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Original Article

Effects of Cilnidipine, an L/N-Type Calcium Channel Blocker, on Carotid Atherosclerosis in Japanese Post-Stroke Hypertensive Patients: Results from the CA-ATTEND Study

Tomohisa Nezu[1], Naohisa Hosomi[1], Shiro Aoki[1], Noriyuki Suzuki[2], Tsukasa Teshima[3], Hitoshi Sugii[3], Shinobu Nagahama[4], Yoshiki Kurose[4], Hirofumi Maruyama[1] and Masayasu Matsumoto[1, 5]

[1]Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan
[2]Medical Affairs Department, Mochida Pharmaceutical Co., Ltd., Tokyo, Japan
[3]Post-Marketing Surveillance, Mochida Pharmaceutical Co., Ltd., Tokyo, Japan
[4]Post-Marketing Medical Research Department, EA Pharma Co., Ltd., Tokyo, Japan
[5]Hoshigaoka Medical Center, Japan Community Healthcare Organization (JCHO), Hirakata, Japan

***Aims*: Although several antihypertensive agents reduced the carotid intima−media thickness (IMT), it remains unclear whether those agents affect the interadventitial diameter (IAD). We aimed to examine whether cilnidipine, an L/N-type calcium channel blocker, reduced the common carotid IMT or IAD in post-stroke hypertensive patients.**

***Methods*: The common carotid IMT and IAD were measured at the start of cilnidipine treatment and 12 months from that. The changes in the mean max-IMT or IAD between baseline and the 12-month follow-up were evaluated and compared between the thick group (max-IMT ≥ 1.1 mm) and the normal group (max-IMT < 1.1 mm).**

***Results*: A total of 603 post-stroke hypertensive subjects (mean age = 69.3 yr, 378 males) were included in the analysis. At baseline, IAD was increased stepwise according to the value of max-IMT (p for trend < 0.001). Among them, 326 subjects were followed up for 12 months. The mean max-IMT from baseline to 12 months did not change in the normal group (−0.01 mm, 95% confidence interval [CI] −0.03 to 0.01, n = 170), whereas a significant reduction was observed in the thick group (−0.09 mm, 95% CI −0.13 to −0.05, n = 156). The mean IAD was significantly reduced during the study period in the normal group (−0.14 mm, 95% CI −0.22 to −0.05) as well as in the thick group (−0.12 mm, 95% CI −0.21 to −0.03).**

***Conclusions*: Cilnidipine promoted the regression of common carotid IMT in post-stroke hypertensive patients, especially in the thick group. Cilnidipine also reduced the IAD in both normal and thick groups.**

Key words: Cilnidipine, Carotid artery, Positive remodeling, Intima-media thickness, Post-stroke hypertensive

Introduction

Atherosclerosis is a major cause of cardiovascular death. Several studies have investigated the indicators of carotid intima−media thickness (IMT) progression, because the common carotid IMT and its progression are considered as surrogate markers for atherosclerosis[1-3]. The progression of IMT was positively associated with the incident stroke[4, 5]. A high IMT also predicts a higher risk of stroke recurrence[6, 7].

Therefore, several trials using antihypertensive or lipid-lowering agents have used the carotid IMT as a clinical endpoint[8, 9]. Although there is accumulating

Address for correspondence: Naohisa Hosomi, Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical and Health Sciences, 1-2-3 Kasumi, Minami-Ku, Hiroshima 734-8551, Japan
E-mail: nhosomi@hiroshima-u.ac.jp
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evidence for the association between carotid IMT and cerebral and cardiovascular events, the associations between carotid IMT regression and clinical outcomes are not conclusive[10]. More recently, several studies have reported that the common carotid interadventitial diameter (IAD) is associated with vascular risk factors, carotid IMT, left ventricular mass, and myocardial infarction[11-13]. In addition, Polak *et al*. showed that IAD was a stronger predictor of ischemic stroke than carotid IMT[14]. However, it remains unclear whether medical intervention reduces the carotid IAD.

The Carotid Atherosclerosis-Antihypertensive Treatment Trial, Effect of N-type Calcium Channel Blocker for Cerebrovascular Disease (CA-ATTEND) study is a 12-month, large-scale (n=2,667), prospective postmarketing surveillance (PMS) study in which the efficacy and safety of cilnidipine were investigated in registered post-stroke hypertensive patients on the basis of pressure (BP) and atherosclerosis of the common carotid arteries[15]. Cilnidipine is a dual L/N-Type calcium channel blocker that can block not only L-type vascular calcium channels but also N-type calcium channels in the sympathetic nerves[16].

In the present study, the effects of cilnidipine on the regression of atherosclerosis, estimated by the carotid IMT or IAD, were evaluated.

Materials and Methods

Study Design and Patients

The study design, patient characteristics, and main BP results of the CA-ATTEND study have been reported elsewhere[15]. This study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000005523). This study was carried out according to the Good Post-marketing Study Practice established by the Ministry of Health, Labour and Welfare of Japan. Briefly, the subjects of this study were hypertensive patients with a history of stroke who newly began cilnidipine treatment between May 2011 and June 2013, and they were recruited from throughout Japan. The observational period was 12 months. The observation items included patient characteristics (sex, age, height, weight, stroke subtype, presence/absence and types of complications, laboratory data related to lifestyle-related disease, etc.), BP, and concomitant agents. The protocol was reviewed and accepted by the ethics committees of the Hiroshima University and by each site where this study was conducted when required from each committee. A written informed consent was not required since this was an observational study in daily medical practice, and not an interventional study.

Carotid Artery Measurements by Ultrasonography

Carotid ultrasonography and measurements on the image were performed according to the methods in the J-STARS Echo study[17]. Ultrasonography was performed before starting treatment and after 12 months of follow-up by expert sonographers. The authorization of qualified sonographers followed the standardized examination criteria in the J-STARS Echo study. Before recruiting the subjects, recorded image data of the common carotid artery of volunteers were submitted to the CA-ATTEND secretariat (CA-ATTEND Central Office, US-ism Co., Ltd., Tokyo, Japan). Participation in this study was allowed for only the sonographers who met the CA-ATTEND criteria, for example, providing scans that clearly showed the long and minor axis views of both common carotid arteries and clearly depicted the arteria vertebralis. Each patient was examined by the same sonographer with the same equipment (high-resolution B-mode ultrasound scanners). The expert sonographers recorded all scans as movies for more than five heart rates and sent them to the CA-ATTEND central office. All saved images were transferred to a personal computer for semiautomated measurements. To avoid interreader variability, all images were read by two of the three observers using the semiautomated digital measurement software (IntimaScope, Version 5.0 R; Media Cross Co, Ltd., Tokyo, Japan)[18]. Two independent observers determined the lumen diameter (LD), IAD, max-IMT, and mean-IMT of the far wall of every bilateral common carotid artery at end-diastole. The coefficients of correlation for the values between the two observers were 1.00 for the left max-IMT ($p<0.001$), 0.99 for the left mean-IMT ($p<0.001$), 0.98 for the left IAD ($p<0.001$), 0.98 for the left LD ($p<0.001$), 0.99 for the right max-IMT ($p<0.001$), 0.99 for the right mean-IMT ($p<0.001$), 0.99 for the right IAD ($p<0.001$), and 0.98 for the right LD ($p<0.001$).

