

Clinical Study Outcomes and the Benefits of Treating Hypercholesterolemia

Encouraging data on outcomes with lipid-lowering therapy have been seen in recent clinical trials, including the Scandinavian Simvastatin Survival Study (4S),¹ the Cholesterol and Recurrent Events (CARE)² trial, and the West of Scotland Coronary Prevention Study group (WOSCOPS).³ These trials were summarized by Peter H. Jones, MD, Associate Professor of Medicine, and Director, American Heart Association Lipid Disorders Training Center at the Baylor College of Medicine in Houston, Texas; and Joseph A. Vita, MD, Associate Professor of Medicine and Associate Director of the Cardiac Catheterization Laboratory, and Director of Catheterization Laboratory Research at Boston University Medical Center in Boston. These well-designed trials showed a clear benefit for treatment with HMG-CoA reductase inhibitors [statins] in reducing mortality and the number of cardiac events in hypercholesterolemic patients with established CHD. Furthermore, the benefits of treatment were evident in subgroups such as women, elderly patients, persons with diabetes, and smokers.

“Observational studies and randomized trials over the past 20 years have shown that cholesterol-lowering and mortality are linked,” said Dr. Vita. The current conventional wisdom is that for every 10% reduction in LDL-C, there is a 20% reduction in mortality in both younger and older patients.

In 1984, the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPT) demonstrated that the greater the reduction in LDL-C, the

greater the observed benefit.⁴ In that trial, an 11% reduction in LDL-C was associated with a 19% CHD benefit, and a 35% reduction in LDL-C was associated with a 49% CHD benefit, continued Dr. Vita. An observational study by Pekkanen et al (1990) showed that the majority of cardiac events occurred in men with an LDL-C of greater than 160 mg/dL.⁵

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In the late 1980s and early 1990s, researchers relied on angiographic studies to determine the effects of lipid-lowering agents on progression or regression of atherosclerosis as reflected by the size of the lumen. These studies showed that small changes in the size of the lumen were associated with a reduction in coronary events, although the studies were not powered to look at coronary events. Examples of such studies are FATS (Familial Atherosclerosis Treatment Study, 1990), STARS (St. Thomas Atherosclerosis Regression Study, 1992), and MARS (Monitored Atherosclerosis Regression Study, 1993).

“Angiographic severity of coronary atherosclerosis fails to correlate with future clinical events. This led researchers to observe that the extent of stenosis was not the whole explanation. Mounting

evidence suggests that as serum cholesterol is reduced, there is a decreased tendency for plaque rupture and thrombosis. Cholesterol lowering will stabilize lesions, and this will reduce the coronary event rate and the need for revascularization," said Dr. Vita.

Recent studies have added to our understanding of the role of elevated LDL-C in coronary events related to rupture of unstable atherosclerotic plaque, explained Dr. Jones. It is now known that the lesions most likely to rupture are those that are mildly to moderately stenotic with a lipid-rich core; these lesions are usually found in patients with elevated LDL-C and other risk factors. Lipid-lowering drugs are thought to reduce the lipid content of these lesions and therefore render them less likely to rupture.

The instability of the atherosclerotic plaque also appears to be related to compromised endothelial function. Functional endothelial cells produce nitric oxide and vasodilation, retard platelet adhesion, suppress vascular cell adhesion, and produce a favorable tPA/PAI ratio. Dysfunctional endothelial cells do just the opposite.

"A person who has had one coronary event is more likely to have another. It has been shown that treatment of hypertension, decreasing LDL-C, increasing HDL-C, and smoking cessation can reverse endothelial dysfunction," continued Dr. Jones.

A recent meta-analysis of 35 cholesterol-lowering trials, which involved more than 75,000 patients, showed that lowering total cholesterol and LDL-C reduced the risk of total and cardiovascular mortality.⁶ Moreover, the magnitude of benefit was related to the degree of cholesterol lowering.

"Every 10% reduction in total cholesterol reduced the total mortality risk by 8% to 10% and the risk of CHD mortality by 13% to 14%. The meta-analysis also suggested that the type of cholesterol-lowering therapy is related to success of treatment. Statins achieved excellent results, while fibrates and

other older drugs were not as good," observed Dr. Jones.

Further evidence of the positive effects of aggressive lipid lowering with statins was provided by three recent trials that included a total of more than 15,000 patients: 4S, CARE, and WOSCOPS.

