DENNIS L. SPRECHER, MD
Before coming to the Cleveland Clinic, where he is head of the Section of Preventive Cardiology, Dr. Sprecher was the site principal investigator for the CARE trial at the University of Cincinnati.

CME CREDIT HOURS

Lipid-lowering therapy for average lipid levels: The CARE trial

The CARE trial indicates that average LDL cholesterol values are too high

Cholesterol-lowering therapy with pravastatin (an HMG-CoA reductase inhibitor or "statin") can prevent major coronary events in patients who have average low-density lipoprotein (LDL) cholesterol levels after a myocardial infarction, according to the results of the recently-completed Cholesterol and Recurrent Events (CARE) trial.[1] Previous trials included only patients with much higher cholesterol levels, whose risk is correspondingly higher.

The CARE findings indicate that average LDL cholesterol levels are too high in patients with coronary artery disease and can contribute to the recurrence of cardiovascular events. They also argue in favor of greater use of cholesterol-lowering drugs in this population.

FINDINGS OF EARLY STUDIES

The Coronary Drug Project in the 1960s[2] and the Lipid Research Clinics Coronary Primary Prevention Trial in the 1980s[3,4] first suggested that cholesterol reduction could decrease the incidence of coronary artery disease and events such as myocardial infarctions. However, these trials used niacin and bile-absorbing resins, which produce side effects that many patients find unacceptable. Only in the late 1980s with the introduction of the first statin (lovastatin) did drugs become available that could lower cholesterol markedly with minimal side effects.[5]

In the 1990s, a series of clinical trials using statins finally convinced physicians that reducing the level of LDL lowers the incidence of both first and recurrent coronary events.

The Scandinavian Simvastatin Survival Study

The Scandinavian Simvastatin Survival Study (4S) included 4444 patients who had experienced a myocardial infarction, who took either simvastatin (20 to 40 mg daily) or placebo. After 5.4 years of therapy, the treated group had LDL levels that were 35% lower than at baseline, and an incidence of fatal or nonfatal myocardial infarction 37% lower than in the placebo group.[6]

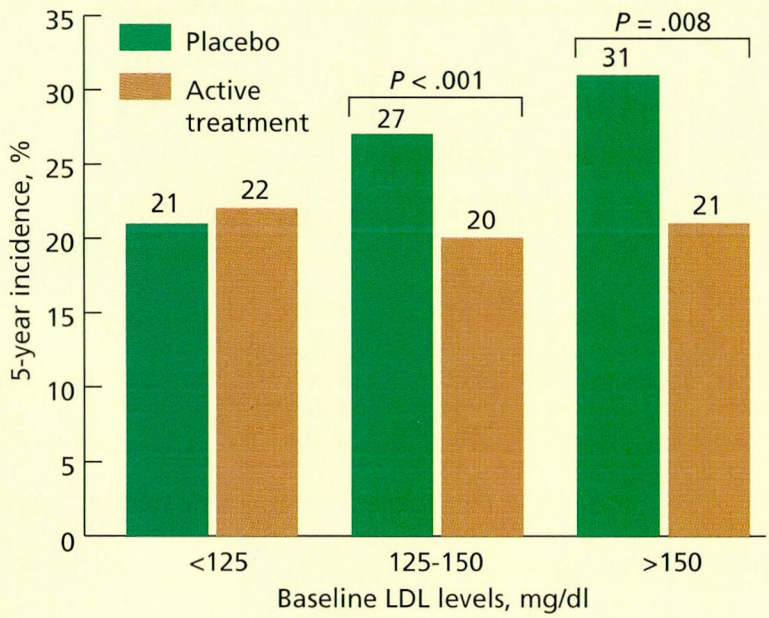
Further, for the first time in this type of study, treatment reduced the mortality rate: 42% fewer persons died of coronary disease and 30% fewer persons died overall in the treated group than in the placebo group. This reduction in mortality was a key factor in convincing many cardiologists and primary care physicians that cholesterol reduction is worthwhile.

The West of Scotland Study

The West of Scotland Study included only patients who had not yet experienced any heart disease.[7] The patients—6595 men—received either pravastatin (40 mg daily) or placebo. In the treated group, LDL levels declined by approximately 26%, and by 4.9 years this group had suffered 31% fewer cases of fatal or nonfatal coronary artery disease

FIGURE

INCIDENCE OF MAJOR CORONARY EVENTS ACCORDING TO BASELINE LDL VALUE IN THE CHOLESTEROL AND RECURRENT EVENTS (CARE) TRIAL. DATA FROM REFERENCE 1.



than did the placebo group, 28% fewer deaths from coronary artery disease, and 22% fewer deaths overall.

THE UNANSWERED QUESTIONS

These two studies indicated that these powerful cholesterol-lowering agents could prevent both first and recurrent coronary events (including deaths) in patients with other risk factors, including cigarette use, low levels of high-density lipoprotein, or obesity. Therefore, the presence of other risk factors should not dissuade us from using statins to lower LDL.

