Statins Reduce Epicardial Adipose Tissue Attenuation Independent of Lipid Lowering: A Potential Pleiotropic Effect

Paolo Raggi, MD, PhD; Varuna Gadiyaram, MD; Chao Zhang, PhD; Zhengjia Chen, PhD; Gary Lopaschuk, PhD; Arthur E. Stillman, MD, PhD

Background—High epicardial adipose tissue (EAT) attenuation (Hounsfield units [HUs]) on computed tomography is considered a marker of inflammation and is associated with an increased risk of cardiovascular events. Statins reduce the volume of EAT, but it is unknown whether they affect EAT HUs.

Methods and Results—We reviewed the chest computed tomographic scans of 420 postmenopausal women randomized to either 80 mg of atorvastatin or 40 mg of pravastatin daily and rescanned after 1 year to measure change in coronary artery calcium score. EAT HUs were measured near the proximal right coronary artery and remote from any area of coronary artery calcium. Computed tomographic images were also queried for subcutaneous adipose tissue (SubQ) attenuation (HUs) change over time. The mean patients’ age was 65±6 years. The baseline EAT HU value was higher than the SubQ HU value (−89.4±24.0 HU versus −123.3±30.4 HU; P<0.001). The EAT HU value decreased significantly in the entire cohort (−5.4±29.7 HU [−6% change]; P<0.001), but equally in the patients given atorvastatin and pravastatin (−6.35±31 HU and −4.55±28 HU; P=0.55). EAT HU change was not associated with change in total cholesterol, low-density lipoprotein cholesterol, coronary artery calcium, and EAT volume (all P—not significant). Change in high-density lipoprotein cholesterol was marginally associated with EAT HU change (P=0.07). Statin treatment did not induce a change in SubQ HUs.

Conclusions—Statins induced a decrease in EAT HUs over time, independent of intensity of low-density lipoprotein cholesterol lowering. The positive effect on EAT and the neutral effect on SubQ suggest that statins induced a decrease in metabolic activity in EAT by reduction in cellularity, vascularity, or inflammation. The clinical significance of the observed change in EAT HUs remains to be demonstrated. (J Am Heart Assoc. 2019;8:e013104. DOI: 10.1161/JAHA.119.013104.)

Key Words: computed tomography • epicardial fat • low-density lipoprotein • statin therapy

Epicardial adipose tissue (EAT) is visceral fat surrounding and in direct contact with the coronary artery adventitia, and it is believed to be implicated in the development of atherosclerosis. In their initial publication, Mazurek et al demonstrated that in patients scheduled to undergo elective coronary artery bypass surgery, EAT is highly inflamed. However, the subcutaneous adipose tissue (SubQ) of the same patients did not show any or only minimal signs of inflammation. Whether EAT contributes directly to the development of atherosclerosis via paracrine effects or via systemic mechanisms remains to be clarified. Nonetheless, there is accumulating evidence that EAT is more plentiful in patients at risk of atherosclerosis or in those with preclinical atherosclerosis and adverse outcomes. Recent investigations correlated a higher computed tomography (CT) attenuation of EAT with coronary artery plaque characteristics and adverse outcomes. In one publication, EAT attenuation was a better predictor of myocardial infarction than EAT volume. A higher CT attenuation may indicate the presence of inflammatory changes and neovascularization in the context of EAT or a different type of adipose tissue in the pericoronary space. If inflammation was the source of such difference in radiodensity, its reversal may be desirable. Statins have been shown to induce a volumetric reduction of EAT, and more aggressive low-density lipoprotein cholesterol (LDL-C) lowering induced a more marked reduction of EAT volume. Whether statins affect the attenuation, hence potentially the inflammatory state of EAT, is unknown. We tested this hypothesis in a subanalysis of a double-blind, randomized, clinical trial designed to investigate the effect of 2 different

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Clinical Perspective

What Is New?

- New evidence suggests that high epicardial adipose tissue attenuation on computed tomography imaging is a marker of inflammation and may promote development of atherosclerosis; however, brown adipose tissue is also present in this fat depot and it has a higher radiological attenuation.

