

Cholesterol Lowering in Atherosclerosis

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Lipid-lowering with statins reduces disease progression, prevents myocardial infarction and other hard end points, and prolongs survival. Data from large-scale trials with these agents further show that lowering low-density lipoprotein (LDL) cholesterol in patients with coronary artery disease reduces the incidence of cardiovascular events and that the lower the LDL cholesterol achieved, the lower the event rate. Currently available evidence supports the National Cholesterol Education Program (NCEP) recommendations for reduction of LDL-cholesterol levels to at least 100 mg/dL in patients with coronary artery disease. The Treating to New Targets

study, which will evaluate the effects of LDL-cholesterol lowering to ≤ 75 mg/dL with atorvastatin, may help clarify if additional benefit accrues with further reductions. However, up to 82% of patients with proven coronary disease are not even at the current NCEP lipid goal. Up to 55% need a >30 -mg/dL reduction in LDL cholesterol to reach that goal. These data suggest that many patients are not receiving a statin or are receiving an inadequate dose. Aggressive lipid lowering, although a desirable goal, does not yet appear to be standard practice. ©2000 by Excerpta Medica, Inc.

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According to the 1994 National Cholesterol Education Program (NCEP) guidelines, treatment decisions for patients with coronary artery disease are based on low-density lipoprotein (LDL)-cholesterol levels.¹ Drug therapy is considered in patients with levels ≥ 130 mg/dL, with a goal of ≤ 100 mg/dL.

After these guidelines were issued, several large-scale trials of the statins were reported. The Scandinavian Simvastatin Survival Study (4S), conducted over 5.4 years in 4,444 patients with angina pectoris or previous myocardial infarction (MI), was the first study to unequivocally demonstrate a reduction in total mortality.² Simvastatin (20–40 mg/day) reduced LDL cholesterol from 188 to 122 mg/dL (35% reduction). The statin group had a 19.4% incidence of combined nonfatal MI, cardiovascular death, or resuscitated cardiac arrest, which corresponded to a 34% reduction versus placebo ($p < 0.00001$).

The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study evaluated the effects of pravastatin 40 mg/day in 9,014 patients with MI (64%) or unstable angina (36%).³ Pravastatin reduced LDL cholesterol from 150 to 112 mg/dL (25% reduction). The statin group had a 12.3% incidence of combined fatal coronary event or nonfatal MI, which corresponded to a 23% reduction versus placebo ($p = 0.001$).

The Coronary and Recurrent Events (CARE) study evaluated the effect of pravastatin 40 mg/day in 4,159 post-MI patients with average cholesterol levels; mean

LDL cholesterol at entry was 139 mg/dL.⁴ Pravastatin 40 mg/day reduced LDL cholesterol to 98 mg/dL (28% reduction). The statin group had a 10.2% incidence of combined fatal coronary event or nonfatal MI, which corresponded to a 24% reduction versus placebo ($p = 0.003$).

SHOULD OUR GOALS BE MORE AGGRESSIVE?

These statin trials show that lowering LDL cholesterol in patients with coronary artery disease reduces the incidence of cardiovascular events and that the lower the LDL cholesterol achieved, the lower the event rate. The data support the reduction of LDL-cholesterol levels to at least 100 mg/dL. The question is whether greater LDL-cholesterol lowering will achieve greater event reduction (Figure 1).^{5,6} An ongoing trial is specifically designed to address this issue. The Treating to New Targets (TNT) study will compare atorvastatin 10 and 80 mg/day in $>10,000$ patients with coronary artery disease. LDL-cholesterol target goals in the 2 arms will be ≤ 100 mg/dL and ≤ 75 mg/dL, respectively. A 5-year follow-up is planned.