We used the max-IMT, mean-IMT, IAD, and LD of the common carotid artery, on the side with the greater max-IMT, for the arteriosclerosis evaluation. Carotid plaque was generally defined as a lesion with a focal IMT of 1.1 mm or more in Japan[19-23]. Therefore, we divided subject into the thick group (max-IMT ≥1.1 mm) and the normal group (max-IMT <1.1 mm). If subjects had the carotid plaques, we measured the max-IMT including it.

Statistical Analysis

The data are expressed as the mean±standard deviation, mean (95% confidence interval [CI]), or median (25th to 75th percentiles). Fisher's exact test or Wilcoxon rank-sum test was used for categorical data, and t-tests were used for continuous data. Dun-

Table 1. Baseline characteristics of subjects

Factors	Total ($n=603$)	Normal group (max-IMT <1.1 mm) ($n=302$)	Thick group (max-IMT ≥ 1.1 mm) ($n=301$)	p value
Age, years	69.3 ± 10.5	68.0 ± 11.4	70.7 ± 9.2	0.002
Male, n (%)	378 (62.7)	187 (61.9)	191 (63.5)	0.736
BMI, kg/m^2	23.5 ± 3.4 ($n=451$)	23.3 ± 3.3 ($n=225$)	23.7 ± 3.5 ($n=226$)	0.213
mRS score	1 (0 to 2)	1 (0 to 2)	1 (0 to 2)	0.466
Concomitant disease				
Dyslipidemia, n (%)	295 (48.9)	133 (44.0)	162 (53.8)	0.018
Diabetes mellitus, n (%)	120 (19.9)	50 (16.6)	70 (23.3)	0.042
Coronary artery disease, n (%)	38 (6.3)	11 (3.6)	27 (9.0)	0.007
Stroke history[a]				
Cerebral infarction, n (%)	475 (78.8)	221 (73.2)	254 (84.4)	0.001
Small vessel occlusion, n (%)	230 (38.1)	109 (36.1)	121 (40.2)	0.315
Large artery atherosclerosis, n (%)	170 (28.2)	70 (23.2)	100 (33.2)	0.007
Cardioembolism, n (%)	26 (4.3)	15 (5.0)	11 (3.7)	0.548
Others, n (%)	52 (8.6)	28 (9.3)	24 (8.0)	0.664
Cerebral hemorrhage, n (%)	94 (15.6)	49 (16.2)	45 (15.0)	0.736
SAH, n (%)	46 (7.6)	35 (11.6)	11 (3.7)	<0.001
Smoking habit[b]	279 (46.3)	131 (43.4)	148 (49.2)	0.165
Drinking habit	220 (36.5)	108 (35.8)	112 (37.2)	0.735
Daily dose of cilnidipine, mg/day	10.2 ± 3.1	10.0 ± 2.9	10.5 ± 3.3	0.056
Anti-hypertensives				
ARBs, n (%)	226 (37.5)	108 (35.8)	118 (39.2)	0.401
CCBs, n (%)	49 (8.1)	21 (7.0)	28 (9.3)	0.301
ACE inhibitors, n (%)	20 (3.3)	9 (3.0)	11 (3.7)	0.658
Diuretics, n (%)	48 (8.0)	30 (9.9)	18 (6.0)	0.097
Statins, n (%)	195 (32.3)	77 (25.5)	118 (39.2)	<0.001
Antiplatelet agents, n (%)	324 (53.7)	146 (48.3)	178 (59.1)	0.009
Warfarin, n (%)	25 (4.1)	14 (4.6)	11 (3.7)	0.684
Office systolic BP, mmHg	152.7 ± 23.3 ($n=553$)	152.6 ± 23.5 ($n=277$)	152.8 ± 23.1 ($n=276$)	0.912
Office diastolic BP, mmHg	84.3 ± 14.6 ($n=550$)	85.9 ± 15.3 ($n=277$)	82.7 ± 13.8 ($n=273$)	0.012
Office pulse rate, beats/min	77.5 ± 13.8 ($n=478$)	77.3 ± 14.7 ($n=238$)	77.6 ± 12.8 ($n=240$)	0.861
eGFR, mL/min/1.73 m^2	68.2 ± 19.5 ($n=388$)	69.7 ± 21.5 ($n=202$)	66.6 ± 17.0 ($n=186$)	0.110
HbA1c, %	6.1 ± 0.9 ($n=270$)	6.0 ± 0.8 ($n=137$)	6.2 ± 1.0 ($n=133$)	0.030
Total cholesterol, mg/dL	191.8 ± 36.5 ($n=325$)	190.3 ± 37.8 ($n=169$)	193.5 ± 35.1 ($n=156$)	0.429
HDL cholesterol, mg/dL	55.0 ± 14.9 ($n=323$)	55.3 ± 14.7 ($n=163$)	54.6 ± 15.1 ($n=160$)	0.644
LDL cholesterol, mg/dL	112.4 ± 31.8 ($n=318$)	109.7 ± 31.2 ($n=165$)	115.3 ± 32.3 ($n=153$)	0.114

Data are shown as the number of subjects (%), the mean ± SD, or median (25th to 75th percentiles).
[a] The clinical subtype of stroke included cases in which more than one subtype of stroke was recorded in the same patient.
[b] Smoking habit, current smoker, and ex-smoker.
Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; CCBs, calcium channel blockers; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; mRS, modified Rankin scale; SAH, subarachnoid hemorrhage.

nett's test was used for multiple comparisons. The Jonckheere–Terpstra test was used for trend analysis. Analysis of covariance (ANCOVA) was used to verify differences in carotid ultrasonography parameters after adjustment for unbalanced baseline subject characteristics. Pearson correlation coefficients were employed to examine the relationships. Multiple linear regression analysis was used to examine the effects of the baseline characteristics (age, sex, smoking habit [current smoker + ex-smoker], dyslipidemia, and diabetes mellitus) or concomitant agents (angiotensin Ⅱ [AⅡ] receptor blockers [ARBs], statins, and antiplatelet agents) on the changes of the max-IMT or IAD. A p-value <0.05 was considered statistically significant.

