Relation of Carotid Artery Wall Thickness to Diabetes Mellitus, Fasting Glucose and Insulin, Body Size, and Physical Activity

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**Background and Purpose** We tested the hypothesis that body mass, waist-to-hip circumference ratio, physical inactivity, diabetes, hyperglycemia, and fasting insulin are each positively associated with asymptomatic carotid artery wall thickness.

**Methods** Average intimal-medial carotid wall thickness (an indicator of atherosclerosis) was measured noninvasively by B-mode ultrasonography in cross-sectional samples of 45- to 64-year-old adults, both blacks and whites, free of symptomatic cardiovascular disease, in four US communities.

**Results** Sample mean carotid wall thickness was approximately 0.7 mm in women (n=7956) and 0.8 mm in men (n=6474). Body mass, waist-to-hip ratio, work physical activity, diabetes, and fasting insulin were associated (P<.05) with carotid wall thickness in the hypothesized direction. Adjusted for age, race, smoking, body mass index, artery depth, and body mass, waist-to-hip circumference ratio, physical inactivity and increased body size are important contributors to insulin resistance and impaired glucose tolerance. Physical inactivity confers almost a two-fold increase in CVD incidence. Body mass has been associated positively with CVD in many studies, although other studies reported a U-shaped or no association. More recently, studies of fat distribution have shown that abdominal adiposity is an important determinant of CVD risk.

**Conclusions** Abdominal adiposity, physical inactivity, and abnormal glucose metabolism are associated positively with carotid intimal-medial wall thickness, suggesting these factors contribute to atherogenesis. (Stroke. 1994;25:66-73.)

**Key Words** • atherosclerosis • insulin • carotid arteries • diabetes mellitus • obesity

Epidemiologic studies have consistently demonstrated a positive association between diabetes mellitus and atherosclerotic cardiovascular disease (CVD). The association seems to be stronger in women than men. Impaired glucose tolerance short of diabetes, on the other hand, is not a firmly established risk factor; there may be a nonlinear or threshold relation between fasting or postload hyperglycemia and CVD incidence. Insulin resistance is another possible CVD risk factor.

Physical inactivity and increased body size are important contributors to insulin resistance and impaired glucose tolerance. Physical inactivity confers almost a two-fold increase in CVD incidence. Body mass has been associated positively with CVD in many studies, although other studies reported a U-shaped or no association. More recently, studies of fat distribution have shown that abdominal adiposity is an important determinant of CVD risk.

A shortcoming of epidemiologic studies employing clinical CVD end points is an inability to disentangle the two processes related to most atherosclerotic events, namely atherosclerosis and thrombosis. Noninvasive techniques such as B-mode ultrasound can more directly assess atherosclerosis. We report here the relation of carotid artery wall thickness to diabetes, fasting hyperglycemia, fasting insulin, body shape and size, and physical activity in a large sample of middle-aged adults.
Measurements

After informed consent, a home interview and clinic examination were conducted. The home interview included assessment of socioeconomic factors, education level, smoking status, medication use, and history of cardiovascular disease and diabetes mellitus. The clinic examination included measurements of cardiovascular risk factors and a B-mode ultrasound examination of selected arterial sites.

Subjects were asked to fast for 12 hours before the clinic examination. Blood specimens were collected into vacuum tubes containing serum separator gel (insulin and glucose) and EDTA (lipids). The tubes were centrifuged at 3000g for 10 minutes at 4°C. After separation, aliquots were quickly frozen at -70°C until analysis within a few weeks. Serum glucose was assessed by the hexokinase method. Serum insulin was assessed using a radioimmunoassay (15 Insulin Kit; Cambridge Medical Diagnostics, Inc, Billerica, Mass). Total cholesterol and triglycerides were measured by enzymatic methods, and low-density lipoprotein (LDL) cholesterol was calculated.10 High-density lipoprotein (HDL) cholesterol was measured after dextran-magnesium precipitation.11 The lipid laboratory participated in the Centers for Disease Control Standardization Program throughout the study.

