Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 19, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.12.051

Effect of Intensive Versus Moderate Lipid-Lowering Therapy on Epicardial Adipose Tissue in Hyperlipidemic Post-Menopausal Women

A Substudy of the BELLES Trial (Beyond Endorsed Lipid Lowering with EBT Scanning)

Nikolaos Alexopoulos, MD,* Bekir H. Melek, MD,* Chesnal D. Arepalli, MD,† Gregory-Randell Hartlage, MD,* Zhengjia Chen, PhD,‡ Sungjin Kim, PhD,‡ Arthur E. Stillman, MD,*† Paolo Raggi, MD§

Atlanta, Georgia; and Edmonton, Alberta, Canada

Objectives This study sought to evaluate the effect of intensive and moderate statin therapy on epicardial adipose tissue (EAT).

Background EAT has been associated with coronary artery disease severity and outcome. It is currently unknown whether EAT volume changes over time when patients are exposed to statin therapy.

Methods Subanalysis of a randomized study of atorvastatin 80 mg/day versus pravastatin 40 mg/day for 1 year in a clinical trial designed to assess the progression of coronary artery calcium (CAC) in hyperlipidemic post-menopausal women. Patients underwent cardiac computed tomography scans at the start and end of the trial period.

Results Of 420 patients, 194 received atorvastatin and 226 pravastatin; the median low-density lipoprotein change was −53.3% and −28.3% with atorvastatin and pravastatin, respectively ($p < 0.001$). Baseline EAT correlated with age, body mass index, hypertension, diabetes mellitus, high-density lipoprotein, triglyceride levels, and CAC ($p < 0.001$). At the end of follow-up, EAT regressed more in the atorvastatin than in the pravastatin group (median, −3.38% vs. −0.83%, $p = 0.025$). The EAT percent change from baseline was significant in the atorvastatin, but not the pravastatin group ($p < 0.001$ and $p = 0.2$, respectively). There was no correlation between lipid lowering and EAT regression. CAC progressed significantly in both groups from baseline.

Conclusions In hyperlipidemic post-menopausal women, statin therapy induced EAT regression, although intensive therapy was more effective than moderate-intensity therapy. This effect does not seem linked to low-density lipoprotein lowering and may be secondary to other actions of statins such as anti-inflammatory effects. (J Am Coll Cardiol 2013;61:1956–61) © 2013 by the American College of Cardiology Foundation

Epicardial adipose tissue (EAT) is a novel marker of coronary atherosclerosis risk and is believed to participate in the pathogenesis of coronary plaque formation through a paracrine effect (1,2). It is associated not only with the presence of but also with some features of vulnerability of atherosclerotic plaques (3–5).

Intensive lipid-lowering therapy with statins has been shown to halt the progression of atherosclerosis (6). We previously reported the effect of intensive versus moderate lipid-lowering therapy on coronary artery calcium (CAC) in a randomized trial of hyperlipidemic post-menopausal women and described the progression of CAC in both study arms with no significant difference between treatments (7).

See page 1962

In the current analysis, we sought to investigate the effect of intensive versus moderate lipid-lowering therapy on EAT in the same population.

Methods

Study population. The study protocol was previously described in detail (7) and is summarized briefly here. The BELLES (Beyond Endorsed Lipid Lowering with Electron

From the *Division of Cardiology, Department of Medicine, Emory University, Atlanta, Georgia; †Division of Cardiothoracic Imaging, Department of Radiology and Imaging Sciences, Emory University, Atlanta, Georgia; ‡Department of Biostatistics and Bioinformatics, Emory University, Atlanta, Georgia; and the §Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 24, 2012; revised manuscript received December 10, 2012; accepted December 16, 2012.

