Letters to the Editor

Statins and Altered Glucose Metabolism
A Laboratory Curiosity or a New Disease?

Koh et al. (1), in a small number of patients given atorvastatin, showed that despite reductions in low-density lipoprotein cholesterol, atorvastatin treatment resulted in significant increases in fasting insulin and glycated hemoglobin levels consistent with insulin resistance in patients with hypercholesterolemia. These results are in agreement with our studies in 345,417 veteran patients (mean age 61 years; 94% men; 6% with diabetes), which showed that in patients without diabetes as well as those with diabetes, fasting blood sugar increased with the use of any statin (p < 0.0001) (2). After adjustment for age and the use of aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors, the change in fasting blood sugar in patients without diabetes using statins was 7 mg/dl (vs. 5 mg/dl in patients not using statins; p < 0.0001), and for patients with diabetes using statins, it was 39 mg/dl (vs. 32 mg/dl in patients not using statins; p < 0.0001).

Sattar et al. (3) found a small but significant increase in diabetes in patients taking statins in an analysis of the results of several randomized controlled trials of statins.

The mechanisms by which statins may influence glucose metabolism are unclear. We suggested that statins may alter glycemic control by decreasing various metabolites, such as isoprenoid, farnesyl pyrophosphate, geranylgeranyl pyrophosphate, and ubiquinone, which enhance glucose uptake via glucose transporter type 4 in adipocytes and impair insulin release (2).

However, further work needs to be done to define the following: 1) Are the outcomes of patients who develop diabetes on statins different from those who do not? In other words, is the rise in fasting blood sugar just a laboratory curiosity or a real disease? 2) Do patients who develop diabetes need to be treated similarly as those who develop diabetes while not taking statins? 3) How soon after starting statins does altered glucose metabolism become evident? 4) Is the altered glucose metabolism related to the dose of statins? and 5) What is the precise mechanism of altered glucose metabolism?

Reply

We thank Dr. Mehta for commenting on our study (1). We agree that it is of significant clinical interest to understand potential mechanisms by which some statins have detrimental effects on glucose homeostasis whereas other statins improve the metabolic phenotype. Sukhija et al. (2) suggested that statins alter glycemic control by decreasing various isoprenoids that enhance glucose uptake via glucose transporter type 4 in adipocytes and contribute to insulin release.

Recent experimental studies have demonstrated that compared with hydrophilic statins, lipophilic statins have pleiotropic actions that cause unfavorable metabolic effects, such as reduction of insulin secretion and exacerbation of insulin resistance (3,4). Sattar et al. (5) showed that risk for the development of diabetes with statins is highest in older participants, while trials with pravastatin have reduced the development of diabetes in participants below a mean age of 65 years. We previously observed that pravastatin improves insulin sensitivity, whereas simvastatin worsens insulin resistance despite comparable improvements in lipid profiles and endothelium-dependent vasodilation in patients with hypercholesterolemia (6). These differential metabolic actions of lipophilic and hydrophilic statins are consistent with recent meta-analyses (7). Among plausible mechanisms that deserve further investigation are potential central nervous system actions of lipophilic statins to impair glucose homeostasis.

Certainly, mechanisms by which atorvastatin treatment results in increased fasting insulin and glycated hemoglobin levels require further investigation. Our observations are consistent with analyses of atorvastatin therapy and the incidence of diabetes (8). It is particularly important to investigate mechanisms of differential metabolic effects of various statins in patients at risk for metabolic diseases, including diabetes, obesity, and metabolic syndrome.

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Prognostic Factors in Patients With Implantable Cardioverter-Defibrillators

We have read with great interest the report by Borleffs et al. (1) about atrial fibrillation (AF) and mortality in patients with implantable cardioverter-defibrillators (ICDs). The investigators found that AF is a prognostic factor in ICD patients, but some issues need to be considered.

The association between higher New York Heart Association (NYHA) functional class and poor outcome in heart failure is well known. Among unselected patients with NYHA functional class II, III, and IV heart failure, mortality was 7.1%, 15.0%, and 28.0%, respectively (2). In the study of Borleffs et al. (1), although the proportion of patients in NYHA functional classes III and IV in the permanent AF group was 56%, this proportion was 35% in the paroxysmal AF group and 33% in the non-AF group. The investigators state that the mortality rates in these groups were 25%, 13%, and 10%, respectively. However, it is possible that independent of other prognostic factors, the discrepancy in the proportions of patients in NYHA functional classes III and IV in AF groups may be a contributing factor to the differing mortality rates. Therefore, specific mortality rates in NYHA groups are needed to correctly interpret the study’s results.

Another important issue is the types of devices used. Although Borleffs et al. (1) state the rates of single- and dual-chamber ICDs, some points are unclear. The investigators concluded that patients with permanent AF showed more than twice the risk for appropriate and inappropriate therapies compared with patients with no histories of AF. However, all ICD patients, without mention of the manufacturers and models of ICDs, were included in the study. It is known that dual-chamber ICDs (DDD[R] ICDs and cardiac resynchronization therapy ICDs) can easily discriminate supraventricular tachycardia from ventricular tachycardia. However, single-chamber ICDs can discriminate supraventricular tachycardia from ventricular tachycardia by using different software algorithms. For example, Medtronic (Minneapolis, Minnesota) ICDs use morphology, stability, onset, and wavelet algorithms; Boston Scientific (Natick, Massachusetts) ICDs use atrial view, stability, and onset algorithms; St. Jude Medical (St. Paul, Minnesota) ICDs use stability, onset, and atrioventricular rate branch algorithms; and Biotronik (Berlin, Germany) ICDs use stability, onset, and sustained ventricular tachycardia timer algorithms (3–6). Therefore, supraventricular tachycardia discrimination performance is also different among manufacturers and models. In addition, some dual-chamber ICDs (e.g., Medtronic’s Virtuso, Secura, and Entrust models and St. Jude’s Current DR and Atlas II models) can convert atrial tachyarrhythmias to sinus rhythm using atrial anti-tachycardia pacing and atrial cardioversion. The use of different manufacturers and device types would result in different AF episodes and appropriate and inappropriate therapies. All of these differences might affect the results of the study by Borleffs et al. (1).

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Reply

We thank Dr. Kalay and colleagues for their interest in and positive comments on our study (1). We fully agree that New York Heart Association (NYHA) functional class should be considered