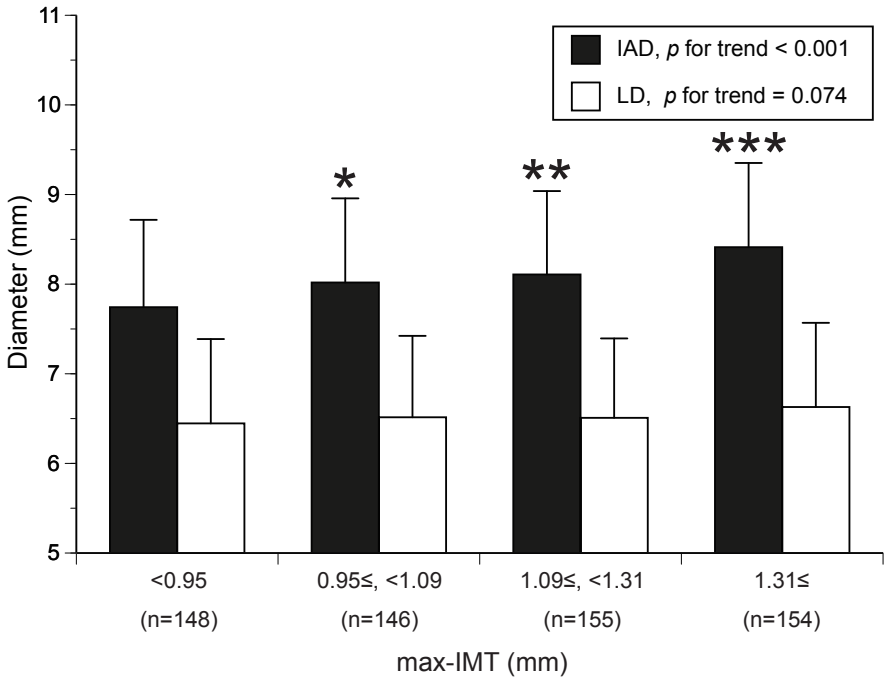

Fig. 1. Changes in IAD and LD at the quartile of max-IMT in the carotid arteries.

The increasing trend of LD or IAD in the quartile of max-IMT was analyzed using the Jonckheere–Terpstra test. The difference in IAD was calculated using Dunnett's test. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs. < 0.95 mm group.

Abbreviations: CI, confidence interval; IAD, interadventitial diameter; IMT, intima-media thickness; LD, lumen diameter.

The primary outcome was the change in the mean common carotid max-IMT or IAD from baseline to 12 months, compared between the thick group (max-IMT ≥ 1.1 mm) and the normal group (max-IMT < 1.1 mm).

All statistical analyses were performed using a statistical software package (JMP, version 12.2.0; SAS Institute, Cary, NC, USA).

Results

Demographic Data and Baseline Max-IMT or IAD

In the CA-ATTEND study, 2,667 patients were registered in 314 hospitals. Of those hospitals, 81 hospitals with trained sonographers recruited the subjects ($n = 618$) with a baseline evaluation of IMT for CA-ATTEND Echo Study. Among them, 15 patients were excluded because they did not have carotid diameter evaluations. The remaining 603 subjects were included in the analysis. The characteristics of the 603 subjects are shown in **Table 1**. The mean age was 69.3 yr, and male patients accounted for 62.7% of the subjects. The mean office systolic BP and diastolic BP were 152.7 and 84.3 mmHg, respectively. In the thick group, the subjects were older than those in the normal group; the incidence of dyslipidemia, diabetes mellitus, coronary artery disease, and cerebral infarction was higher; and the incidence of subarachnoid hemorrhage was lower. The diastolic office BP was lower, and glycated hemoglobin (HbA1c) was higher in the thick group. The coadministration ratio of statins or antiplatelet agents was higher in the thick group. The other baseline patient characteristics were not different between the thick and normal groups. The baseline mean max-IMT was 1.20 mm (95% CI 1.17 to 1.24, $n = 603$), and baseline IAD was 8.07 mm (95% CI 8.00 to 8.15, $n = 603$). The relationships between laboratory data and max-IMT or IAD are shown in **Supplementary Figs. 1** and **2**. The baseline max-IMT and baseline IAD were positively associated with age ($r = 0.17$, $p < 0.001$, $n = 603$; and $r = 0.20$, $p < 0.001$, $n = 603$, respectively) and negatively with estimated glomerular filtration rate ($r = -0.14$, $p = 0.005$, $n = 388$; and $r = -0.17$, $p = 0.001$, $n = 388$, respectively). Additionally, the baseline IAD was positively associated with body mass index ($r = 0.11$, $p = 0.021$, $n = 451$). All subjects were divided into quartiles on the basis of the baseline max-IMT values. IAD was increased stepwise according to the value of max-IMT (p for trend < 0.001, $n = 603$, **Fig. 1**). However, no association with LD was observed in these quartiles (p for trend = 0.074, $n = 603$).

Table 2. Baseline and follow-up carotid measures

	Total ($n=326$)	Normal group (max-IMT < 1.1 mm) ($n=170$)	Thick group (max-IMT ≥ 1.1 mm) ($n=156$)	Difference	p value
Max-IMT (mm)					
Baseline	1.18 (1.14 to 1.22)	0.93 (0.92 to 0.95)	1.45 (1.38 to 1.51)		
12 months	1.13 (1.08 to 1.17)	0.92 (0.90 to 0.94)	1.35 (1.28 to 1.43)		
Mean change	−0.05 (−0.07 to −0.03)	−0.01 (−0.03 to 0.01)	−0.09 (−0.13 to −0.05)	−0.08	<0.001
Mean-IMT (mm)					
Baseline	0.91 (0.88 to 0.94)	0.77 (0.75 to 0.78)	1.07 (1.03 to 1.11)		
12 months	0.88 (0.85 to 0.90)	0.76 (0.74 to 0.77)	1.01 (0.97 to 1.05)		
Mean change	−0.03 (−0.05 to −0.02)	−0.01 (−0.03 to 0.00)	−0.06 (−0.08 to −0.04)	−0.05	0.001
IAD (mm)					
Baseline	8.04 (7.93 to 8.14)	7.85 (7.70 to 8.00)	8.24 (8.09 to 8.39)		
12 months	7.91 (7.80 to 8.01)	7.71 (7.58 to 7.84)	8.12 (7.97 to 8.27)		
Mean change	−0.13 (−0.19 to −0.07)	−0.14 (−0.22 to −0.05)	−0.12 (−0.21 to −0.03)	0.02	0.799
LD (mm)					
Baseline	6.53 (6.43 to 6.64)	6.46 (6.32 to 6.60)	6.61 (6.47 to 6.76)		
12 months	6.47 (6.37 to 6.57)	6.41 (6.28 to 6.54)	6.54 (6.39 to 6.69)		
Mean change	−0.06 (−0.13 to 0.00)	−0.05 (−0.14 to 0.04)	−0.08 (−0.17 to 0.02)	−0.02	0.723

Data are shown as the mean and 95% confidence interval or mean only.
Abbreviations: IAD, interadventitial diameter; IMT, intima-media thickness; LD, lumen diameter.