What Are the Clinical Implications?

- We demonstrated that statins reduce the attenuation of epicardial adipose tissue independent of reduction in low-density lipoprotein levels.
- This may be caused by an anti-inflammatory and a positive pleiotropic effect of statins, or it could reflect inhibition of brown adipose tissue physiological features by these drugs; in this case, it could represent a negative influence of statins.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

Details of the study protocol have been published before and are summarized in brief here. The purpose of the BELLES (Beyond Endorsed Lipid Lowering With Electron Beam Tomography Scanning) trial was to investigate whether aggressive lipid lowering treatment with 80 mg daily of atorvastatin than with a more moderate LDL lowering attained with 40 mg daily of pravastatin, 40 mg/d, and matching atorvastatin placebo. The second CT scan was performed after 12 months from randomization. The study was approved by the ethics review committee of each participating institution, and the subjects gave informed consent to participate.

CT Imaging for CAC and EAT Assessment

Imatron (GE Imatron, San Francisco, CA) C-150 electron beam CT scanners were used to perform the baseline and follow-up scans for all patients using a standard imaging protocol. Scanning started at the bronchial carina and extended to the diaphragm for a total of 36 to 40 slices. The CAC score was calculated as a volume score, as previously described.

The EAT volume and attenuation were measured on the same axial images used for CAC scoring. The EAT volume was calculated using the Volume Analysis software of a Leonardo workstation (Siemens, Erlangen, Germany), as previously described. The EAT volume was assessed after manually tracing the epicardium in each successive axial slice in the craniocaudal direction, using a threshold of −190 to −30 Hounsfield units (HU). The fat voxels from each slice were then summed to obtain the total EAT volume (in mL).

The EAT attenuation was measured in HUs in the vicinity of the proximal right coronary artery (Figure 1). A region of interest was drawn in the EAT located in the space separating the right atrium from the right ventricular outflow tract. The region of interest was drawn in an area not contiguous with CAC and not affected by streak or motion artifacts. The location and surface area of the region of interest were kept identical for the baseline and follow-up scans. Similar procedures were followed to measure SubQ HUs. In this case, the region of interest was drawn in an area of thoracic subcutaneous tissue, mostly along the midaxillary line (Figure 1).

The same experienced investigator (G.V.) performed all measurements of adipose tissue attenuation. The same investigator also performed repeated measurements of attenuation on a random sample of 100 CT scans selected...
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in a blinded manner. The intrareader variability of the measurements was <1%, demonstrating a high degree of reproducibility.

Statistical Analysis

Mean and SD were calculated for normally distributed numerical variables; medians were calculated for nonnormally distributed variables. Frequency and percentages were used to describe categorical variables. The variables CAC, EAT volume, EAT HUs, and SubQ HUs were measured at baseline and at 1 year from randomization in all patients. The percentage change for each parameter was calculated as [(final-baseline)/baseline]*100%. One-way ANOVA test and Kruskal-Wallis test were used to compare numerical variables in univariable analyses, as appropriate. The paired t-test was used to compare baseline and follow-up CAC, EAT volume, EAT HUs, and SubQ HUs. The Pearson correlation coefficient was used to test the association between percentage EAT HU change and percentage change in CAC score, EAT volume, SubQ HUs, total cholesterol, high-density lipoprotein cholesterol (HDL-C), LDL-C, and total triglycerides. Differences in categorical variables between treatment arms were compared by means of $\chi^2$ test or Fisher’s exact test, where appropriate. A multivariate linear regression model was fit by a backward variable selection method with an $\alpha=0.20$ removal criterion, to estimate the association of EAT HU change in the whole group, the atorvastatin group, and the pravastatin group with age, race, diabetes mellitus, hypertension, smoking, baseline use of hormone replacement therapy, body mass index, and history of cardiovascular disease (angina, coronary artery angioplasty or bypass, or peripheral vascular disease). Scatterplots were drawn to show the relationship between percentage EAT HU change and percentage change in LDL-C and HDL-C in the entire cohort. The same analyses performed for EAT HU change were applied to assess change in SubQ HU. The significance level was set at $P<0.05$. The SAS statistical package, version 9.4 (SAS Institute, Inc, Cary, NC), was used for data management and analysis.

