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Coronary Artery Disease and Carotid Artery Disease Progress Despite Normal Lipid Levels by Standard Statin Therapy in Asymptomatic Patients without Known Coronary Artery Disease: Implications for Statin Therapy

Kohichiro Iwasaki, MD1* and Takeshi Matsumoto, RT1

[1]Department of Cardiology, Okayama Kyokuto Hospital

Abstract

Many mega-trials of statin therapy demonstrate that a 28% drop in LDL-cholesterol (LDL-C) in 5-year statin trial is associated with a 25% to 35% drop in CAD risk, leaving a substantial residual risk. We studied whether standard statin therapy would prevent progression of coronary artery disease (CAD) and carotid artery disease in asymptomatic patients without known CAD. We retrospectively selected 45 patients who continued statin therapy for one year and underwent multidetector computed tomography and carotid ultrasound measurement one year apart. Follow-up period was 1.37±0.49 (1.0 to 2.5) years. Total cholesterol changed from 213.2±46.2mg/dl to 196.0±34.3mg/dl (p=0.045). Triglyceride changed from 125.5±72.3mg/dl to 107.1±58.2mg/dl (p=0.184). HDL-cholesterol changed from 60.8±15.8mg/dl to 60.0±12.3mg/dl (p=0.789). LDL-cholesterol changed from 101.7±25.2mg/dl to 102.7±23.0mg/dl (p=0.844). However coronary calcium score significantly increased (230.1±414.5 to 298.3±479.2, p=0.009) and the number of coronary plaques significantly increased (2.5±1.7 to 3.0±1.7, p=0.001). Also carotid IMT significantly increased (1.42±0.81 to 1.78±0.92, p=0.049) and the number of carotid plaques significantly increased (0.5±1.1 to 1.1±1.5, p=0.001). In conclusion, our results showed that CAD and carotid artery disease progressed significantly despite normal lipid values using standard statin therapy in asymptomatic patients without known CAD. This suggests that more intense lipid lowering will be needed to prevent progression of CAD and carotid artery disease.

Keywords

Carotid intima-media thickness; Coronary artery calcium; Coronary artery disease; Multidetector computed tomography; Statin

*Corresponding author: Kohichiro Iwasaki, MD, Department of Cardiology, Okayama Kyokuto Hospital, 567-1, Kurata, Naka-ku, Okayama, Japan, Tel:+81-86-276-3231; FAX:+81-86-274-1028; E-mail: kiwasaki@kyokuto.or.jp

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Abbreviations

ACE-I: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; CACS: Coronary Artery Calcium Score; CCB: Calcium Channel Blocker; CKD: Chronic Kidney Disease; IMT: Mean Intima Media Thickness; LDL-C: Low-Density Lipoprotein Cholesterol; Ca: Calcified; CACS: Coronary Artery Calcium Score; BS: Blood Sugar; HbA1c: Hemoglobin, A1c; HDL-C: High-Density Lipoprotein Cholesterol; IMT: Intima Media Thickness; LDL-C: Low-Density Lipoprotein Cholesterol; MDCT: Multidetector Computed Tomography; nCa: non-Calcified; TC: Total Cholesterol; TG: Triglyceride; TC: Total Cholesterol

Statin is a mainstay in the treatment of patients with coronary artery disease (CAD). Many mega-trials of statin therapy demonstrate that a 28% drop in LDL-cholesterol (LDL-C) in 5-year statin trial is associated with a 25% to 35% drop in CAD risk, leaving a substantial residual risk [1]. Statins are particularly suited for primary prevention in high risk patients with subclinical atherosclerosis because they not only dramatically decrease LDL-C but also exert pleiotropic effect on plaque stabilization and atherosclerotic regression [2-4]. Recent studies suggest that an early and long-term reduction in LDL-C lead to a substantial reduction in coronary events, namely the efficacy of a lifetime lowering of LDL-C level [5]. If therapeutic lowering of LDL-C had a similar long-term impact in higher risk asymptomatic individuals, this could result in a major reduction in cardiac events.

Coronary artery calcification (CAC) and carotid intima-media thickness (IMT) are two surrogate markers of cardiovascular events [6,7]. Thus we studied whether standard statin therapy would prevent progression of coronary artery disease and carotid artery disease in asymptomatic patients without known CAD by measuring not only CAC and IMT but also the number of coronary and carotid plaques.

Methods

Patients

From April 2011 through August 2013, 721 patients underwent 64-multidetector computed tomography (MDCT) in our hospital. We retrospectively selected the following patients. 1) asymptomatic patients without known CAD, 2) patients who underwent MDCT and carotid IMT measurement twice one year apart, 3) patients whose laboratory data was complete, 4) patients who continued standard statin therapy during the study period, 5) patients whose LDL-C was less than 130mg/dl during the study period. Thus we selected 45 patients.