Changes in Max-IMT or IAD

Among the 603 subjects evaluated, 326 subjects had carotid ultrasonography at 12 months of follow-up. The subjects with follow-up had some considerable differences from the subjects without follow-up (**Supplementary Table 1**). The subjects with follow-up had a lower modified Rankin scale score at enrollment. The proportion of subjects with antiplatelet agents was high, and warfarin was low in the subjects with follow-up. Additionally, the subjects with follow-up had lower office systolic BP, diastolic BP, and HbA1c. In 326 subjects who had follow-up carotid ultrasonography, changes in IMT and carotid diameters were evaluated (**Table 2**). The characteristics of 326 subjects, 170 subjects in the normal group and 156 subjects in the thick group, are shown in **Supplementary Table 2**. The mean change in max-IMT, mean-IMT, and IAD from baseline to 12 months were −0.05 mm (95% CI −0.07 to −0.03, $n=326$), −0.03 mm (95% CI −0.05 to −0.02, $n=326$), and −0.13 mm (95% CI −0.19 to −0.07, $n=326$), respectively. However, the mean LD did not decrease significantly (−0.06 mm, 95% CI −0.13 to 0.00, $n=326$). The change in max-IMT from baseline to 12 months after cilnidipine treatment was negatively correlated with baseline max-IMT ($r=-0.21$, $p<0.001$, $n=326$, **Supplementary Fig. 3A**). The change in IAD from baseline to 12 months after cilnidipine treatment was also negatively correlated with baseline IAD ($r=-0.36$, $p<0.001$, $n=326$, **Supplementary Fig. 3B**).

The mean max-IMT from baseline to 12 months did not change in the normal group (−0.01 mm, 95% CI −0.03 to 0.01, $n=170$), whereas a significant reduction was observed in the thick group (−0.09 mm, 95% CI −0.13 to −0.05, $n=156$) but not LD (−0.08 mm, 95% CI −0.17 to 0.02, $n=156$, **Table 2**). The mean IAD from baseline to 12 months significantly decreased in both groups (thick group −0.12 mm, 95% CI −0.21 to −0.03; normal group −0.14 mm, 95% CI −0.22 to −0.15). There was a significant difference in the change in mean max-IMT between the thick and normal groups (mean difference between groups −0.08 mm, $p<0.001$). A significant difference was also shown in the mean mean-IMT between the two groups (mean difference between groups −0.05 mm, $p=0.001$). No differences between groups were observed in the mean IAD and LD. These differences between the two groups were not affected by statistical adjustment for each of the baseline subject characteristics that differed between the groups (ANCOVA, data not shown).

Office systolic BP decreased markedly in both groups (thick group −16.0 mmHg, 95% CI −19.9 to −12.0, $n=126$; normal group −19.5 mmHg, 95% CI −23.2 to −15.7, $n=145$), and its reductions were not different between both groups (mean difference between groups 3.5 mmHg, 95% CI −1.9 to 8.9). There was no significant association between decrease in max-

Table 3. Multiple linear regression analysis for change in max-IMT or IAD

Covariates	max-IMT					
	Total ($n=326$)			Thick group ($n=156$)		
	Estimates of beta coefficient	95% CI	p value	Estimates of beta coefficient	95% CI	p value
Age	0.001	−0.002 to 0.003	0.555	0.002	−0.003 to 0.006	0.508
Sex (male)	0.036	−0.019 to 0.090	0.199	0.070	−0.031 to 0.170	0.174
Smoking[a]	−0.047	−0.099 to 0.005	0.077	−0.044	−0.139 to 0.051	0.360
Dyslipidemia	0.017	−0.041 to 0.074	0.568	0.062	−0.046 to 0.170	0.256
Diabetes Mellitus	−0.014	−0.072 to 0.044	0.635	0.004	−0.088 to 0.096	0.931
ARBs	−0.042	−0.088 to 0.003	0.067	−0.112	−0.192 to −0.033	0.006
Statins	−0.018	−0.078 to 0.042	0.549	−0.073	−0.179 to 0.034	0.181
Antiplatelet agents	−0.010	−0.054 to 0.035	0.675	−0.018	−0.099 to 0.063	0.664
Covariates	IAD					
	Total ($n=326$)			Thick group ($n=156$)		
	Estimates of beta coefficient	95% CI	p value	Estimates of beta coefficient	95% CI	p value
Age	0.001	−0.005 to 0.008	0.714	−0.684	−1.467 to 0.099	0.086
Sex (male)	0.080	−0.083 to 0.244	0.334	0.006	−0.005 to 0.017	0.274
Smoking[a]	−0.047	−0.203 to 0.109	0.552	0.156	−0.082 to 0.395	0.198
Dyslipidemia	0.123	−0.047 to 0.294	0.156	0.001	−0.223 to 0.226	0.991
Diabetes Mellitus	0.021	−0.152 to 0.193	0.814	0.188	−0.068 to 0.444	0.148
ARBs	0.009	−0.127 to 0.144	0.898	0.108	−0.111 to 0.326	0.333
Statins	−0.131	−0.309 to 0.048	0.151	−0.010	−0.199 to 0.179	0.916
Antiplatelet agents	0.080	−0.054 to 0.214	0.239	−0.233	−0.485 to 0.019	0.070

[a] Smoking: current smoker + ex-smoker.
Abbreviations: ARBs, angiotensin II receptor blockers; CI, confidence interval; IAD, interadventitial diameter; IMT, intima-media thickness.

IMT and reduction in systolic BP in all subjects ($r=-0.07$, $p=0.278$, $n=271$). Any significant relationship was also not observed between decrease in IAD and reduction in systolic BP in all subjects ($r=0.05$, $p=0.403$, $n=271$).

Combined Action of Cilnidipine with Concomitant Agents in the Change of Max-IMT or IAD

To evaluate the effects of concomitant agents (ARBs, statins, and antiplatelet agents) on the reduction in max-IMT or IAD, multivariate regression analysis was used. After adjustment for age, sex, smoking habit, dyslipidemia, diabetes mellitus, statins, and antiplatelet agents, ARBs was the only independent determinant on the reduction in max-IMT in the thick group but not in all subjects (**Table 3**). After addition of angiotensin-converting enzyme inhibitors to ARBs as covariate, the result of multivariate regression analysis was not different from that of ARBs only on the reduction in max-IMT in the thick group (estimates of beta coefficient −0.106, 95% CI −0.185 to −0.027, $p=0.009$). In the thick group, the decrease in the mean max-IMT was −0.16 mm (95% CI −0.23 to −0.09) in subjects taking ARBs ($n=60$) and −0.05 mm (95% CI −0.09 to −0.01) in subjects not taking ARBs ($n=96$); the difference in the reduction between the two groups was 0.11 mm (95% CI 0.03 to 0.18).

Discussion

We have found that cilnidipine, an L/N-type calcium channel blocker, promoted the regression of carotid IMT in post-stroke hypertensive patients in the thick group during 12 months. In addition, there was a significant reduction in IAD in any post-stroke hypertensive patients taking cilnidipine. Although the relevance between carotid IMT regression and clinical outcomes has not yet been concluded, the accumulation of medical outcomes as to what kind of medical intervention can reduce carotid IMT or IAD is important in carotid arteriosclerosis treatment.

