The National Cholesterol Education Panel Adult Treatment III guidelines,1 which were released earlier this year, recommend that the number of Americans who should be treated with cholesterol-lowering drugs increase from 13 million to 36 million. This action is justified because coronary disease remains the leading cause of death in this country and because of the overwhelming evidence from clinical trials that statins reduce coronary events and are safe. Many of the additional individuals for whom drug treatment is now recommended have diabetes or other factors that increase their risk to the level of patients with documented atherosclerosis. Calibrating the intensity of treatment to the level of risk is a rational and efficient approach.

See p 2660

One feature of the guidelines that has not changed is the target of LDL levels <100 mg/dL for patients with documented atherosclerosis. This cut point was selected before the publication of any of the major statin trials, and no compelling data has emerged since then to indicate that it should be adjusted either upward or downward. The guidelines also continue to recommend that diet and other lifestyle interventions be used to attain this goal and that drugs also be used when the LDL cholesterol level exceeds 130 mg/dL.

The guidelines leave to the discretion of the physician whether drug treatment is prescribed for patients whose LDL-cholesterol remains between 100 and 130 mg/dL. In one study of 8500 men with coronary disease, the authors estimated that 37% of their cohort would have LDL-cholesterol values within this range after successful treatment with diet.2 Thus, physicians commonly face the decision of whether or not they should begin a statin or increase the intensity of drug therapy for patients with LDL-cholesterol levels in this range. The article by White et al3 in the present issue of Circulation and several other recent studies are relevant to this question.

The article by White et al3 in the present issue of Circulation and several other recent studies are relevant to this question. From the Division of Cardiology, San Francisco General Hospital, and the Department of Medicine, University of California, San Francisco, San Francisco.

Dr Waters has received investigator-initiated research support from Astra-Zeneca, Merck, and Pfizer and honoraria for lectures from Astra-Zeneca, Merck, and Pfizer. Dr Hsue has received investigator-initiated research funding from Astra-Zeneca and honoraria for lectures from Pfizer.

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(Circulation 2001;104:2635-2637.)

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Low-Density-Lipoprotein Cholesterol Goals for Patients With Coronary Disease

Treating Between the Lines

David D. Waters, MD; Priscilla Y. Hsue, MD

Drawing the Line at 130 mg/dL

The Cholesterol and Recurrent Events (CARE) investigators randomized 4159 postinfarction patients to 5 years of treatment with placebo or pravastatin 40 mg/d.4 They reported a 24% reduction in the primary end point of coronary death and nonfatal myocardial infarction in the pravastatin group overall, but no reduction in the primary end point among the 851 patients with a baseline LDL cholesterol level <125 mg/dL.4 They concluded: “Although our finding cannot be considered definitive and requires confirmation, it suggests that an LDL-cholesterol level of 125 mg/dL may be an approximate lower boundary for a clinically important influence of LDL-cholesterol on coronary heart disease.”

The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) investigators randomized 9014 coronary patients to 5 years of treatment with placebo or pravastatin 40 mg/d.5 They also reported a 24% reduction in the primary end point of coronary death and nonfatal myocardial infarction. As part of the prespecified subset analyses, they found a 16% reduction in events (95% CI, ~4% to 32%) in pravastatin-treated patients with a baseline LDL-cholesterol level <135 mg/dL.

In a pooled analysis of the CARE and LIPID data,6 the reduction in coronary death and nonfatal infarction was 22% (95% CI, 7% to 34%; P=0.005) in patients with LDL-cholesterol <135 mg/dL at baseline. The event rate for patients with LDL-cholesterol <125 mg/dL was 12.6% with placebo and 12.2% with pravastatin, a 5% reduction. However, when baseline LDL-cholesterol was between 125 and 138 mg/dL, this difference widened to 14.4% versus 10.6% (a 26% reduction), only to narrow again to 13.8% versus 11.1% for those with levels between 139 and 150 mg/dL.6 Clearly, these subgroup estimates lack precision; nevertheless, the data from CARE and LIPID suggest that treating to an LDL-cholesterol level of 125 mg/dL may be sufficient and that further LDL-cholesterol lowering might not provide additional benefit.