Results

The clinical characteristics of the 420 patients enrolled in this study are shown in Table 1. The randomization was effective, and there were no significant clinical or demographic differences between patients in the 2 treatment arms. The characteristics of the 55 patients excluded because of poor image quality were identical to the 420 patients included. The LDL-C and triglycerides lowering of atorvastatin were superior to those of pravastatin (48±18% versus 25±18% [$P<0.001$] and 22.8±33% versus 9.7±30% [$P<0.001$], respectively). There was no significant difference in the CAC increasing effect between the 2 statins. We previously demonstrated that both statins reduced the EAT volume from baseline, although pravastatin was more effective than atorvastatin.9 Similarly, statins reduced (made more negative) the EAT attenuation (−9.4±24 HUs at baseline versus −94.7±21 HUs at follow-up; average change for the entire cohort, −5.4±29.7 HUs [−6% change]; $P<0.001$). However, the 2 statins were equally effective and there was no significant difference in the EAT attenuation change induced by treatment (atorvastatin versus pravastatin, −6.35±31 HUs versus −4.55±28 HUs; $P=0.55$). Among the clinical categorical variables, only diabetes mellitus was marginally correlated with change in EAT attenuation ($P=0.067$). Among the continuous variables, percentage change in EAT attenuation was marginally correlated with percentage change in HDL-C ($P=0.073$; Table 2), but no other variable. Figures 2 and 3 show the correlation between change in EAT HUs and change in LDL-C and HDL-C for the entire cohort.

The multivariable model for the entire cohort did not produce any variable significantly associated at the 0.05 level with change in EAT attenuation. The only 2 variables marginally associated with EAT attenuation change were age and percentage change in HDL-C ($P=0.084$ and $P=0.086$, respectively). Although there were no significant predictors of change in EAT attenuation in the pravastatin group, in the atorvastatin group, history of diabetes mellitus ($\beta=18.8$; $P=0.039$), age ($\beta=-0.94$; $P=0.045$), and change in HDL-C ($\beta=-0.64$; $P=0.003$) were predictive of EAT change.

The subcutaneous tissue of the 420 patients included in this subanalysis had a lower attenuation at baseline than EAT (−123±30 versus −89±24 HUs; $P<0.001$). This observation supports the notion that the tissue composition of the 2 fat compartments is substantially different. Treatment with
Table 1. Patients’ Baseline Clinical Characteristics by Treatment Arm