Compensatory enlargement of the artery, which

reflects vascular remodeling, is recognized as an important adaptive process in early atherosclerosis[24]. This positive remodeling is characterized by increases in IMT and IAD[25]. A wider IAD was associated with an increased IMT in the present study. Additionally, the baseline max-IMT, mean-IMT, and IAD were greater in the thick group than in the normal group. In this study, no change in baseline LD was observed with increasing max-IMT. Several studies also reported that the LD remained constant with increasing IMT of the carotid artery[25-28]. Our findings of baseline carotid artery ultrasonographic parameters might reflect that the carotid artery in the thick group was experiencing the positive remodeling characteristic of early atherosclerosis. After 12 months of treatment with cilnidipine, a significant reduction in mean max-IMT was observed in the thick group, whereas no significant change was observed in the normal group, and the difference was significant between the groups. In the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial, the L-type calcium channel blocker, amlodipine, significantly inhibited the progression of common carotid artery atherosclerosis in 825 participants with coronary artery disease[29]. Kaneshiro *et al*. reported that after 12 months of treatment with cilnidipine, the common carotid max-IMT decreased in a small number of hypertensive patients ($n = 50$)[30]. However, to the best of our knowledge, few studies have investigated the effects of calcium channel blockers on the progression of carotid IMT in post-stroke hypertensive patients. No group differences were observed in the change in office systolic BP, even though the thick group experienced a greater reduction in max-IMT. Therefore, the decrease in office systolic BP is not associated with the reduction in max-IMT. The decrease in max-IMT did not accompany changes in LD in the present study. Because a lowered BP leads lower wall tension and apparently increases the IMT in the carotid arteries[31], "a true regression" in vascular mass by antihypertensive agents is defined as a decrease in IMT unrelated to a change in LD in a report from American Society of Echocardiography and Society for Vascular Medicine and Biology[32]. Therefore, we believe that a true regression of early atherosclerosis in the common carotid artery after 12 months of cilnidipine treatment was observed in the thick group.

More recently, some studies showed that the IAD of the common carotid artery was associated with ischemic stroke as well as cardiovascular events. It was shown that the IAD was a stronger predictor of ischemic stroke than carotid IMT from the results of the Multi-Ethnic Study of Atherosclerosis[14]. On the other hand, Eigenbrodt *et al*. reported that the presence of both a large IAD and large a IMT was the strongest predictor of stroke incidence in the general population[33]. In this study, we separately analyzed the effects of cilnidipine on IAD. The significant decreases in mean IAD after 12 months of cilnidipine treatment were shown not only in the thick group but also in all subjects. No linear relationship was observed between a reduction of IAD and a decrease in office systolic BP in all subjects. Only a few studies have investigated the association between medical interventions and carotid IAD[34, 35]. Cooper *et al*. showed that the common carotid IAD as well as IMT decreased with weight loss intervention in severely obese adults[34]. Lloyd *et al*. reported that estrogen replacement therapy decreased common carotid IAD in overweight or obese postmenopausal women[35]. Because there have been few studies evaluating the effects of agents for lifestyle-related diseases on carotid IAD in a high-risk population, further accumulation of evidence for medical intervention is needed to establish the therapeutic position of IAD in carotid atherosclerosis.

ARBs[36-38], statins[39, 40], and antiplatelet agents[41] have been reported to promote the regression or inhibition of progression of the IMT in the common carotid artery, and the effects of these agents have also been reported in the meta-analysis[8, 42-44]. In the present study, these agents were coadministered in approximately one-third to one-half of subjects in the thick group. Therefore, the effects of the concomitant agents (ARBs, statins, and antiplatelet agents) on the regression of the max-IMT were investigated to clarify their combined action with cilnidipine by using multiple linear regression analysis. The association between the coadministration of ARBs and the decrease in the max-IMT remained statistically significant after adjustment for other concomitant agents in the thick group but not in all subjects. It seems that the combination of ARBs and cilnidipine will be essential in the regression of atherosclerosis of the common carotid artery in post-stroke hypertensive patients. Interestingly, there was no association between the coadministration of ARBs and the decrease in IAD in not only all subjects but also the thick group. Moreover, the decrease in IAD was observed in both normal and thick groups, and the decrease in max-IMT was shown only in the thick group. Kawamoto *et al*. reported that common carotid enlargement may reflect the ability of adaptive remodeling to atherosclerosis before plaque formation[45]. Therefore, from our results, the pathophysiology of IAD enlargement and increase of IMT may be different in common carotid arteries of post-stroke hypertensive patients.

A few studies have found that N-type calcium channels are distributed not only in sympathetic nerve ends[46] but also in podocytes[47], adrenal cortex[48], pan-

creatic alpha cells[49], and endothelial cells[50]. In aortic endothelial cell lines, cilnidipine suppressed the production of AII-induced reactive oxygen species through blocking N-type calcium channels[50]. However, the pathophysiological roles of N-type calcium channels, which can be inhibited by cilnidipine, have not been elucidated in carotid artery plaque or adventitia. Further studies are needed to clarify the pharmacological actions of triple-blocking AII receptors, and N-type and L-type calcium channels in the atherosclerotic carotid artery. In the future, larger-scale and longer-term randomized, controlled trials are needed to establish the clinical usefulness of cilnidipine for reversing the progression of carotid atherosclerosis in hypertensive patients with stroke.

This study had certain limitations. At first, the PMS study had no control group. Therefore, a relative evaluation of the efficacy of cilnidipine was not possible. Second, the large proportion of subjects did not have a carotid ultrasonography at 12 months of follow-up. Additionally, there were several factors that were different between the subjects with follow-up and the subjects without follow-up. These factors may cause a considerable selection bias. Third, we could not analyze the effects of antidiabetic agents on max-IMT or IAD. Since many kinds of antidiabetic agents were used in this study, the number of patients for each agent and its combination was small, which was inconvenient for analysis. Finally, we could not evaluate the BP change in all subjects with follow-up carotid ultrasonography. Therefore, the associations between decrease in max-IMT or IAD and reduction of systolic BP might be affected by selection bias.

Conclusion

In conclusion, as a result of the ultrasonographic investigation of the common carotid artery of 326 post-stroke hypertensive subjects undergoing cilnidipine treatment, the reduction in the max-IMT at 12 months was observed only in the thick group (max-IMT $\geq$ 1.1 mm) but not the normal group (max-IMT $<$ 1.1 mm). The reduction in IAD was observed in both groups. The treatment with cilnidipine, an L/N-type calcium channel blocker, promoted the regression of carotid atherosclerosis in post-stroke hypertensive patients.

Conflicts of Interest

Naohisa Hosomi reports an honorarium from Mochida Pharmaceutical Co., Ltd. Hirofumi Maruyama reports grants from Daiichi Sankyo Co., Ltd. Masayasu Matsumoto reports grants from Takeda Pharmaceutical Co., Ltd., Sanofi K.K., Mochida Pharmaceutical Co., Ltd., Otsuka Pharmaceutical, and Daiichi Sankyo Co., Ltd. and honoraria from Sanofi K.K., Bayer Health Care, and Daiichi Sankyo Co., Ltd. The other authors declare no conflicts of interest. Tsukasa Teshima, Hitoshi Sugii, and Noriyuki Suzuki are employees of Mochida Pharmaceutical Co., Ltd. Shinobu Nagahama and Yoshiki Kurose are employees of EA Pharma Co., Ltd.