Scandinavian Simvastatin Survival Study (4S)

The 4S trial included 4,444 patients with CHD and elevated cholesterol levels after 1 month of dietary treatment, 81% of whom were male and 19%, female. At entry, mean total cholesterol level was 260 mg/dL and mean LDL-C level was 188 mg/dL. Patients were randomized to receive either simvastatin or placebo. The starting dose of simvastatin was 20 mg/day; during the study, patients were titrated up to 40 mg/day or down to 10 mg/day according to LDL-C level, with the average dose being 26 mg daily.¹

The 4S trial was the first cholesterol-lowering trial to show a benefit in total mortality, with a risk reduction of 30%. In addition, coronary mortality was reduced by 42% with simvastatin treatment compared to placebo.

"In this trial, patients lived longer because they didn't die of CHD. A significant reduction in every single endpoint was achieved by aggressive LDL-lowering treatment (ie, a 35% reduction in LDL-C)," emphasized Dr. Jones.

The difference between treatment groups was evident by 2 years, after which the two groups continued to diverge and widen (Figure 1). "The study was only 5 years long. These results suggest that if you treat longer than 5 years, the benefit would be even greater," noted Dr. Jones.

Positive results were seen across all patient types. The benefit was similar in patients over the age of 60 years as well as those under 60. A 34% reduction in coronary events was seen in patients older than 65. Women achieved as great a benefit as men regarding major coro-

nary events, but there were not enough women in the study to assess the statistical significance for total mortality. Smokers achieved a 31% reduction in risk of cardiac events, and patients with diabetes had a 55% reduction in event rates. In addition, patients taking aspirin and/or beta-blockers also enjoyed additive effects of aggressive cholesterol lowering.

The data also suggest that aggressive LDL lowering reduces the incidence of stroke, continued Dr. Jones. The incidence of thrombotic stroke was lower in those patients treated with simvastatin versus placebo.

In the placebo group, the higher the LDL-C level, the greater the number of events. "When the treatment group was compared to placebo, it didn't matter where the LDL level was; if you lowered it by 35%, you reduced the number of events," emphasized Dr. Jones (Figure 2).

The number of hospitalizations was significantly reduced with simvastatin (32% reduction), and there was less utilization of hospitalization and ancillary healthcare services in the simvastatin-treated group compared to placebo patients.

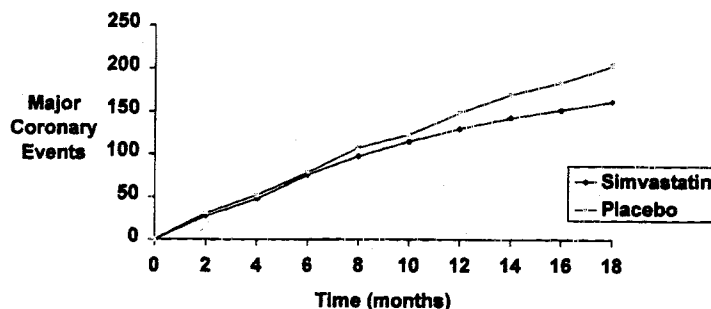
One message from the 4S trial is that lipid-lowering treatment with simvastatin reduced coronary deaths by 78 lives, major coronary events by 191 events, revascularization by 131 procedures, and CHD hospital days by 3,848 days, said Dr. Jones.

Cholesterol And Recurrent Events (CARE)

CARE was a large, randomized, double-blind, placebo controlled trial that enrolled 4,159 MI survivors without markedly elevated cholesterol levels (mean total cholesterol level was 209 mg/dL; mean baseline LDL level was 139 mg/dL).² "These cholesterol levels are similar to those found in the typical American CHD patient treated in the community," observed Dr. Vita.

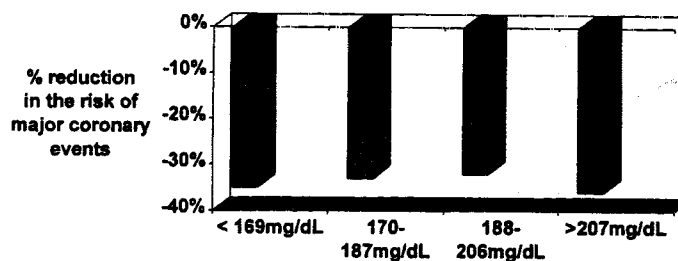
Patients were randomized to receive either 40 mg of pravastatin or placebo

Figure 1. 4S: Separation of Events



Scandinavian Simvastatin Survival Group. *Lancet* 1994;344:1383-1389.

Figure 2. Simvastatin Reduced the Risk of Major Coronary Events* Regardless of Baseline LDL Cholesterol



*Incidence of major coronary events, including coronary mortality and nonfatal MI, was the secondary endpoint of the study. *Lancet* 1995;345:1274-1275.

and treated for 5 years. Pravastatin 40 mg treatment was associated with a 24% risk reduction in fatal CHD or nonfatal MI, a 25% risk reduction in total MI, and a 27% risk reduction in the need for coronary artery bypass grafts (CABG) and percutaneous transluminal coronary angioplasty (PTCA).