Body mass index (kg/m²) was computed from height and weight. Circumferences of the waist (umbilical level) and hip (maximum buttocks) were measured to the centimeter. The ratio of waist-to-hip circumferences was calculated as a measure of fat distribution.

Physical activity was assessed by interview using a questionnaire developed by Baecke.15 The questionnaire included 16 items about usual exertion, and three indexes ranging from 1 (low) to 5 (high) were derived for physical activity at work, during leisure time, and in sports. Leisure time physical activity showed no relation with carotid atherosclerosis, so associations are shown for the work and sport indexes only. Systolic and diastolic fifth phase blood pressures were measured three times in the right arm of seated participants. The mean of the last two measurements was used in analysis.

Prevalent hypertension was defined as systolic pressure ≥ 140 mm Hg or diastolic pressure ≥ 90 mm Hg or use of antihypertensives. Because an oral glucose tolerance test was not performed, glycerinemia status was defined by fasting values and self-reported medical history. Prevalent diabetes mellitus was defined as a fasting glucose ≥ 7.8 mmol/L (≥ 140 mg/dL), a nonfasting glucose ≥ 11.1 mmol/L (≥ 200 mg/dL), and/or a history of or treatment for diabetes. Hyperglycemia was defined as a fasting glucose of 6.4 to 7.7 mmol/L (115 to 139 mg/dL) and no history of or treatment for diabetes. Prevalent CVD was defined as a positive history of angina or intermittent claudication by the Rose questionnaire;16 a self-reported physician-diagnosed history of a heart attack or stroke; evidence of old myocardial infarction by electrocardiogram; or a self-reported history of cardiovascular surgery or angioplasty.

Carotid artery atherosclerosis was determined by high resolution B-mode ultrasound.17 Trained technicians in each field center scanned the extracranial carotid arteries bilaterally (and one popliteal artery, not reported here). The carotid arteries were divided into three segments: the distal 1.0-cm straight portion of the common carotid artery, the carotid bifurcation, and the proximal 1.0 cm of the internal carotid artery. Thus, including both sides, six artery segments were scanned. B-mode ultrasound data were recorded onto high-resolution 3/4-in. cassettes and interpreted by trained readers according to a standardized protocol.18 Using magnified images, readers recorded for each segment up to 11 coordinate points from each echogenic interface that identified an arterial boundary. Between-reader and within-reader coefficients of reliability for average artery wall thickness in the three segments were all r > .90.16

Our primary interest was the average intimal-medial thickness of the far wall of the six carotid artery segments. The rationale for this measure as an indicator of early atherosclerosis has been described,17 as has its strong association with major cardiovascular risk factors.18 Poor visualization of carotid boundaries led to missing information in part of the six segments on some subjects and a greater degree of missingness for deeper arteries or participants with greater body mass index. However, controlling for race, sex, body mass index, and artery depth, degree of visualization was not strongly associated with standard coronary heart disease risk factors. We therefore assumed that, conditional on race, sex, body mass index, and artery depth, missingness was random.

Statistical Methods

This analysis was restricted to participants with usable ultrasound data who reported their race as black or white. We excluded glucose and insulin values from analysis for subjects who had not fasted at least 8 hours. Insulin values were also excluded if the subject reported current pharmacologic treatment for diabetes. The final sample size was 14,430 of the 15,800 original participants.

The characteristics of the entire ARIC cohort were described as sex- and race-specific means and standard deviations or prevalence estimates. Differences in characteristics of those with prevalent CVD versus no CVD at baseline were compared using χ² or t-tests. Analysis of the B-mode ultrasound data were restricted to those without prevalent CVD at baseline. To include in analysis all participants with wall thickness data in at least one of the six sites, multivariate normal maximal likelihood techniques were applied to fit models of site-specific wall thickness as a function of potential risk factors and adjusting variables, using the EM algorithm in BMDP5V.19 Models were performed sex-specific and always controlled for body mass index, artery depth, and race to more nearly assure that missingness in the B-mode ultrasound data was random. Risk factor stratum-specific age-adjusted (imputed) mean wall thickness was computed by ANCOVA using SAS PROC GLM.20

Results

A description of ARIC participants is given in Table 1. Among women, blacks had greater adiposity than whites, lower sport physical activity, and higher levels of work activity, fasting glucose, insulin, and diabetes prevalence. Among men, there were virtually no racial differences in adiposity and insulin. However, similar to women, black men had lower sport physical activity than white men and higher glucose levels and diabetes prevalence.

