

## Converting Clinical Lipid Trials into the Practical Management of High-Risk Patients: New NCEP Thoughts on Treating CHD Patients

Based on a presentation by Scott Grundy, MD, PhD

### *Presentation Summary*

The National Cholesterol Education Program (NCEP) guidelines published in 1993 made low-density lipoprotein cholesterol (LDL-C) the primary target of intervention. This decision was based on observations in familial hypercholesterolemia and on data from primary, secondary, and angiographic trials conducted prior to 1993. NCEP set the target goal for LDL-C as 100 mg/dL or less for secondary prevention and 130 mg/dL or less for primary prevention. Large-scale, well-designed, cholesterol-lowering

trials conducted since 1993 substantiate these goal levels. In particular, the Scandinavian Simvastatin Survival Study and the Cholesterol and Recurrent Events trial showed that LDL-cholesterol-lowering with HMG-CoA reductase inhibitors (statins) reduced coronary events, coronary deaths, and total mortality in patients who had established coronary heart disease (CHD) with both elevated and normal cholesterol levels. These data, together with the NCEP guidelines, underscore the need for aggressive lipid-lowering therapy in patients at risk for CHD.

**T**he purpose of the National Cholesterol Education Program (NCEP) was to develop a central framework for a cholesterol education program. Scott Grundy, MD, PhD, described the goal, both established and new, of the NCEP. Dr. Grundy was one of the principal authors of the original NCEP guidelines. A faculty member at the University of Texas Southwestern Medical Center in Dallas, Dr. Grundy holds the titles of Professor of Medicine, Chairman of the Department of Clinical Nutrition, Director of the Center for Human Nutrition, and Professor of Medicine and Biochemistry.

The NCEP Adult Treatment Panel (ATP)-II guidelines,<sup>1</sup> developed before the publication of recent clinical trials,

made low-density lipoprotein cholesterol (LDL-C) the primary target for intervention. This decision was based partly on studies in familial hypercholesterolemia showing that a single gene

*[Study] data, together with the NCEP guidelines, underscore the need for aggressive lipid-lowering therapy in patients at risk for CHD.*

defect producing elevated LDL-C led to the development of premature coronary heart disease (CHD) in the absence of other known risk factors.

"The NCEP regarded LDL as the center of the atherogenic process. On

the basis of studies of familial hypercholesterolemia and a lot of additional data, it appeared that LDL was the initiating factor that drives the atherosclerotic process," Dr. Grundy said.

Epidemiologic evidence suggests that in the presence of elevated LDL-C,

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other risk factors accentuate the rate of atherogenesis. These include hypertension, low levels of high-density lipoprotein cholesterol (HDL-C), smoking, and diabetes. Studies have shown that in populations with very low LDL-C, there is a low incidence of CHD even if other risk factors are present.

#### **LDL-C Late in the Atherosclerotic Process**

One question experts have asked, Dr. Grundy told listeners, is whether LDL-C is important at every stage of atherogenesis or only in the beginning. It was previously thought that LDL-C initiated the atherogenic process, but that other risk factors determined whether events occurred. Several decades ago, this line of reasoning led to the assumption that intervention late in the course of atherosclerosis might not be of benefit.

A number of well-designed clinical trials have been conducted over the past 25 years to test the validity of this assumption. The accumulated evidence from these trials provides firm evidence that treatment late in the process is beneficial in reducing cardiac morbidity and mortality, Dr. Grundy said. These trials can be divided into three categories: primary prevention, secondary prevention, and angiographic trials.

Primary prevention trials evaluate strategies that prevent new onset of CHD; secondary prevention trials

evaluate strategies to prevent recurrent disease in people with manifest CHD; angiographic trials assess whether cholesterol or LDL lowering reverses or prevents progression of atherosclerosis.

#### **Primary Prevention Trials**

Over the past 10 or 12 years, primary prevention trials have shown that lipid-lowering therapy achieves a reduction in new coronary events. A major primary prevention trial, the Lipid Research Clinic Coronary Primary Prevention Trial (LRC-CPPT),<sup>2</sup> showed a significant reduction in coronary events with cholestyramine treatment. However, most primary prevention trials were not sufficiently powered to determine mortality. Some investigators conceded that cholesterol lowering prevented coronary disease, but were skeptical that it would improve survival.