64-Multidetector Computed Tomography (MDCT)

All patients were scanned with a 64-MDCT scanner (SOMATOM Sensation 64 Cardiac, Siemens Medical Solutions, Erlangen, Germany). Patients with a heart rate >70beats/min received oral metoprolol 20mg before the 64-MDCT scan. To achieve coronary vasodilation we administered sublingual nitroglycerin 0.8mg before the scan. A native scan without contrast dye was performed to determine the total calcium burden of the coronary tree (sequential scan with 32×0.6-mm collimation, tube current 60 mAs at 120 kV). Contrast-enhanced CT angiography data were acquired with the use of a spiral scan with 32×0.6-mm collimation, 330-ms gantry rotation, pitch of 0.2, and tube voltage at 120 kV. A total of 64 overlapping 0.6-mm slices per rotation were acquired with the use of a focal spot periodically moving in the longitudinal direction (z-flying focal spot). Tube current was modulated according to the ECG, with a maximum current of 850 to 950 mAs during a time period of approximately 330 ms centered at 375 ms before the next R-wave and reduction by 80% during the remaining cardiac cycle. Contrast agent (60 to 70ml; 370mg iodine /ml) was injected intravenously (4.0 ml/s) followed by a 30-ml saline chaser. Transaxial images were reconstructed using an ECG-gated half-scan reconstruction algorithm (temporal resolution 164 ms) and kernel B30f.

64-MDCT Image Interpretation

CT data sets were transferred to an offline workstation (Aquarius NetStation, Terarecon In, San Meteo, CA, USA) for image analysis. Total calcium score of all patients were calculated with dedicated software and expressed as coronary calcium score (CCS). The CCS is a commonly used scoring method that calculates the total amount of calcium on the basis of the number, areas, and peak Hounsfield units of the detected calcified lesions [8]. Two reviewers independently evaluated the contrast-enhanced 64-MDCT scans with maximum intensity and curved multiplanar reconstruction techniques along multiple longitudinal axes and transversely. Calcified atherosclerotic plaque was defined as any structure with a density of 130 HU or more that could be visualized separately from the contrast-enhanced coronary lumen, that could be assigned to the coronary artery wall, and that could be identified in at least two independent planes. Noncalcified atherosclerotic plaque was defined as any discernible structure that could be clearly assignable to the vessel wall, that had a CT density less than the contrast-enhanced coronary lumen but greater than the surrounding connective tissue, and that could be identified in at least two independent planes [9]. Standard display settings were used for the evaluation of the contrast-enhanced 64-MDCT scans (window width 800 Hounsfield units; window center 250 HU).

Carotid Ultrasound Examinations

Ultrasound scans were obtained with a Prosound α 10 ultrasound system (ALOKA, Tokyo, Japan). All examinations were carried out by the same operator. B-mode ultrasonography of the left and right common carotid arteries was performed. The image was focused on the far wall of the common carotid arteries. A magnified image was recorded from the angle showing the greatest distance between the lumen-intima interface and the media-adventitia interface. At least four measurements of the common carotid far wall were taken 10mm proximal to the bifurcation to derive mean carotid IMT [10]. Maximum IMT was defined as maximum IMT of the two carotid arteries. Mean IMT was calculated as an average of these measurements. Plaque was defined as a distinct area of the vessel wall protruding into the lumen >50% of the adjacent intima-media layer. We studied the changes of laboratory data, MDCT data (CCS and number of coronary plaques), and carotid IMT data (IMT and number of carotid plaques).

Statistical Analysis

Data are Expressed as Mean±SD

Continuous variables in the laboratory data were compared by two group t-test. Because the data for coronary calcium score, number of coronary plaques, carotid IMT, and the number of carotid plaques did not show a normal distribution, the Wilcoxon signed-ranks test was used to determine the differences between the two groups. Discrete variables were expressed as counts or percentage and compared with chi-square or the Fisher's exact test. A p value <0.05 was considered to be statistically significant.

Results

Clinical characteristics of studied patients are shown in Table 1. Follow-up period was 1.37±0.49 (1.0 to 2.5) years. As for compliance, these patients received statin therapy at least 90% of the study period. Thirty-five patients (77.8%) received statin treatment at least one year before the study period. Table 2 shows the changes of laboratory data, MDCT data, and carotid IMT data. There was a significant decrease of total cholesterol levels during the study period. There were no significant changes in blood levels of triglyceride, HDL-cholesterol, LDL-cholesterol, blood sugar, and HbA1c. However, the CCS and carotid IMT increased significantly between the two periods. Also the number of coronary plaques and carotid plaques increased significantly.

n (%)	
age (y.o.)	67.9±8.9
male	25 (55.6%)
hypertension	24 (53.3%)
hyperlipidemia	24 (53.3%)
diabetes	11 (24.4%)
smoking	7 (15.6%)
obesity	12 (26.7%)
CKD	8 (17.8%)
CACS=0	3 (6.7%)
IMT<1.0mm	11 (24.4%)
LDL-C<100mg/dl	21 (46.7%)
medication	
aspirin	37 (82.2%)
statin	45 (100%)
CCB	17 (37.8%)
ACE-I/ARB	25 (55.6%)
β-blocker	4 (8.9%)
oral diabetes agent	11 (24.4%)

Table 1. Patient characteristics (n=45)

Discussion

Our results showed that CAD and carotid artery disease progressed significantly despite normal lipid values using standard statin therapy in asymptomatic patients without known CAD. This suggests that residual risk of statin therapy may be associated with CAD progression despite normal lipid levels.

