HMG-CoA Reductase Inhibitors
Issues in Assessing Their Benefits in Coronary Heart Disease

Antonio M. Gotto Jr
Department of Medicine, Baylor College of Medicine, Houston, Texas, USA

In Pedersen and Tobert's article on page 11[1] of this issue, the general conclusions about the benefits of lowering total cholesterol and low density lipoprotein (LDL) cholesterol in hypercholesterolaemic patients with coronary heart disease (CHD) centre on the impressive benefits reported in the Scandinavian Simvastatin Survival Study (4S).[2] This trial was conducted in patients with established CHD and total cholesterol levels of 5.5 to 8.0 mmol/L. It demonstrated the benefit of simvastatin therapy in various clinical endpoints, including a significant 30% reduction in all-cause mortality, the primary endpoint. 4S therefore supports a strong impetus begun in the US and Europe to manage hypercholesterolaemia aggressively in patients with CHD. One question is 'how aggressively should it be managed?' – an issue that I will take up later in this editorial.

1. Primary Prevention

The West of Scotland Coronary Prevention Study (WOSCOPS) results, recently reported at the American Heart Association Scientific Sessions and published in the New England Journal of Medicine,[3] extend the benefit of treating hypercholesterolaemic patients with an HMG-CoA reductase inhibitor, or statin, in this case pravastatin, to patients without established CHD. WOSCOPS participants had no history of myocardial infarction and had LDL cholesterol levels of at least 4.0 mmol/L on 2 assessments despite dietary therapy, at least 4.5 mmol/L on at least 1 assessment, and no more than 6.0 mmol/L on 1 assessment. As noted by Pedersen and Tobert,[1] prior to WOSCOPS there was not a strong mandate for primary prevention. Concern about increased noncardiovascular mortality had been raised on the basis of some earlier trials of lipid-regulating therapy. At least for hypercholesterolaemic patients, WOSCOPS lays these concerns to rest. There was no increase in deaths from trauma, suicide, cancer, or other non-cardiovascular causes in the pravastatin-treated patients. The results in these asymptomatic individuals with moderate hypercholesterolaemia were dramatic: pravastatin lowered plasma cholesterol levels by 20% and LDL cholesterol levels by 26%. There was a significant 31% reduction in risk for the combined primary endpoint of either nonfatal myocardial infarction or CHD death as a first event, a significant 31% reduction in risk for non-fatal myocardial infarction, and a significant 33% reduction in the risk for definite or suspected CHD death. All-cause mortality was reduced by 22% (p = 0.051).

2. Who Should be Treated?

In a meta-analysis of randomised controlled clinical trials of lipid-regulating therapy, Law et al.[4] concluded that a lag period of 2 years is required before an effect is seen on clinical events and that a dose-response association exists between reduction in cholesterol level and reduction in CHD events. The reduction in CHD events is achievable in patients with or without ischaemic heart disease, whether the cholesterol lowering is accomplished by diet or drug therapy. The trials in this meta-analysis did not include the recent HMG-CoA reductase inhibitor pharmacological
monotherapy trials, and the degree of cholesterol lowering achieved in these earlier trials was considerably less than that obtained in 4S and WOSCOPS. In the recent Drugs Affecting Lipid Metabolism (DALM) symposium in Houston, Texas, Law extended his previous meta-analysis to include 4S. With the more potent cholesterol lowering, a greater reduction in CHD events was demonstrated, as Pedersen and Tobert predict in the present issue of this publication. Because of the consistency of the findings in patients with established CHD, in whom cost-benefit is much more efficient on the basis of cost per year of life saved compared with patients without established CHD, Law suggested treating all individuals with established CHD with a statin as standard therapy, regardless of serum cholesterol level or even without necessarily measuring the serum cholesterol level.

What are the assumptions and the implications of such a drastic approach? One assumption is that total cholesterol can be used as a surrogate measure for LDL cholesterol, and another is that all patients with CHD would benefit from LDL cholesterol lowering, even those with LDL cholesterol levels 2.6 mmol/L or lower. The data from 4S that have been published to date and the data from WOSCOPS do not allow the degree of LDL cholesterol lowering to be related to the degree of event reduction. This is a reasonable hypothesis, but what is proven by data should be distinguished from what is an extrapolation. Until the data are analysed in such a way as to enable the relation between the degree of LDL cholesterol lowering and event reduction to be determined, we cannot be confident that lowering the LDL cholesterol of a patient whose LDL cholesterol level is already below 2.6 mmol/L will confer further benefit.

The results of the Cholesterol and Recurrent Events (CARE) trial, anticipated to be reported in 1996, should provide valuable information about the benefit of treating patients with established CHD and lower levels of LDL cholesterol. Lipid criteria for patients in the CARE trial include an LDL cholesterol level of 3.0 to 4.5 mmol/L. In both 4S and WOSCOPS, the mean LDL cholesterol levels were approximately 4.9 mmol/L. Whether the same degree of benefit will be obtained in a population with lower LDL cholesterol levels remains to be established.

The total cholesterol level and indeed the LDL cholesterol level may not tell the entire story. For example, patients with CHD are at high risk for CHD events even at lower levels of LDL cholesterol. Factors besides total cholesterol and LDL cholesterol levels, including high density lipoprotein (HDL) cholesterol level, level of triglyceride-rich lipoproteins, prolonged postprandial lipaemia, insulin resistance, and oxidised LDL, among many other lipid and lipoprotein factors, may contribute significantly to the increased risk for CHD events.

In my opinion, it is a mistake to consider the total cholesterol level as representing all these factors, although its value as a surrogate for LDL cholesterol in epidemiological studies is unquestioned.

**3. Benefits Achieved Earlier Than Expected**

Unlike the 2-year lag period reported by Law et al., which is based on trials preceding those that used a statin as pharmacological monotherapy, in 4S the curves appear to diverge as early as 1 year after the initiation of drug treatment, and in WOSCOPS, surprisingly, as early as 6 months. It had previously been assumed that a period of 2 years would be required before cholesterol or LDL cholesterol lowering would be expected to change the atherosclerotic plaques sufficiently to allow a measurable difference in CHD events. An effort is now under way to study effects of aggressive LDL cholesterol lowering and treatment of dyslipidaemia at much earlier times. Such treatment has been shown to improve endothelial function and vascular reactivity, possibly by increasing nitric oxide production and possibly also by decreasing the inflammatory or immune type of response in the arterial wall and decreasing thrombogenicity, all of which would be expected to result in plaque stabilisation. This has actually been shown in a number of angiographic, or 'regression', studies.