Compared with those who were free of CVD at baseline (Table 2), those who reported CVD had a greater mean body mass index and waist-to-hip ratio, lower sport and work activity indexes, higher fasting glucose and insulin concentrations, and a 1.4-to 2.6-fold greater prevalence of diabetes. These findings were statistically significant (P < .05) for most race-sex groups, given the large ARIC sample size.

The remaining analyses were performed after excluding those with prevalent CVD to focus on early carotid atherosclerosis in asymptomatic subjects. The distribution of carotid artery intimal-medial wall thickness was slightly right-skewed. The sample mean (SD) wall thickness in those without CVD was 0.69 (0.16) mm in white women (n = 4340), 0.72 (0.15) mm in black women (n = 1682), 0.79 (0.20) mm in white men (n = 3645), and 0.77 (0.17) mm in black men (n = 1047). The respective medians were 0.66, 0.69, 0.75, and 0.75 mm.

Figs 1 and 2 illustrate for the four race-sex groups the association of age-adjusted average carotid wall thickness with body mass, waist-to-hip ratio, the sport index,
TABLE 1. Selected Baseline Characteristics of Participants by Race and Sex in the ARIC Study, 1987 to 1989

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>White (n=5520)</th>
<th>Black (n=2436)</th>
<th>White (n=4984)</th>
<th>Black (n=1510)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.0±5.7</td>
<td>53.4±5.7</td>
<td>54.8±5.7</td>
<td>53.9±6.0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.6±5.5</td>
<td>30.8±6.5</td>
<td>27.4±4.0</td>
<td>27.8±4.9</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.89±0.08</td>
<td>0.90±0.08</td>
<td>0.97±0.05</td>
<td>0.94±0.06</td>
</tr>
<tr>
<td>Sport index*</td>
<td>2.4±0.8</td>
<td>2.1±0.7</td>
<td>2.7±0.8</td>
<td>2.3±0.8</td>
</tr>
<tr>
<td>Work index*</td>
<td>2.0±0.9</td>
<td>2.3±1.0</td>
<td>2.3±0.9</td>
<td>2.3±1.0</td>
</tr>
<tr>
<td>Fasting serum glucose, mmol/L</td>
<td>5.7±1.6</td>
<td>6.3±2.7</td>
<td>6.0±1.5</td>
<td>6.2±2.2</td>
</tr>
<tr>
<td>Fasting serum insulin, mmol/L</td>
<td>68±54</td>
<td>105±75</td>
<td>80±57</td>
<td>82±61</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>6.3</td>
<td>14.7</td>
<td>7.4</td>
<td>12.6</td>
</tr>
<tr>
<td>Plasma LDL cholesterol, mmol/L</td>
<td>3.5±1.0</td>
<td>3.6±1.1</td>
<td>3.6±0.9</td>
<td>3.6±1.1</td>
</tr>
<tr>
<td>Plasma HDL cholesterol, mmol/L</td>
<td>1.5±0.5</td>
<td>1.5±0.5</td>
<td>1.1±0.3</td>
<td>1.3±0.4</td>
</tr>
<tr>
<td>Cigarette smoking, pack-years</td>
<td>12±18</td>
<td>8±15</td>
<td>24±25</td>
<td>20±25</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>26.1</td>
<td>55.7</td>
<td>28.5</td>
<td>54.8</td>
</tr>
</tbody>
</table>

ARIC indicates Atherosclerosis Risk in Communities; LDL, low-density lipoprotein; and HDL, high-density lipoprotein. Values are mean±SD or percent.

*Range 1 to 5 (low to high).
†Excludes pharmacologically treated diabetics.
§Reported and/or treated diabetes, fasting glucose ≥7.8 mmol/L, or nonfasting glucose ≥11.1 mmol/L.