Beam Tomography Scanning) trial (7) enrolled 615 hyperlipidemic post-menopausal women to study the effect of moderate versus aggressive lipid-lowering treatment with statins on the progression of CAC, and 475 of the patients enrolled completed the study. For the purpose of the current analyses, we reviewed all available chest computed tomography (CT) scans of adequate quality to measure EAT. Thus, the study population consisted of 420 women with either surgically induced or spontaneous menopause, and serum levels of low-density lipoprotein (LDL) >130 mg/dl if they had known coronary heart disease or a 10-year Framingham risk score >10%; the serum LDL level at enrollment could be >160 mg/dl if the 10-year Framingham risk score was <10% (7). Of the original 475 patients, 55 patients were excluded from these analyses because of an error that occurred at the time the CT images were stored in DICOM format; this error rendered the interpretation of the images impossible. The clinical characteristics of the 55 excluded patients were identical to those of the 420 patients included in these analyses.

Patients underwent an initial screening visit, which included an assessment of their medical history, coronary heart disease risk profile, and laboratory testing. If they met the inclusion/exclusion criteria, they were then eligible to undergo the baseline chest CT scan and be randomized. Patients were randomized to a double-blind treatment with either atorvastatin 80 mg/day and matching pravastatin placebo or pravastatin 40 mg/day and matching atorvastatin placebo, all taken at bedtime. A follow-up CT scan was scheduled at 12 months after randomization. The study was approved by the review committee of each participating institution, and the subjects gave informed consent to participate.

CT imaging for CAC and EAT assessment. Electron beam CT scanning was performed with C-150 Imatron scanners (GE Imatron, San Francisco, California). Both baseline and follow-up scans were performed using a standard imaging protocol, as previously described (7). A total of 36 to 40 slices spanning from the carina to the diaphragm, 3-mm thick, were obtained during a single breath hold. A calcified coronary plaque was considered present if at least 3 contiguous pixels with a minimal attenuation of 130 Hounsfield units were detected along the course of the coronary artery tree and the calcium volume score (CVS) was calculated as previously described (8).

The EAT volume was measured on the same axial images as those used for CAC scoring (Fig. 1), using the Volume Analysis software of a Leonardo workstation (Siemens, Erlangen, Germany), as previously described (9). All slices from the bifurcation of the pulmonary artery to the diaphragm were used for the analyses. The region of interest containing the heart and the surrounding EAT was assessed by manually tracing the epicardium in the axial slices; a threshold of −190 to −30 HU units was then applied to isolate the fat-containing voxels. The fat voxels were summed to obtain the total EAT volume in milliliters. All measurements were made by 3 experienced investigators blinded to the patients' treatment and all other clinical data, as previously described (3,9). A random sample of 50 patient scans was selected for the 3 investigators to perform repeat, blinded readings. This allowed the calculation of intra- and inter-reader repeatability of EAT measurements. The average intrareader variability for all investigators was <1% (between 0.6% and 0.8%), representing a high degree of reliability in the repeat measurements.

Abbreviations and Acronyms

BMI = body mass index
CAC = coronary artery calcium
CT = computed tomography
CVS = calcium volume score
EAT = epicardial adipose tissue
HDL = high-density lipoprotein
LDL = low-density lipoprotein

Statistical analysis. Continuous variables are presented as median and range, whereas categorical variables are presented as frequencies and percentages. The variables CAC, EAT, total cholesterol, triglycerides, HDL, and LDL had 2 data points (baseline and final) for each subject. The percent change between 2 data points for each individual parameter in each subject was calculated as (final − baseline)/baseline · 100 and used for the analysis. Non-HDL cholesterol was calculated as total cholesterol − HDL. Wilcoxon rank sum test was used to compare the percent change of CVS, EAT, total cholesterol, triglycerides, HDL, non-HDL, and LDL between the 2 treatment arms (atorvastatin vs. pravastatin). A chi-square test or Fisher exact