Three other ongoing studies may also provide relevant data. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, 2,100 patients who present with unstable angina or non-Q-wave MI have been randomized to receive either placebo or atorvastatin 80 mg/day beginning within the first 96 hours.⁷ A 16-week treatment with follow-up is planned. Preliminary results may be available in 2000. The Study of the Effectiveness of Additional Reductions of Cholesterol and Homocysteine (SEARCH) will compare simvastatin 20 and 80 mg/day in 12,000 patients with a history of MI. A 5-year follow-up is planned. Finally, the Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) trial will compare atorvastatin 80

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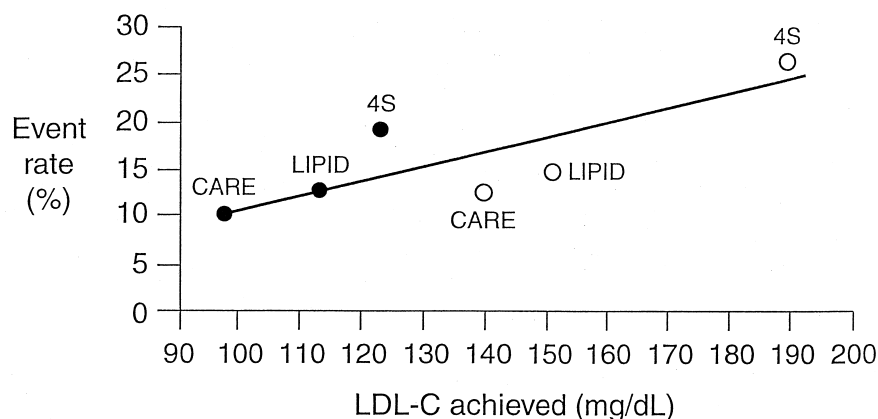


FIGURE 1. Event rates by low-density lipoprotein (LDL)-cholesterol level in secondary-prevention trials with statins. The data demonstrate a linear relation between LDL-cholesterol (LDL-C) level achieved and event rate. CARE = The Coronary and Recurrent Events study; 4S = Scandinavian Simvastatin Survival Study; LIPID = The Long-term Intervention with Pravastatin in Ischemic Disease study. (Adapted with permission from *Am J Cardiol*.⁵)

mg/day and simvastatin 20–40 mg/day in 7,600 patients at high risk of coronary artery disease.

THE MANDATE FOR REACHING TARGET LEVELS: INSIGHTS FROM RECENT TRIALS

The Post Coronary Artery Bypass Graft (Post-CABG) study randomly assigned 1,351 patients to aggressive or moderate lipid-lowering treatment, warfarin, or placebo in a 2 × 2 factorial design.⁸ Study subjects had undergone bypass surgery 1–11 years before study entry and had LDL-cholesterol levels of 130–175 mg/dL. The aggressive lipid-lowering arm received lovastatin 40–80 mg/day plus cholestyramine 4–8 g/day and had a target goal of ≤85 mg/dL. The moderate lipid-lowering arm received only lovastatin 2.5–5 mg/day and had a target goal of 130–140 mg/dL. Over the 4 years of the study, mean LDL-cholesterol levels were 134–136 mg/dL (moderate group) and 93–96 mg/dL (aggressive group). However, despite not reaching target lipid goals, aggressive lipid lowering was associated with significant benefit (see the article by Popma et al⁹).

The Atorvastatin Versus Revascularization Treatments (AVERT) study randomized 341 patients with 1- or 2-vessel disease to angioplasty plus usual care or atorvastatin 80 mg/day plus optional aspirin and anti-anginal therapy.¹⁰ There was an 18-month follow-up. At some point during the study, 130 of 177 patients (73%) in the angioplasty group received lipid-lowering medication; in 125 of these patients (71%), their lipid-lowering treatment included a statin (median dose of 20 mg/day). However, the angioplasty group did not reach the NCEP lipid goal. At study end, the mean LDL-cholesterol levels in the 2 groups were 77 mg/dL (atorvastatin group) and 119 mg/dL (angioplasty group). Treatment with atorvastatin was associated with a significantly longer time to first ischemic event, corresponding to a risk reduction of 36% versus angioplasty plus usual care ($p = 0.03$). The difference

between the 2 groups became more noticeable after 6 months. During months 6–18, 6% in the atorvastatin group and 11% in the angioplasty group experienced an ischemic event, which corresponded to a 46% risk reduction ($p = 0.09$).

