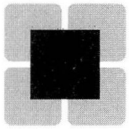

Cholesterol lowering: perspectives on the 4S and West of Scotland studies

TWO RECENT STUDIES have resolved any lingering doubts about the benefit of cholesterol-lowering therapy in patients both with[1] and without[2] definite coronary heart disease, and support the 1993 recommendations of the National Cholesterol Education Program.[3] Patients in both studies who were treated with HMG-CoA reductase inhibitors ("statins") experienced fewer coronary events, deaths due to coronary heart disease or cardiovascular disease, and deaths from all causes than did patients receiving placebo.[2] In contrast, earlier studies, which used other cholesterol-lowering drugs, had demonstrated lesser reductions in coronary events and no effect on overall mortality. The key appears to be reducing low-density lipoprotein (LDL) levels as much as possible.

THE SCANDINAVIAN SIMVASTATIN SURVIVAL STUDY

The Scandinavian Simvastatin Survival Study (4S)[1] was a randomized, double-blind, placebo-controlled trial in patients with angina pectoris or previous myocardial infarction and hypercholesterolemia despite diet therapy. The mean LDL level at baseline was 188 mg/dL, and simvastatin therapy lowered this by 35%. At 5.4 years of follow-up, the relative risk of all deaths in the treated group as compared to the placebo group was 0.70 (95% confidence interval [CI] 0.58 to 0.85, $P = .0003$). Other endpoints were significantly reduced as well (*Table*).

The 4S was the first study to show a decrease in all-cause mortality during the planned follow-up period. The Coronary Drug Project, completed in the 1960s, had shown an 11% lower rate of all-cause mortality in men with a history of myocardial infarction treated with niacin compared to those who received placebo ($P = .0004$), but only after 15 years of follow-up. This benefit had not been evident at 6 years.[4]

Numerous other studies have demonstrated that aggressive lipid management can cause regression of atherosclerosis and reduce cardiovascular events. A meta-analysis of these trials showed a trend toward fewer deaths that was not statistically significant.[5]

THE WEST OF SCOTLAND STUDY

The West of Scotland Coronary Prevention Study[2] addressed the role of cholesterol lowering in middle-aged men who had not had a myocardial infarction (although 10% of the subjects had a history of angina pectoris and 6% had a history of intermittent claudication). Patients were randomized to receive either pravastatin 40 mg every evening or placebo. Before treatment, the mean LDL cholesterol concentration was 192 mg/dL; after pravastatin treatment, it was 142 mg/dL, a 26% decrease.

During an average follow-up of 4.9 years, there were 248 definite coronary events (nonfatal myocardial infarction or death from coronary heart disease) in the placebo group and 174 in the pravastatin group, a risk reduction of 31% (95% CI 17% to 43%, $P < .001$). There were 31% fewer nonfatal myocardial infarctions ($P < .001$) and 32% fewer deaths from all cardiovascular causes ($P = .033$) in the pravastatin-treated group, and no excess deaths from noncardiovascular causes. The pravastatin group also had 22% fewer deaths from any cause

TABLE
SUMMARY OF THE WEST OF SCOTLAND STUDY AND THE 4S

Feature	Scandinavian Simvastatin Survival Study (4S)[1]	West of Scotland Coronary Prevention Study[2]
Design		
Number of patients	4444	6595
Gender	81% men, 19% women	100% men
Age (years)	35–70	45–64
Lipid-lowering agent	Simvastatin 20–40 mg daily	Pravastatin 40 mg daily
Mean follow-up (years)	5.4	4.9
Primary prevention	...	90%
Secondary prevention	100% (angina or myocardial infarction)	10% had angina
Change in lipid levels		
Total cholesterol	–25%	–20%
Low-density lipoprotein cholesterol	–35%	–26%
High-density lipoprotein cholesterol	+8%	+5%
Triglycerides	–10%	–12%
Endpoints (% risk reduction)		
Nonfatal myocardial infarction or death from coronary heart disease	34% ($P < .00001$) for men, 35% for women ($P = .01$)	31% ($P < .001$)
Percutaneous transluminal coronary angioplasty or coronary artery bypass grafting	37% ($P = .0001$)	37% ($P = .009$)
Coronary heart disease death (definite and suspected)	42% ($P = .0001$)	33% ($P = .042$)
Death from any cause	30% ($P = .0003$)	22% ($P = .051$)

(95% CI 0% to 40%, $P = .051$). The reduction in risk extended to patients without multiple risk factors (risk reduction 37%, $P < .001$) and those without preexisting vascular disease (risk reduction 33%, $P < .001$). The investigators calculated that cholesterol-lowering treatment for middle-aged men with asymptomatic dyslipidemia was as beneficial as treating hypertension in middle-aged patients with mild hypertension.

GREATER LDL REDUCTIONS, GREATER BENEFIT

The reductions in LDL cholesterol in both studies were much more substantial than in earlier studies, due to the more-effective, more-tolerable cholesterol-lowering drugs now available. The greater reductions in LDL cholesterol might explain the more marked reductions in cardiovascular events and all-cause mortality.

For example, in the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT),[6,7] there were 19% fewer primary endpoints (definite nonfatal myocardial infarction and coronary heart disease deaths) among patients treated with cholestyramine than in the placebo group ($P < .05$); coronary heart disease deaths and nonfatal myocardial infarctions were reduced by 24% and 19% respectively. The all-cause mortality rate, however, was not different between the two groups. The degree of cholesterol reduction was modest: the mean cholesterol levels were 275 mg/dL and 277 mg/dL at 1 and 7 years, respectively, in the placebo group and 239 mg/dL and 257 mg/dL at 1 and 7 years, respectively, in the cholestyramine group.

