Journal of the American College of Cardiology
© 1999 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 34, No. 1, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(99)00183-7

VIEWPOINT

How Much to Lower Serum Cholesterol: Is It the Wrong Question?

C. Tissa Kappagoda, MD, PHD, Ezra A. Amsterdam, MD
Sacramento, California

Although the management of cardiovascular disease contains numerous controversies, there are two issues that cardiologists appear to agree on: the link between serum cholesterol and coronary atherosclerosis and the efficacy of the statin drugs in lowering serum cholesterol concentration. These drugs have been tested in several well designed clinical trials of secondary prevention (1–3), and each has shown favorable findings involving a consistent decrease in serum cholesterol concentration and a concurrent reduction in coronary events. In fact, the three major secondary prevention trials (1–3) have resulted in a pattern of approximately 1% decrease in events for each 1% decline in LDL-cholesterol. As this evidence accumulates, emphasis has shifted from "Can we reduce serum cholesterol concentration?" to "How low should we go?" This comment is written to open a dialogue on this issue with reference to the management of patients with known coronary artery disease.

Cardiologists recognize two aspects of preventive cardiology: one dealing with primary risk in individuals having no previous evidence of coronary disease and the other concerning secondary risk in patients with clinical evidence of disease (4,5). In 1990, Pekkanen and his colleagues (6) addressed this issue using the data base of the Lipid Research Clinics Program Prevalence Study (LRCPPS), and identified the relationships between serum cholesterol concentration and the death rate from coronary artery disease (per 1,000 individuals/year). They identified two distinct relationships between coronary mortality and serum cholesterol level in individuals with no history of coronary artery disease and in patients with documented coronary disease (Fig. 1). As illustrated, mortality is closely related to serum cholesterol concentration, and the correlation is stronger in patients with, than in patients without, coronary disease. These relationships form the raison d'etre for attempting to "treat" elevations in serum cholesterol. The implication in these two relationships is that a reduction in serum cholesterol will diminish the risk of death from coronary artery disease. The observations from the placebo arms of several large trials (7–9) and observational studies (10) relating to coronary atherosclerosis have since confirmed this disparate relationship between serum cholesterol and mortality in symptomatic compared with asymptomatic individuals (Fig. 1). It is of interest to consider the findings of the major lipid lowering studies involving statins against this background. Figure 2A shows the results of three recent studies plotted against the relationship defined by Pekkanen et al. (6) in patients who have evidence of coronary artery disease. Each trial showed significant reductions in both serum cholesterol and death rate (1–3). However, the slopes of these relationships are considerably lower than those defined by Pekkanen et al. (6).

The patients recruited into the LRCPPS usually had multiple cardiovascular risk factors that were broadly similar to those present in recruits in the three trials under consideration (Table 1). The curve described by Pekkanen's data defines the interplay of multiple coronary risk factors, of which serum lipid level is but one. Modification of one factor, such as serum cholesterol, would permit the remaining risk factors to continue their interactions and does not guarantee that the dependent variable (mortality) would traverse down the trajectory defined by the original relationships (Figs. 1 and 2) (6). Such an argument could explain why the statin-treated and placebo groups form a curve with a flatter slope than that described by Pekkanen (Fig. 2A).

The current debate on lipid lowering therapy focuses on the degree of the response to treatment. If one were to stay within the limits imposed by the data, it is clear that it would not be possible to extrapolate to serum cholesterol values significantly lower than 170 mg/dl (Fig. 2). Even at a total cholesterol of 160 mg/dl, a value not achieved in any of the trials reported thus far, it is evident that these patients would still retain a risk of approximately six-fold compared with that anticipated from the LRCPPS data (Fig. 2B). A similar relationship exists for LDL concentrations (Fig. 3). The current controversy with respect to treatment for serum cholesterol (both total and LDL) relates to matters that could influence the relationship between lipid levels and death rates within the confidence intervals of the regression lines (11–13) (Fig. 2B).

In addition to the current preoccupation with statins, the issue that requires attention is whether one should look beyond these drugs at other secondary preventive measures. Over the past few years there has been considerable interest

From the Division of Cardiovascular Medicine, Department of Internal Medicine, University of California (Davis) Medical Center, Sacramento, California.

JACC Vol. 34, No. 1, 1999
July 1999:289–92

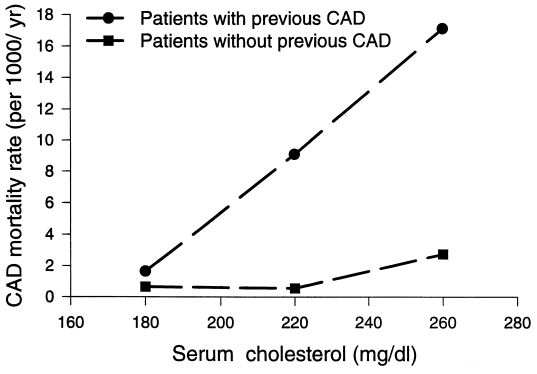

Figure 1. Relationship between coronary artery disease mortality rate and serum cholesterol. The patients with previous evidence of coronary artery disease (CAD) have a steeper relationship compared with those without. This data is obtained from the Lipid Research Clinics Program Prevalence Study, in which patients receive no lipid lowering treatment (6).

in the potential effects of "lifestyle modification" programs on the prognosis of patients with coronary atherosclerosis (14–16). These programs integrate conventional outpatient cardiac care with several other treatment modalities such as exercise training, dietary management and maneuvers designed to reduce psychosocial stress. Many of these regimens include medications to lower cholesterol concentrations. The American Heart Association and the American College of Cardiology have recognized the value of some aspects of such a multidisciplinary approach in their consensus statement on secondary prevention of atherosclerotic disease (17).

