Journal of the American College of Cardiology Vol. 61, No. 19, 2013

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.02.024

EDITORIAL COMMENT

Statins

Still in Pursuit of Pleotrophic Effects*

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Statins have long been known to have multiple pleotrophic effects, those beyond lowering cholesterol alone. These additional benefits of statins (i.e., inflammation reduction, plaque stabilization, endothelial function improvement) have most likely been partially responsible for the cardiovascular benefits of this class of agents. Inflammation substudies from 2 secondary prevention trials—PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection-TIMI 22) (1) and REVERSAL (Reversing Atherosclerosis With Aggressive Lipid Lowering) (2)—have shown that intensive therapy with atorvastatin 80 mg compared with pravastatin 40 mg achieves a greater decrease in low-density lipoprotein (LDL) cholesterol and C-reactive protein (CRP) levels, and together, they are associated with a greater reduction in clinical events and progression of atherosclerotic plaque burden.

See page 1956

However, just evaluating CRP has proved to be a poor predictor of cardiovascular events and is unlikely the primary mechanism of benefit (3). New research suggests that statins modify the epicardial adipose tissue (EAT), which is the visceral fat around the heart, and this effect may be independent of a lipid-lowering effect. Alexopoulos et al. (4) in this issue of the *Journal*, show the differential effect of high- and moderate-dose statins (using the same statin doses as those used in both PROVE-IT and REVERSAL) on the epicardial fat surrounding the heart. This study demonstrated that statin therapy induced EAT regression, and intensive therapy (atorvastatin 80 mg/day) was more effective than moderate-intensity therapy (pravastatin 40 mg/day). The investigators conclude that this effect does not seem to be linked to LDL lowering. This raises the interesting questions of whether this represents another pleotrophic effect of the statins and whether this is a direct anti-inflammatory effect, manifesting by decreasing the volume of the paracrine or endocrine organ responsible for the production of cytokines.

There have been several notable failures in the attempt to discern the relative benefit of the nonlipid-lowering pleotrophic effects of statins. Notably, the aforementioned PROVE-IT trial (1) demonstrated that the lower LDL attained with atorvastatin was associated with fewer cardiovascular events (CVEs), despite a hypothesis that pravastatin, a statin previously shown to have significant pleotrophic properties, would be at least as good in decreasing CVEs. Following this, the JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial (5) demonstrated reverse epidemiology for an anti-inflammatory effect benefit. In those persons with high-sensitivity CRP (hsCRP) levels above a median of 4.3 mg/dl randomized to rosuvastatin, there was significantly less benefit than in those who started with an hsCRP level below the median ($p = 0.015$). Kaul et al. (5) demonstrated that "the benefit is significantly greater in those with an hsCRP level lower than the median (4.2 mg/l) and nonsignificantly greater in those with an hsCRP level lower than 3 mg/l. These data imply an inverse dose-response of hsCRP in the treatment arm." This undermines the concept of statins' effect on CVEs being related to inflammation reduction directly and higher levels of inflammation predicting better CVE reduction. JUPITER demonstrated that those patients with lower hsCRP had a greater benefit from rosuvastatin, and, unfortunately, those with hsCRP <2 mg/dl were excluded. Furthermore, JUPITER failed to demonstrate any benefit in the subset of patients with an isolated CRP increase. Thus, if we hope to have a better understanding of the true benefits of therapies, we need better biomarkers to evaluate their individual effects.

Although numerous studies have documented the prognostic value of coronary artery calcium on noncontrast computed tomography of the heart, more recent studies are reporting the independent and incremental prognostic importance of the fat surrounding the heart (6). This EAT (or pericardial fat) is associated with multiple markers of inflammation, vascular dysfunction, and oxidative stress and also predicts major CVEs (6–8). Investigators have suggested that excessive nonsubcutaneous fat deposition may play a role in the function of surrounding tissues and organs through the inflammatory cytokines and free fatty acid secretion, leading to ischemia, cardiovascular disease, and coronary obstruction (7–9).

Epicardial fat volume, as a direct measure on computed tomography, may afford us newer insights into the differential effects of commonly used therapies. The potential use in evaluating drug therapy on cardiovascular disease risk and metabolism is significant. Newer oral hypoglycemic, anti-inflammatory, and lipid-lowering therapies can all potentially benefit from better techniques to evaluate their noncholesterol benefits. This study further validates the need to add to serum biomarkers with better techniques that can

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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visualize changes associated with improved outcomes. However, before we use this new technique in clinical practice, outcome studies validating that progression of EAT is associated with increased CVEs and/or regression is associated with cardiovascular protection need to be conducted.

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Key Words: atherosclerosis ■ epicardial adipose tissue ■ statins.