at 21% but do not mention that the negative predictive value of the tool is 99%; hence, the tool is highly reliable at excluding LADA and has a sensitivity of 90%, meaning that most LADA patients can be identified with the assistance of this noninvasive and cost-free clinical screening tool.

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Efficacy and Safety of Atorvastatin in the Prevention of Cardiovascular End Points in Subjects With Type 2 Diabetes: The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN)

Response to Knopp

We read with interest the results of the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) (1). The composite primary end point rate (10 mg/day atorvastatin versus placebo) showed a hazard ratio of 0.90 (95% CI 0.73–1.12, $P = 0.34$) after 4 years. Knopp et al. (1) highlight some of the differences between ASPEN and previous atorvastatin trials (Collaborative Atorvastatin Diabetes Study and Anglo-Scandinavian Cardiac Outcomes Trial) also involving diabetic individuals without established coronary heart disease (2,3).

Other differences may also be relevant. In ASPEN, 78.3% of those on atorvastatin and 76.4% of those in the placebo group were included in the analysis. This represents a substantial "drop-out" rate. Furthermore, by the end of the study, medication was taken by 67.5% of those in the atorvastatin group and 57.6% of those in the placebo group. The "drop-in" rate in ASPEN was also high; 26.9% of those on placebo and 15.4% of those in the atorvastatin group took concomitant hypolipidemic agents. Nevertheless, LDL cholesterol was reduced by 29% with atorvastatin relative to placebo. Is it possible that among the patients on atorvastatin, some took a second statin? If so, how many of the placebo-treated patients were taking a statin and for how long?

In the ASPEN study (1), blood pressure was well controlled (mean 133/77 mmHg). The blood pressure in the Collaborative Atorvastatin Diabetes Study and the Anglo-Scandinavian Cardiac Outcomes Trial was ~138/78 and 143/80 mmHg, respectively (2,3). This difference may influence any benefit accruing from lipid lowering in ASPEN. There was also a change in protocol during the ASPEN study. Did this lead to a difference in the duration of follow-up in the primary and secondary prevention groups?

The differences outlined above, together with those mentioned by the ASPEN authors (1), may have contributed to the nonsignificant reduction in events reported in this trial.

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Efficacy and Safety of Atorvastatin in the Prevention of Cardiovascular End Points in Subjects With Type 2 Diabetes: The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN)

Response to Gazi and Mikhailidis

We appreciate the interest of Gazi and Mikhailidis (1) in the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) and their proposed reasons for the nonsignificant results (2).

We mention in our article the high rates of treatment "drop in" and "drop

out" and the potential impact on the primary end point (mostly due to changing guidelines and study design changes). While Gazi and Mikhailidis correctly state that there was a high incidence of dropouts, we should clarify that all subjects (including those who withdrew) were included in the final analysis. The authors ask if the substantial differential LDL cholesterol decrease of 29% between active and placebo groups could reflect active subjects taking a second statin. Of the 15% of atorvastatin-treated subjects taking concomitant lipid-lowering medications, the vast majority took an additional statin. However, considered on its own, this would not explain the 29% reduction in LDL cholesterol compared with placebo. Of the 26.9% of subjects in the placebo group who were taking concomitant lipid-lowering medications (mostly statins), 19.7% took them for ≥30 days. It is likely more important that 42% of subjects with cardiovascular events in the atorvastatin group had stopped their randomized medication >1 year before their event.

We agree that lower blood pressure, as well as lower baseline LDL cholesterol, younger age, lower smoking rates, and a smaller proportion of men combined to place primary prevention subjects in the ASPEN at lower CVD risk than those in the Collaborative Atorvastatin Diabetes Study (3). Despite this apparent lower risk, a greater incidence of cardiovascular events was observed in placebo-treated primary prevention subjects in ASPEN (10.8%) than in CARDS (9.0%), indicating inclusion of "softer" end points, such as hospitalization for angina pectoris and interventions. Nonetheless, trends in CVD event reduction with atorvastatin were at the expected rates for the fatal and nonfatal myocardial infarction end point and in the secondary prevention cohort (2).

The subjects in the secondary prevention group entered the study before the primary prevention group. Secondary prevention subjects would have remained in the study longer were it not for the Safety and Data Monitoring Board recommendation late in the study to stop the study drug in the secondary prevention cohort and begin active treatment. As a result, the durations of follow-up were similar: 4.50 and 4.38 years for secondary versus primary prevention subjects taking atorvastatin and 4.38 and 4.46 years, respectively, for those taking placebo.

The nonsignificance of the ASPEN results has many possible explanations. Nonetheless, the ASPEN study reminds us that the many risk factors for heart disease in diabetes require individualized management for a complete treatment approach.

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Prediction of Diabetic Foot Ulcer Occurrence Using Commonly Available Clinical Information

Response to Boyko et al.

In their article, Boyko et al. (1) describe a foot ulcer prediction tool that will be useful in practice, as it is based on simple clinical criteria. The tool is well validated but limited by the patients examined, who were predominantly male (98%), mainly with type 2 diabetes, and were recruited from a hospital diabetes clinic. We have already addressed these problems in a previous publication (2) using a similar, clinically focused foot ulcer prediction tool (3) that included many of the criteria recommended by the International Working Group on the Diabetic Foot (4). Our grading scheme categorized 3,526 patients into low, moderate, or high risk of ulceration. High-risk patients "were 83 times more likely to ulcerate than low risk" patients, and the chance of "low-risk" patients remaining ulcer-free after 2.4 years was 99.7% (2). This tool was valid for type 1 and type 2 diabetic male and female subjects in a population-based cohort. Such foot ulcer prediction tools are thus useful for "all-comers" in a general community setting, as well as in specialized hospital clinics.

Boyko et al. also raised the issue that patients at high risk of ulceration may be at increased risk of death. We demonstrated that the crude mortality rate for high-risk patients was 19.1% compared with 3.4% for low-risk patients (2). Thus, high risk of ulceration is associated with increased death rate as suspected by Boyko et al., which may result in an underestimation of the predictive value of these clinical tools, as patients may die before they develop foot ulcers.

These two studies complement each other by demonstrating that the overall foot ulcer risk assessment is greater than any individual criteria (1) and that the tool is valid in routine clinical practice for all patients in the community (2) and specialized centers (1,2). Foot ulcer prediction tools may be useful in directing educational initiatives and scarce health care resources to those at greatest need.

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