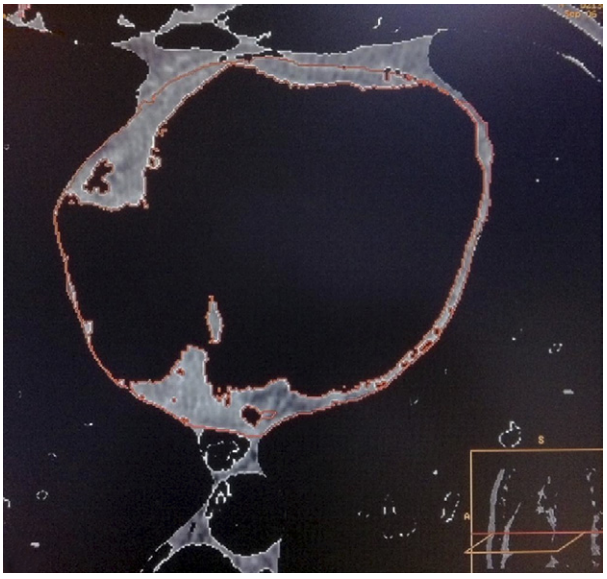

Figure 1 Example of Epicardial Adipose Tissue Extraction From Computed Tomography Images

Single axial image of the heart showing epicardial adipose tissue **(gray filling)** between the **orange lines**. After applying an attenuation threshold of −190 to −30 Hounsfield units, all myocardial structures except for fat-containing voxels are removed. The **gray areas** outside the **orange lines** and adjacent to the parietal pericardium represent paracardial adipose tissue. The **inset** shows at what level of the myocardium the axial slice was obtained.

JACC Vol. 61, No. 19, 2013
May 14, 2013:1956–61

Table 1 Baseline Characteristics in the 2 Treatment Groups

Characteristic	Atorvastatin (n = 194)	Pravastatin (n = 226)	p Value
Age, yrs	64.5 (52.6–79.6)	65.4(50.3–77.7)	0.548*
BMI, kg/m^2	27.6 (17.4–46.4)	28.2 (15.9–47.5)	0.194*
Race			0.224†
Asian	3 (1.55)	0 (0)	
Black	10 (5.15)	8 (3.56)	
Hispanic	6 (3.09)	6 (2.67)	
Other	0 (0)	2 (0.89)	
White	175 (90.21)	209 (92.89)	
HRT	46 (23.7)	51 (22.6)	0.781‡
Hypertension	75 (38.7)	98 (43.4)	0.329‡
Diabetes	26 (13.4)	35 (15.5)	0.546‡
History of MI	5 (2.6)	4 (1.8)	0.738†
CABG	1 (0.5)	2 (0.9)	1.000†
Angina	14 (7.2)	15 (6.6)	0.815‡
PVD	11 (5.7)	18 (8.0)	0.355‡
Smoker	114 (58.8)	131 (58)	0.869‡
Cholesterol			
Total	269 (148–395)	262 (147–470)	0.428*
LDL	174.5 (55–287)	171 (76–318)	0.333*
HDL	56 (28–110)	57 (32–103)	0.358*
Non-HDL	210 (70–337)	204 (105–436)	0.223*
TGs	164 (65–618)	157 (46–674)	0.419*
EAT volume	105.0 (34.9–271.6)	103.6 (39.5–307.4)	0.950*
CVS	136.2 (10.3–3,057.5)	173.3 (0–4,586.6)	0.071*

Values are median (range) or n (%). *p value is calculated by Wilcoxon rank sum test. †p value is calculated by the Fisher exact test. ‡p value is calculated by the chi-square test.

BMI = body mass index; CABG = coronary artery bypass grafting; CVS = calcium volume score; EAT = epicardial adipose tissue; HDL = high-density lipoprotein; HRT = hormone replacement therapy; LDL = low-density lipoprotein; MI = myocardial infarction; PVD = peripheral vascular disease; TGs = triglycerides.

