prevents the onset of silent brain infarction in Japanese subjects with Type II diabetes

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Abstract

Aims/hypothesis. This study aimed to evaluate the effect of a phosphodiesterase inhibitor, cilostazol, on the prevention of silent brain infarction in diabetic patients without symptoms of vascular events.
Methods. A total of 89 subjects were allocated at random to the cilostazol group ($n = 43$) or the control group ($n = 46$).
Results. After the study period (3.2 ± 0.5 years), carotid intima-media thickness (IMT) (means ± SD) had increased ($p < 0.01$) by 0.18 ± 0.19 mm in the control group. In the cilostazol group, intima-media thickness showed almost no change (-0.00 ± 0.16 mm). In the control group, 2 out of 46 subjects showed symptomatic brain infarctions and 10 out of 34 subjects without infarct-like region assessed by standard brain MRI examination showed silent brain infarctions after the observation period. On the other hand, no subjects in the cilostazol group showed silent brain infarction or strokes during the study period. Both at the beginning and end of the study period, the number of infarct-like regions positively correlated with IMT ($r = 0.335$, $p < 0.001$ or $r = 0.347$, $p < 0.001$ respectively). The progression of infarct-like regions was directly related to the increase in IMT during the study period ($r = 0.299$, $p = 0.004$).
Conclusion/interpretation. These data demonstrated that cilostazol could prevent the onset of silent brain infarction in Japanese subjects with Type II (non-insulin-dependent) diabetes mellitus. Also, an increase in intima-media thickness of the carotid artery wall could be able to predict the onset of silent brain infarction. [Diabetologia (2002) 45: 188–194]

Keywords Silent brain infarction, intima-media thickness, Type II diabetes, antithrombotic drug.

Silent brain lesions detected by magnetic resonance imaging (MRI) are fairly common not only in first-ever stroke but also in normal elderly subjects without any symptoms [1–5]. It has been shown that a considerably higher incidence of white matter lesions exist in neurologically normal subjects with several risk factors for stroke than in those without risk factors. Recently, subclinical silent brain infarction has been identified as a risk factor for clinical stroke [6]. Thus, the detection of silent brain lesion is a useful clinical predictor of stroke. Antithrombotic drugs, such as aspirin and ticlopidin, can effectively reduce the recurrence of brain infarction in subjects with brain infarction or coronary heart disease. Diabetic patients without previous myocardial infarction have as high a risk of myocardial infarction as nondiabetic subjects with previous myocardial infarction [7]. The Stroke Council of the American Heart Association recently recommended antithrombotic drugs to prevent stroke in subjects with a high risk of atheroscle-

Received: 10 July 2001 and in revised form: 3 October 2001

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Abbreviations: API, ankle pressure index; APTT, anti-prothrombin time; dBP, diastolic blood pressure; HDL-Chol, HDL cholesterol; IMT, intima-media thickness of the carotid artery; sBP, systolic blood pressure; T-Chol, total cholesterol; TG, triglycerides

rosis [8]. However, there have been no data on the effect of antithrombotic drugs on the primary prevention of stroke.

The intima-media thickness (IMT) of the carotid artery is used as a surrogate of definite atherosclerosis in subjects with a high risk of vascular events [9–12]. The risk of brain infarction increases continuously with increasing IMT of the common carotid artery [13]. Also, the Cardiovascular Health Study pointed out that the infarct-like lesions detected by MRI show strong and consistent relationships with increasing carotid IMT and stenosis degree [14]. We have recently shown that long-term antithrombotic therapy with aspirin or ticlopidine can reduce progression of the IMT of subjects with Type II diabetes [15]. Thus, antithrombotic therapy could lessen the progression of early atherosclerosis and thus lessen the progression of brain infarction especially in patients with Type II diabetes.

The new antithrombotic drug, cilostazol, shows beneficial effects such as increasing peripheral blood flow [16] and the inhibition of the proliferation of vascular smooth muscle cells [17] as a type 3 phosphodiesterase inhibitor as well as ameliorating insulin resistance [18, 19]. In this study, therefore, we aimed to clarify the effect of cilostazol on the primary prevention of brain infarction of subjects with Type II diabetes. We conducted a randomized intensive study of antithrombotic drug on patients with Type II diabetes and found that cilostazol can reduce the appearance and progression of infarction-like lesions as well as IMT of the carotid artery in subjects with Type II diabetes.