CARE included patients up to the age of 75. A 20% risk reduction was found in those under 60 years of age, and a 26% risk reduction was seen in those ages 60 to 75. Benefits of pravastatin treatment were found in women, smok-

ers, hypertensives, and patients previously treated with CABG/PTCA.

"In this trial, LDL reduction was beneficial in patients with or without risk factors. There was a reduction in total CHD event rates associated with pravastatin treatment," said Dr. Jones.

West Of Scotland Coronary Prevention Study (WOSCOPS)

WOSCOPS included 6,595 men up to the age of 64 years with no CHD but with elevated cholesterol levels (mean cholesterol: 272 mg/dL). Patients were randomized to receive either pravastatin 40 mg or placebo. Pravastatin 40 mg treatment achieved statistically significant risk reductions for the endpoint of nonfatal MI or CHD death (31% risk reduction); nonfatal MI (31% risk reduction); all cardiovascular deaths (32% risk reduction); and total mortality (22% risk reduction).³ Both smokers and non-smokers had a 31% risk reduction in nonfatal MI or CHD death.

Summary of 4S, CARE, and WOSCOPS

In all three trials, the magnitude of LDL reduction was correlated with the degree of benefit. Patients with the highest lipid levels at baseline benefited the most from aggressive treatment with statins. The 4S trial included patients with high LDL levels who were treated with aggressive lipid lowering, and this resulted in a 42% risk reduction in CHD mortality. WOSCOPS achieved a 31% risk reduction in patients with no evidence of CHD but with high LDL.

CARE achieved a 24% risk reduction in patients with CHD but without elevated cholesterol levels (Table 1).

"It is clear from the results of these trials that very aggressive LDL-C reduction in a high LDL-C population has profound effects. There is still some benefit if the LDL-C is lower, but it is not quite as great. CARE included patients with the lowest cholesterol levels at baseline, and treatment achieved a lower reduction in CHD events; but there was still some benefit," noted Dr. Jones.

"Very few interventions in medicine give us the cumulative benefit we have seen with the statins," continued Dr. Jones. For every 1,000 patients treated for 5 years, 35 CHD deaths were prevented in 4S, 11 CHD deaths were prevented in CARE, and seven in WOSCOPS. In 4S, 67 nonfatal MIs were prevented, compared with 26 in CARE and 20 in WOSCOPS. Fifty-nine revascularizations were prevented in 4S, compared to 46 in CARE, and eight in WOSCOPS.

Dr. Jones commented that results of these trials suggest the distinction between primary prevention and secondary prevention may hinder appropriate management of patients at risk for coronary events. "Each of these trials included a different patient population with regard to CHD status and lipid levels. These studies show us that we should not wait until an event has occurred in such patients before we treat with a lipid-lowering agent. On any given morning, a patient may be considered in the primary prevention state, but if that person suffers an MI that afternoon, he shifts to the secondary prevention state. High-risk patients in the primary prevention state, as in WOSCOPS, are still of concern and should be treated," observed Dr. Jones.

The data from these trials provide further support for current NCEP guidelines, he continued, and they show that both absolute LDL-C values achieved and percentage of LDL-C lowered are important. Patients with

Table 1. Comparison of Risk Reduction in 4S, CARE, WOSCOPS

	4S	WOSCOPS	CARE
Nonfatal MI or CHD Death	34% (men)	31%	45% (women)
	34% (women)	(men only)	20% (men)
PTCA or CABG	37%	37%	27%
CHD Death	42%	33%	20%
Death from any Cause	30%	22%	24%

LDL levels greater than 160 mg/dL who have CHD or carotid disease clearly benefit from the percentage of LDL lowered (as shown by ACAPS and 4S). Patients with LDL levels between 130 and 160 mg/dL and CHD benefit from both the absolute LDL level achieved and the percentage of LDL lowering (4S and CARE). In patients with LDL-C levels greater than 160 mg/dL and no CHD, the percentage of LDL lowering is beneficial (WOSCOPS). "The high-risk primary prevention patient should be considered for lipid-lowering treatment," he added.

"The NCEP ATP II guidelines and the clinical data are mutually supportive. Both the percent lowering and absolute lowering should be considered in treating patients with a lipid-lowering agent" Dr. Jones emphasized. "Clinical data show that LDL-C lowering is the most important factor in preventing cardiac morbidity and mortality."

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