test was used to compare patient binary or categorical characteristics between the 2 treatment arms. A paired Student *t* test was used to test the significance of the percent change from the pre- to post-treatment in CVS or EAT within each treatment group. Analysis of variance or Pearson correlation coefficient was used to examine the relationship of baseline EAT with total cholesterol, LDL, HDL, non-HDL, triglycerides, body mass index (BMI), CVS, age, presence or absence of diabetes, hypertension, and smoking. Pearson correlation coefficients were estimated to measure the relationship between the percent change in EAT with the percent change in total, LDL and non-HDL cholesterol, and triglycerides within the whole group, the atorvastatin group, and pravastatin group. A general linear model was used to estimate the adjusted relationship of the percent change in EAT with the percent change in CVS, non-HDL, triglycerides, and LDL in the whole group, the atorvastatin group, and the pravastatin group after adjusting for BMI and other variables. A logistic regression analysis was used to identify the best independent predictors of a minimum EAT change of 1% among the following variables: age, BMI, hypertension, diabetes mellitus, baseline and change in serum levels of LDL and non-HDL cholesterol. The significance level was set at 0.05 for all tests. The SAS statistical package version 9.2 (SAS Institute, Inc., Cary, North Carolina) was used for data management and analysis.

Results

Of the 420 patients, 194 received atorvastatin and 226 pravastatin. The clinical characteristics of the 2 groups are presented in Table 1.

The median and range EAT volumes at baseline were not different between the atorvastatin (105, 34.9 to 271.6 ml) and pravastatin (103.6, 39.5 to 307.4 ml) groups ($p = 0.95$); at baseline, EAT was larger in hypertensive than in normotensive patients (median and range: 113, 35 to 307 vs. 98, 36 to 272 ml; $p < 0.001$) and in diabetic than in nondiabetic patients (119, 71 to 248 ml vs. 102, 35 to 307 ml; $p < 0.001$). EAT volume was weakly but significantly correlated with age ($r = 0.206$), BMI ($r = 0.469$), HDL ($r = -0.239$), triglyceride levels ($r = 0.213$), and CVS ($r = 0.214$) ($p < 0.001$ for all correlations).

At the end of follow-up (Table 2), the atorvastatin group experienced a greater percent decrease compared with the pravastatin group in total cholesterol (median: −39.2% vs. −19.6%; $p < 0.001$), LDL cholesterol (median: −53.3% vs. −28.3%; $p < 0.001$), triglycerides (median, −28.2% vs. −13.6%; $p < 0.001$), and non-HDL cholesterol (median: −49.7% vs. −25.5%; $p < 0.001$) levels; there was a small HDL cholesterol increase that was nonsignificantly different between treatment groups (median: 2.1% atorvastatin vs. 4% pravastatin; $p = 0.18$). At the end of treatment, the percent EAT reduction was significantly greater in the atorvastatin-

Table 2 Effect of Atorvastatin and Pravastatin on Lipid Serum Levels, CAC, and EAT

Parameter	Atorvastatin (n = 194)	Pravastatin (n = 226)	p Value
Percent change in TC	−39.2 (−57.9 to 15.7)	−19.6 (−42.6 to 43.5)	<0.001*
Percent change in LDL	−53.3 (−69.4 to 20.2)	−28.3 (−54.8 to 73.7)	<0.001*
Percent change in non-HDL	−49.7 (−65.7 to 15.4)	−25.5 (−53.0 to 50.5)	<0.001*
Percent change in HDL	2.1 (−33.3 to 41.7)	4.0 (−28.1 to 52.6)	0.181*
Percent change in TG	−28.2 (−79.1 to 157.7)	−13.6 (−73.4 to 135.8)	<0.001*
Percent change in CVS	12.1 (−63.4 to 207.8)	12.7 (−75.1 to 358.3)	0.45*
Percent change in EAT	−3.38 (−30.1 to 40.1)	−0.83 (−37.9 to 62.8)	0.025*

Values are median (range). *p value is calculated by the Wilcoxon rank sum test.

CVS = calcium volume score; TC = total cholesterol; other abbreviations as in Table 1.

treated patients than in the pravastatin-treated patients (median: −3.38% vs. −0.83%; p = 0.025, Table 2). The percent EAT change from baseline was significant in the atorvastatin (p < 0.001), but not in the pravastatin (p = 0.2) group. Identical results were obtained when using absolute change rather than relative change in EAT (data not shown). Although the serum lipids were lowered significantly in both statin groups, there was no significant correlation between reduction in total, LDL, non-HDL cholesterol, triglycerides, and EAT reduction in either treatment arm (Fig. 2). The CVS progressed significantly from baseline in both treatment arms (p < 0.001 for both treatment arms from baseline; p = 0.45 between groups) (Table 2).

