

Secondary Prevention

Based on a presentation by John S. Banas, Jr., MD, FACC

Presentation Summary

Landmark trials in secondary prevention—the Scandinavian Simvastatin Survival Study (4S), the Cholesterol and Recurrent Events (CARE) study, and the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study—have consistently demonstrated that lowering low-density lipoprotein cholesterol (LDL-C) reduces the number of coronary events among patients with coronary heart disease (CHD). The Pravastatin Atherosclerosis and Myocardial Infarction (MI) Reduction Analysis, which pooled data from four atherosclerosis regression trials, revealed that the rate of MI decreased 62% after 3 years and that all-cause mortality decreased by 46%. The CARE study, the first trial with a North American population, demonstrated significant reduction in risk for fatal (CHD) or nonfatal MI (24%), total MI (25%), revascularization procedures (27%), and stroke (31%). The LIPID, the largest statin trial to date, demonstrated significant reductions in total

mortality (23%), and stroke (20%). The results of these trials are explored in detail, and a comparison of the populations in the 4S and CARE trials is provided.

The issue of what level of LDL-C reduction provides maximum benefit is addressed. Although clinical trials have demonstrated that statins are efficacious, safe, and well tolerated, there is potential for drug-drug interactions. Pravastatin is metabolized in a different manner than the other statins and therefore has fewer drug-drug interactions and serious adverse effects.

Pravastatin, with more than 50,000 patient-years of experience in confirmed clinical trials, is shown to be an optimal therapeutic choice in secondary prevention for managed care organizations. It reduces the costs of managing CHD-related events and is cost effective in the treatment of most CHD patients and compared with other cardiovascular interventions. Improving physician involvement in secondary prevention is a challenge that must be met.

Each year, 1.5 million Americans experience a myocardial infarction (MI).¹ Despite medical advances, 30% to 50% of people who experience MI die. Fifty percent die within 1 hour of onset of symptoms,¹

before they reach a hospital or a physician's office. "These statistics underscore the need for not only primary but also secondary prevention," said John S. Banas, Jr., MD, Professor of Clinical Medicine at the College of Physicians

and Surgeons at Columbia University and Chairman of the Department of Cardiovascular Medicine at Morristown Memorial Hospital, during his presentation "Secondary Prevention." In many cases, clinical markers indicate atherosclerosis before MI occurs, whether the patient has cardiovascular disease or peripheral vascular disease.

The goals of secondary prevention among patients with a history of coronary heart disease (CHD) and prior MI are to limit the progression of atherosclerosis, reduce the number of secondary MIs, reduce cardiovascular deaths, and reduce the need for coronary intervention. Twenty percent to 40% of people who have MI have another cardiovascular event, either reinfarction or unstable angina, within 6 years of the first MI.¹ Secondary prevention not only reduces morbidity and mortality, but also reduces the staggering costs of coronary interventions in the United States.

The relation between an increasing cholesterol level and increasing coronary events has been known for many years. Clinical trials in secondary prevention have demonstrated that reducing cholesterol reduces the number of acute clinical events. Landmark trials in secondary prevention—the Scandinavian Simvastatin Survival Study (4S), the Cholesterol and Recurrent Events (CARE) study, and the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study—have consistently demonstrated that lowering low-density lipoprotein cholesterol (LDL-C) reduces the number of coronary events among patients with CHD. The CARE and LIPID trials used pravastatin as the cholesterol-lowering agent. The CARE study was important because it was the first CHD secondary prevention trial to involve a North American population. Baseline LDL-C levels in these trials were 188 mg/dL for 4S, 139 mg/dL for the CARE study, and 151 mg/dL for the LIPID study. The Pravastatin Atherosclerosis and MI Reduction Analysis, which pooled data from four atherosclerosis regression tri-

als, provided additional evidence for the use of pravastatin in reducing acute coronary events. Dr. Banas provided a brief historical review of each of these trials.

The Scandinavian Simvastatin Survival Study

The results of the 4S trial, a secondary prevention trial involving patients with angina pectoris or previous MI or both, were published in *Lancet* in 1994.² Patients placed followed an appropriate lipid-lowering diet and then were randomized to receive either placebo or simvastatin. There were no differences between the baseline characteristics of the treatment and placebo groups, each of which comprised 2200 men and women. About 50% of the patients were older than 60 years. At baseline, LDL-C level was 188 mg/dL in both arms of the trial. The trial results demonstrated that patients taking simvastatin had a highly statistically significant decrease in total mortality, coronary mortality, serious coronary events, and need for revascularization procedures and prolongation of an event-free survival period.