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Author Contributions

T.N. and N.H. wrote the introduction, methods, results, and discussion.

S.A., N.S., and S.N. contributed to the discussion.

T.T and H.S. collected the data.

Y.K. analyzed the results under the guidance of medical professionals, M.M. and N.H.

N.H., H.M., and M.M. reviewed/edited the manuscript and contributed to the discussion.

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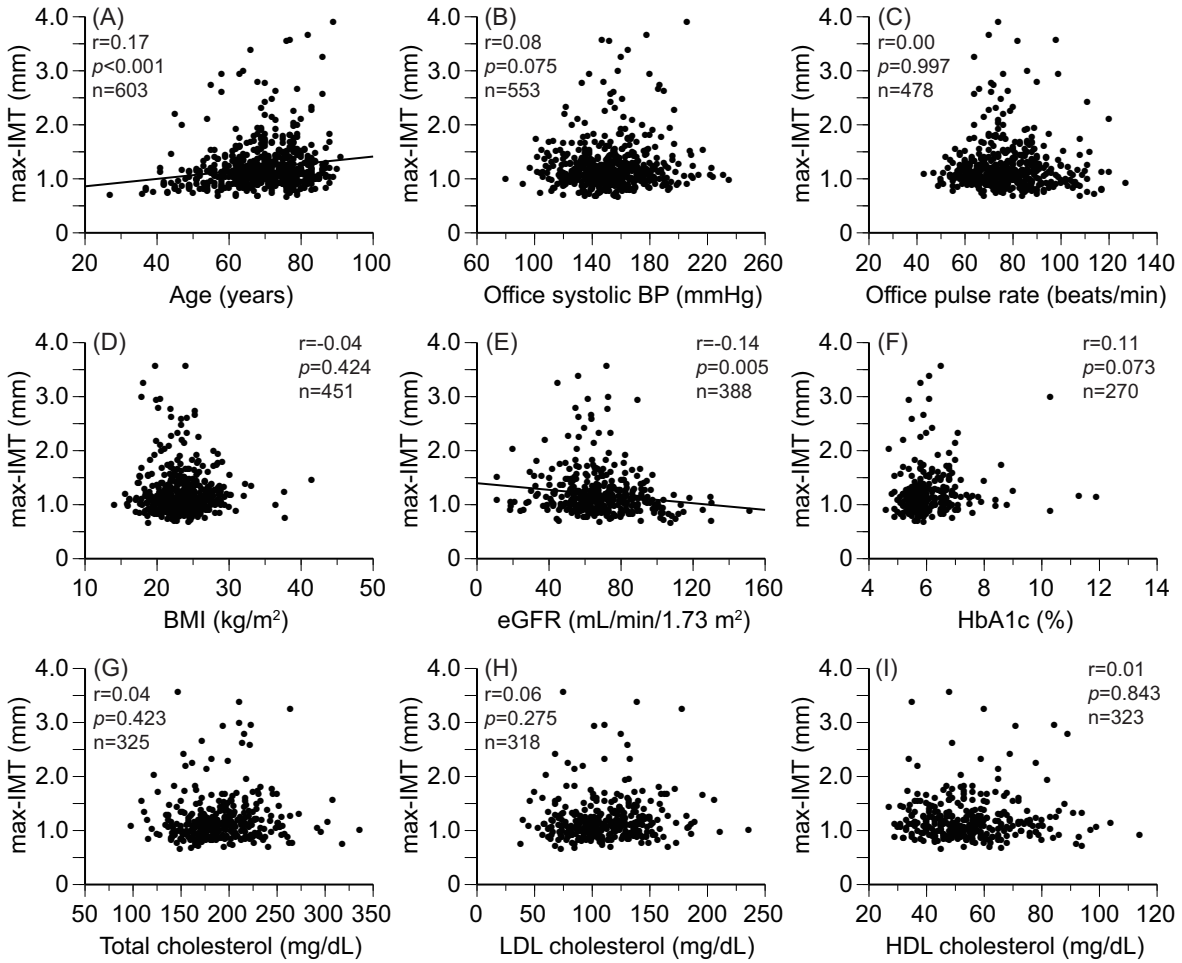
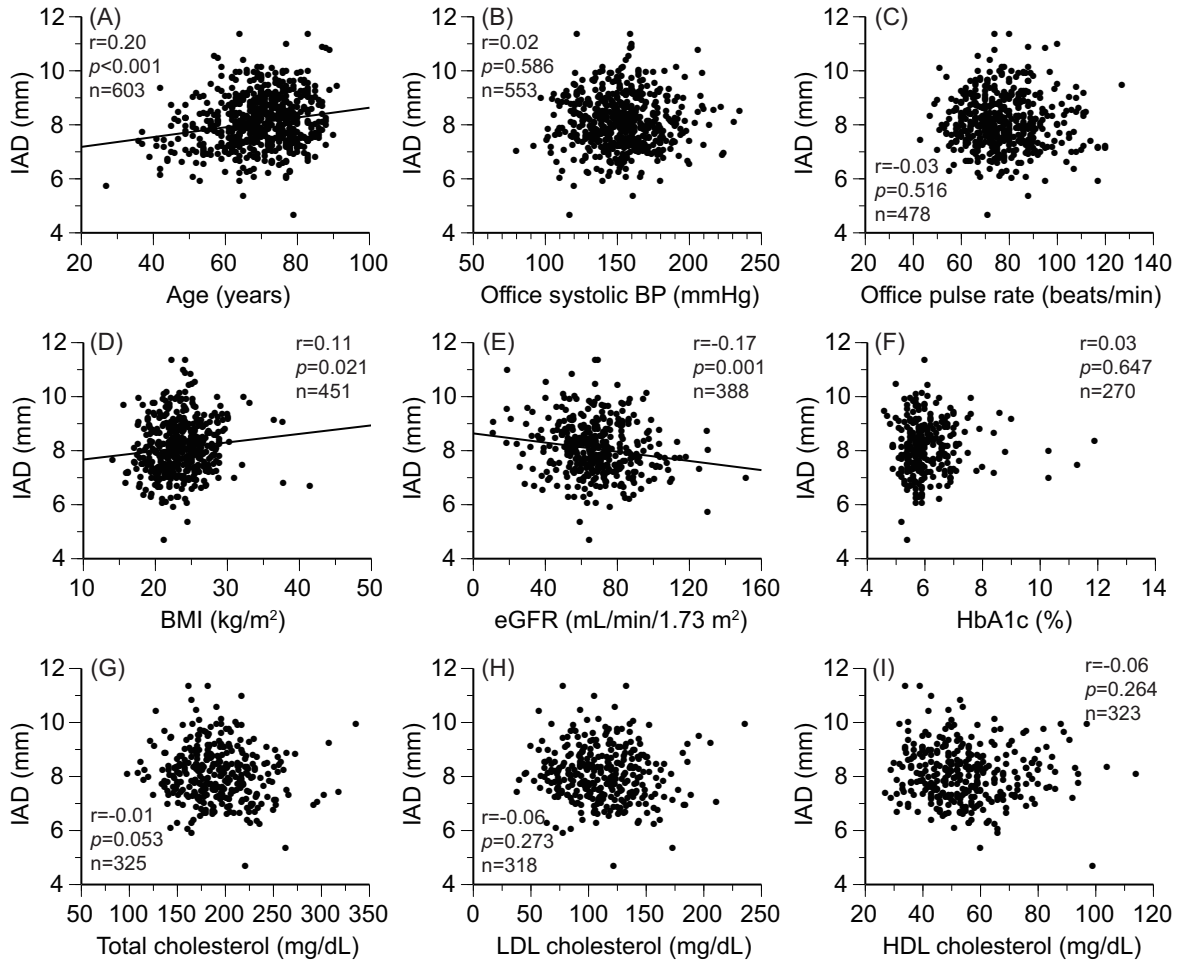


