

Lessons Learned from Lipid-Lowering Trials That Have Included Women

Based on presentations by Thomas A. Pearson, MD, PhD, and Tatu A. Miettinen, MD

Presentation Summary

While only a handful of primary prevention trials have evaluated the effects of lipid lowering on coronary heart disease (CHD) risk in women, a growing number of secondary prevention trials with meaningful numbers of women has shown that lipid abnormalities are as predictive of CHD in women as they are in men. In general, these studies have also shown that lipid-lowering drugs affect men and women similarly in modifying lipid abnormalities and in reducing the risk for CHD and stroke.

Two studies that have evaluated the lipid-lowering effects of HMG-CoA reductase inhibitors (statins) in postinfarction patients, including a substantial number of women, are the

Cholesterol and Recurrent Events (CARE) trial and the Scandinavian Simvastatin Survival Study (4S).

In the CARE study, the reduction of CHD risk was found to be greater in women than in men (46% versus 20%, $P < 0.05$). In the landmark 4S trial, the reduction in risk for CHD death, nonfatal myocardial infarction, and the need for a revascularization procedure was virtually identical in men and women. There was also a significant decrease of 39% in hospital bed days for cardiovascular disease in women receiving simvastatin compared with placebo.

Because there are so few data regarding primary prevention of CHD in women, however, many issues remain unresolved.

Although there are only a handful of primary prevention studies that have evaluated the effects of lipid-lowering therapy in women, increasing numbers of secondary prevention studies that have included women are providing useful data in this regard, said Thomas A. Pearson, MD, PhD, of the Mary Imogene Bassett Hospital Research Institute and Preventive Cardiology Clinic in Cooperstown, New York.

To underscore the paucity of data on primary prevention in women, Dr. Pear-

son described a recent case in which a 68-year-old woman with a documented 15-year history of untreated hypercholesterolemia above 350 mg/dL presented to her primary care provider at a health maintenance organization (HMO) with chest pain, which was misdiagnosed. The woman died and her survivors sued the HMO for negligence. They were awarded \$400,000 by an Oregon court on May 1, 1996.

"It is ironic that the first lawsuit settled for nontreatment of hypercholes-

terolemia involves a patient in just about the only group—that is, older women—in which we do not have adequate clinical trials of primary prevention,” Dr. Pearson said.

Secondary prevention lipid-lowering trials that have included women, however, have provided some valuable lessons, he said, and these lessons can be categorized into four general areas: gender and risk, gender and efficacy, prevention of coronary heart disease (CHD) in women, and unresolved issues.

Gender and Risk

Two underlying questions regarding gender and risk are whether lipid abnormalities are as strongly associated with CHD in women as they are in men and whether there is any etiologic basis for being concerned about cholesterol in women.

In a review of 13 prospective studies enrolling men and women under 65 years of age, Manolio et al¹ found that 12 of these studies demonstrated relative risks above 1.0 for total cholesterol values above 240 mg/dL compared with values below 200 mg/dL in women. In 10 of these studies, the differences were statistically significant, with the mean relative risk for cholesterol levels above 240 mg/dL being 2.0 in women (above that found in men).

In terms of the relative risks of various lipid comparison groups—low levels of high-density-lipoprotein cholesterol (HDL-C) versus high levels, high levels of low-density-lipoprotein cholesterol (LDL-C) versus low levels, and high levels of triglycerides versus low levels—the studies found the risks to be similar in both men and women for low HDL-C and higher in women for elevated LDL-C and triglycerides.

Thus, on the basis of these and other studies, one can conclude that serum levels of total cholesterol, LDL-C, and

Table 1. Changes in LDL-C and HDL-C After Treatment With Lipid-Lowering Drugs in Two Angiographic Trials

Study	Intervention	LDL-C Reduction*		HDL-C Increase*	
		Men	Women	Men	Women
CCAIT	Lovastatin	28%	32%	8%	5%
SCOR	Various regimens	38%	40%	28%	26%

*Compared with pretreatment levels.