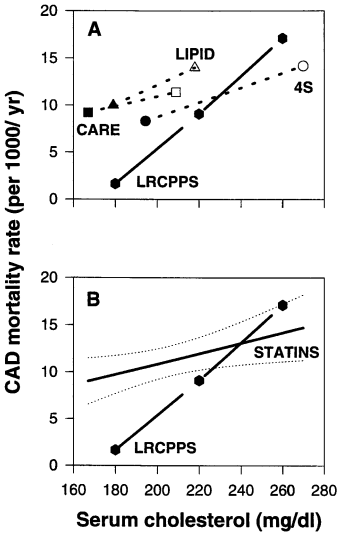

Figure 2. (A) The effect of statins on serum cholesterol and coronary artery disease (CAD) mortality in three clinical trials, 4S (1), CARE (2) and LIPID (3). In each instance, the **open symbols** (△, ○, □) represent the placebo-treated groups and the **closed symbols** (▲, ●, ■) represent the drug-treated groups. The **interrupted line** is the data from LRCPPS (6), showing the relationship between serum cholesterol and CAD mortality. **(B)** Comparison of the regression lines in the relationship between statin-treated groups **(solid regression line)** and the data from LRCPPS (**interrupted line** [6]). The confidence intervals for each line are shown. At serum cholesterol concentrations of approximately 180 mg/dl, there appears to be a six-fold increase in risk in the statin-treated group compared with LRCPPS cohort.

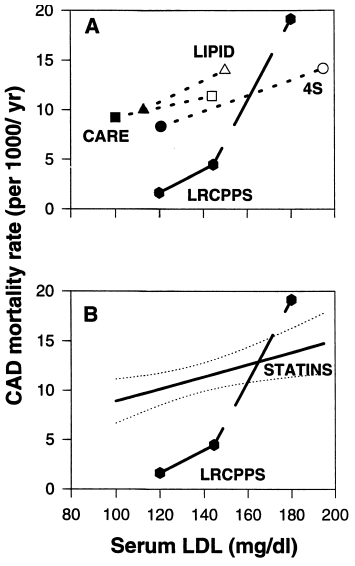

Figure 3. (A) The effect of statins on serum LDL and coronary artery disease (CAD) mortality in three clinical trials, 4S (1), CARE (2) and LIPID (3). In each instance, the open symbols (△, ○, □) represent the placebo-treated groups and the **closed symbols** (▲, ●, ■) represent the drug-treated groups. The **interrupted line** is the data from LRCPPS (6), showing the relationship between serum cholesterol and CAD mortality. **(B)** Comparison of the regression line in the relationship between statin-treated groups (the **solid regression line**) and the data from LRCPPS (**interrupted line** [6]). The confidence intervals for the statins are also shown. At serum LDL concentrations of approximately 100 mg/dl there appears to be a 6-fold increase in risk in the statin-treated group compared to LRCPPS cohort.

These lifestyle modification studies, however, appear to have limited results because they are usually small and the number of patients recruited is insufficient to evaluate effects

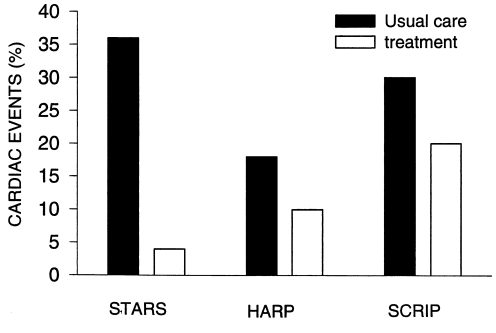

Figure 4. Effect of three lifestyle modification trials (SCRIP [13], HARP [14], AND STARS [15]) and cardiac events. **Solid bars** indicate usual care groups and **open bars** indicate treatment groups.

