Do Statins Reduce the Risk for Diabetes by Improving Exercise Capacity?

To the Editor:

In the January 23, 2001, issue of Circulation, Freeman et al undertook a retrospective analysis of data from the West of Scotland Coronary Prevention Study (WOSCOPS) and showed that assignment to pravastatin therapy resulted in a 30% reduction (P=0.042) in the hazard of developing diabetes. They suggested that lowering plasma triglyceride levels may favorably influence the development of diabetes and speculated that the antiinflammatory properties of pravastatin in combination with its endothelial effects may also play a part. In an accompanying editorial, Haffner suggested that the perceived benefit of such an intervention "is likely to be markedly underestimated." 1

It should be noted, however, that the absolute risk reduction in this post hoc analysis was only 0.86% (2.76% in the pravastatin group and 1.90% in the placebo group). As such, 116 subjects would need to be treated for 5 years to prevent 1 case of diabetes. Moreover, the authors' Kaplan-Meier plots showing the percentage of patients developing diabetes (Figure, D) are nearly parallel after 3 and a half years, 2 which suggests that treatment may only delay the development of diabetes for about 1 year.

Lack of exercise is a powerful predictor of risk for diabetes. 3 Increases in physical activity have been shown to prevent progression to diabetes. 4 Thus, one alternative explanation for the modest but unexpected effect found by Freeman et al is the impact that statin therapy has on patients' capacity for physical activity. Angina and other cardiac end points, such as heart failure, have a significant impact on exercise capacity. Improvements in such end points have been shown to result in increased exercise tolerance. A recent meta-analysis of clinical outcomes in 17 statin treatment trials shows an odds benefit ratio of 0.70 (95% CI, 0.65 to 0.76) for angina. 5 Improvements in such end points have been shown in clinical trials to maintain higher levels of physical activity. Other possible mechanisms of action include the reduced risk for diabetes seen by Freeman et al. 1

The practical implication of this is that the antidiabetic properties of statin therapy may be a result of the drug's capacity for improving clinical outcomes in heart disease, rather than any pleiotropic effect specific to pravastatin.

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Response

We welcome the contribution of Drs Ur and Shlossberg to our discussion on the impact of pravastatin on the prevention of new type 2 diabetes mellitus. As we clearly indicated in our article, 1 our conclusions were based on a post hoc analysis of the West of Scotland Coronary Prevention Study (WOSCOPS) database. As such, our aim in publishing was to raise the possibility that pravastatin may have an important preventive effect on the development of this serious condition, in addition to its now well-known effects on the reduction of cardiovascular and cerebrovascular disease risk. In so doing, we hoped to open the debate and stimulate further, more definitive research in this area.

The importance of lifestyle factors on the development of type 2 diabetes in high-risk individuals should not be forgotten. 2 Drs Ur and Shlossberg suggest that an indirect effect of statin therapy may have been to allow patients treated with pravastatin in WOSCOPS to maintain higher levels of physical activity. This possible mechanism of action cannot be excluded by our current analyses, and it deserves further examination, as do the other possible mechanisms of action that we have put forward relating to the lipid-lowering effects of the drug and its effects on endothelial function and inflammatory processes. Only in detailed prospective studies can the potentially beneficial effects of pravastatin be examined fully.

Currently, we are conducting the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). 3 Analyses of this study will allow further evaluation of the different hypotheses that have been generated to explain the important observation in WOSCOPS that subjects receiving pravastatin therapy experienced a statistically significant reduction in their risk of developing type 2 diabetes mellitus during the course of the study. We look forward to continuing this debate when further data are available at the conclusion of PROSPER in 2002.

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Circulation. 2001;104:e104-e105
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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