The single best independent predictor of a minimum EAT change of ≥1% was the baseline non-HDL cholesterol level (odds ratio: 0.991; 95% confidence interval: 0.985 to 0.996; p = 0.002) in a model containing age, BMI, hypertension, diabetes mellitus, and baseline and change in serum levels of LDL and non-HDL cholesterol.

Discussion

We showed that intensive lipid-lowering therapy with atorvastatin for 1 year was associated with a significant reduction in EAT volume in postmenopausal women. This effect was not observed in the group that received more moderate statin treatment; the difference between the 2 treatment arms was significant. Even in the absence of a significant regression from baseline, the pravastatin group may have benefitted from treatment. In fact, extrapolating from a previous publication (10), the average yearly EAT percent change approximated 3% in 249 subjects with stable body weight followed for 4 years. This is substantially larger than the 3% regression we observed in the atorvastatin-treated patients, but also larger than what we observed in the pravastatin-treated arm.

EAT has emerged as a novel marker of coronary atherosclerosis risk; it has been associated with subclinical coronary atherosclerosis, coronary obstructive disease (11), and adverse cardiac events (12). It has been suggested that EAT may play a pathogenetic role in the inception and progression of coronary atherosclerosis through paracrine effects and by supporting local inflammatory activities (2,13,14). Of interest, EAT volume has been shown to be larger in patients with coronary atherosclerotic lesions demonstrating features of vulnerability such as low-density cores, positive remodeling, and spotty calcification (4,5), and in patients with acute coronary syndromes (15).

Several primary and secondary prevention trials have demonstrated the ability of statins to reduce cardiovascular events in a broad range of populations. Intensive lipid lowering with statins inhibited the progression of atherosclerotic plaques in the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering Therapy) (16) and the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) (17) trials; furthermore, intensive statin therapy has been linked with a greater reduction in cardiovascular events compared with moderate lipid-lowering treatment (18). This has been attributed mainly to the larger cholesterol-lowering effect achieved with intensive lipid-lowering treatment; however, there is evidence that statins exert an anti-inflammatory effect that may play an important role in risk reduction (19,20). Of note, a greater reduction in CRP was found in patients receiving atorvastatin compared with pravastatin in

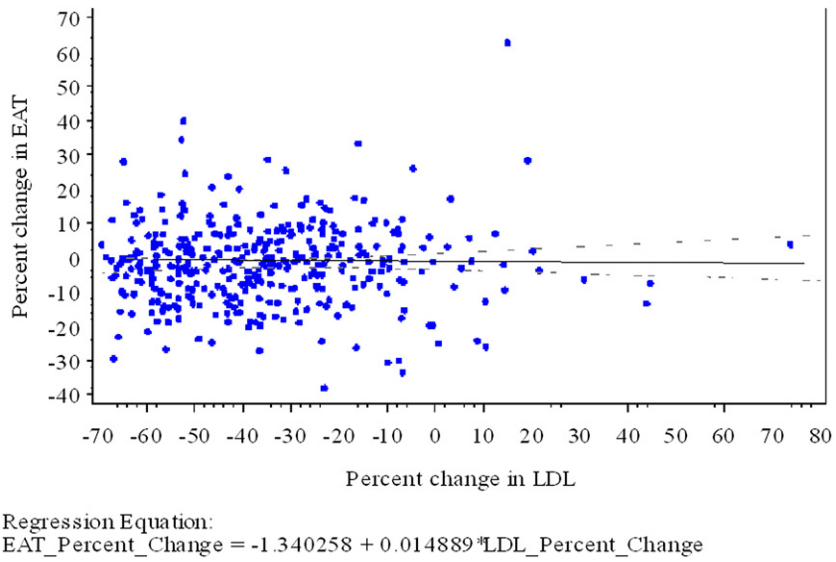

Figure 2 **Correlation of EAT and LDL Change**

Scatterplot of the percent change in epicardial adipose tissue (EAT) and low-density lipoprotein (LDL) for all patients showing no correlation between these 2 endpoints.

a previous study (18). This is relevant to our study as there is evidence that epicardial visceral fat is a source of inflammatory mediators.