Materials and methods

Ultrasonographic scanning of the carotid arteries was performed using an echotomographic system (EUB-450, Hitachi Medico, Tokyo, Japan) with an electrical linear transducer (midfrequency of 7.5 MHz). The axial resolution of this system was at least 0.3 mm. Scanning of the extracranial common carotid artery, carotid bulb, and internal carotid artery in the neck was performed bilaterally from three different longitudinal projections (ie. anterior-oblique, lateral and posterior-oblique) as well as the transverse projection, as reported in our previous studies [20–22]. All the images were photographed. The scanning session lasted for an average of 30 min. The detection limit of this echo system using 7.5 MHz is 0.1 mm.

The intima-media thickness (IMT) defined by Pignoli et al. [23–25] was measured as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line. The first line represents the lumen-intimal interface, and the second line is produced by the collagen-containing upper layer of the tunia adventitia. For each longitudinal projection, the site of the greatest thickness including a plaque lesion was sought along the near and far arterial walls from the common carotid artery to the internal carotid artery. Three measurements of intima-media thickness were conducted at the site of the greatest thickness and at two points, 1 cm upstream and 1 cm downstream from this site. These three measurements were averaged. The greatest value among the six averaged intima-media thicknesses (three from the left and three from the right) was used as the representative value (IMT) for each individual. All scans were conducted by physicians who were unaware of the clinical characteristics of the subjects. Determination of IMT on the photograph was performed by a physician. The reproducibility of the IMT measurement was examined by conducting another scan on eight participants 1 week later. The mean difference in IMT between these two determinations was 0.01 mm, and the standard deviation was 0.04 mm, demonstrating good reproducibility for repeated measurements, as described previously [20]. The threshold of IMT for normal subjects were less than 1.1 mm [20, 21].

Table 1. Baseline patient characteristics

	Control (46)	Cilostazol (43)	*p*
Age (years)	61.0 ± 7.2	60.3 ± 7.9	
Gender (female/male)	18/28	26/17	
Duration (years)	12.7 ± 12.6	10.4 ± 9.6	
BMI (kg/m2)	23.1 ± 4.66	22.9 ± 4.10	
HbA_{1c} (%)	7.63 ± 1.73	7.33 ± 1.87	
T-Chol (mmol/l)	5.34 ± 1.09	5.36 ± 0.70	
TG (mmol/l)	1.57 ± 1.21	1.51 ± 1.23	
HDL-Chol (mmol/l)	1.46 ± 0.59	1.39 ± 0.47	
sBP (mmHg)	134 ± 14	138 ± 13	
dBP (mmHg)	77.1 ± 7.1	80.3 ± 8.0	0.0462
Fibrinogen (mg/l)	283 ± 66	296 ± 52	
Treatment	16/8	15/7	
Hypertension (–/ +)	26/20	25/18	
Hyperlipidaemia (–/ +)	12/34	15/28	
Nephropathy (–/ +)	37/9	34/9	
MRI[a]	34/8/2/2/0	27/8/7/1/0	
API	0.97 ± 0.18	0.98 ± 0.10	
IMT (mm)	1.09 ± 0.29	1.10 ± 0.34	

[a] MRI was shown as number of patients who had brain lesions or showed an increase in number of brain lesions as follows (no lesion/1 lesion /2 lesions /3 lesions /4 lesions or more)

MRI was done using 1.5-T MRI. We used the T2-weighted image (TR, 4000 ms; TE, 102 ms) and T1-weighted image (TR, 500 ms; TE 15 ms; flip angle 82) of coronal slices (6 mm thick). We considered a focal and sharply demarcated high intensity on a T2-weighted image of larger than 3 mm to be brain infarction when it coincided with low density area of the a T1-weighted image. Hyperintense images visible only on T2 images were not counted as infarctions so as to exclude perivascular space. The number of infarct-like lesions in each patient was counted in a blinded fashion. The physicians evaluating MRI findings were unaware of patients' characteristics and IMT evaluation.