#### **Secondary Prevention Trials**

Of the eight trials carried out in secondary prevention, no single trial had sufficient power to detect differences in mortality. Most suggested a benefit for lipid-lowering therapy, but this was not statistically significant.

In 1990, a meta-analysis of secondary prevention trials<sup>3</sup> showed that cholesterol lowering achieved a 25% reduction in recurrent CHD and coronary deaths, no increase in non-CHD deaths, and a trend toward reduction in total deaths. Furthermore, there appeared to be no deleterious effects of cholesterol-lowering therapy in patients with established CHD.

"These results were obtained with the relatively modest cholesterol-lowering agents available at that time. This meta-analysis suggested that lowering cholesterol levels even in the presence of extensive atherosclerotic disease does a lot of good," said Dr. Grundy.

These data are similar to those seen in trials of aspirin, a widely used agent for secondary prevention. A meta-analysis of aspirin trials showed a 25% reduction in recurrent events and a 10% reduction in total mortality.<sup>4</sup>

**Angiographic Trials**

A large number of angiographic trials have been carried out to determine whether aggressive cholesterol lowering produced changes in the degree of atherosclerosis. [See page S84.] Results showed on average that a slight regression in atherosclerotic plaque occurred with treatment, whereas some progression of atherosclerosis was seen in the placebo or control groups. However, a striking reduction in coronary events occurred with drug treatment that was unexpected with the small change in atherosclerotic plaque measurements seen on quantitative angiography.

“Something was being produced by cholesterol lowering that went beyond angiographic changes. It appeared as though cholesterol lowering had a beneficial effect on coronary arteries not reflected by total gross lesion measurements,” observed Dr. Grundy.

The angiographic trials suggested that the benefit of lipid-lowering therapy was because of plaque stabilization. Cholesterol lowering is thought to stabilize lipid-rich atherosclerotic plaques and prevent them from rupturing, thus reducing the likelihood of unstable angina and myocardial infarction (MI).

“Acute events are what kill patients, and the major benefit of cholesterol-lowering therapy is a reduction in acute events,” noted Dr. Grundy.

The NCEP ATP-II guidelines were based on studies published up to 1993. The guidelines placed increased emphasis on CHD risk status for obtaining cholesterol screening. Patients at highest risk of CHD appear to get the most immediate and greatest reduction in absolute risk.

“Patients with established CHD or other atherosclerotic disease have a five- to seven-fold increased risk of dying from CHD, and they deserve the most aggressive therapy,” stated Dr. Grundy.

**The 4S Study**

Since publication of the NCEP ATP-II recommendations in 1993, several new trials have supported the recom-

mendations. Perhaps the most important was the Scandinavian Simvastatin Survival Study (4S),<sup>5</sup> which evaluated the effects of simvastatin versus placebo in patients with established CHD. The majority of patients received simvastatin 20 mg/day, but some required a higher dose. The goal of treatment in these hypercholesterolemic patients was to reduce the total cholesterol to less than 200 mg/dL or the LDL-C 130 mg/dL or less.

Results showed that simvastatin achieved a 34% reduction in risk of new CHD events, which was highly significant, statistically. A 42% reduction was seen in cardiovascular deaths. There was no increase in noncardiovascular deaths, and no evidence of toxicity or increase in cancer associated with drug treatment. Of extreme importance, was a 30% reduction in total deaths (Table 1).

4S was the first trial to show not only a reduction in coronary events and coronary death, but also a reduction in total overall mortality, Dr. Grundy pointed out. These results were obtained with simvastatin, which appears to have more powerful cholesterol-lowering efficacy than older agents.