The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT) was a multicenter, randomized, double-blind, placebo-controlled 2 × 2 factorial trial in patients with normal cholesterol levels; 230 patients received simvastatin and 230 received placebo.^{11,12} The average follow-up was 4 years. Atherosclerosis progression was assessed by quantitative coronary angiography. Patients were categorized into quartiles according to the percent change in their lipids. A dose response relationship was noted, with patients in the highest quartile exhibiting the greatest changes in mean diameter ($p = 0.042$ for trend) and minimum diameter ($p = 0.016$ for trend). Change in percent diameter stenosis followed a similar but nonsignificant trend. Of patients on simvastatin, 20.1% showed progression, 7.2% showed regression, 13.6% had a mixed response, and 8.2% showed no change; the corresponding values for placebo patients were 26.7%, 5.4%, 14.1%, and 4.6%, respectively ($p = 0.036$ for trend). While angiography is a less sensitive measure of disease burden than intravascular ultrasound, these data suggest that long-term cholesterol lowering with a statin may result in reduction in coronary atherosclerosis burden. The ongoing Reversal of Atherosclerosis with Lipitor (REVERSAL) is also evaluating this hypothesis (see the article by Nissen¹³).

These trials support the desirability of aggressive lipid lowering but illustrate the difficulty of achieving that even within the highly structured context of a controlled clinical trial. In clinical practice, available data suggest that our success rate is even lower. The Lipid Treatment Assessment Project (L-TAP) was a large epidemiologic study, conducted in 1996, that examined 4,888 hypercholesterolemic patients from a primary care setting.¹⁴ Of 1,460 patients with cor-