A total of 91 subjects with Type II diabetes between 41 and 75 years of age were recruited from among outpatients of Bellland Hospital and Osaka University Hospital. The determination of Type II diabetes was based on World Organization criteria. Each patient in this study fulfilled the following criteria: no episodes of ketoacidosis and absence of ketonuria; diagnosis of diabetes after 30 years of age; insulin therapy (if any) started after duration of diabetes for at least 5 years; absence of overt diabetic nephropathy or other renal tract disease; and absence of active diabetic proliferative retinopathy. The subjects were allocated at random into two groups with and without cilostazol. The subjects in the cilostazol group received cilostazol at a dose of 100–200 mg/day, while those in the control group did not receive any antithrombotic drugs. Informed consent was obtained from the subjects studied. Patient characteristics are shown in Table 1. This study is approved by the Osaka University Ethics Committee.

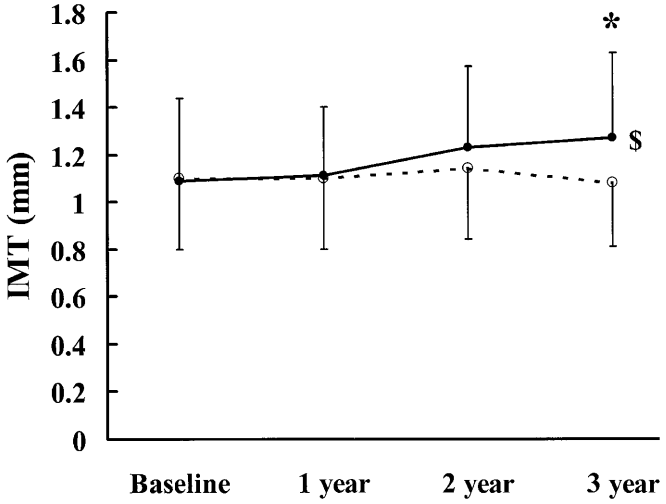

Fig. 1. Annual change in IMT of subjects with Type II diabetes with (○) and without (●) cilostazol. Data are shown as means ± SD. * Indicates a significant ($p < 0.01$) difference between with and without cilostazol. $ indicates a significant difference between before and after the observation period

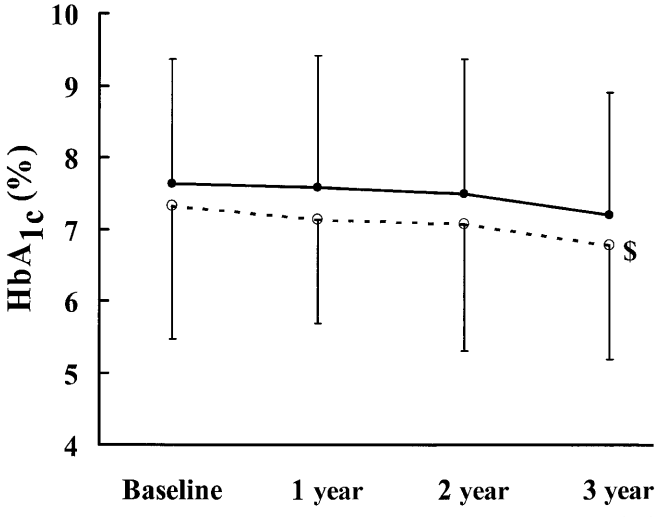

Fig. 2. Annual change in HbA_{1c} of diabetic subjects with (○) and without (●) cilostazol. Data are shown as means ± SD. $ indicates a significant difference between before and after the observation period