HDL-C predict CHD in women at least as well as they predict CHD in men, Dr. Pearson stated. Triglyceride levels may be predictive only in men.

Gender and Efficacy

A major question regarding gender and efficacy is whether lipid-lowering agents affect LDL-C and HDL-C levels similarly in women and men. As shown in Table 1, data from the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT)² and the Specialized Center of Research (SCOR) study³ demonstrate that lipid-lowering drugs are equally efficacious in both men and women.

In addition, there is no evidence that a low-cholesterol diet, which remains the first step in correcting lipid abnormalities, is either more or less effective in one gender compared with the other, [HN Ginsberg, et al, unpublished data, January 1997], Dr. Pearson said. Nevertheless, some patients, particularly those with familial hypercholesterolemia, will require therapy with lipid-lowering agents in addition to diet, he added.

Gender and Prevention of CHD

With the results of several recent trials that have enrolled substantial numbers of women, it is now possible to answer the question, “Do lipid-lowering drugs prevent CHD in women?” in the affirmative. Even with these more recent trials, however, “we had to look very carefully to find enough female

subgroups to make sense of the data," Dr. Pearson pointed out.

As Furberg has demonstrated in a "pyramid of risk" [personal communication, 1995] lipid-lowering therapy was able to prevent the manifestations of cardiovascular disease, including CHD and stroke, in all subgroups of patients at varying levels of risk (Figure 1). Included in the subgroups were patients with CHD, stroke, peripheral vascular disease, carotid artery thickening or

other indices of subclinical atherosclerosis, and multiple risk factors. Because all patients at risk stand to benefit from therapy with lipid-lowering agents, the issue is not efficacy, but cost effectiveness, Dr. Pearson stressed.

In addition to demonstrating the efficacy of lipid-lowering agents in both men and women, the CCAIT and SCOR studies also showed angiographically that such treatment could halt progression, prevent the formation of new lesions, and even promote regression of stenosed coronary arteries.

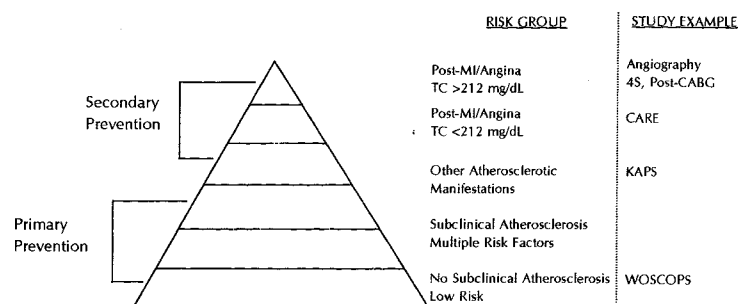
In the SCOR study, which employed multiple risk factor interventions in patients with familial hypercholesterolemia, there was a modest effect of treatment in men versus controls, but a more substantial effect of treatment in women over men," Dr. Pearson said.

Similarly, women in the CCAIT study, in which a baseline coronary arteriogram was followed by diet, randomization to the HMG-CoA reductase inhibitor lovastatin or placebo, and a repeat arteriogram at 2 years, showed a substantial reduction in disease progression and a huge reduction in the formation of new lesions.

Although there were no statistically significant differences between men and women, the findings suggest that women benefit at least as much as men from interventions that affect the natural history of coronary atherosclerosis, he observed.