Pravastatin Atherosclerosis and MI Reduction Analysis

When data from four clinical trials—Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I); Pravastatin, Lipids, and Atherosclerosis in the Carotoid Arteries (PLAC II); Regression Growth Evaluation Statin Study (REGRESS); and Kuopio Atherosclerosis Prevention Study (KAPS)—were pooled in a predetermined analysis, the Pravastatin Atherosclerosis and MI Reduction Analysis revealed that the number of MIs decreased dramatically within 1 year, the rate of non-fatal MI decreased 62% after 3 years, and all-cause mortality decreased 46% (Figure 1).³ The results of the study were published in *Circulation* in 1995. These effects were evident among younger and older patients, men and women, and patients with and without hypertension.³ The analysis included

1891 patients with confirmed CHD and mildly to moderately elevated lipid levels.

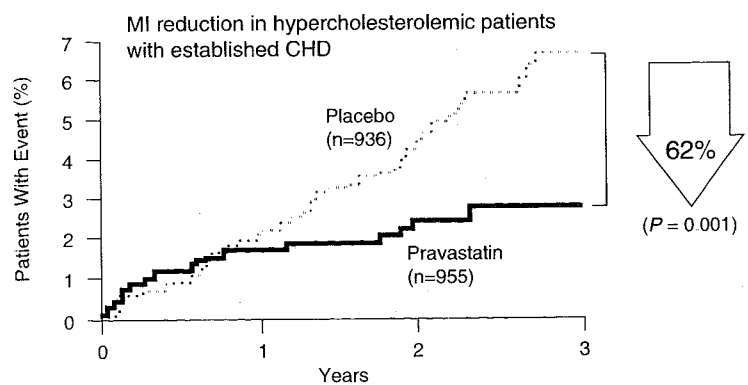
The endpoints in the Pravastatin Atherosclerosis and MI Reduction Analysis were nonfatal or fatal MI, total mortality, and stroke. The four trials were originally powered to measure regression or progression or lack thereof in the coronary arteries. Two of the trials also measured regression or progression in the peripheral vessels as manifested by disease in the carotid arteries. B-mode ultrasonography was used to identify plaque in the carotid arteries, and coronary angiography was used to quantitatively evaluate lesions in the coronary arteries. "This particular analysis is important because it not only evaluates clinical events but also looks at the pathology of the disease process," said Dr. Banas.

The PLAC I study and the REGRESS were investigations of the effect of pravastatin therapy on disease progression or regression in the coronary arteries. The PLAC II study and the KAPS were examinations of the effect of pravastatin therapy on atherosclerosis in the carotid arteries. The pooled data showed a significant reduction in disease progression in the coronary arteries and a highly significant reduction in progression of the disease in the carotid arteries. It was concluded that pravastatin reduces risk for cardiovascular events among patients with CHD, making a strong case for secondary prevention. Evidence also suggested that pravastatin might provide benefit beyond lowering LDL-C.

The Cholesterol and Recurrent Events Study

Early trials with cholesterol-lowering agents lacked relevance in the United States because they enrolled patients with higher cholesterol levels than are typically found in American clinical practice. "We were in desperate need of a trial to evaluate the impact of lipid lowering in the patient population that we see," said Dr. Banas. In 1996, the results of the CARE trial, a landmark

Figure 1. Pravastatin Atherosclerosis and MI Reduction Analysis Results



Byington et al. *Circulation* 1995;92:2419-2425.

5-year study involving 4159 US and Canadian patients with average elevations in cholesterol, were published in the *New England Journal of Medicine*.⁴ The study was designed to demonstrate whether cholesterol lowering with pravastatin reduces the number of MIs among patients who have had an MI and have average elevations in cholesterol (<240 mg/dL). The patient population represented most patients who had had an MI and were receiving aggressive intervention in American managed care organizations. The primary endpoints were fatal coronary disease or nonfatal MI.

The CARE study was predominantly a US trial with some sites in Canada. Men and women up to the age of 75 years from all types of demographic areas were recruited for the study. The mean baseline LDL-C was 139 mg/dL, and the mean baseline total cholesterol was 209 mg/dL. "This was really striking, because up until the CARE trial, I think the vast majority of physicians would say 209 to 220 mg/dL was great and send the patient on his or her way," said Dr. Banas.