The current study was a subanalysis of the BELLES trial designed to address the effect of aggressive versus moderate statin therapy on CAC progression in post-menopausal hyperlipidemic women. As reported in the original publication, intensive lipid-lowering therapy did not reduce CAC progression compared with moderate lipid-lowering therapy (7), an effect later confirmed in a study including both men and women (21). These publications demonstrated that sequential CAC imaging is the wrong surrogate marker to assess the effectiveness of lipid-lowering therapies. Indeed, a healing plaque may be accumulating calcium to replace the lipid core (22,23).

In contrast, in these subanalyses of the BELLES trial, we demonstrated that EAT can be reduced with intensive statin therapy. The mechanisms involved in the observed EAT regression are not known at this time and only speculative considerations can be offered. In animal experiments, statins have been shown to reduce inflammation in the visceral adipose tissue as well as the arterial wall (24,25); obese mice treated with statins exhibited a lower adipose tissue mass (25). However, a short-term study of atorvastatin therapy in patients with documented atherosclerosis did not show an effect on visceral adipose tissue (26), whereas weight loss was associated with a reduction in EAT in a small patient sample (10). In the BELLES trial, body weight and BMI were measured only at baseline; therefore, we are unable to determine whether the measured change in EAT volume was accompanied by a parallel decrease in body weight. However, to our knowledge, there is currently no evidence that statin use is associated with weight loss, although such a question has been addressed in several multicenter statin trials. Finally, in a recent publication, Takase et al. (27) demonstrated a reduction in visceral abdominal fat tissue after 6 months of treatment with ezetimibe compared with placebo. The reduction was not correlated with LDL lowering, as seen in our study, and patients did not show any weight change while on treatment. The reduction in visceral abdominal fat tissue was also associated with an increase in adiponectin and was not accompanied by a parallel reduction in subcutaneous fat.

Our findings may support the notion that atherosclerosis is a perivascular disease rather than an intravascular phenomenon (28–30). In fact, experimental evidence suggests that lipids may be brought into the intima via the vasa vasorum penetrating from the adventitia through the vessel wall (27–29). Furthermore, recent research suggests that intensive lipid-lowering therapy reduces the concentration of vasa vasorum around the human carotid artery (31).

In the present study, we used noncontrast-enhanced electron beam CT scans previously obtained to measure CAC with a standardized protocol. EAT can be measured easily on the same scans without adding unnecessary radiation exposure, time, and cost for the patient. EAT can be measured on either noncontrast or contrast-enhanced cardiac CT images, with very good reproducibility (32), and our investigators demonstrated a high-degree of accuracy. We used the term epicardial to denote all adipose tissue surrounding the heart, but confined within the parietal layer of the pericardium; this is in line with previous publications from our research group (2,3,9,33) as well as others (4,15,34,35).

Study limitations. The BELLES trial enrolled only post-menopausal hyperlipidemic women, and our results do not automatically extend to men and other populations with a different risk profile. The original study was not designed to measure EAT sequentially, and power calculations were based on the expected change in CAC score over a year's time. Weight and BMI were measured only at baseline, and although we have no repeat measurements, weight and BMI never showed a significant change in any of the major statin trials. We did not measure serum high-sensitivity C-reactive protein or other inflammatory markers in our study population; however, it is reasonable to expect a significant reduction in high-sensitivity C-reactive protein with intensive lipid-lowering therapy (36). Furthermore, even in the absence of a systemic effect, the regional effect on adipose tissue would be of greater interest, but this could only be tested with pericardial biopsies that are obviously impractical. All patients enrolled in the BELLES trial were treated with 1 of 2 statins, and the absence of a placebo control prevented us from assessing the natural history of EAT over time. The fact that EAT is positively associated with age, however, suggests that there is a natural tendency for EAT to increase over time, and the negative trend shown by patients in both treatment arms suggests an actual impact of active therapy on this marker.