Fasting insulin, fasting glucose, and diabetes. Tables 3 and 4 show the associations by sex from regression modeling. Twelve separate models were run, two (models 1 and 2) for each characteristic considered separately. Simultaneous adjustment was viewed as inappropriate because body size, physical activity, and glucose and insulin metabolism are causally intertwined; yet adjustment for body mass index was required to account for possible nonrandom missing wall thickness data (see “Methods”). Therefore, the most appropriate assessment of the overall associations is model 1, which adjusted for age, race, pack-years of smoking, artery depth, ARIC field center, and body mass index. Model 2 assessed whether the associations in model 1 might be explained by several mediating factors, ie, HDL cholesterol, LDL cholesterol, and hypertension. The regression coefficients, for the most part, were larger for men than for women. Most of the associations were statisti-

cally significant in model 1, given the large sample size. Adjustment for hypertension, LDL cholesterol, and HDL cholesterol reduced the associations.

Age-adjusted average carotid intimal-medial wall thickness increased steadily with increasing body mass and waist-to-hip ratio in each sex-race group. From model 1, the predicted increase in wall thickness for a 5-kg/m² (1 SD) increase in body mass was about 0.017 mm for women and about 0.026 mm for men. The predicted increase in wall thickness for an increase of 0.07 unit (1 SD) in waist-to-hip ratio was 0.020 mm in women and 0.029 mm in men. (To place these in perspective, a 0.02-mm increase would represent about a 3% increase in average carotid wall thickness.) Both the body mass and waist-to-hip ratio associations with wall thickness were reduced but remained statistically significant (P<.01) after adjustment for other major risk factors.

Wall thickness decreased with increasing physical exertion at work for both men and women; by model 1

TABLE 3. Adjusted Regression Coefficients (β) for Multiple Linear Regressions of Average Carotid Artery Intimal-Medial Wall Thickness (mm) on Selected Characteristics in Women Free of Cardiovascular Disease in the ARIC Study, 1987 to 1989

<table>
<thead>
<tr>
<th>Characteristic* (separately considered)</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Body mass index, kg/m²</td>
<td>0.0033</td>
<td>&lt;.01</td>
<td>0.0021</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>(2) Waist-to-hip ratio, 1 unit</td>
<td>0.2885</td>
<td>&lt;.01</td>
<td>0.2135</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>(3) Work index, 1 unit</td>
<td>-0.0063</td>
<td>.03</td>
<td>-0.0060</td>
<td>.03</td>
</tr>
<tr>
<td>(4) Sport index, 1 unit</td>
<td>-0.0009</td>
<td>.78</td>
<td>0.0011</td>
<td>.75</td>
</tr>
<tr>
<td>(5) Diabetes (yes vs no)</td>
<td>0.0716</td>
<td>&lt;.01</td>
<td>0.0605</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Hyperglycemia (yes vs no)†</td>
<td>0.0203</td>
<td>.08</td>
<td>0.0113</td>
<td>.32</td>
</tr>
<tr>
<td>(6) Fasting insulin, mmol/L‡</td>
<td>0.00017</td>
<td>&lt;.01</td>
<td>0.00009</td>
<td>.66</td>
</tr>
</tbody>
</table>

*pAverage wall thickness was the dependent variable, and 12 separate regression models were run with the six listed characteristics as separately considered independent variables adjusted successively for two sets of covariates.

Model 1 coefficients were adjusted for age, race, pack-years of smoking, artery depth, Atherosclerosis Risk in Communities (ARIC) field center, and body mass index [except (1)]. Model 2 coefficients were adjusted also for hypertension (yes, no), plasma low-density lipoprotein cholesterol, and plasma high-density lipoprotein cholesterol.

†Hyperglycemia = fasting glucose 6.4 to 7.7 mmol/L.

‡Excludes pharmacologically treated diabetes.

estimation, the decrease was 0.006 to 0.010 mm per unit increase in the work index. Inclusion of the other major risk factors (model 2) did not appreciably alter this estimate. The association for sports participation, however, was not statistically significant in either sex.