Exposure to smoking was estimated as the mean number of cigarettes smoked daily. Blood pressure was measured with a mercury sphygmomanometer. After a supine rest of 5 min, three measurements in the sitting position were conducted, and the mean value was used. Ankle pressure index (API) was calculated as systolic blood pressure measured on ankle divided by systolic blood pressure measured on brachial artery. At the baseline determination, blood was withdrawn for analyses of serum total cholesterol and HDL cholesterol, serum triglycerides, plasma glucose, haemoglobin A_{1c} (HbA_{1c}), fibrinogen, activated partial thromboplastin time, prothrombin time, and antithrombin III by standard laboratory techniques. Urinary albumin of a fasting urine specimen and a specimen collected at least 4 weeks later was measured by radioimmunoassay. The concentration of albumin in urine was divided by the urinary creatinine concentration and expressed as milligrams per gram of creatinine. The existence of nephropathy was determined if urinary albumin excretion rate was more than 30 mg / g creatinine. During the observation period of 3.2 ± 0.5 years, the lipid profile, blood pressure, IMT and API were determined every year. Brain MRI was taken at the beginning and end of the study period.

Forty-five randomly selected patients with diabetes were given cilostazol. After oral administration of cilostazol, two subjects who showed side effects (headache) were advised to terminate drug administration and were excluded from this study. Forty-three diabetics were controlled with diet only, 31 with oral hypoglycaemic agents, 15 with insulin injection once or more daily. Thirty-eight patients showed hypertension (systolic blood pressure greater than 160 mmHg or diastolic blood pressure above 145 mmHg) or were given anti-hypertensive drugs (diuretics, beta-blockers, alpha-blockers, Ca-channel blockers, and angiotensin converting enzyme inhibitors). Sixty-two patients showed dyslipidaemia (total cholesterol greater than 220 mg/dl or HDL cholesterol less than 40 mg/dl) or were given anti-hyperlipidaemic drugs (clofibrates, probucol, and 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitors). The same doses of drugs are administered during the observation period.

Data are presented as means ± SD. The laboratory data were compared by Student's and paired *t* test or one-way ANOVA. The difference in number of brain lesions was evaluated by Wilcoxon's rank-sum test. Stepwise multivariate regression analyses were performed to account for the effects and interactions of different variables on foci of silent brain infarction in diabetic patients treated with and without cilostazol. In this analysis, F values for inclusion and exclusion of variables were set at 2.0. These statistical analyses were carried out using the HALBAU (Gendai Sugaku-sha, Kyoto, Japan) statistical package on a personal computer. A p value of less than 0.05 or as an F value greater than 2.0 for stepwise multivariate regression analyses were considered to be statistically significant.

Results

Diabetic patients not given an antithrombotic drug (control group) showed a significant progression of intima-media thickness during the observation period (0.17 ± 0.19 mm). However, diabetic patients given cilostazol (cilostazol group) showed almost no progression of IMT (0.00 ± 0.20 mm), which was significantly ($p < 0.001$) smaller than that in the control group. Thus, after the observation period, the IMT of the subjects given cilostazol were significantly lower than those of the subjects not given it (1.08 ± 0.27 vs 1.27 ± 0.36 mm, $p < 0.001$, Fig. 1). During the study period, HbA_{1c} and diastolic blood pressure decreased significantly in cilostazol group (Fig. 2). However, the differences in change of HbA_{1c} (–0.43 ± 1.56 vs –0.54 ± 1.15 %, respectively) and diastolic blood pressure (1.1 ± 12.1 vs –2.9 ± 12.4 mmHg, respectively) between the control group and the cilostazol group showed no statistical significances. Also, both groups showed a significant increase in total cholesterol level. API increased but not significantly in both groups (Table 2).