Conclusions

We demonstrated that intensive lipid-lowering therapy with atorvastatin induced significant EAT regression in a subanalysis of a large randomized clinical trial of hyperlipidemic post-menopausal women; moderate-intensity lipid-lowering therapy did not attain equal results. Although the extent of EAT has been associated with the presence of subclinical atherosclerosis and adverse outcomes, there is currently no knowledge of the prognostic impact of EAT regression or the extent of EAT regression that might be linked with an improved outcome; future studies should address this interesting question. EAT volume modulation may be one of the unsuspected mechanisms whereby statins influence a patient's outcome. Due to its ease of measurement, especially compared with intravascular imaging methodologies, sequential EAT measurements may become a useful method to assess the effectiveness of risk-reduction therapies.

Reprint requests and correspondence: Dr. Paolo Raggi, Mazankowski Alberta Heart Institute, University of Alberta School of Medicine, 8440-112 Street, Suite 4A7.050, Edmonton, Alberta T6G2B7, Canada. E-mail: raggi@ualberta.ca.

REFERENCES

1. Iacobellis G, Sharma AM. Epicardial adipose tissue as new cardiometabolic risk marker and potential therapeutic target in the metabolic syndrome. Curr Pharm Des 2007;13:2180–4.
2. McLean DS, Stillman AE. Epicardial adipose tissue as a cardiovascular risk marker. Clin Lipidol 2009;4:55–62.
3. Alexopoulos N, McLean DS, Janik M, Arepalli CD, Stillman AE, Raggi P. Epicardial adipose tissue and coronary artery plaque characteristics. Atherosclerosis 2010;210:150–4.
4. Oka T, Yamamoto H, Ohashi N, et al. Association between epicardial adipose tissue volume and characteristics of non-calcified plaques assessed by coronary computed tomographic angiography. Int J Cardiol 2012;161:45–9.
5. Schlett CL, Ferencik M, Kriegel MF, et al. Association of pericardial fat and coronary high-risk lesions as determined by cardiac CT. Atherosclerosis 2012;222:129–34.
6. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004; 291:1071–80.
7. Raggi P, Davidson M, Callister TQ, et al. Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). Circulation 2005;112:563–71.
8. Callister TQ, Cooil B, Raya SP, Lippolis NJ, Russo DJ, Raggi P. Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. Radiology 1998;208: 807–14.
9. Lipson A, Alexopoulos N, Hartlage GR, et al. Epicardial adipose tissue is increased in patients with systemic lupus erythematosus. Atherosclerosis 2012;223:389–93.
10. Nakazato R, Rajani R, Cheng VY, et al. Weight change modulates epicardial fat burden: a 4-year serial study with non-contrast computed tomography. Atherosclerosis 2012;220:139–44.
11. Taguchi R, Takasu J, Itani Y, et al. Pericardial fat accumulation in men as a risk factor for coronary artery disease. Atherosclerosis 2001;157: 203–9.
12. Ding J, Hsu FC, Harris TB, et al. The association of pericardial fat with incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr 2009;90:499–504.
13. Iacobellis G, Ribaudo MC, Assael F, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 2003;88:5163–8.
14. Baker AR, Silva NF, Quinn DW, et al. Human epicardial adipose tissue expresses a pathogenic profile of adipocytokines in patients with cardiovascular disease. Cardiovasc Diabetol 2006;5:1.
15. Harada K, Amano T, Uetani T, et al. Cardiac 64-multislice computed tomography reveals increased epicardial fat volume in patients with acute coronary syndrome. Am J Cardiol 2011;108:1119–23.