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Statistics</th>
<th>Level</th>
<th>Treatment (N=194)</th>
<th>Pravastatin (N=226)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mean±SD</td>
<td></td>
<td>65.2±6.5</td>
<td>65.5±6.0</td>
<td>0.548</td>
</tr>
<tr>
<td>Race</td>
<td>No. (%)</td>
<td>White</td>
<td>175 (90)</td>
<td>209 (93)</td>
<td>0.606</td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>Black</td>
<td>10 (5)</td>
<td>8 (3.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>Other</td>
<td>9 (4.6)</td>
<td>8 (3.6)</td>
<td></td>
</tr>
<tr>
<td>HRT</td>
<td>No. (%)</td>
<td>Yes</td>
<td>46 (24)</td>
<td>51 (23)</td>
<td>0.781</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No. (%)</td>
<td>Yes</td>
<td>75 (39)</td>
<td>98 (43)</td>
<td>0.329</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>No. (%)</td>
<td>Yes</td>
<td>26 (13.4)</td>
<td>35 (15.5)</td>
<td>0.546</td>
</tr>
<tr>
<td>Prior MI</td>
<td>No. (%)</td>
<td>Yes</td>
<td>5 (2.6)</td>
<td>4 (1.8)</td>
<td>0.738</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>No. (%)</td>
<td>Yes</td>
<td>1 (0.5)</td>
<td>2 (0.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Prior angina</td>
<td>No. (%)</td>
<td>Yes</td>
<td>14 (7.2)</td>
<td>15 (6.4)</td>
<td>0.815</td>
</tr>
<tr>
<td>Prior PVD</td>
<td>No. (%)</td>
<td>Yes</td>
<td>11 (6)</td>
<td>18 (8)</td>
<td>0.355</td>
</tr>
<tr>
<td>Smoking</td>
<td>No. (%)</td>
<td>Never</td>
<td>80 (41)</td>
<td>95 (42)</td>
<td>0.748</td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>Ex/current</td>
<td>114 (59)</td>
<td>131 (58)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/cm²</td>
<td>Mean±SD</td>
<td></td>
<td>28.6±5.5</td>
<td>29.2±5.8</td>
<td>0.194</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>Mean±SD</td>
<td></td>
<td>6.95±0.95</td>
<td>6.88±0.98</td>
<td>0.491</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>Mean±SD</td>
<td></td>
<td>1.47±0.36</td>
<td>1.5±0.36</td>
<td>0.357</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>Mean±SD</td>
<td></td>
<td>4.55±0.88</td>
<td>4.47±0.88</td>
<td>0.332</td>
</tr>
<tr>
<td>Total triglycerides, mmol/L</td>
<td>Mean±SD</td>
<td></td>
<td>2.1±1.0</td>
<td>2.0±1.1</td>
<td>0.419</td>
</tr>
<tr>
<td>EAT volume, mL</td>
<td>Mean±SD</td>
<td></td>
<td>111.3±46.8</td>
<td>110.3±43.2</td>
<td>0.950</td>
</tr>
<tr>
<td>EAT HUs</td>
<td>Mean±SD</td>
<td></td>
<td>−88.07±26</td>
<td>−90.73±22</td>
<td>0.097</td>
</tr>
<tr>
<td>SubQ HUs</td>
<td>Mean±SD</td>
<td></td>
<td>−121.8±32</td>
<td>−124.7±28</td>
<td>0.275</td>
</tr>
<tr>
<td>CAC score</td>
<td>Mean±SD</td>
<td></td>
<td>262.9±386</td>
<td>348.9±549</td>
<td>0.071</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CABG, coronary artery bypass grafting; CAC, coronary artery calcium; EAT, epicardial adipose tissue; HDL-C, high-density lipoprotein cholesterol; HRT, hormone replacement therapy; HU, Hounsfield unit; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PVD, peripheral vascular disease; SubQ, subcutaneous adipose tissue.

Discussion

In this subanalysis of a randomized clinical trial, we report, for the first time, a change in EAT attenuation under treatment with statins that was independent of their effect on serum lipid levels, with the exception of a borderline association between EAT HU decrease and HDL-C increase. The SubQ in the same patients had a lower radiodensity at baseline and was not affected by treatment with statins.

The interaction of EAT with the cardiovascular system in health and disease is complex. EAT can be both a friend (providing thermogenic and nourishing support to the coronary arteries and myocardium) and a foe. The influence of obesity, systemic inflammation, hyperlipidemia, and smoking can promote a phenotypic change in the EAT adipocytes and induce a secretome responsible for the production of proinflammatory cytokines that replace the anti-inflammatory adiponectin. In this new state, EAT and visceral fat are believed to have both paracrine and autocrine activities that may promote atherosclerosis and myocardial fibrosis.

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attenuation have been associated with an increased risk of all-cause and cardiovascular mortality.\textsuperscript{22,24} A higher fat attenuation has long been interpreted as a surrogate marker of inflammation, after an initial report that visceral fat showed an increased radiodensity in patients with pancreatitis.\textsuperscript{25} Accordingly, recently, Antonopoulos et al\textsuperscript{23} reported that higher pericoronary artery attenuation, measured with a novel CT method, reflects a state of inflammation in the context of the vessel wall.