Supplementary Fig. 1. The associations between baseline max-IMT and patient characteristics.

A. The association between max-IMT and age.
B. The association between max-IMT and office systolic blood pressure (BP).
C. The association between max-IMT and office pulse rate.
D. The association between max-IMT and body mass index (BMI).
E. The association between max-IMT and estimated glomerular filtration rate (eGFR).
F. The association between max-IMT and glycated hemoglobin (HbA1c).
G. The association between max-IMT and total cholesterol.
H. The association between max-IMT and low-density lipoprotein (LDL) cholesterol.
I. The association between max-IMT and high-density lipoprotein (HDL) cholesterol.
Pearson's correlation coefficients (r) and the associated *p* values are shown.
Abbreviation: IMT, intima-media thickness.



Supplementary Fig. 2. The associations between baseline IAD and patient characteristics.

A. The association between IAD and age.
B. The association between IAD and office systolic blood pressure (BP).
C. The association between IAD and office pulse rate.
D. The association between IAD and body mass index (BMI).
E. The association between IAD and estimated glomerular filtration rate (eGFR).
F. The association between IAD and glycated hemoglobin (HbA1c).
G. The association between IAD and total cholesterol.
H. The association between IAD and low-density lipoprotein (LDL) cholesterol.
I. The association between IAD and high-density lipoprotein (HDL) cholesterol.
Pearson's correlation coefficients (r) and the associated *p* values are shown.
Abbreviation: IAD, interadventitial diameter.

Supplementary Table 1. Baseline characteristics of subjects with and without follow-up

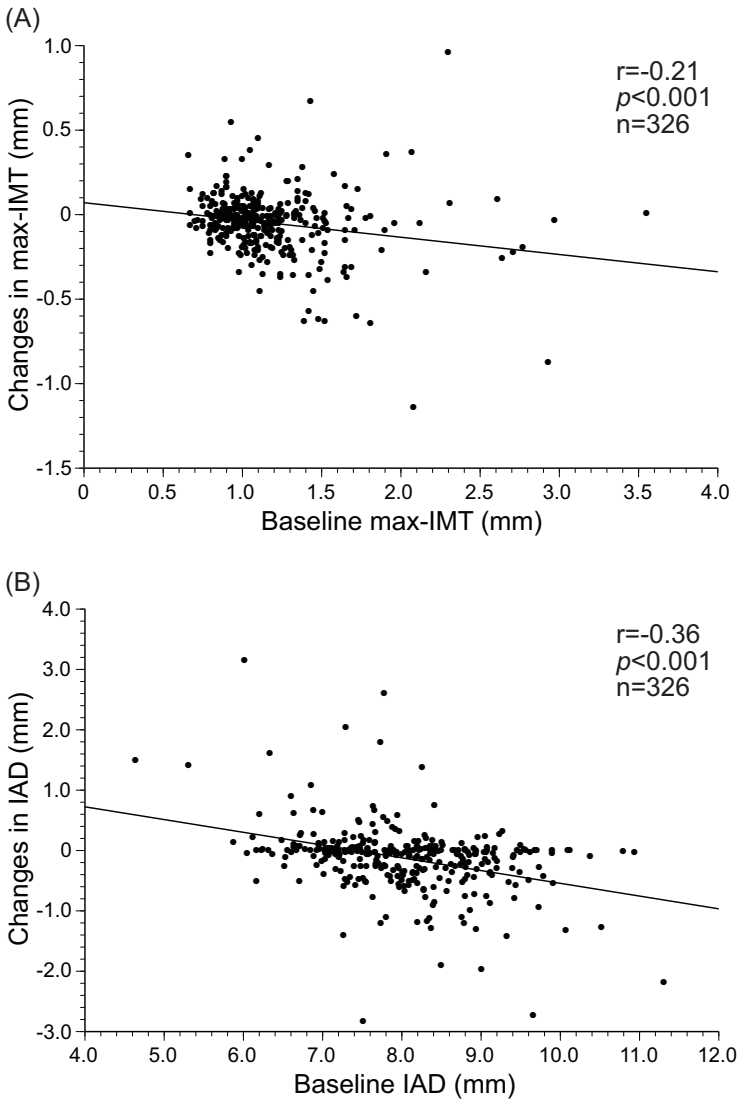
Factors	Subjects with follow-up ($n=326$)	Subjects without follow-up ($n=277$)	p value
Age, years	69.1 ± 9.6	69.6 ± 11.4	0.527
Male, n (%)	209 (64.1)	169 (61.0)	0.448
BMI, kg/m^2	23.5 ± 3.2 ($n=261$)	23.5 ± 3.7 ($n=190$)	0.927
mRS score	1 (0 to 1.25)	1 (0 to 2)	0.011
Concomitant disease			
Dyslipidemia, n (%)	171 (52.5)	124 (44.8)	0.061
Diabetes mellitus, n (%)	57 (17.5)	63 (22.7)	0.125
Coronary artery disease, n (%)	20 (6.1)	18 (6.5)	0.868
Stroke history[a]			
Cerebral infarction, n (%)	257 (78.8)	218 (78.7)	1.000
Small vessel occlusion, n (%)	129 (39.6)	101 (36.5)	0.450
Large artery atherosclerosis, n (%)	97 (29.8)	73 (26.4)	0.365
Cardioembolism, n (%)	8 (2.5)	18 (6.5)	0.016
Others, n (%)	25 (7.7)	27 (9.7)	0.385
Cerebral hemorrhage, n (%)	46 (14.1)	48 (17.3)	0.311
SAH, n (%)	30 (9.2)	16 (5.8)	0.125
Smoking habit[b]	155 (47.5)	124 (44.8)	0.513
Drinking habit	112 (34.4)	108 (39.0)	0.270
Daily dose of cilnidipine, mg/day	10.3 ± 3.0	10.2 ± 3.2	0.622
Anti-hypertensives			
ARBs, n (%)	117 (35.9)	109 (39.4)	0.399
CCBs, n (%)	28 (8.6)	21 (7.6)	0.765
ACE inhibitors, n (%)	11 (3.4)	9 (3.2)	1.000
Diuretics, n (%)	20 (6.1)	28 (10.1)	0.096
Statins, n (%)	113 (34.7)	82 (29.6)	0.191
Antiplatelet agents, n (%)	190 (58.3)	134 (48.4)	0.017
Warfarin, n (%)	8 (2.5)	17 (6.1)	0.038
Office systolic BP, mmHg	150.6 ± 21.6 ($n=299$)	155.1 ± 24.9 ($n=254$)	0.025
Office diastolic BP, mmHg	83.0 ± 13.9 ($n=298$)	85.8 ± 15.3 ($n=252$)	0.027
Office pulse rate, beats/min	77.2 ± 13.6 ($n=263$)	77.8 ± 14.1 ($n=215$)	0.614
eGFR, mL/min/1.73 m^2	66.9 ± 17.7 ($n=223$)	70.0 ± 21.6 ($n=165$)	0.117
HbA1c, %	6.0 ± 0.7 ($n=173$)	6.4 ± 1.2 ($n=97$)	< 0.001
Total cholesterol, mg/dL	194.6 ± 38.2 ($n=200$)	187.5 ± 33.3 ($n=125$)	0.087
HDL cholesterol, mg/dL	55.3 ± 14.5 ($n=194$)	54.4 ± 15.4 ($n=129$)	0.563
LDL cholesterol, mg/dL	113.2 ± 33.5 ($n=187$)	111.3 ± 29.3 ($n=131$)	0.604