However, patients entering both studies had mean LDL levels well above normal—188 mg/dL in the 4S trial and 192 mg/dL in the West of Scotland Study. These values are in the top 5th percentile for western countries.

That left many important clinical questions unanswered. The risk of coronary artery disease increases with increasing serum levels of total cholesterol and LDL,[8,9] yet most cases of coronary artery disease occur in persons with lipid levels that are normal or only slightly elevated.

Therefore, clinicians need to know if "normal" LDL levels are too high in such patients. And would the potential benefit of lipid-lowering therapy outweigh its risks? These were the questions the CARE investigators set out to answer.

THE CARE TRIAL

The CARE trial[1] included only persons who had experienced a myocardial infarction and whose LDL cholesterol values were between 110 and 175 mg/dL—a range that would include 60% to 70% of post-myocardial infarction patients. The mean baseline LDL value was 139 mg/dL. In all, 4159 patients received either pravastatin 40 mg/day (which decreased the LDL level by approximately 28%) or placebo.

After 5 years of follow-up, 10.2% of patients receiving pravastatin had suffered a fatal coronary event or a nonfatal myocardial infarction, compared with 13.2% of the patients receiving placebo—a 24% difference ($P = .003$). Further, 20% fewer treated patients had died of coronary artery disease, but this difference was not statistically significant.

Benefit greater at higher LDL levels

The percentage reduction in risk was greater in patients with higher baseline LDL values (**FIGURE**), in contrast to the findings in the 4S study. The 4S study (in which the lowest LDL values were 145 mg/dL) did not find a difference in risk reduction related to baseline cholesterol levels. According to the Framingham frequency curve, a reduction in benefit might be expected as the baseline LDL cholesterol values become low. When the total cholesterol

is below 160 mg/dL and the LDL is approximately 100 mg/dL, the curve outlining the relationship between cholesterol level and coronary heart disease is flat.

Further, even though the CARE study investigators concluded that patients with baseline LDL levels less than 125 mg/dL did not derive any benefit from therapy, this conclusion may be premature. The power with which one can make conclusions in persons with lower baseline LDL values is weaker because a lower percentage of patients would be expected to suffer. At present, I would still follow the guidelines from the National Cholesterol Education Program[10]: if a patient has suffered a coronary event and has an LDL value greater than 100 mg/dL, I would begin diet therapy and perhaps drug therapy as well, with a goal LDL level of less than 100 mg/dL.

Benefit in women

Women, who comprised 19% of the patients in the 4S and 14% of the patients in the CARE study, derived as much benefit from cholesterol-reducing therapy as men did, if not more.[1,6]

OTHER STUDIES SHOW ANGIOGRAPHIC BENEFIT

As yet unpublished results from the Lipoprotein and Coronary Atherosclerosis Study (LCAS) study,[11] presented at the 1996 American Heart Association meeting, revealed that LDL-lowering therapy with fluvastatin resulted in angiographic regression of coronary artery disease in approximately 400 subjects with LDL levels as low as 115 mg/dL (mean 146 mg/dL).

The Post Coronary Artery Bypass Graft trial[12] indicated that lowering the LDL level from approximately 160 mg/dL to 95 mg/dL with lovastatin produced angiographic benefit in saphenous vein grafts, beyond that observed when the LDL was reduced only to 135 mg/dL.

NEW STATINS TO BE RELEASED

One new lipid-lowering drug was recently approved by the FDA (atorvastatin) and another is expected to be released in 1997 (cerivastatin), bringing the total number of available statins to six (along with fluvastatin, lovastatin, pravastatin, and simvastatin).

Although each drug may have some unique properties, all of them lower LDL values, an effect that has been shown to reduce cardiovascular events. Given that 75% to 80% of patients with coronary artery disease are not properly treated for their LDL cholesterol value, the specific drug used may not be quite as important as using them at all, for sustained periods, in more patients for whom they are appropriate. ■

REFERENCES

1. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996; 335:1001–1009.
2. Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. JAMA 1975; 231:360–381.
3. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984; 251:351–364.
4. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984; 251:365–374.
5. Grundy SM. HMG-CoA reductase inhibitors for treatment of hypercholesterolemia. N Engl J Med 1988; 319:24–33.
6. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344:1383–1389.
7. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995; 333:1301–1307.
8. Gordon T, Kannel WB, Castelli WP, Dawber TR. Lipoproteins, cardiovascular disease, and death: the Framingham study. Arch Intern Med 1981; 141:1128–1131.
9. Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk factor Intervention Trial (MRFIT). JAMA 1986; 2823–2828.
10. National Cholesterol Education Program. Second report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation 1994; 89:1329–1445.
11. Herd JA, Ballantyne CM, Farmer JA, et al. The effect of fluvastatin on coronary atherosclerosis. The Lipoprotein and Coronary Atherosclerosis Study (LCAS) [abstract]. Circulation 1996; 94(Suppl I):I-597.
12. The Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. N Engl J Med 1997; 336:153–162.