In the Helsinki Heart Study,[8] the fibric acid derivative gemfibrozil produced a 9% decrease in total cholesterol and a 8% decrease in LDL cholesterol. There was a 34% lower incidence of fatal and nonfatal myocardial infarction and cardiac death in the treated group than in the placebo group, a greater reduction than one would expect with such a small reduction in LDL cholesterol. The most likely reason for this degree of reduction in cardiac event rates was the beneficial effect of gemfibrozil on high-density lipoprotein (HDL) cholesterol (a 10% increase) and triglycerides (a 34% decrease). However, as in the LRC-CPPT, the overall mortality rate was no different between the placebo group and the treated group.

IS LIPID LOWERING HARMFUL?

Both the LRC-CPPT and the Helsinki Heart Study reported higher rates of violent or accidental

deaths in the groups receiving cholesterol-lowering agents than in the groups receiving placebo. Wysowski and Gross[9] examined this effect and found little evidence of a causal relationship between cholesterol-lowering drugs and accidental or violent deaths.

There does appear to be a J- or U-shaped relationship between serum cholesterol and all-cause mortality. Increased mortality has been noted only with total cholesterol levels lower than 160 mg/dL. Some investigators suggest this apparent effect is due in part to the low serum cholesterol levels that occur in patients with cancer or liver disease.[10,11] A National Institutes of Health consensus conference concluded that there was little evidence of an adverse effect of cholesterol-lowering therapy.[12]

Link with cancer disputed

Newman and Hulley[13] recently suggested that cholesterol-lowering medications (fibric-acid derivatives and statins) cause cancer in rodents at doses similar to those used in humans, and recommended these medications be reserved for patients at short-term risk of coronary heart disease death. Dalen and Dalton[14] contest these findings, citing three meta-analyses.[15–17] Davey Smith and Pekkanen[15] reviewed six clinical trials that included 13 359 patients and calculated the relative risk of cancer death as 1.31 (95% CI 0.92 to 1.86) in patients undergoing dietary treatment and 1.33 (95% CI 0.93 to 1.89) in patients receiving lipid-lowering drugs. Similarly, Kritchevsky and Kritchevsky[16] reviewed 14 clinical trials involving 25 269 patients and found a 23% excess in cancer deaths with dietary therapy and a 26% excess with lipid-lowering drugs. More recently, Law and colleagues[17] reviewed the largest randomized trials and cohort studies and concluded there were no excess cancer deaths in the treatment groups. In these trials, the relative risk of cancer death was 1.07 (95% CI 0.90 to 1.26), but only 0.85 (95% CI 0.74 to 1.05) in clinical trials with extended follow-up. Two clinical trials (the World Health Organization Clofibrate Study[18] and the Los Angeles dietary trial[19]) accounted for most of the excess cancer deaths in these three meta-analyses. If these two studies were not included, there would be no significant excess cancer deaths.

Dalen and Dalton[14] also interpreted the rodent toxicity data quite differently than did Newman and Hulley, stating that "the doses used for lovastatin and gemfibrozil were 312 and 10 times the human recommended dose, respectively. When lovastatin was administered at 12.5 to 62.5 times the recommended dose [resulting in a drug exposure (area under the curve) ranging from 0.3 to 2.0 times that observed in humans], no increase in tumors was observed."

RECOMMENDATIONS...AND QUESTIONS

The 4S and the West of Scotland Study lend support to the 1993 recommendations of the National Cholesterol Education Program Adult Treatment Panel II,[3] which call for drug treatment if the LDL level is 130 mg/dL or greater in patients with definite coronary heart disease. In patients without coronary heart disease, the threshold LDL level is 190 mg/dL if fewer than two risk factors are present, 160 mg/dL if two or more risk factors are present.

Numerous questions regarding lipid management remain. For example, we still do not know whether treatment of isolated low HDL levels would be beneficial. Another issue is whether women would derive as much benefit from cholesterol-lowering therapy. Women accounted for 18.6% of the 4S study population and achieved a similar reduction in major coronary event rates as did men. However, no reduction in all-cause mortality could be detected in women because their overall mortality rate was low.

Until further studies with larger numbers of women become available regarding the role of cholesterol-lowering therapy in the prevention of coronary heart disease, there should be no differences in the treatment offered to patients based upon gender. If atherosclerosis is present in the coronary or peripheral circulation, an aggressive program to reduce total and LDL cholesterol should be instituted with a goal LDL cholesterol of < 100 mg/dL.

Trials to date have also included very few elderly patients (older than 75 years). There are really no good data to guide us on how to treat elevated blood lipids in the elderly patient with no clinical evidence (primary prevention) of coronary heart or other vascular disease. However, if the elderly patient demonstrates evidence of coronary heart disease or atherosclerosis elsewhere, the guidelines as outlined in the National Cholesterol Education Program Adult Treatment Panel II should be followed.

Clinical trials (primary and secondary prevention) with larger numbers of women and elderly patients are necessary to determine whether cholesterol lowering is effective in decreasing coronary

heart disease events and death and all-cause mortality in these groups.

Given the availability of effective drugs with minimal side effects to lower cholesterol levels, does diet therapy still have a role? Although many patients find it easier to take a pill than to adhere to a diet, diet therapy should be emphasized to all patients with lipid abnormalities and all patients with cardiovascular disease. A diet low in cholesterol and saturated fat not only lowers cholesterol values but augments the effects of cholesterol-lowering medications.

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