In the Japan Lipid Intervention Trial, 52 421 subjects with total cholesterol levels ≥220 mg/dL were treated with simvastatin, usually at a dose of 5 mg/d, for 6 years. Approximately 10% of the subjects had coronary disease at baseline. The incidence of myocardial infarction did not decrease once on-treatment LDL-cholesterol levels fell below 140 mg/dL. In the 47 294 subjects without coronary disease at baseline, total mortality was higher when LDL-cholesterol levels were <70 mg/dL on treatment.7 The absence of a control group severely limits the value of this trial. The accumulated epidemiological evidence suggests that low cholesterol or
lowering cholesterol does not increase mortality, but rather
that low blood cholesterol levels may be a consequence of
chronic diseases that increase mortality.8

**Drawing the Line at 100 mg/dL**
The Post Coronary Artery Bypass Graft (Post-CABG) Trial randomized 1351 patients with at least one patent saphenous vein bypass graft and an LDL-cholesterol level between 130 and 175 mg/dL to aggressive or moderate LDL-cholesterol lowering.9 Patients received lovastatin 40 mg or 2.5 mg/d as initial therapy, with dose increases and supplemental cholestyramine to attain LDL-cholesterol goals of <85 mg/dL and <140 mg/dL, respectively. During 4.3 years of treatment, LDL-cholesterol levels averaged 93 to 97 mg/dL and 132 to 136 mg/dL in the 2 groups, and significantly less progression of saphenous vein bypass graft narrowing was seen in the aggressively treated group.

After 7.5 years of follow-up, cardiovascular death or nonfatal infarction had occurred less often in the aggressively treated patients: 15.1% versus 20.3% (P=0.03).10 The secondary composite end point of death, nonfatal infarction, stroke, or coronary revascularization was also lower in the aggressive group: 30.6% versus 40.2% (P=0.001). These results provide powerful evidence that an LDL-cholesterol level <100 mg/dL is preferable to a level of 130 mg/dL in patients with saphenous vein grafts. However, the atherosclerosis that occurs in vein grafts differs from native coronary atherosclerosis in several respects, including the rate at which it progresses.11 Extrapolating these results to native coronary arteries may not be justified.

The report by White et al13 indicates that native coronary arteries, not just venous bypass grafts, benefit from the lower LDL-cholesterol levels. These investigators measured the left main coronary artery before and after treatment using quantitative methods in a random sample of 402 Post-CABG patients. Minimum lumen diameter narrowed by a mean of 0.084 mm in the aggressively treated group compared with 0.224 mm in the moderate group (P=0.0003). Substantial progression, which is defined as a worsening of at least 0.4 mm in lumen diameter, occurred in 13.8% of patients in the aggressively treated group and 24.1% of patients in the moderate group (P=0.008). Progression of at least 0.4 mm has been shown to be a strong, independent predictor of future cardiac death or nonfatal infarction.12

At least 3 other recent studies have randomized patients to treatments that lower LDL-cholesterol substantially below 100 mg/dL or to a more conservative degree of cholesterol lowering. In the German Atorvastatin Intravascular Ultrasound (GAIN) Study,13 131 patients were randomized to aggressive cholesterol lowering with atorvastatin or to usual care. LDL-cholesterol was reduced to a mean of 86 mg/dL in the atorvastatin group and to 140 mg/dL in the usual care group. Plaque volume, as assessed by intracoronary ultrasound at baseline and after 1 year of treatment, increased by 1.2±30 mm³ in the atorvastatin group and by 9.6±28 mm³ (P=NS) in the usual care group among the 99 patients with follow-up studies. The hyperechogenicity index, which may be a marker of plaque stability, increased more in the aggressively treated group compared with the usual care (P=0.02). A trial that is likely to be more definitive, entitled REVERSAL, has randomized 600 patients with coronary disease to either atorvastatin 80 mg/d or pravastatin 40 mg/d; the primary end point is percent change in coronary plaque volume as measured by intracoronary ultrasound between baseline and 18 months.