Applying this novel imaging method in a derivation and validation study, Oikonomou et al\textsuperscript{24} confirmed that this index of vascular inflammation is predictive of all-cause and cardiac mortality, after adjustment for several clinical characteristics and risk factors. Both in experimental animals\textsuperscript{26,27} and in human observations,\textsuperscript{28} statins have been shown to have a direct anti-inflammatory effect on adipose tissue. Parisi et al\textsuperscript{28} showed a direct correlation between EAT thickness and inflammasome expression within the EAT and further demonstrated an in vitro anti-inflammatory effect of atorvastatin on cultured EAT adipocytes. Atorvastatin had no effect on subcutaneous tissue, in line with our observations in the present study. We previously showed that statins reduced the volume of EAT\textsuperscript{9} and suggested that a reduction of inflammation and/or partial disappearance of vasa vasorum in the perivascular fat surrounding the coronary arteries\textsuperscript{29} may have contributed to our findings. If interpreted in this light, the current results can be seen as a positive pleotropic action of statins on EAT. In fact, a reduction in tissue attenuation could reflect a reduction in EAT inflammation, hence an

### Table 2. Continuous Variables Associated With Change in EAT Attenuation in the Entire Patient Cohort

<table>
<thead>
<tr>
<th>Change</th>
<th>Pearson CC</th>
<th>Pearson $P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAT volume</td>
<td>-0.003</td>
<td>0.954</td>
</tr>
<tr>
<td>SubQ HUs</td>
<td>-0.004</td>
<td>0.941</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-0.063</td>
<td>0.241</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-0.096</td>
<td>0.073</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-0.042</td>
<td>0.433</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.034</td>
<td>0.526</td>
</tr>
<tr>
<td>CAC</td>
<td>0.029</td>
<td>0.570</td>
</tr>
</tbody>
</table>

All parameters are expressed as percentage change. CAC indicates coronary artery calcium; CC, correlation coefficient; EAT, epicardial adipose tissue; HDL-C, high-density lipoprotein cholesterol; HU, Hounsfield unit; LDL-C, low-density lipoprotein cholesterol; SubQ, subcutaneous adipose tissue.