Patients were randomized to receive placebo or pravastatin and participated

in a follow-up study for 5 years. The two groups were well matched with regard to age, risk factors, total cholesterol, and LDL-C. The CARE study demonstrated significant risk reduction in fatal CHD or nonfatal MI (24%), total fatal or nonfatal MI (2% to 5%), revascularization procedures (27%), and stroke (31%), among patients who had had an MI who were treated with pravastatin (Figure 2). Women taking pravastatin had a nearly 50% decrease in coronary events. Patients with unusually high rates of coronary events—smokers, those with hypertension, and patients with left ventricular dysfunction—also exhibited significant event reduction. The change in CHD risk was maximized with a 10% to 20% reduction in LDL-C. “Evidence now shows that lowering LDL-C to 100 mg/dL may not be necessary in producing a favorable decrease in cardiac events,” said Dr. Banas.

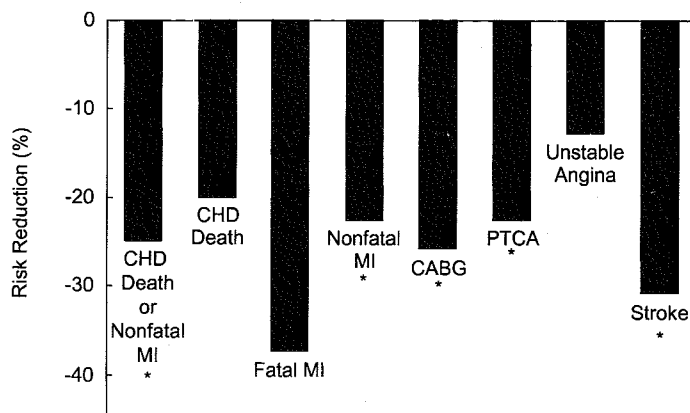
Comparing 4S and CARE

Both baseline lipids and study populations differed in the 4S and CARE studies.^{2,4} Baseline levels in the 4S trial were 188 mg/dL for LDL-C and 260

mg/dL for total cholesterol, compared with 139 mg/dL for LDL-C and 209 mg/dL for total cholesterol in the CARE trial. Eighty percent of 4S patients versus 100% of CARE patients had suffered an MI. Eight percent of 4S patients had undergone revascularization compared with 54% of CARE patients. Thirty-seven percent of 4S patients were taking aspirin therapy versus 83% of CARE patients. The benefit provided by pravastatin went beyond what is considered optimal therapy today, according to Dr. Banas.

Dr. Banas compared the 4S and CARE trials by identifying the population of patients that met the criteria for both trials, which he referred to as CARE:4S eligible. Reduction of LDL-C was greater for 4S patients than for the CARE:4S eligible patients. The CARE:4S eligible patients had slightly greater reductions in risk for coronary events (43%) than either CARE (24%) or 4S (34%) patients alone. The risk reduction was greater for CARE:4S eligible patients. Even though CARE patients had lower baseline LDL-C levels, the benefit of pravastatin therapy was superimposed on the high frequency of revascularization procedures and secondary prevention with drugs such as aspirin. This again suggests that an alternative protective mechanism beyond LDL-C lowering may contribute to coronary event risk reduction.

Figure 2. CARE Results: Reduction in Cardiovascular Events



*P < 0.05.
Sacks et al. *N Engl J Med* 1996;335:1001-1009

Is Lower Better?

In the West of Scotland Coronary Prevention Study (WOSCOPS), a primary prevention study, a decrease of about 24% in LDL-C provided the maximum benefit in coronary event reduction.⁵ A similar preliminary analysis in the CARE study revealed that the reduction in coronary events remained the same when LDL-C was lowered 10% to 19%, 20% to 29%, or more than 30%. (Sacks F, personal communication). “It’s possible that because CARE recruited a group of patients with a lower LDL-C and total cholesterol, we are beginning to see the lower plateau

of the event-reduction curve, and as a result the differences in decreases in LDL-C may not be translated into significantly greater event reduction," said Dr. Banas.

The National Cholesterol Education Program (NCEP) guidelines for secondary prevention call for a target LDL-C of 100 mg/dL. The guidelines explicitly state, however, that lowering LDL-C to 100 mg/dL may not be necessary for every patient with coronary disease. Since the NCEP guidelines were written, evidence from the WOSCOPS and the CARE study has shown that there may be limits to the amount of reduction in LDL-C that will provide coronary event risk reduction benefits.