Table 2. Patients' characteristics before and after follow-up period

	Control (n = 46)			Cilostazol (n = 43)		
	before	after	p*	before	after	p*
BMI (kg/m2)	23.1 ± 4.66	22.7 ± 4.38		22.9 ± 4.10	22.8 ± 4.06	
HbA_{1c} (%)	7.63 ± 1.73	7.20 ± 1.71		7.33 ± 1.87	6.78 ± 1.60	0.0045
T-Chol (mmol/l)	5.34 ± 1.09	5.65 ± 0.91	0.0032	5.36 ± 0.70	5.67 ± 0.70	0.0121
TG (mmol/l)	1.57 ± 1.21	1.41 ± 0.69		1.51 ± 1.23	1.40 ± 1.30	
HDL-Chol (mmol/l)	1.43 ± 1.21	1.60 ± 0.59	0.0036	1.39 ± 0.47	1.51 ± 0.35	
sBP (mmHg)	134 ± 14	135 ± 10		138 ± 13	134 ± 10	
dBP (mmHg)	77.1 ± 7.1	76.0 ± 6. 3		80.3 ± 8.0	77.4 ± 6.9	0.0283
Bleeding time (sec)	150 ± 65	158 ± 72		140 ± 57	143 ± 47	
Prothrombin time (sec)	20.9 ± 43.0	10.9 ± 3.7		10.8 ± 0.5	10.2 ± 0.4	
APTT (%)	37.0 ± 45.1	35.8 ± 3.3		29.2 ± 2.2	39.2 ± 35.8	
Antithrombin III	95.5 ± 21.8	98.2 ± 32.2		103 ± 11	97.8 ± 12.3	
Fibrinogen (mg/l)	283 ± 66	290 ± 41		296 ± 52	279 ± 77	
IMT (mm)	1.09 ± 0.29	1.27 ± 0.36	< 0.001	1.10 ± 0.34	1.08 ± 0.27	
MRI[a]	34/8/2/2/0	24/10/5/4/3	< 0.001	27/8/7/1/0	27/8/6/1/1	
Change in MRI[a]	30/8/6/2/0	41/2/0/0/0				
API	0.97 ± 0.18	1.05 ± 0.13	0.0418	0.98 ± 0.10	1.00 ± 0.14	

Data are shown as means ± SD
[a]MRI and change in MRI were shown as number of patients who had brain lesions or showed the increase in number of brain lesions as follows (no lesion/1 lesion /2 lesions /3 lesions / 4 lesions or more).
*p before vs after

Table 3. Multivariate regression analysis to evaluate efficacy of cilostazol, IMT, blood pressures in affecting progression of infarct-like lesions by MRI

	Initial MRI findings			Final MRI findings			Progression of MRI findings		
Parameter	Partial regression coefficient (mm/years)	p value	Partial correlation coefficient	Partial regression coefficient	p value (mm/year)	Partial correlation coefficient	Partial regression coefficient (mm/year)	p value	Partial correlation coefficient
Initial IMT (per 1 mm)	0.767	0.003	0.312	0.945	0.006	0.294	0.320	0.142	0.161
Change in IMT (per 1 mm)							0.781	0.034	0.230
Initial sBP (per 1 mmHg)	0.022	0.006	0.292	0.046	< 0.001	0.436	0.024	< 0.001	0.382
Initial dBP (per 1 mmHg)	– 0.033	0.024	– 0.242	– 0.063	0.001	– 0.337	– 0.032	0.011	– 0.276
Cilostazol (per administration)				– 0.341	0.114	– 0.172	– 0.399	0.009	– 0.281
R^2	0.191			0.291			0.316		

Stepwise multivariate regression analysis was done on 89 diabetic subjects

In the control group, 16 out of 46 subjects had an increased number of infarct-like lesions detected by MRI at the end of the study. In the cilostazol group, 2 out of 43 subjects showed increases in the number of infarct-like lesions. The difference was statistically significant ($p < 0.001$). At the baseline examination, IMT was significantly related to the number of infarct-like lesions ($r = 0.335$, $p = 0.001$). After the observation period, IMT was significantly related to the number of infarct-like lesions ($r = 0.347$, $p = 0.001$) in both groups. During the observation period, the progression of IMT correlated significantly and positively with the increase in the foci of infarct-like lesions ($r = 0.299$, $p = 0.004$, Fig. 3). During the observation period, the change in systolic blood pressure did not significantly correlate with the increase in the foci of infarct-like lesions (Fig. 4). In the control group, 10 out of 34 subjects without infarct-like lesions at the baseline MRI examination showed such lesions after the observation period. On the other hand, in the cilostazol group, none of the 28 subjects without infarct-like lesions at the baseline MRI examination showed such lesions after the observation period ($p = 0.001$).