16. Schoenhagen P, Tuzcu EM, Apperson-Hansen C, et al. Determinants of arterial wall remodeling during lipid-lowering therapy: serial intravascular ultrasound observations from the Reversal of Atherosclerosis with Aggressive Lipid Lowering Therapy (REVERSAL) trial. Circulation 2006;113:2826–34.
17. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006;295:1556–65.
18. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–504.
19. Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005;352:20–8.
20. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.
21. Schmermund A, Achenbach S, Budde T, et al. Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. Circulation 2006;113: 427–37.
22. Corti R, Fayad ZA, Fuster V, et al. Effects of lipid-lowering by simvastatin on human atherosclerotic lesions: a longitudinal study by high-resolution, noninvasive magnetic resonance imaging. Circulation 2001;104:249–52.
23. Zhao XQ, Yuan C, Hatsukami TS, et al. Effects of prolonged intensive lipid-lowering therapy on the characteristics of carotid atherosclerotic plaques in vivo by MRI: a case-control study. Arterioscler Thromb Vasc Biol 2001;21:1623–9.
24. Abe M, Matsuda M, Kobayashi H, et al. Effects of statins on adipose tissue inflammation: their inhibitory effect on MyD88-independent IRF3/IFN-beta pathway in macrophages. Arterioscler Thromb Vasc Biol 2008;28:871–7.
25. Khan T, Hamilton MP, Mundy DI, Chua SC, Scherer PE. Impact of simvastatin on adipose tissue: pleiotropic effects in vivo. Endocrinology 2009;150:5262–72.
26. Wu YW, Kao HL, Huang CL, et al. The effects of 3-month atorvastatin therapy on arterial inflammation, calcification, abdominal adipose tissue and circulating biomarkers. Eur J Nucl Med Mol Imaging 2012;39:399–407.
27. Takase H, Dohi Y, Okado T, Hashimoto T, Goto Y, Kimura G. Effects of ezetimibe on visceral fat in the metabolic syndrome: a randomised controlled study. Eur J Clin Invest 2012;42:1287–94.
28. Stary HC, Blankenhorn DH, Chandler AB, et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation 1992;85: 391–405.
29. Subbotin V. Neovascularization of coronary tunica intima (DIT) is the cause of coronary atherosclerosis. Lipoproteins invade coronary intima via neovascularization from adventitial vasa vasorum, but not from the arterial lumen: a hypothesis. Theor Biol Med Model 2012;9:11.
30. Moreno PR, Purushothaman K-R, Sirol M, Levy AP, Fuster V. Neovascularization in human atherosclerosis. Circulation 2006;113: 2245–52.
31. Dong L, Kerwin WS, Chen H, et al. Carotid artery atherosclerosis: effect of intensive lipid therapy on the vasa vasorum-evaluation by using dynamic contrast-enhanced MR imaging. Radiology 2011;260: 224–31.
32. Nichols JH, Samy B, Nasir K, et al. Volumetric measurement of pericardial adipose tissue from contrast-enhanced coronary computed tomography angiography: a reproducibility study. J Cardiovasc Comput Tomogr 2008;2:288–95.
33. Janik M, Hartlage G, Alexopoulos N, et al. Epicardial adipose tissue volume and coronary artery calcium to predict myocardial ischemia on positron emission tomography-computed tomography studies. J Nucl Cardiol 2010;17:841–7.
34. Gorter PM, de Vos AM, van der Graaf Y, et al. Relation of epicardial and pericoronary fat to coronary atherosclerosis and coronary artery calcium in patients undergoing coronary angiography. Am J Cardiol 2008;102:380–5.
35. Yerramasu A, Dey D, Venuraju S, et al. Increased volume of epicardial fat is an independent risk factor for accelerated progression of sub-clinical coronary atherosclerosis. Atherosclerosis 2012; 220:223–30.
36. Ray KK, Cannon CP, McCabe CH, et al. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2005;46:1405–10.

Key Words: atherosclerosis ■ epicardial adipose tissue ■ statins.