These trials and the LIPID trial provided nearly 100,000 patient years of experience with pravastatin, which has demonstrated an impressive safety profile. In the CARE trial, the level of discontinuation caused by adverse effects was greater for patients taking placebo than for those taking pravastatin.⁴ Because of its design, the CARE study was a landmark trial important for its relevance to American managed care organizations. The CARE study provided additional evidence for the efficacy of pravastatin in secondary prevention.

Long-Term Intervention with Pravastatin in Ischaemic Disease Study

Results of the largest statin trial to date, the LIPID study, were presented in November 1997 at the American Heart Association meeting (Tonkin AM, personal communication). The LIPID study included 9014 patients with MI or unstable angina pectoris from Australia and New Zealand who had modest elevations in cholesterol. The LIPID investigators sought to evaluate the effect of 40 mg of pravastatin and dietary therapy on coronary events. The trial was scheduled to continue for 7 years, but it was stopped prematurely because the benefits of pravastatin made it unethical to continue giving patients placebo.

The LIPID study added much to the secondary prevention literature because of the large number of patients enrolled, the level of baseline cholesterol (a mean total cholesterol of 219 mg/dL and a mean LDL-C of 150 mg/dL), and the diverse population used, which included older patients, female patients, and patients with unstable angina. Patients received standard aggressive concomitant therapy with aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and revascularization procedures. The placebo and pravastatin groups were similar in composition. The results demonstrated that patients taking pravastatin had significant reductions in total mortality (23%), CHD mortality (24%), fatal CHD or nonfatal MI (23%), and stroke (20%) (Tonkin AM, personal communication).

In all of the secondary prevention trials conducted with pravastatin, the drug consistently lowered LDL-C levels and reduced coronary events (Table 1). "The studies clearly demonstrate the clinical benefit of pravastatin in an extraordinarily large number of patients worldwide, including the patient population that you and I see," said Dr. Banas.

Drug-Drug Interactions with HMG Coenzyme A Reductase Inhibitors

Large clinical trials and extensive clinical experience with statins demonstrate that they are efficacious, safe, and well tolerated. There are differences among the statins, however, which lead to differences in their potential for drug-drug interactions. Three-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMGs) are metabolized by the cytochrome P450 enzymes, which are important catalysts of oxidative drug biotransformation processes. Clinically important differences exist among the HMGs in their interactions with the cytochrome P450 system. The cytochrome P4503A4 family is responsible for many drug-drug interactions.

Pravastatin has a lower potential for drug-drug interaction than other statins.

Table 1. Summary of Results of Major Pravastatin Clinical Intervention Trials

Study	Number of Patients	Duration (yr)	Percentage Reduction in LDL-C	Coronary Event Endpoint	Percentage Event Reduction
<i>Secondary Prevention for Patients with Established Coronary Artery Disease</i>					
CARE	4159	5	28	Fatal/nonfatal MI	24 ($P = 0.003$)
Pravastatin MI Reduction Analysis	1891	3	28	Fatal/nonfatal MI	62 ($P = 0.001$)
<i>Atherosclerosis Studies in Patients with Established Coronary Artery Disease*</i>					
PLAC I	408	3	28	Fatal/nonfatal MI	60 ($P \leq 0.05$)
PLAC II	151	3	28	Fatal/nonfatal MI	80 ($P = 0.018$)
REGRESS	885	2	29	CV events	42 ($P = 0.002$)
KAPS	447	3	29	Fatal/nonfatal MI	62 ($P = NS$)

*Atherosclerosis studies included coronary angiographic and carotid ultrasound studies; primary endpoints were atherosclerosis change and cardiovascular event reduction measured as a secondary endpoint

Lovastatin, simvastatin, atorvastatin, and cervirastatin are all metabolized by the cytochrome P4503A4 isozyme. Fluvastatin is metabolized by the cytochrome P4502C9 isozyme. Pravastatin, however, is not significantly metabolized through the cytochrome P450 system.³ Whether this is related to its molecular configuration or in part to the fact that pravastatin is the only truly water-soluble statin is undetermined. Whatever the reason, the result is a lower potential for drug-drug interaction, because many commonly prescribed drugs inhibit the cytochrome P450 system. These include the antifungal drugs itraconazole and ketoconazole; antibiotics erythromycin, clarithromycin, troleandomycin, and ciprofloxacin; the cardiovascular drug diltiazem; the ulcer drug cimetidine; and the organ transplant rejection drug cyclosporine.

