EDITORIAL COMMENT

In the Statin Era, How Important Are Intense Lifestyle Changes?*

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The patient sitting across from me in my office seems to have lipids controlled with a reasonable diet and a daily statin. He asks, “Doctor, can I have an occasional steak, and an occasional hot fudge sundae?” As a believer in the importance of quality of life, I am likely to concur with such a request. In my mind I am probably rationalizing that the statin will easily cover such indiscretions because of its powerful effects in both primary and secondary prevention.

In this issue of the *Journal*, Sdringola et al. (1) suggest that my attitude may be too cavalier. They make a case for intense lifestyle changes bringing added benefit to patients on top of statin therapy. A total of 409 consecutive unselected patients with coronary artery disease (CAD) had baseline positron emission tomography imaging, repeat imaging at about two and half years, with additional follow-up for five more years. The level of treatment during this time was classified as: *poor* = no dietary control or lipid-active drugs; *moderate* = diet (<10% of calories as fat), regular exercise, weight loss, monthly follow-up, and lipid-active drugs dosed to target cholesterol goals (LDL [low-density lipoprotein] <90 mg/dl). Over the five-year period, coronary events occurred in 6.6%, 20.3%, and 30.6% of patients in the maximal, moderate, and poor treatment groups, respectively. This data is first of all an affirmation that lipid-lowering is beneficial in reducing coronary events.

Similarly, lipid-lowering improved myocardial perfusion judged by PET scan (2). This effect presumably occurred by improved endothelial function and/or plaque regression. The new question of importance, however, is the potential independent benefit from intense lifestyle changes (3).

One of the difficulties in answering the question posed by Sdringola et al. (1) is that this was not a randomized trial. In their introduction, the investigators make a compelling case as to why randomization would be difficult if not impossible. Nevertheless, this remains a major problem with the present study. We have recent examples of how observational studies have been strongly contradicted by subsequent prospective, placebo-controlled, randomized trials. Observational studies of vitamin E intake strongly suggested benefit from taking this antioxidant vitamin (4–6). The rationale seemed intuitive that an antioxidant vitamin would counter the adverse effects of oxidized LDL cholesterol. However, the large placebo-controlled Heart Outcomes Prevention Evaluation (HOPE) (7) and Heart Protection Studies (8) failed to show any benefit from vitamin E.

In a similar way, observational studies of hormone replacement therapy (HRT) have suggested considerable benefit in protecting postmenopausal women from cardiovascular events (9–11). Again, the rationale seems indisputable. Prior to menopause the female hormones seem to be protective, by a number of mechanisms, thus explaining the higher risk in men. After menopause there is a catch-up phenomenon, whereby women have more events than men, a sequence so easily explained by the loss of their protective hormones. Thus, it was quite a surprise when the Heart and Estrogen/progestin Replacement Study (HERS) (12) and the Women’s Health Initiative (13) failed to show protection with HRT in women, and in fact were suggestive of harm.

These two recent examples remind us of a major pitfall of nonrandomized observational studies: you simply cannot control for, or know, all of the variables that affect outcome. In the two observational examples cited above, the patients who benefited from vitamin E (4–6) or HRT (9–11) were probably doing other “healthy things,” which improved the outcome. In the present trial (1), intense lifestyle changes may have been the other “healthy things” that improved the outcome, but we cannot prove it by this study design.

Missing data in this study are the baseline lipids, although there is a similar distribution of patients in the three groups, those who have “hypercholesterolemia,” “hypertriglyceridemia,” and “low high-density lipoprotein (HDL).” When examining the follow-up lipid data, the simplest explanation for the difference in clinical events is the difference in lipids (Table 2 in Sdringola et al. [1]). For the maximal, moderate, and poor treatment groups the total cholesterol levels were 140, 184, and 226 mg%, and the LDL cholesterol levels were 74, 111, and 143 mg%, respectively. This leaves the unanswered question: If lipid levels were the same in all three groups (by adjusting statins), would there have been a similar clinical event rate? In other words, is lowering lipids by intense lifestyle changes to the same extent as statins equally protective?

Another question related to the study by Sdringola et al. (1) is whether all the benefit is related to the level of lipids achieved. In the Scandinavian Simvastatin Survival Study (4S) study with simvastatin in patients with known vascular disease and very high levels of LDL cholesterol, there was a similar percentage reduction in clinical events in patients from all quartiles of initial LDL cholesterol (14). Conversely, in the Cholesterol And Recurrent Events (CARE) trial (15) postmyocardial infarction, it appeared that pravachol was beneficial only in patients with an initial baseline

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LDL cholesterol >125 mg%. However, in the much larger Heart Protection Study (16) there was an equal percent benefit from simvastatin in each tertile of LDL cholesterol, including patients who started below 100 mg%. This suggests that LDL goal levels may be overemphasized since the use of statins may be the key. This may reflect other beneficial effects of statins, such as anti-inflammatory and antithrombotic effects, among other benefits. Relative to the present study, the use of statins in the maximal, moderate, and poor treatment groups was 89%, 64%, and 15%, respectively. Thus, the markedly differing use of statins may have played a role in the results cited by the investigators (1). In contrast, intense lifestyle changes such as exercise, diet, and weight loss may also have other independent benefits besides lowering cholesterol.

Conclusions. In summary, the study by Sdringola et al. (1) is very important in emphasizing the benefit of lifestyle changes and risk factor reduction along with lipid-lowering therapy. It seems reasonable to employ a broad-based approach to both primary and secondary prevention, rather than to depend only on a pill. Because the study by Sdringola et al. (1) was not randomized, it cannot unequivocally prove the added benefit of lifestyle changes. Nevertheless, I agree with the investigators in their important findings that a combination of lifestyle changes and lipid-lowering therapy caused an optimal reduction in clinical events.

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