Using data from a recent review by Walsh and Grady,⁴ Dr. Pearson reviewed total cholesterol and relative risk

Figure 1. Pyramid of Risk



TC = total cholesterol; 4S = Scandinavian Simvastatin Survival Study; Post-CABG = Post-Coronary Artery Bypass Grafts; CARE = Cholesterol and Recurrent Events; KAPS = Kuopio Atherosclerosis Prevention Study.
From Furberg C (personal communication, 1995)

Table 2. Reduction in Total Cholesterol and Relative Risk in Five Secondary Prevention Trials Using Clinical Endpoints

Trial	Women	Men	Intervention	Reduction in Total Cholesterol	Relative Risk of Intervention
Stockholm	103	452	Clofibrate	13%	0.64
Scottish Society of Physicians	124	593	Clofibrate	16%	0.17
Newcastle-upon-Tyne	97	400	Clofibrate	NA	0.29
4S	827	3,617	Simvastatin	28%	0.65
CARE	582	3,579	Pravastatin	20%	0.54

Adapted from: Walsh JME, Grady D. Treatment of hyperlipidemia in women. *JAMA* 1995;274:1152-1158.

reductions in five studies employing different cholesterol-lowering modalities in men and women (Table 2). He then focused on the findings of the Cholesterol and Recurrent Events (CARE) trial⁵ and the Scandinavian Simvastatin Survival Study (4S) study,⁶ the two studies with the largest numbers of women. Both studies demonstrated the powerful effects of HMG-CoA reductase inhibition (pravastatin in CARE and simvastatin in the 4S) in women as well as in men, with the enormous reduction in risk in both studies also reaching statistical significance.

In the CARE study, which enrolled postinfarction patients with relatively normal cholesterol levels, there was a 20% reduction in relative risk for CHD events in men, with the onset of benefit occurring at 2.5 years. For women, the reduction in relative risk was 46%, with the onset of benefit occurring as early as 6 months.

"This suggests that lowering cholesterol may be more effective in women than in men, and that treatment in women may prevent substantially more clinical myocardial infarctions (MIs), more strokes, and perhaps more bypasses and angioplasties in women than in the group as a whole," Dr. Pearson remarked.

In the 4S trial, which Dr. Pearson characterized as a "landmark trial in every sense of the word," 4444 patients with MI or angina who remained hypercholesterolemic after a lipid-lowering diet were randomized to simvastatin or placebo.

In terms of the major cardiac endpoint and whether lowering cholesterol with simvastatin could reduce coronary events, the risk reductions were virtually identical in women and in men. Both groups benefited equally, he said.

Subgroup Analysis of Women in the 4S Trial

Tatu A. Miettinen, MD, Professor of Medicine at the University of Helsinki in Finland, agreed. In a separate presentation that focused on reduced chole-

sterol levels for the women who participated in the 4S study, he pointed out that women in the study derived "striking benefits from aggressive lipid lowering and benefited from treatment similarly to men."

Dr. Miettinen presented a subgroup analysis of the 827 women in the 4S trial, who constituted 18.6% of the total study population of 4444 (Table 3). Of all the secondary prevention trials evaluating lipid-lowering therapy in CHD patients, the 4S trial enrolled the largest number of women (Table 2).

All women in the study had docu-

Table 3. Clinical Findings in 827 Women in the Scandinavian Simvastatin Survival Study

Event Category	Simvastatin Patients (n = 407)	Placebo Patients (n = 420)
All-cause mortality	28	25
CHD mortality	14	17
Major coronary events (CHD death plus nonfatal MI)	60	91
Revascularization procedure	21	42
Hospital days	1,457	2,391

mented coronary artery disease and elevated cholesterol levels, and were between 35 and 70 years of age. The age range is especially important since there are so few data on women with CHD over the age of 65. Of the 827 women in the trial, 407 received 20 mg to 40 mg of simvastatin a day and 420 received placebo. Drug treatment lowered total cholesterol by 26% from an average recorded baseline level of 267 mg/dL. LDL-C was reduced by 37%, HDL-C was increased by 7%, triglycerides were reduced by 16%, and the LDL-C to HDL-C ratio was reduced by 39%. In addition, treatment reduced fatal and nonfatal MIs by 34%, Dr. Miettinen noted.

There were 49% fewer coronary bypass procedures and angioplasties in the treatment group, as well as less cardio-

vascular morbidity, as evidenced by a 39% reduction in hospital days, he added.