Concomitant use of most HMGs and these drugs increases plasma concentrations of HMGs, which increases the potential for adverse clinical effects, such as myalgia, myositis, rhabdomyolysis, and myopathy. Plasma levels of pravastatin are not significantly elevated when the drug is used concomitantly with HMG drugs. The low potential of pravastatin for drug-drug interactions translates into reduced potential for se-

rious adverse events among patients taking concomitant medications, multiple medications (for CHD), and those whose condition is compromised (transplant recipients).

Improving Physician Involvement in Secondary Prevention

Despite the well-known relation between an increasing cholesterol level and increasing risk for coronary events and the ever-increasing body of clinical trial evidence to support the link between reduction in cholesterol and reduction in clinical events, physician involvement in secondary prevention is sadly lacking, according to Dr. Banas. The results of a 1995 survey⁶ show that less than 30% of all physicians are prescribing any type of therapy, including diet, for patients who meet all criteria, even by the most conservative standards, for lipid lowering. In primary prevention, only 3% of physicians are prescribing lipid-lowering drugs to those patients who meet the criteria conservatively. "We have much to do from the standpoint of education of ourselves, our peers, and our patients," said Dr. Banas. Managed care organizations can play a leading role by encouraging their physicians to become more involved in secondary prevention. If they choose not to do so, however, govern-

ment or regulatory intervention is likely to be necessary to change physicians' attitudes and behavior.

Conclusions

In addition to the effectiveness of pravastatin in reducing CHD events among patients who have had an MI, these secondary prevention trials demonstrate that use of pravastatin also reduces the cost of managing CHD-related events. They also show that use of the drug is cost effective in the care of most patients with CHD and compared with other cardiovascular interventions. The favorable safety and tolerability profile of pravastatin translates into a reduced frequency of liver function test monitoring (Pravachol Prescribing Information, Bristol-Myers Squibb), a low potential for drug-drug interactions, and fewer problems that waste the time and resources of managed care organizations, providers, and patients.

FACULTY QUESTION-AND-ANSWER SESSION

Question: *One of the hesitations that physicians have in prescribing medication for patients who have high cholesterol and coronary disease is this issue of diet. Diet gets in the way of the trial data. Should we tell patients to follow a low cholesterol diet and write a prescription at the same time?*

Answer (Dr. Banas): Diet is vitally important with or without drug therapy. If your patients follow an appropriate diet, they'll have a greater effect at a lower dose with fewer side effects. A simple pill isn't going to allow them to maintain their visits to McDonald's.

Comment: *At one of the hospitals I work at, when someone comes in with an acute MI, the residents don't even check the cholesterol because of the old thought that it's an acute phase reaction.*

Answer (Dr. Banas): LDL-C and the lipid profile should be obtained. There's no question that an acute event can cause perturbations in lipid levels. But if a patient comes in with a coronary event and has abnormal lipid levels, this provides evidence for how to proceed with treatment. For those MI patients who have very low lipids, the recommendation is to still take the lipid profile and then do follow-up lipid profiles somewhere around 6 to 8 weeks later.

Question: *Why do patients spend five times the money to purchase unproved over-the-counter remedies and we see such poor compliance with the statins?*

Comment: If you said it was a natural statin, you could get patients to take it. All they want is something that comes off of a dead tree or bark.

Comment: Physicians aren't doing a good job. Patients aren't satisfied with the care they're getting so they're turning to alternative medicine. They're buying colistin, one of the yeast statins that's made in China and has no supporting documentation of any sort, like crazy.

Comment: If ever there is a case where the cost of treatment is zero or saves money for every patient treated, it's in this population, where the likelihood of a second event being costly is much higher than in the general population. Yet many patients who have had MIs with this borderline total cholesterol and an elevated LDL-C are untreated. It should be a public health issue to go after those patients.

Comment: We brought in an outside consultant to our group who picked 40 charts at random from each of our seven cardiologists. He put the charts on a computer to measure the parameters you've been discussing—diagnostic, follow-up, patient compliance, doctor relationship to that. The very appearance of

this person in the back room going through the charts prompted our cardiologists to practically wear out our cholesterol machine from overwork. Just the suggestion of Big Brother was enough to change things.

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