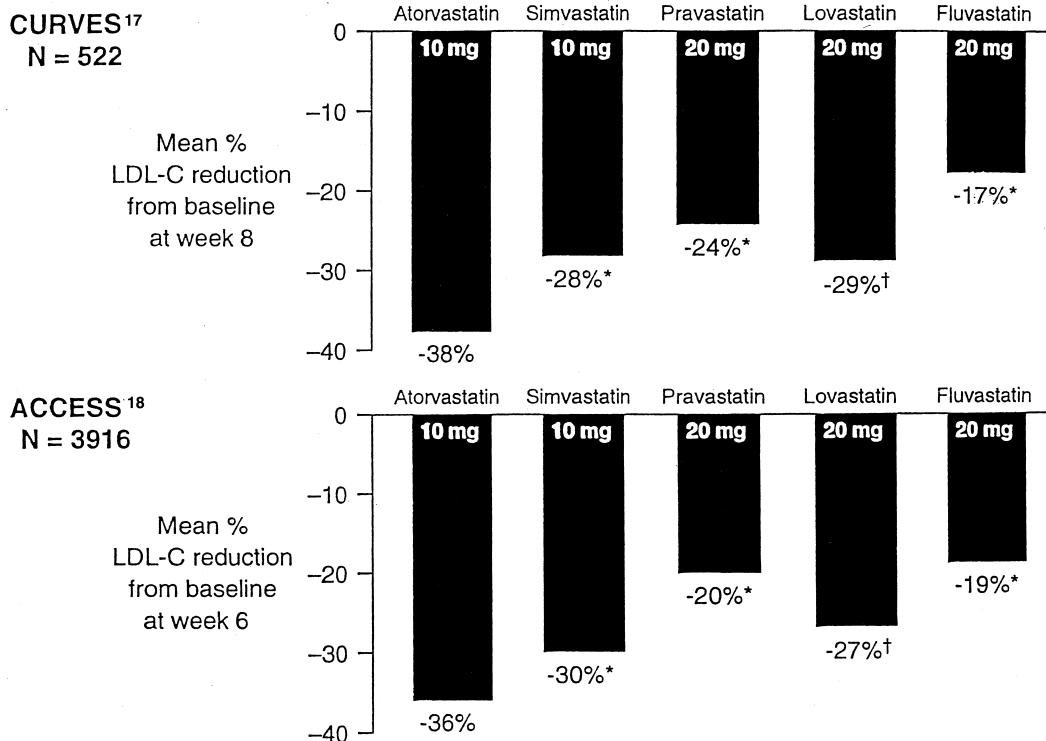


FIGURE 2. Low-density lipoprotein cholesterol (LDL-C) reductions achieved in 2 studies of patients with hypercholesterolemia given usual starting doses of atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. * $p \leq 0.0001$ versus atorvastatin 10 mg; † $p \leq 0.0019$ versus atorvastatin 10 mg. ACCESS = Atorvastatin Comparative Cholesterol Efficacy and Safety Study; CURVES = Comparative Dose Efficacy Study of Atorvastatin versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin. (Adapted from data published in *Am J Cardiol*¹⁷ and the *J Am Coll Cardiol*.¹⁸)

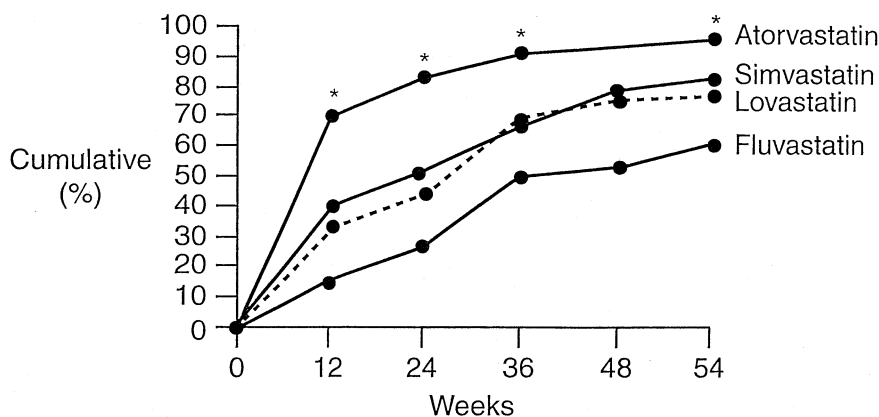


FIGURE 3. Patients reaching National Cholesterol Education Program (NCEP)-recommended low-density lipoprotein (LDL)-cholesterol goal with statin treatment. Success rates increase with increasing statin potency. Doses used: atorvastatin 10–80 mg, fluvastatin 20–40 mg, lovastatin 20–80 mg, simvastatin 10–40 mg. Addition of colestipol to reach NCEP target LDL-cholesterol goal was required in 2% of atorvastatin, 67% of fluvastatin, 24% of lovastatin, and 24% of simvastatin patients. * $p < 0.05$ for atorvastatin versus other statins. (Adapted with permission from *J Fam Pract*.¹⁹)

onary artery disease, 82% did not reach their goal and 55% needed a >30 mg/dL reduction in LDL cholesterol to reach that goal. The mean LDL-cholesterol level in this group was 140 mg/dL (3.62 mmol/L). Frolkis et al conducted a retrospective review of 225 randomly selected charts of patients

admitted in 1996 to the coronary care unit of Midwest Medical Center.¹⁵ At admission, 23 patients met the NCEP treatment criteria but only 14% were actually receiving lipid-lowering drugs. In addition, 48% of this group were discharged without lipid-lowering drugs. Finally, a study of 63 secondary-

prevention patients at a Veterans Affairs Medical Center, all of whom were receiving statins, found that 76% were not at goal.¹⁶

These findings suggest that many patients are not receiving lipid-lowering treatment or are receiving inadequate doses of a statin. Statins vary in the maximum LDL-cholesterol reduction that can be achieved at a given dose (Figure 2),^{17,18} and there is evidence that relative potency may have an impact on the number of patients who reach goal (Figure 3).^{18,19}

CONCLUSIONS

All patients with coronary artery disease should receive optimal medical therapy, regardless of whether they undergo a coronary interventional procedure. In particular, aggressive lipid lowering can improve morbidity and mortality as well as prevent costly procedures. However, although this is a desirable goal, it does not yet appear to be standard practice.

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