Stepwise multivariate regression analysis was done to evaluate the risk factors for the infarct-like lesions detected by MRI. The initial IMT, baseline systolic blood pressure and baseline diastolic blood pressure were significant risk factors for the infarct-like lesions at the baseline examination. For the infarct-like lesions of the final MRI examination, the initial IMT, baseline systolic blood pressure, baseline diastolic blood pressure and administration of cilostazol were deduced as being significant factors. Baseline systolic and diastolic blood pressures, the change in IMT, and administration of cilostazol affected ($p < 0.05$) the increase in the number of infarct-like lesions (Table 3).

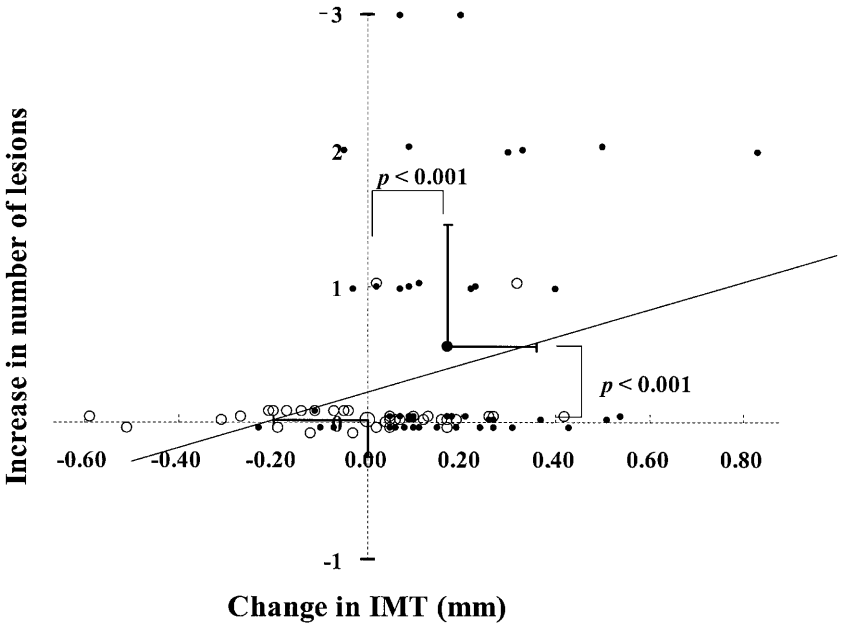

Fig. 3. Relationship between the change in IMT and the increase in number of infarct-like lesions in subjects diabetic subjects with (○) and without (●) cilostazol after the observation period. Average data were given with SD of IMT and SD of the number of lesions

Discussion

This is the first study showing the effectiveness of antithrombotic agents on arresting the appearance or progression of silent brain infraction as well as arresting progression of the carotid intima-media thickness of subjects with Type II diabetes without symptomatic coronary vascular diseases.

In this study, cilostazol, a type 3 phosphodiesterase inhibitor, could prevent the progression of carotid IMT of subjects with Type II diabetes (from 0.17 ± 0.19 to -0.0 ± 0.2 mm/3 years). Recently, we showed that aspirin at a small dose or ticlopidin could reduce the progression of IMT by almost 50% [15]. Cilostazol also shows an antiatherogenic effect on endothelial cells and vascular smooth muscle cells. Because type 3 phosphodiesterase is present not only in platelets but also in endothelial cells and smooth muscle cells, the inhibition of this enzyme by cilostazol administration results in increased blood flow [16] and attenuation of smooth muscle cell proliferation [17]. Together with these antiatherogenic effects on endothelial cells and vascular smooth muscle cells, cilsotazol could prevent the progression of carotid IMT.

Gene disruption of endothelial nitric oxide synthase causes insulin resistance in mice [26]. Cilostazol increases NO synthesis in smooth muscle cells [27].Thus, cilostazol might improve insulin sensitivity [18, 19]. In this study, HbA_{1c} decreased significantly after administration of cilostazol. It also decreased in subjects not given cilostazol but not significantly. However, according to a previous multiple regression analysis on the effectiveness of the reduction of HbA_{1c} on the inhibition of IMT progression, the decrease of the HbA_{1c} might be too small to arrest the IMT progression shown in this study [15].