By model 1 estimation, in both sexes, diabetic subjects had carotid artery walls about 0.07 mm thicker and subjects with fasting glucose equal to 6.4 to 7.7 mmol/L had artery walls about 0.02 mm thicker than subjects with fasting glucose <6.4 mmol/L (Fig 2 and Tables 3 and 4). Adjustment for hypertension and plasma lipids reduced these estimates somewhat. Among those not pharmacologically treated for diabetes, a 100-mmol/L greater fasting insulin was associated in model 1 with thicker carotid artery walls by about 0.017 mm in women and 0.016 mm in men.

It has been suggested that the sex difference in cardiovascular disease may be due to a lower waist-to-hip ratio in women and is greatly diminished in diabetic subjects. However, the waist-to-hip ratio and diabetes graphs in Figs 1 and 2 suggest that carotid atherosclerosis is higher in men than women both for each level of waist-to-hip ratio and for participants with diabetes. In a linear regression model that included age, race, pack-years of smoking, body mass index, artery depth, and ARIC field center, women were predicted to have a 0.08-mm lower average wall thickness than men. When a term for waist-to-hip ratio was added to the model, this male/female difference was mildly reduced to 0.06 mm. Alternatively, when terms for hyperglycemia and diabetes were added, the male/female difference of 0.08 mm was unchanged.

We also ran model 1 regressions separately for the average wall thickness of the common carotid, the bifurcation, and the internal carotid artery segments. Associations tended to be in the same direction for all

TABLE 4. Adjusted Regression Coefficients (β) for Multiple Linear Regressions of Average Carotid Artery Intimal-Medial Wall Thickness (mm) on Selected Characteristics in Men Free of Cardiovascular Disease in the ARIC Study, 1987 to 1989

<table>
<thead>
<tr>
<th>Characteristic* (separately considered)</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Body mass index, kg/m²</td>
<td>0.0052</td>
<td>&lt;.01</td>
<td>0.0037</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>(2) Waist-to-hip ratio, 1 unit</td>
<td>0.4155</td>
<td>&lt;.01</td>
<td>0.3632</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>(3) Work index, 1 unit</td>
<td>-0.0102</td>
<td>&lt;.01</td>
<td>-0.0053</td>
<td>.01</td>
</tr>
<tr>
<td>(4) Sport index, 1 unit</td>
<td>-0.0043</td>
<td>.31</td>
<td>-0.0034</td>
<td>.42</td>
</tr>
<tr>
<td>(5) Diabetes (yes vs no)</td>
<td>0.0731</td>
<td>&lt;.01</td>
<td>0.0698</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Hyperglycemia (yes vs no)†</td>
<td>0.0184</td>
<td>.12</td>
<td>0.0147</td>
<td>.21</td>
</tr>
<tr>
<td>(6) Fasting insulin, mmol/L‡</td>
<td>0.00016</td>
<td>.01</td>
<td>0.00013</td>
<td>.04</td>
</tr>
</tbody>
</table>

*pAverage wall thickness was the dependent variable and 12 separate regression models were run with the six listed characteristics as separately considered independent variables adjusted successively for two sets of covariates.

Model 1 coefficients were adjusted for age, race, pack-years of smoking, artery depth, Atherosclerosis Risk in Communities (ARIC) field center, and body mass index [except (1)]. Model 2 coefficients were adjusted also for hypertension (yes, no), plasma low-density lipoprotein cholesterol, and plasma high-density lipoprotein cholesterol.

†Hyperglycemia indicates fasting glucose of 6.4 to 7.7 mmol/L.

‡Excludes pharmacologically treated diabetes.
three arterial segments, but there was some variation in the strength. For example, associations of wall thickness with hypertension status, the sex of index, and waist:hip ratio were generally stronger for the bifurcation and internal carotid segments than for the common carotid.