Data are shown as the number of subjects (%), the mean ± SD, or median (25th to 75th percentiles).
[a]The clinical subtype of stroke included cases in which more than one subtype of stroke was recorded in the same subject.
[b]Smoking habit, current smoker, and ex-smoker.
Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; CCBs, calcium channel blockers; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; mRS, modified Rankin scale; SAH, subarachnoid hemorrhage.

Supplementary Table 2. Baseline characteristics of subjects in the normal and thick groups

Factors	Total (n=326)	Normal group (max-IMT <1.1 mm) (n=170)	Thick group (max-IMT ≥1.1 mm) (n=156)	p value
Age, years	69.1±9.6	68.1±10.3	70.2±8.6	0.052
Male, n (%)	209 (64.1)	106 (62.4)	103 (66.0)	0.563
BMI, kg/m^2	23.5±3.2 (n=261)	23.4±3.0 (n=133)	23.6±3.4 (n=128)	0.495
mRS score	1 (0 to 1.25)	1 (0 to 1)	1 (0 to 2)	0.451
Concomitant disease				
Dyslipidemia, n (%)	171 (52.5)	81 (47.6)	90 (57.7)	0.076
Diabetes mellitus, n (%)	57 (17.5)	20 (11.8)	37 (23.7)	0.005
Coronary artery disease, n (%)	20 (6.1)	5 (2.9)	15 (9.6)	0.019
Stroke history[a]				
Cerebral infarction, n (%)	257 (78.8)	125 (73.5)	132 (84.6)	0.015
Small vessel occlusion, n (%)	129 (39.6)	62 (36.5)	67 (42.9)	0.258
Large artery atherosclerosis, n (%)	97 (29.8)	43 (25.3)	54 (34.6)	0.070
Cardioembolism, n (%)	8 (2.5)	5 (2.9)	3 (1.9)	0.725
Others, n (%)	25 (7.7)	16 (9.4)	9 (5.8)	0.298
Cerebral hemorrhage, n (%)	46 (14.1)	23 (13.5)	23 (14.7)	0.753
SAH, n (%)	30 (9.2)	24 (14.1)	6 (3.8)	0.002
Smoking habit[b]	155 (47.5)	75 (44.1)	80 (51.3)	0.222
Drinking habit	112 (34.4)	58 (34.1)	54 (34.6)	1.000
Daily dose of cilnidipine, mg/day	10.3±3.0	10.0±2.8	10.6±3.2	0.080
Anti-hypertensives				
ARBs, n (%)	117 (35.9)	57 (33.5)	60 (38.5)	0.358
CCBs, n (%)	28 (8.6)	12 (7.1)	16 (10.3)	0.328
ACE inhibitors, n (%)	11 (3.4)	5 (2.9)	6 (3.8)	0.763
Diuretics, n (%)	20 (6.1)	12 (7.1)	8 (5.1)	0.498
Statins, n (%)	113 (34.7)	47 (27.6)	66 (42.3)	0.007
Antiplatelet agents, n (%)	190 (58.3)	87 (51.2)	103 (66.0)	0.007
Warfarin, n (%)	8 (2.5)	5 (2.9)	3 (1.9)	0.725
Office systolic BP, mmHg	150.6±21.6 (n=299)	151.2±21.5 (n=155)	150.0±21.9 (n=144)	0.627
Office diastolic BP, mmHg	83.0±13.9 (n=298)	85.0±14.7 (n=155)	80.9±12.7 (n=143)	0.009
Office pulse rate, beats/min	77.2±13.6 (n=263)	76.5±13.8 (n=135)	77.9±13.4 (n=128)	0.401
eGFR, mL/min/1.73 m^2	66.9±17.7 (n=223)	67.7±19.4 (n=119)	66.0±15.5 (n=104)	0.481
HbA1c, %	6.0±0.7 (n=173)	5.8±0.5 (n=91)	6.1±0.8 (n=82)	0.010
Total cholesterol, mg/dL	194.6±38.2 (n=200)	192.6±40.8 (n=108)	196.8±35.1 (n=92)	0.440
HDL cholesterol, mg/dL	55.3±14.5 (n=194)	56.0±14.2 (n=101)	54.6±14.9 (n=93)	0.501
LDL cholesterol, mg/dL	113.2±33.5 (n=187)	109.8±33.8 (n=101)	117.2±32.9 (n=86)	0.134

Data are shown as the number of subjects (%), the mean±SD or median (25th to 75th percentiles).
[a]The clinical subtype of stroke included cases in which more than one subtype of stroke was recorded in the same subject.
[b]Smoking habit, current smoker, and ex-smoker.
Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; CCBs, calcium channel blockers; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; mRS, modified Rankin scale; SAH, subarachnoid hemorrhage.



Supplementary Fig. 3A. The association between the changes in max-IMT and baseline max-IMT.

Pearson's correlation coefficient (r) and the associated *p* value are shown for all subjects (*n* = 326).
Abbreviation: IMT, intima-media thickness.

Supplementary Fig. 3B. The association between the changes in IAD and baseline IAD.

Pearson's correlation coefficient (r) and the associated *p* value are shown for all subjects (*n* = 326).
Abbreviation: IAD, interadventitial diameter.