Table 1. Comparison of Pertinent Clinical Data in the LRCPPS Patients (6) With Those of Three Statin Trials—4S(1), CARE (2), LIPID (3)

	LRCPPS	4S	CARE	LIPID
Variable				
Age (mean/yr)	52	59	59	62
Male/Female	100:0	81:19	86:14	83:17
BMI	26.6 ± 0.19	26.0 ± 3.3	28	?
History of MI (%)	18	62	62	64
History of angina/+ ETT (%)	68	?38	?	36*
History of smoking (%)	33	30	43	73
History of hypertension (%)	45	26	43	42
History of hyperlipidemia (%)	100	100	100	100
Diabetes mellitus (%)	0	4	14	9
Medication				
Lipid lowering meds (%)	0	zocor	pravachol	pravachol
Beta-blockers (%)				48
Ca^{++} blockers (%)				36
Nitrates (%)				36
ACE inhibitors (%)				16
Anti-platelet drugs (%)				82
Total cholesterol (mg%)	227 ± 2.0	270	209	218
LDL (mg%)	151 ± 1.6	195	139	150
HDL (mg%)	47 ± 0.8	48	39	36
Endpoint	Death/1,000/yr	Death/1,000/yr	Death/1,000/yr	Death/1,000/yr

Blank cells indicate that data was unavailable. ? indicates that a reliable estimate could not be made from the information in the published report. * = unstable angina.

on "hard" primary end-points such as mortality. The statin trialists avoided this problem by resorting to a multicenter format that permits much larger numbers of recruits for the investigations. Because of the relatively simple nature of the intervention involved, it is possible to maintain an appropriate level of quality control in these studies.

Lifestyle modification programs and trials, in contrast, place great emphasis on the concept that patients exercise personal responsibility for their health by playing a significant role in implementing the intervention. These considerations make it difficult to conduct large, multicenter clinical trials in which lifestyle modification is the main intervention. Therefore, investigators have been forced to rely on small trials and surrogate end-points, such as the total cardiovascular event rate, to demonstrate therapeutic efficacy. These provisos notwithstanding, the general consensus that has emerged from these investigations, which were not limited to lipid lowering strategies (14–16), is that such programs are effective in reducing the incidence of major cardiac events (Fig. 4) despite a very modest influence on the angiographic appearance of patients' coronary arteries.

By resorting to less stringent endpoints such as total cardiovascular events (e.g., hospitalizations for therapeutic interventions and revascularizations) supported by careful documentation, it may be possible to undertake clinical trials in which treatment with a lifestyle modification program is compared with lipid lowering medication alone. In both instances, patients could be titrated to a single serum cholesterol window. If such a design is adopted, it will be possible for these studies to be completed in those individual centers that possess infra-structures by which these services can be implemented. This approach will help us focus attention away from the limited goal of specific serum cholesterol levels to a more comprehensive risk intervention (16–18) in defining therapeutic end points.

Reprint requests and correspondence: Dr. C. T. Kappagoda, Division of Cardiovascular Medicine, 4860 Y Street, Suite 0200, Sacramento, California 95817. E-mail: ctkappagoda@ucdavis.edu.

REFERENCES

1. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344: 1383–9.
2. 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;335:1001–9.
3. The Long Term Intervention with Pravastatin in Ischemic Heart Disease (Lipid) Study Groups. Prevention of cardiovascular events and death with pravastatin in patients with coronary artery disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349–57.
4. Amsterdam EA, Hyson D, Karragoda CT. Nonpharmacologic therapy for coronary artery atherosclerosis: results of primary and secondary prevention trials. Am Heart J 28:1344–52.
5. Amsterdam EA, Deedwania PC. A perspective on hyperlipidemia: concepts of management in the prevention of coronary artery disease. Am J Med 1998;105:69S–74S.
6. Pekkanen J, Linn S, Heiss G, et al. Ten year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. N Engl J Med 1990; 332:1700–7.

JACC Vol. 34, No. 1, 1999
July 1999:289–92

7. Waters D, Lesperance J, Francetich M, et al. A controlled clinical trial to assess the effect of a calcium channel blocker on the progression of coronary atherosclerosis. Circulation 1990;82:1940–53.
8. Stephens NG, Parsons A, Schofield PM, et al. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). Lancet 1996;347:781–5.
9. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in post menopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605–13.
10. Stamler J, Wentworth D, Neaton JD, for the MRFIT Research Group. Is 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;256:2823–3014.
11. Grundy SM. Statin trials and goals of cholesterol-lowering therapy. Circulation 1998;97:1436–9.
12. Pedersen TR, Olsson AG, Faergeman O, et al., for the Scandinavian Simvastatin Survival Study Group. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). Circulation 1998;97: 1453–60.
13. West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). Circulation 1998;97: 1440–5.
14. Alderman EL, Haskell WL, Fiar JM, et al. Beneficial angiographic and clinical response to multi factor modification in the Stanford Coronary Risk Intervention Project (SCRIP). Circulation 1992;86:1–11.
15. Sacks FM, Pasternak RC, Gibson CM, Rosner B, Stone PH. Effect on coronary atherosclerosis of decrease in plasma cholesterol concentrations in normocholesterolaemic patients. Lancet 1994; 344:1182–6.
16. Watts GF, Lewis B, Brunt JNH, et al. Effects on coronary artery disease of lipid-lowering diet or diet plus cholesteramine in the St. Thomas' Atherosclerosis Regression Study (Stars). Lancet 1992;339: 563–9.
17. Smith SC, Jr., Blair SN, Criqui MH, et al. Consensus panel statement: preventing heart attack and death in patients with coronary disease. Circulation 1995;92:2–4.
18. Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary artery disease? The Lifestyle Heart Trial. Lancet 1990;336:129–33.