The Atorvastatin Versus Revascularization Treatments (AVERT) Trial randomized 341 patients with no worse than class 2 angina and an LDL-cholesterol level ≥115 mg/dL to atorvastatin 80 mg/d or to angioplasty plus usual care.14 The mean on-treatment LDL-cholesterol levels were 77 mg/dL in the atorvastatin group and 119 mg/dL in the angioplasty/usual care group. The coronary event rate during the 18-month follow-up period was 13.4% in the atorvastatin group and 20.9% in the angioplasty group, a difference of borderline statistical significance. This trial was designed to compare 2 treatment strategies, so the outcome difference between the groups might not be attributable only to differences in cholesterol levels.

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study randomized 3086 patients with unstable angina or non–Q-wave infarction to atorvastatin 80 mg/d or placebo.15 The mean LDL-cholesterol level at the end of the 16-week follow-up period was 72 mg/dL in the atorvastatin group and 135 mg/dL in the placebo group. The primary composite end point was reduced with active treatment (relative risk, 0.84; 95% CI, 0.7 to 1.0; P=0.048). The results of this short-term trial in patients with unstable coronary disease are unlikely to apply to patients with stable coronary disease who are treated over longer periods of time.

**Upcoming, Definitive Studies**
On the basis of the currently available clinical trial data summarized above, it is not possible to claim with certainty that LDL-cholesterol lowering to <100 mg/dL with drugs will produce incremental benefit beyond lowering to <130 mg/dL. However, several ongoing trials are certain to resolve this quandary.

The Medical Research Council/British Heart Foundation Heart Protection Study randomized 20 536 men and women with total cholesterol levels ≥135 mg/dL (3.5 mmol/L) to simvastatin 40 mg/d or to placebo between 1994 and 1997.16 Two thirds of the patients have documented coronary disease, and they overlap with the one third who have an LDL-cholesterol level ≤115 mg/dL (3.0 mmol/L). The results of this trial will be presented at the American Heart Association meeting this November.

The Treating to New Targets (TNT) Study has enrolled 10 000 patients with clinically evident coronary disease and LDL-cholesterol levels between 130 and 250 mg/dL. Patients were randomized to atorvastatin 10 mg/d or 80 mg/d, with the expectation that LDL-cholesterol levels on therapy will be ≤100 mg/dL and 75 mg/dL on the low and high doses, respectively. The primary end point is coronary death or nonfatal myocardial infarction, and the study is due to be completed after a follow-up of ≈5 years, in 2004.

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial has enrolled
12,000 survivors of myocardial infarction with LDL-cholesterol levels >135 mg/dL. They were randomized to 20 mg/d or 80 mg/d of simvastatin and also to folie acid plus vitamin B12 or corresponding placebo. The 5-year follow-up is scheduled to finish at the end of 2004.

The Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) trial randomized 8888 patients with previous myocardial infarction to simvastatin 20 mg/d, increasing to 40 mg/d if total cholesterol remains >190 mg/dL, or to atorvastatin 80 mg/d. The primary end point is coronary death or nonfatal myocardial infarction, and the study will be finished in early 2005, with a mean follow-up of 5.5 years.

A Broader Perspective
This editorial has focused narrowly on LDL cholesterol. Hypertriglyceridemia and other risk factors are also targets for treatment, increasingly so as the prevalence of obesity and type II diabetes increase. However, LDL cholesterol remains the easiest risk factor to treat successfully, and lowering LDL cholesterol reduces coronary events in patients with other risk factors, such as diabetes, low HDL cholesterol, or hypertriglyceridemia.

Historically, as clinical trial evidence has accumulated, treatment goals for systolic and diastolic blood pressure, diabetes, LDL cholesterol, and triglycerides have moved in only one direction: downward. Systolic hypertension in the elderly used to be considered normal, and hypercholesterolemia used to start at 250 or even 300 mg/dL. The current guidelines accurately reflect the current evidence, but both 130 and 100 mg/dL may turn out not to be lines etched in stone.

References

Key Words: Editorials ☐ cholesterol ☐ coronary disease
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Circulation. 2001;104:2635-2637
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/104/22/2635

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