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**Figure 2.** Percentage change in epicardial adipose tissue attenuation vs percentage low-density lipoprotein cholesterol (LDL-C) change for the entire study population. EAT indicates epicardial adipose tissue; HU, Hounsfield unit.
antiatherosclerotic action of statins. However, there is at least one other explanation for our findings that needs careful consideration. Imaging and histological studies suggest that the perivascular fat of epicardial coronary arteries is composed of brown adipose tissue (BAT) with dispersed beige cells (white adipose tissue [WAT] cells that express a BAT phenotype). BAT is essential for the production of nonshivering thermogenesis via the action of several enzymes, the most important of which is UCP-1 (uncoupling protein-1). By burning large quantities of free fatty acids and glucose, BAT contributes to better cardiometabolic health overall, improved glucose homeostasis, and insulin sensitivity. Indeed, its stimulation with a β-3 adrenergic receptor agonist in mice stymied the development of experimental atherosclerosis. The adipocytes found in BAT contain more mitochondria and are smaller than those of WAT. This is likely due to the fact that they have smaller triacylglycerol stores because BAT cells oxidize rather than store fatty acids. Furthermore, activation of BAT induces a several fold increase in blood flow through it, for the purpose of delivering free fatty acids and glucose for consumption. The end result is a higher radiological attenuation of BAT than WAT, both at rest and especially after stimulation. A surprising recent study suggested that statins may reduce the expression of genes necessary for thermogenesis within BAT and that the mechanism may reside in inhibition of the geranylgeranyl pyrophosphate cascade. Balaz et al reported that hydroxy methyl-glutaryl coenzyme A synthase 2 is highly expressed in human BAT and is correlated with expression of UCP-1. Blockade of the hydroxy methyl-glutaryl coenzyme A synthase 2 with statins, both in murine and in in vitro adipose tissue experiments, led to a marked decrease in the expression of UCP-1, hence a reduction in the thermogenetic potential of BAT. In in vivo murine experiments, Balaz et al further demonstrated that fluvastatin and simvastatin inhibited “browning of WAT,” essentially inhibiting a phenotypic transformation of WAT adipocytes into BAT adipocytes. Of interest, the negative influence of statins on UCP-1 expression could be rescued with geranylgeranyl pyrophosphate, suggesting a non–cholesterol-related action of statins on BAT. In a retrospective analysis of 738 patients submitted to multiple positron emission tomography/CT scans with 18F-fluorodeoxyglucose over a year’s time, Balaz et al further showed a lower BAT activity in patients receiving statins compared with statin-naïve patients. Finally, in 16 volunteers with high baseline BAT activity, 2 weeks of fluvastatin therapy effectively reduced total cholesterol and LDL-C levels, but it also blocked UCP-1 expression, whereas there was no difference
in expression of inflammatory markers. Taken together, these data suggest that what we observed in our analyses potentially was a loss of activity of BAT that resulted in reduction in the CT attenuation of EAT. Although the deactivation of BAT may be a negative collateral effect of statins, these drugs obviously have a proven record of cardiovascular safety. Whether the inhibition of BAT and browning of WAT are a potential other pathway leading to the development of diabetes mellitus in patients receiving statins remains to be studied in detail. In obesogenic states, even BAT can become inflamed. In addition, experiments in apolipoprotein E knockout mice showed that stimulation of BAT with cold induced a striking increase in hepatic production of hydroxy methyl-glutaryl coenzyme A reductase and serum LDL-C, intermediate-density lipoprotein cholesterol, and very low density lipoprotein-cholesterol. The end result was promotion of atherosclerosis development, apparently via an adiponectin-sensitive mechanism. Hence, it is possible that BAT itself may become proatherogenic in some disease states, such as hypercholesterolemia and obesity. Finally, the separation of WAT, beige adipose tissue, and BAT into separate depots may be somewhat artificial; and it has been proposed that adipocytes of all types are likely present in every compartment.

The SubQ in our patients had a lower attenuation at baseline and did not respond to treatment with statins compared with EAT. These observations support the notion that subcutaneous fat is mainly constituted of WAT, and it may not be as inflamed as EAT. In their original report, Mazurek et al noted that the SubQ of patients referred for elective coronary artery bypass surgery was not inflamed, whereas the EAT expressed a large number of proinflammatory mRNAs and was densely infiltrated with monocytes and lymphocytes. Our observation appears to be consistent with theirs.

A few limitations of the current report should be highlighted. This was a subanalysis of a previously randomized clinical trial in postmenopausal women, with hypercholesterolemia and CAC; hence, our findings cannot be automatically extended to other patient groups. In the parent trial, we did not collect serum markers of inflammation. Other investigators reported an anti-inflammatory action of statins on EAT, but without histological confirmation our observations remain hypothesis generating. Patients were randomized to 2 different statins, but there was no placebo arm. We measured EAT and SubQ attenuation in a relatively small region of interest, although we made it as large as possible and we also ensured that the areas chosen were free from artifacts. Selecting smaller regions of interest in the pericoronal space would have increased the SD and the error in the measurement.

This study also had a few positive connotations. The randomization followed strict criteria, and the 2 groups were perfectly matched. All imaging studies were performed with the same CT scanner brand and model, thus avoiding variability caused by different types of image reconstruction and x-ray tube voltage.

In summary, we showed that moderate to aggressive treatment with statins reduced the EAT attenuation by ≈6% after 1 year of treatment in a cohort of postmenopausal women with subclinical atherosclerosis and hypercholesterolemia.

The SubQ fat attenuation was not affected by statin treatment. Because a higher EAT attenuation has been shown to be associated with an unfavorable outcome, a decrease in attenuation with treatment may represent another beneficial pleotropic action of statins. On the other hand, whether the changes we described are suggestive of a potential adverse effect of these popular drugs, that in rare cases induce development of diabetes mellitus, will require further clarification.

Disclosures
None.

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