

Growing body of evidence shows benefits of aggressive lipid management in high-risk patients



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An increasing body of evidence from various trials of coronary heart disease (CHD) has made it clear that aggressive lipid-lowering treatment produces substantial reductions in coronary events and death for patients at high risk for such events. The effectiveness of the statins in safely reducing low-density lipoprotein (LDL) cholesterol to levels <100 mg/dL has been a major boon to patients who have had myocardial infarction (MI) or those who have known risk factors for MI and other cardiac events.

Several medical trials have been key to understanding the benefits of aggressive lipid-lowering therapy for patients with elevated LDL cholesterol levels, said W. Virgil Brown, MD.

"The Post-Coronary Artery Bypass Graft [Post-CABG] trial was important because it was the first to actually titrate patients to a goal with regard to their LDL cholesterol," said Dr. Brown. This randomized, double-blind, multicenter study examined the impact of lovastatin on venous grafts. Patients were given high (40 to 80 mg/day) or low (2.5 to 5 mg/day) doses of lovastatin and followed for a mean initial period of 4.3 years. A quantitative angiography was performed at baseline and then in 85% of patients at the end of follow-up. Separate data sets were created for diabetic and nondiabetic patients.

In patients treated with low doses of lovastatin, LDL cholesterol stabilized within the first few months, at a mean of 134 to 136 mg/dL. In those treated aggressively, LDL cholesterol dropped

to a mean of 93 to 96 mg/dL. Those levels remained consistent in both groups for the remainder of the trial.

Of the 226 patients with diabetes, 43.3% of those randomized to low-dose lovastatin experienced substantial atherosclerotic progression of vein grafts, compared with 27% of patients treated with the higher doses. In nondiabetic patients (n = 2,452), 39% of the low-dose group and 27.8% of the high-dose group had substantial progression of stenosis.

Aggressive lipid lowering in stable CHD

Lipid lowering in stable CHD was the focus of the Atorvastatin Versus Revascularization Treatments (AVERT) trial. "The question here was whether very aggressive treatment with atorvastatin would be equivalent to or better than angioplasty in patients with coronary stenosis greater than 50%, followed by treatment according to the judgment of the physician," explained Dr. Brown. Patients in the AVERT trial had stenotic lesions >50% in one or two coronary arteries, but not in the left main artery. Their LDL cholesterol levels were >115 mg/dL and averaged 146 mg/dL.

Patients were randomized to either 80 mg/day of atorvastatin plus usual medical therapy or angioplasty plus usual care; usual care included lipid-lowering medication in 73% of the angioplasty group at some point, generally at lower doses. In the atorvastatin group, mean LDL cholesterol was reduced from 145 mg/dL at baseline to 77 mg/dL at the end of the 18-month study. In the angioplasty patients, LDL cholesterol was decreased from 147 to 119 mg/dL.

End points included death from cardiac causes, resuscitation after a

cardiac arrest, nonfatal MI, stroke, need for bypass grafting, angioplasty, or hospitalization with worsening angina verified by objective evidence. During the trial, ischemic events occurred in 21% of the angioplasty patients and 13% of the atorvastatin patients, a relative difference of 36% ($p = .048$, which was not statistically significant after interim analyses adjustments). In measuring the time elapsed before the first ischemic event, Dr. Brown noted, a greater divergence was seen between the two groups after 6 months (Figure).

Unstable angina

Patients with unstable angina who have suffered a non-Q-wave MI have been shown to be at greatly increased risk of death or recurrent nonfatal MI in the short term, Dr. Brown pointed out. In light of the success of the early statin studies, some researchers hypothesized that early, rapid, and profound cholesterol-lowering therapy could reduce early recurrent ischemic events in patients with unstable angina or non-Q-wave acute MI. This was the premise of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial, reported in 1998.

The effectiveness of the statins in safely reducing LDL cholesterol to levels <100 mg/dL has been a major boon to patients who have had MI or those who have known risk factors for cardiac events.

The trial enrolled 3,086 high-risk patients (those with non-Q-wave MI or with unstable angina) after treatment for acute coronary syndrome. Patients were randomized to atorvastatin 80 mg/day, or placebo and diet. Baseline LDL cholesterol levels were at a mean of 124 mg/dL. By week 6, the levels had dropped to about 60 mg/dL in the atorvastatin group while remaining at slightly above 120 mg/dL in the placebo-plus-diet group; the levels then remained relatively stable in both groups through the end of the 16-week trial.