"The 4S study clearly shows benefit of treatment in women and provides extremely important information for physicians and their patients."

— Tatu A. Miettinen, MD

"The magnitudes of the relative risk reductions in fatal and nonfatal events and the need for revascularization procedures were equivalent to or greater than those observed in men," Dr. Miettinen pointed out. "The 4S study clearly shows benefit of treatment in women and provides extremely important information for physicians and their patients," he continued, adding that women with CHD should receive lipid-lowering therapy even if their cholesterol levels are not elevated.

Unresolved Issues

Despite the findings of the 4S, CARE, and other secondary prevention trials that demonstrate the benefits of lipid-lowering therapy in women with CHD, several issues remain unresolved, said Dr. Pearson. The first is that there are no primary prevention studies

evaluating current lipid-lowering therapies in women.

"This leaves us with a huge hole in our research database," he declared.

The second issue concerns triglycerides. It is still not known whether the reduction in triglyceride levels also lowers CHD risk in women or whether cholesterol-lowering drugs that are particularly effective in lowering triglyceride levels are more effective in women than in men.

It is also not known whether there are certain side effects of lipid-lowering therapies that are unique to women. This is a matter of some concern, Dr. Pearson said, because a large percentage of prescriptions for lipid-lowering agents are written for women even though there is no database to provide answers regarding side effects.

The fourth unresolved issue is the interaction between lipid-lowering therapies and estrogen replacement therapy in postmenopausal women. While there appears to be a "cooperative" effect between these two therapies, the interactions between the two are not completely understood, he said.

Reminding the audience that there are no recent primary prevention studies in women and a paucity of data in women with CHD, Dr. Pearson said that such studies were clearly needed. He then presented a "wish list" of factors that should be addressed in any

Table 4. Factors to be Addressed in Primary Prevention Studies in Women

- Identification of appropriate subgroups who would benefit from intervention
- Assessment of baseline risk
- Identification of cost-effective interventions (atherosclerosis prevention vs atherosclerosis treatment)
- Evaluation of effective therapeutic agents (ie, HMG-CoA reductase inhibitors), preferably as monotherapy
- Role of diet
- Compliance issues
- Cost of pharmacologic treatment per patient
- Interval to benefit
- Cost of nontreatment
- Minimization of competing risk

primary prevention study of women (Table 4).

In identifying women at high risk, he suggested that investigators look at 65-year-old women instead of 55-year-old men since the risks for these two groups are about the same.

Minimizing competing risk is also an important factor because the goal of lipid-lowering therapy is to reduce CHD events, not precipitate or exacerbate another disorder, he continued. This issue was raised in the CARE trial, where there were 12 cases of breast cancer in the pravastatin group and one case in the placebo group. There were no cases of breast cancer among the women in the 4S trial. Since the HMG-CoA reductase inhibitors in general have not been associated with an excess risk of breast cancer, the finding is "probably a fluke," Dr. Pearson said.

Conclusion

Based on the available evidence, Dr. Pearson drew a few conclusions. First, serum levels of total, LDL-C and HDL-C are as predictive of CHD in women as in men. Second, there is no gender difference in the efficacy of lipid-lowering therapy to alter serum lipid levels. Third, the 4S and CARE trials have shown that HMG-CoA reductase inhibitors are at least as effective, if not more so, in reducing CHD in women as compared with men. Fourth, there are few relevant data concerning the primary prevention of CHD in women, with the reason for this more likely to be an issue of cost effectiveness than an issue of efficacy. Fifth, several issues specific to women remain unresolved.

In the absence of primary prevention data in women, Dr. Pearson recommended that clinicians extrapolate findings from secondary prevention trials so that women with lipid abnormalities do not go untreated.

"If you have a body of secondary prevention trials showing efficacy, it is silly not to extrapolate those data to primary prevention. In fact, most secondary prevention studies have paralleled primary prevention studies quite well. Besides, they are the only data we have at the moment," he said.

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