**Table 1.** Percentage of Reductions with Statin Treatment in 4S

Events or Procedures	% Reduction
Major Coronary Events	-34%
Coronary Deaths	-42%
Revascularization Procedures	-37%
Major Coronary Events in Diabetic Patients	-54%
Major Coronary Events in Patients 65 or Older	-34%
Total Mortality	-30%

The benefits of simvastatin were evident across the board in older and younger patients, women and men, and people with diabetes. Diabetic patients had a 54% reduction in major coronary events. About 70% of adults with diabetes in the United States have high or

borderline-high total cholesterol levels. Most diabetic patients also have multiple risk factors and are at high risk of CHD. Some investigators believe aggressive cholesterol lowering to a goal LDL-C level of less than 100 mg/dL is as important for diabetic patients as for those with established CHD.

4S also showed that the same results were obtained with drug treatment regardless of initial total cholesterol or LDL-C levels. Patients with LDL-C levels 100 mg/dL to 160 mg/dL got the same benefit from cholesterol lowering as those with higher levels. This is important, said Dr. Grundy, because most American patients with established CHD have cholesterol levels in the lower and middle ranges, not in the higher ranges common among people in Scandinavian countries.

### The CARE Trial

Results of the Cholesterol and Recurrent Events (CARE) trial bolster the finding that CHD patients who have so-called normal cholesterol levels achieve the same benefit with cholesterol-lowering therapy as those with elevated cholesterol.<sup>6</sup> CARE randomized patients to either pravastatin or placebo. The study population included male and female patients who had sustained a previous MI and had an average total cholesterol level of 209 mg/dL and LDL-C levels between 115 mg/dL and 174 mg/dL. This is the range seen in most patients with established CHD. The majority of patients tended to have relatively normal or slightly elevated triglycerides.

Cholesterol lowering with pravastatin produced significant lowering of cholesterol, not quite as big a magnitude as with simvastatin in the 4S trial, but a marked LDL-C lowering effect was seen in treated patients. Results were similar to those of the 4S trial: a 24% reduction in CHD and nonfatal MI; a 26% reduction in the need for percutaneous transluminal coronary angioplasty (PTCA); and an 18% reduction in total CHD deaths (Table 2). The CARE study confirmed results obtained in 4S in patients with established CHD and extended the results to show that patients with CHD and normal cholesterol levels also receive a major benefit from lipid-lowering statin therapy.

"Evidence from CARE supports the target goal of LDL-C <math>100\text{ mg/dL}</math> in secondary prevention," emphasized Dr. Grundy.

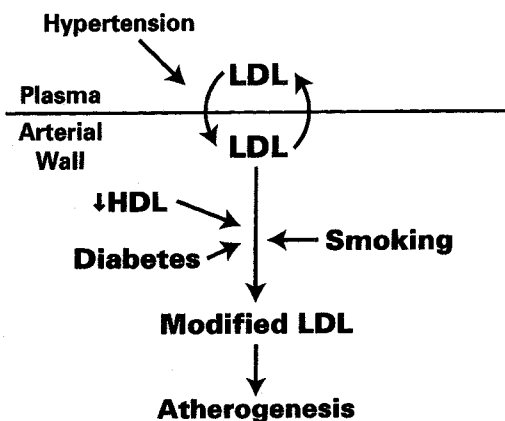
### Conclusion

LDL-C is the primary driving factor in atherogenesis. Recent clinical trials, such as 4S and CARE, show that initiating LDL-C-lowering therapy, even in patients with advanced CHD, achieves a marked benefit in outcome. Lowering LDL-C is an important goal of secondary prevention; agents that have been shown to be effective in accomplishing this goal should move to the top of the

**Table 2.** Percentage of Reductions with Statin Treatment in CARE

Event or Procedure	% Reduction
Fatal CHD or Nonfatal MI	-24%
CABG	-26%
PTCA	-23%
Confirmed Nonfatal MI	-23%

**Figure 1.** Risk Factors that Affect the LDL-C Axis



list of modalities for secondary prevention therapy, Dr. Grundy concluded.

Other risk factors also affect the LDL-C axis. For example, smoking appears to accelerate oxidation of LDL-C; HDL-C protects against oxidation of LDL-C; diabetes promotes the modification of LDL-C; and hypertension drives more LDL-C into the artery wall (Figure 1). These risk factors may act to promote progression of the atherosclerotic pathway leading to premature atherosclerosis. Thus, it is important to lower LDL-C with drug therapy and dietary changes and also to modify other risk factors that influence the atherosclerotic process.

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