Discussion

Epidemiologic studies of atherosclerotic diseases typically study clinical end points, such as myocardial infarction or coronary heart disease death. However, among those with underlying atherosclerosis, clinical atherosclerotic events occur only infrequently, usually because of rupture of a plaque and subsequent thrombosis. A theoretical advantage of B-mode ultrasound is that risk factors for atherosclerosis might be directly quantifiable. Indeed, the clinical use of B-mode in measuring symptomatic carotid artery stenoses is well established. However, because most ARIC participants do not have stenotic carotid lesions, we measured average carotid intimal-medial wall thickness. It is possible that greater than average wall thickness may represent not only early atherosclerosis, but also medial hypertrophy or hyperplasia from other causes such as hypertension. The validity of intimal-medial wall thickness as a measure of atherosclerosis and its reliability in the ARIC Study have been described. Wall thickness, in ARIC, is strongly associated with atherogenic lipids and smoking, as well as hypertension, suggesting that the atherosclerotic process is reflected in intimal-medial wall thickness. The preliminary ARIC data also suggest that carotid intimal-medial thickness predicts coronary disease prospectively (unpublished data).

There are, nevertheless, drawbacks of B-mode carotid wall thickness as an end point. Although atherosclerosis in the carotid arteries is correlated with atherosclerosis in the coronaries and elsewhere, the carotid represents only a small segment of the arterial system. Frequently, the boundaries of the arterial tissues were not fully identifiable in the B-mode image (see "Methods"), so the ARIC investigators had to impute missing boundaries from the existing boundaries. Finally, this particular analysis may be susceptible to the usual biases of cross-sectional studies; however, we believe the likelihood was reduced by the exclusion of participants with symptomatic CVD.

The strengths of ARIC are its size and its biracial population-based samples. We found that greater body mass and waist-to-hip ratio, less physical activity, greater fasting insulin and glucose, and diabetes were all related to prevalent CVD, as is generally accepted. More importantly, our main findings were that these factors for maximal intimal-medial thickening. Body mass index was not an independent risk factor. We reported average intimal-medial thickness here, and confirmed that along with atherogenic lipids, smoking, and hypertension, diabetes was a risk factor. To a lesser degree so were body mass index, waist-to-hip ratio, fasting insulin, and physical exertion at work, although lack of sports participation was not. Salonen and Salonen did not report whether waist-to-hip ratio, exercise, or fasting insulin concentrations were related to carotid wall thickness. However, these investigators did demonstrate an association between carotid atherosclerosis and reduced whole-body glucose uptake (a measure of insulin resistance) in a recent substudy of 30 nonobese subjects with atherosclerosis and 13 control subjects.

Atherosclerosis has a greater predilection for the carotid bifurcation than the internal or common carotid segments. Tell et al have recently reported that risk factors for carotid plaques vary somewhat by segment. Giral et al have shown variations among risk factors for plaques in the carotid, aorta, and the femoral arteries among hypercholesterolemic men. We also observed some differences in the association of examined risk factors with the wall thickness of three carotid segments.

Comparisons of carotid wall thickness between men and women should be made cautiously because normal artery wall thickness may be greater in men than women. We nevertheless tested in regression models whether sex differences in waist-to-hip ratio, or hyperglycemia and diabetes, may explain the sex difference in wall thickness. Accounting for hyperglycemia and diabetes had no effect on the sex difference in wall thickness. Accounting for waist-to-hip ratio reduced the sex difference in carotid thickness somewhat but did not eliminate it. Thus, the data are consistent with this.
factor being partly responsible for sex differences in CVD.

There are several mechanisms by which the examined risk factors may be associated with atherosclerosis. Theories of atherosclerosis suggest that two crucial steps are endothelial injury and LDL uptake by subendothelial macrophages to form foam cells and eventually atherosclerotic plaques. Greater body mass, waist-to-hip ratio, physical inactivity, fasting insulin, and diabetes all tend to be associated with higher blood pressure, which may injure endothelium. They are also associated with higher plasma triglycerides and LDL, and with lower HDL.4,44 Observed associations with wall thickness were weakened when hypertension and plasma lipids were included in the regressions (model 2), suggesting that hypertension and atherogenic lipids may indeed partly mediate the associations. It is also possible that the examined risk factors directly promote endothelial injury, LDL uptake, or smooth muscle proliferation. For example, insulin has been shown to enhance cholesterol transport into arteriolar smooth muscle cells, and to increase the proliferation and cholesterol synthesis of these cells. Furthermore, it is considered.

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