Aggressive Lowering of Low-Density Lipoprotein Cholesterol: Do the Studies Apply to the Elderly?

Dennis L. DeSilvey, MD
Address for correspondence: Dennis L. DeSilvey, MD, Consultants in Cardiology, 108 Houston Street, Suite B, Lexington, VA 24450
E-mail: dl.desilvey@pcvmed.com

Results of the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial\textsuperscript{1,2} and the PRavastatin Or AtorVastatin Evaluation and Infection Therapy (PROVE IT) trial\textsuperscript{3,4} add significantly to our understanding of how far low-density lipoprotein (LDL) cholesterol levels should be lowered in the secondary prevention of vascular disease. Both studies demonstrated that reducing LDL cholesterol to levels below the accepted guideline of <100 mg/dL to levels in the 70 mg/dL range led to significant improvements in the progression of coronary artery disease, as measured by intravascular ultrasound in REVERSAL and by cardiovascular events in PROVE IT. Can the results of these trials be applied to the treatment of cardiovascular disease in elderly persons?

The designs of the trials were remarkably similar. In REVERSAL, one arm of the treatment group received 40 mg pravastatin and the other arm received 80 mg atorvastatin. The intent of the trial was not to demonstrate that one drug was better than the other, but to choose two drugs with different abilities to lower LDL cholesterol. Subjects receiving pravastatin achieved, on average, a 25\% reduction of LDL cholesterol level to an average 110 mg/dL. Subjects receiving atorvastatin achieved a 45\%–50\% reduction with a final value of 77 mg/dL.

PROVE IT enrolled 4162 patients hospitalized for acute coronary syndrome within the preceding 10 days and compared the efficacy of 40 mg pravastatin (standard therapy) to 80 mg atorvastatin (aggressive therapy). The primary end points were death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, early revascularization within 30 days, and stroke. In this trial, the pravastatin group achieved a median LDL cholesterol level of 95 mg/dL and the atorvastatin group achieved a median LDL cholesterol level of 62 mg/dL. The rates of the primary end points at 2 years were 26.3\% in the pravastatin group and 22.4\% in the atorvastatin group, representing a 16\% reduction in the hazard ratio in favor of atorvastatin.

Can one apply these very favorable results to an elderly population? We can begin by looking at the age groups evaluated in these two landmark studies. In REVERSAL, the mean age in both groups was 56 ± 9.8 years. In PROVE IT, the mean age was 58 ± 11.2 years. In PROVE IT, participants older than age 65 years had an insignificant benefit, 28.8\% events for the atorvastatin group and 29.5\% in the pravastatin group. Selecting an age of 75 years as elderly, it is immediately apparent that these results cannot be applied to elderly persons where drug metabolism is usually impaired. Even among the most healthy of the group, multiple drug interactions are more frequent, and side effects are more common and often more devastating. Even in the younger population in PROVE IT, aggressive lipid lowering came with a cost of more frequent side effects, with 3.3\% of patients receiving atorvastatin having elevations in alanine aminotransferase levels compared with 1.1\% in the pravastatin group, and myalgias or elevation of creatinine kinase requiring discontinuation of the study medication in 3.3\% of the atorvastatin group compared with 2.7\% of the pravastatin group. There were no cases of rhabdomyolysis in either group.
There are currently several trials looking at an elderly population, and it is premature to apply the results of these two trials to a population over age 70–75 years without a great deal of thought regarding the risk–benefit analysis. The current National Cholesterol Education Program guidelines recommend an LDL cholesterol level <100 in secondary prevention, recognizing, as noted, that those goals should be achieved within the limitations of patient safety and tolerance. Based on current data, the only time a more aggressive goal in the elderly is necessary is if there is evidence of further progression of disease or new acute events when on optimal therapy according to current guidelines.

A provocative aspect of these trials is whether they suggest that all statins do not provide equal benefit. This message should not be lost in the translation. In REVERSAL, even with a relatively similar reduction in LDL cholesterol level (77 mg/dL for atorvastatin and 88 mg/dL for pravastatin), the reduction in C-reactive protein was greater for the atorvastatin group, and this was accompanied by lesser or no progression of disease by intravascular ultrasound. In PROVE IT, C-reactive protein values for the atorvastatin group were 1.3 mg/L and were 2.1 mg/L in the pravastatin group. What is now needed is a trial of pravastatin at 20-mg and 40-mg doses plus ezetimibe 10 mg to see if an aggressive LDL cholesterol-lowering strategy with fewer side effects might have significant benefit in a population including the young and the elderly.

REFERENCES