Coronary artery calcification (CAC) and carotid intima-media thickness (IMT) are two surrogate markers of cardiovascular events. Coronary artery calcification signifies the presence of coronary atherosclerosis and a strong linear correlation exists between total coronary artery atherosclerotic plaque burden and the extent of coronary artery calcification [11,12]. Coronary artery calcification has been found to be the most powerful predictor of cardiac events, providing independent and incremental information over risk factor-based assessment of the asymptomatic patients [6,13]. Carotid IMT correlates with the degree of carotid atherosclerosis measured at autopsy and has been found to correlate with atherosclerotic vascular disease in other arterial beds [14,15]. Thus, ultrasound-derived carotid IMT is considered a surrogate for systemic atherosclerotic disease burden [16]. IMT findings have been demonstrated to correlate with cardiac and cerebrovascular outcomes [7]. Recent studies found that coronary calcification had significant correlations with carotid IMT [17,18]. In a substudy of Cardiovascular Health Study, Newman et al. [18] found that internal carotid IMT was most closely related to coronary artery calcium. CAC progression rate in our patients was 20.6% during follow-up period of 1.37±0.49 years, which means annual CAC progression rate of 15.0%. Previous studies showed that annual CAC progression rate was 20 to 30% in patients at average Framingham risk without statin therapy [19-21].

Laboratory data	Baseline	Follow-up	P
TC (mg/dl)	213.2±46.2	196.0±34.3	0.045
TG (mg/dl)	125.5±72.3	107.1±58.2	0.184
HDL-C (mg/dl)	60.8±15.8	60.0±12.3	0.789
LDL-C (mg/dl)	101.7±25.2	102.7±23.0	0.844
BS (mg/dl)	113.2±36.4	110.9±30.4	0.745
HbA1c (%)	6.01±1.80	5.98±1.07	0.923
MDCT findings			
CACS	230.1±414.5	298.3±479.2	0.009
coronary plaques (n)	2.5±1.7	3.0±1.7	0.001
Ca plaques (n)	2.2±1.7	2.6±1.6	0.005
nCa plaques (n)	0.3±0.5	0.4±0.7	0.206
carotid ultrasound findings			
carotid IMT (mm)	1.42±0.81	1.78±0.92	0.049
carotid plaques (n)	0.5±1.1	1.1±1.5	0.001

Table 2. Changes of laboratory data, MDCT findings, and carotid IMT findings

There are several therapeutic studies demonstrating the effects of statin therapy on CAC in patients [22-28]. In these studies, achieved LDL-C level was 65 to 129mg/dl in statin group and 122 to 147mg/dl in placebo group. Most studies showed that statins reduced progression rate of CAC compared with placebo. However most studies were observational and were non-randomized prospective studies. Also studies which compared intensive statin therapy with standard statin therapy showed no significant change in progression rate of CAC and no correlation of CAC with changes in LDL-C levels. Thus statins have been unsuccessful in reducing CAC progression. McEvory et al. [29] suggest that pathologically statins have been shown to promote microcalcification, which might lead to CAC increase even when total atherosclerosis is reduced on statin therapy. It is possible that statin therapy acts more quickly to slow progression of non-calcified plaques. Actually our results showed that the number of calcified plaques significantly increased but that of non-calcified plaques did not increase. Nissen et al suggested that studies investigating coronary plaque volume using intravascular ultrasound showed that plaque regression occurred below the LDL-C level of 80mg/dl [30]. Thus intensive lowering of LDL-C below 80mg/dl may prevent the progression of CAC.

Our results also showed that carotid IMT increased and number of carotid plaque increased in spite of normal lipid values by statin therapy. There are many trials demonstrating effects of statin therapy on carotid IMT in patients with known CAD [31-35]. Achieved LDL-C level was 76 to 120mg/dl in statin group and 110 to 167mg/dl in placebo group in these studies. Most studies showed regression of carotid IMT in statin group and progression in placebo group. In our patients LDL-C level was 65 to 128mg/dl in the second period, which is similar to the previous statin groups.

There are several limitations in our study. First, this is a retrospective therapy and the number of patients is small. Second, study period is brief. Long-term follow up to five or more years may be needed to assess properly the impact of statin on the long-term progression of coronary artery disease and carotid artery disease. Third, we do not investigate cardiovascular event because of small number of patients. Fourth, we selected asymptomatic stable patients without known CAD, who had moderate CAD. Perhaps patients with acute coronary syndromes would have shown a different result.

In conclusion, our results showed that CAD and carotid artery disease progressed significantly despite normal lipid values using standard statin therapy in asymptomatic patients without known CAD. This suggests that more intense lipid lowering will be needed to prevent progression of CAD and carotid artery disease.

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