Cross-sectional study before and after the observation period showed a positive relationship ($p < 0.001$) between the number of infarct-like lesions and the carotid IMT ($r = 0.335$ or $r = 0.347$, respectively). These results were comparable with the observation that carotid artery IMT is a risk factor for myocardial infarction and stroke in older adults [12]. This study is the first to show that the change in infarct-like lesion after the observation period was significantly and positively related with the change in carotid IMT ($r = 0.299$, $p = 0.004$). This points to the possibility that the increase in carotid IMT could predict the appearance of silent brain infarction.

The diabetic patients without cilostazol had an increase of infarct-like lesions ($p < 0.001$). However, the diabetic patients given cilostazol showed a negligible appearance of infarct-like lesions in the observation period of up to 3 years. These results offer support for the secondary prevention study using cilostazol at 200 mg/day showing a reduction in the appearance of stroke by 43.4% compared with the placebo group [28].

Multivariate regression analysis showed that the initial systolic blood pressure is the primary risk factor (its partial regression coefficient was 0.024) for the progression of MRI finding of subjects with Type II diabetes and also the initial diastolic blood pressure is negatively (its partial regression coefficient was -0.032) responsible for the progression of MRI.

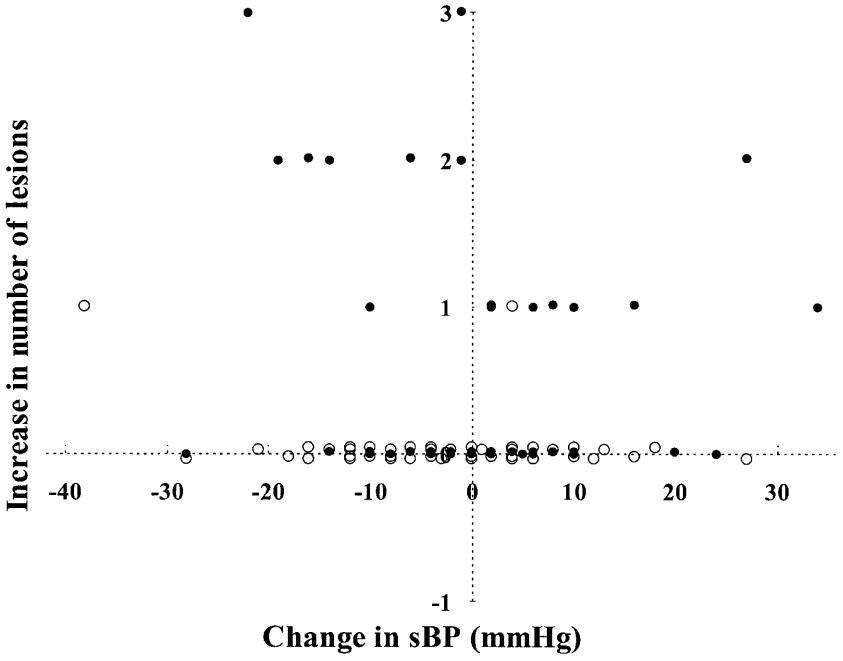

Fig. 4. Relationship between the change in systolic blood pressure and the increase in number of infarct-like lesions in diabetic subjects with (○) and without (●) cilostazol after the observation period

This observation could be comparable to the report showing that the thickening of the media of arteries in hypertension is a response to the raised tension in their walls [29]. The patients in the cilostazol group did not show a significant reduction of systolic blood pressure and the change in systolic blood pressure did not correlate with the change in brain lesions. Thus, the reduced appearance of brain lesions in the cilostazol group could not be accounted for by changes in systolic blood pressure.

This study is the first primary prevention study showing that cilostazol is effective for arresting the appearance of silent brain infarction of diabetic patients without symptomatic coronary vascular events. As already described in detail, cilostazol could have favourable antiatherogenic effects, such as improving impaired endothelial function, increasing blood flow, and inhibiting vascular smooth muscle proliferation. It could also improve insulin resistance in Type II diabetic subjects. However, to establish the usefulness of cilostazol for primary prevention in Type II diabetic patients, a large-scale intervention study is needed.

Acknowledgements. We would like to thank Drs H. Hougaku and K. Kitagawa for their excellent suggestions to this study.

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