

EDITORIAL



Low-Density Lipoprotein Cholesterol in Patients with Stable Coronary Heart Disease — Is It Time to Shift Our Goals?

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The evidence of the effectiveness of statins in the treatment of stable coronary heart disease (CHD) continues to grow. Large-scale, randomized, secondary-prevention trials involving patients with CHD have shown that statins reduce the clinical consequences of atherosclerosis, including death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina pectoris and heart failure, as well as the need for coronary revascularization. Current guidelines recommend a low-density lipoprotein (LDL) cholesterol level of less than 100 mg per deciliter (2.6 mmol per liter) as the goal for patients with stable CHD and a goal of 70 mg per deciliter (1.8 mmol per liter) in patients at particularly high risk.¹ Many clinicians, however, have suggested a goal of 70 mg per deciliter in patients with stable CHD on the basis of comparative epidemiologic studies and the effectiveness of high-dose statins, such as 80 mg of atorvastatin daily, in patients with acute coronary syndromes.² The Treating to New Targets (TNT) Trial reported by LaRosa et al.³ in this issue of the *Journal* provides further insight into the effectiveness and safety of reducing LDL cholesterol levels in patients with stable CHD to less than 70 mg per deciliter, as compared with the current goal of 100 mg per deciliter.

In the TNT study, 15,464 patients with stable CHD and a mean LDL cholesterol level at baseline of 130 to 250 mg per deciliter (3.4 to 6.5 mmol per liter) entered an eight-week period of open-label treatment with 10 mg of atorvastatin per day. At the end of the run-in phase, 10,001 patients with an LDL cholesterol level of less than 130 mg per deciliter (3.4 mmol per liter; mean, 99 mg per deciliter [2.6 mmol per liter]) were randomly assigned in a double-blind fashion to continue to take 10 mg of

atorvastatin per day or to receive 80 mg of atorvastatin per day. After a median follow-up of 4.9 years, patients who received 10 mg of atorvastatin per day had an LDL cholesterol level of 101 mg per deciliter (2.6 mmol per liter), whereas those who received 80 mg of atorvastatin per day had an LDL cholesterol level of 77 mg per deciliter (2.0 mmol per liter). The greater reduction in LDL cholesterol levels with the higher dose of atorvastatin was also associated with a relative reduction in the risk of a major cardiovascular event, including death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, and fatal or nonfatal stroke, of 22 percent ($P < 0.001$). There was also a reduction in the risk of several of the components of the composite end point with the 80-mg dose of atorvastatin, as compared with the 10-mg dose, including a 22 percent relative reduction in the risk of nonfatal non-procedure-related myocardial infarction ($P = 0.004$) and a 25 percent relative reduction in the risk of fatal or nonfatal stroke ($P = 0.02$). There was, however, no reduction in overall mortality. The reduction in cardiovascular risk associated with the 80-mg dose of atorvastatin was accomplished with an increase in the incidence of persistent elevations in liver-enzyme levels (1.2 percent, as compared with 0.2 percent in the group given 10 mg of atorvastatin; $P < 0.001$) but no significant increase in creatine kinase levels or the incidence of myalgia or rhabdomyolysis. LaRosa et al. conclude that in patients with stable CHD, the use of 80 mg of atorvastatin per day to lower LDL cholesterol levels below currently recommended levels to approximately 70 mg per deciliter could further reduce the health care burden associated with cardiovascular events and cerebrovascular disability.

Before this strategy can be adopted, however, sev-

eral issues are worthy of discussion. Most important, clinicians will need to ask themselves how compelling the new information provided by the TNT Trial is for clinical practice and whether it is sufficient to change our current goals for LDL cholesterol levels in patients with stable CHD. Although the risk of CHD events was reduced by treatment with 80 mg of atorvastatin per day, the overall risk of death was not. The TNT Trial was not adequately powered to compare the effect on overall mortality of high-dose atorvastatin with that of low-dose atorvastatin, and there was no significant increase in the number of deaths due to cancer, accidents, or suicide or any other particular category of death in the former group. Still, although the number of deaths from CHD was reduced by 26 among patients assigned to 80 mg of atorvastatin per day, as compared with those assigned to receive 10 mg of atorvastatin, the number of deaths from noncardiovascular causes in this group was increased by 31. Although this increase in deaths from noncardiovascular causes could be due to chance, it is a matter of concern. If, indeed, there is an increase in the risk of death from noncardiovascular causes associated with the 80-mg dose of atorvastatin, as compared with the 10-mg dose, in patients with stable CHD, further efforts will be needed to select the subgroups that are at increased risk for an adverse cardiovascular event in order to preserve the benefits of this dose on myocardial infarction and stroke.

In view of the lack of an effect of the 80-mg dose of atorvastatin on overall mortality, it is reasonable to ask whether other means of achieving an LDL cholesterol level of 70 mg per deciliter will be equally beneficial with respect to cardiovascular events but possibly safer. One might also ask whether the effects of the 80-mg dose are due entirely to a reduction in LDL cholesterol levels or to the pleiotropic effects of high-dose atorvastatin. Some patients with stable CHD should be able to reduce their LDL cholesterol level to 70 mg per deciliter through dietary and lifestyle changes. However, this goal is probably not attainable by such means in most patients, who would therefore require a high-dose statin, and the goal may not be safely or easily reached with the use of any individual statin at its maximally approved dose.

Some clinicians may choose to add an agent such as ezetimibe,⁴ which reduces resorption of cholesterol from the intestine, to a lower dose of a statin in the belief that this combination is as effec-

tive as 80 mg of atorvastatin per day in lowering LDL cholesterol but is safer. The effectiveness and safety of ezetimibe and a low-dose statin as compared with those of 80 mg of atorvastatin per day with respect to the risk of cardiovascular events has, however, yet to be determined. The relative safety and efficacy of other strategies to lower LDL cholesterol levels and increase high-density lipoprotein (HDL) cholesterol levels, such as by treatment with nicotinic acid derivatives, fibrates, HDL cholesterol mimetics, and inhibitors of cholesterol ester transfer protein in combination with a low-dose statin, will also need to be compared with the safety and efficacy of the 80-mg dose of atorvastatin. One might also ask whether LDL cholesterol is the most effective target of lipid-lowering strategies. Studies^{5,6} have suggested that the ratio of apolipoprotein B to apolipoprotein A-I may be a better indicator of cardiovascular risk than are LDL cholesterol levels. These are, however, questions for the future.

Until the safety and effectiveness of an 80-mg daily dose of atorvastatin have been established, patients and their physicians will need to carefully weigh the benefits of a reduction in the risk of cardiovascular events, including myocardial infarction and stroke, with their attendant disability, against the uncertainty of an increase in the risk of death from noncardiovascular causes. We need further reassurance as to the safety of this approach before we can advocate a major shift in our current goals for LDL cholesterol levels in patients with stable CHD.

Dr. Pitt reports having served as a consultant for AstraZeneca, Novartis, and Pfizer.

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