With end points similar to the AVERT trial, 17.4% of placebo-diet patients experienced an event by the

TABLE

Heart Protection Study: Persons in high-risk categories

Preexisting disease categories	n (%)
Myocardial infarction	8,510 (41)
Cerebrovascular disease	3,288 (16)
Peripheral vascular disease	6,748 (33)
Diabetes mellitus	5,963 (29)
Treated hypertension	8,455 (41)
Other major subgroups	
Women	5,082 (25)
Elderly, 65–80 years of age at entry	9,515 (46)
Baseline LDL-C < 3.0 mmol/L	6,888 (34)

LDL-C = low-density lipoprotein cholesterol.
Source: MRC/BHF Heart Protection Study Collaborative Group. *Eur Heart J* 1999;20:725.

end of the trial, compared with 14.8% in the statin group—a 16% relative reduction in the statin group. The major end point for about half of the patients was hospitalization for worsening angina with new objective evidence of ischemia. At 16 weeks, the atorvastatin patients had a 26% ($p = .02$) lower incidence of this end point compared with the placebo-diet patients.

The Heart Protection Study

The recently completed Heart Protection Study (HPS; Table) has evaluated 40 mg/day of simvastatin versus placebo (with or without an antioxidant combination of vitamin E, vitamin C, and beta-carotene) in about 20,000 high-risk patients over 5 years.

Cardiovascular mortality was reduced by 17% and all-cause mortality by nearly 12% in the simvastatin-treated patients. Major vascular events were reduced by 24%; after correction for noncompliance and allocation of placebo patients to lipid-lowering therapy by primary care physicians, the reduction in vascular events associated with simvastatin was 33%. This benefit was still accruing at the end of the 5-year trial.

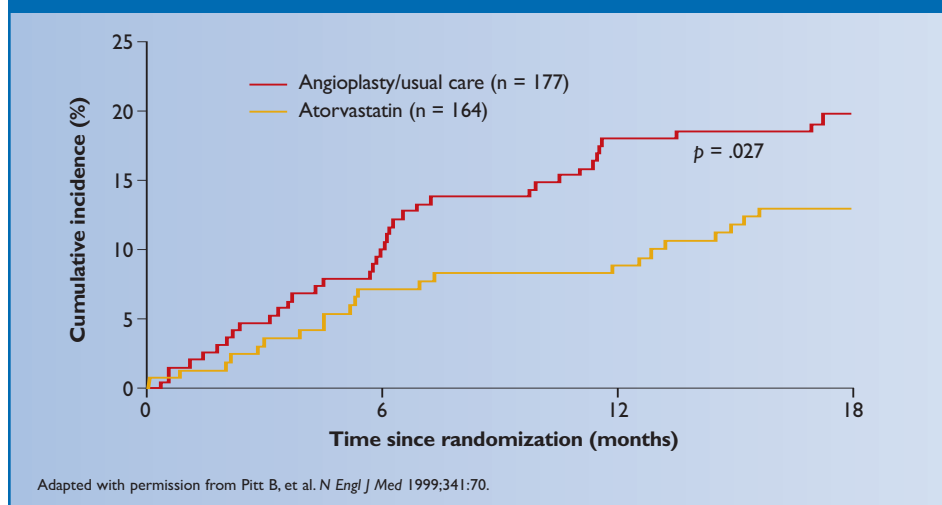
The HPS findings show that patients with a baseline LDL cholesterol level <100 mg/dL and those with LDL cholesterol between 100 and 130 mg/dL benefited as much from statin therapy in terms of risk reduction as did those with baseline LDL cholesterol level >130 mg/dL. Similar effectiveness was demonstrated across age and gender groups.

An important remaining question is what attained LDL cholesterol levels

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FIGURE

Time to first ischemic event in the AVERT trial



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are necessary to achieve optimum reduction in cardiovascular events? Currently, the Study of the Effectiveness of Additional Reductions of Cholesterol and Homocysteine (SEARCH) and Treating to New Targets (TNT) trials are comparing the

effect of moderate- versus high-dose statins on the rate of clinical events.

Adverse effects

The major concern surrounding the statins has been the risk of rhabdomyolysis. According to the U.S. Food and

Drug Administration, the statin associated with the highest rate of rhabdomyolysis fatalities was cerivastatin (3.16 cases per 1 million prescriptions), which was removed from the worldwide market in 2001. The other statins have rhabdomyolysis fatality rates of

between 0 and 0.19 per 1 million prescriptions. Of approximately 12 million people taking statins, 772 reported cases of rhabdomyolysis occurred between October 1997 and December 2000; of these, 72 cases were fatal, including 20 involving cerivastatin. ■