Dietary Treatment of Cholesterolemia

The dietary treatment of hypercholesterolemia has been reviewed elsewhere (72). Cholesterol-lowering diets involve the reduction of overall fat and cholesterol intake, and the substitution of polyunsaturated vegetable oils for saturated fats and complex carbohydrates for sugars (116). Many people have reduced their cholesterol levels dramatically by diet alone. However, when averaged across many individuals, the reduction in serum cholesterol in the randomized trials of dietary interventions has been modest. In the Multiple Risk Factor Intervention Trial (MRFIT), diet reduced the cholesterol level by an average of about 7 percent.

Dietary treatment, although generally safer than pharmacologic approaches, is not entirely without cost. Significant changes in eating habits may reduce the quality of life. The monetary and utility costs of dietary modification have not been well studied. Other than the potential for loss of pleasure in eating, however, dietary changes have few known side effects.

Oat bran is a soluble fiber that reduces serum cholesterol. With a dietary intake of 1 to 1.5 cups of dry bran per day, serum cholesterol falls by 13 to 19 percent (7,9, 10,67,89). When used with other soluble fibers, the sustained reduction in serum cholesterol can be 20 to 25 percent. At current prices, a 90 gm daily dose of oat bran costs less than $0.40, if purchased in bulk. The cost does not include the time or money required to convert the oat bran to palatable food, such as bread or muffins.

Certain foods, especially fish containing omega-3 fatty acids, may have a beneficial effect on serum cholesterol (46,52,53,112). In one study *of* healthy persons, a fish diet reduced low-density lipoprotein (LDL) cholesterol and very low-density lipoprotein (VLDL) cholesterol with variable effects on high-density lipoprotein (HDL) cholesterol (124). There have been no reported long-term studies of omega-3 fatty acids in hypercholesterolemic patients (125).

Drug Treatment of hypercholesterolemia

Bile Acid Sequestrants: Cholestyramine and Colestipol

The bile acid sequestrants, which interrupt the circulation of bile acids in the body and cause the liver to synthesize new bile acids from cholesterol, are commonly used to reduce the LDL-cholesterol level. These drugs can reduce total serum cholesterol by 20 percent and LDL-cholesterol by 27 percent if taken in full doses (77), with a proportionate loss in effect when compliance is imperfect (79).

The bile acid sequestrants are difficult to take regularly, in part because some people have difficulty swallowing the slurry in which they are administered and in part because of minor but unpleasant side effects. The resin is administered in a liquid suspension and must be drunk quickly to avoid settling. Nausea, abdominal discomfort, and indigestion are common, and constipation occurs in as many as 45 percent of patients treated with cholestyramine (77). Impaction of stool may occur and be particularly troublesome in the elderly. The resins also bind other drugs in the intestine, decreasing their absorption. Despite their favorable effects on the LDL cholesterol, bile acid sequestrants can raise the triglyceride level.

Nicotinic Acid

Nicotinic acid (niacin) is an inexpensive and effective cholesterol-lowering medication.

The frequent occurrence of side effects has limited its acceptance. Nicotinic acid lowers the levels of plasma triglycerides and LDL cholesterol and raises HDL cholesterol. Nicotinic acid reduced total serum cholesterol by an average of 10 percent in the Coronary Drug Project (26) but can reduce cholesterol by as much as 40 percent in combination with bile acid sequestrants (61).

In the Coronary Drug Project, the incidence of the most common side effects of nicotinic acid, skin flushing and itching, were 92 and 49 percent, respectively. These side-effects may be less common when the dose is gradually escalated, or when each dose is preceded by a dose of aspirin. Vomiting, diarrhea, and dyspepsia (indigestion) are also common. Nicotinic acid can cause hepatitis (rarely), elevate serum liver enzyme levels without causing apparent disease, and raise blood sugar levels in diabetics.

HMG CoA reductase inhibitors

The enzyme 3-hydroxy-3-methyl glutaryl coenzyme-A (HMG CoA) reductase regulates the rate of cholesterol synthesis in humans. The drugs that inhibit this enzyme lower total and LDL cholesterol by reducing the rate of cholesterol synthesis. Formerly known as mevinolin, lovastatin is the first HMG CoA reductase inhibitor to be released in the United States. Lovastatin raises or does not affect plasma HDL.

There have been several multicenter trials of lovastatin (80,82,123). In one of these studies, there was a dose-dependent reduction of 32 percent in total cholesterol and 39 percent in plasma LDL cholesterol (80). HDL cholesterol increased 13 percent. When patients take cholestyramine in addition to lovastatin, plasma LDL cholesterol falls by 50 percent.

Side effects of lovastatin are uncommon and usually mild. None of the 101 patients in one study had a side effect that required stopping the drug. Liver enzymes (the transaminases) often rise in patients treated with lovastatin, but the enzyme levels seldom exceed twice the upper limit of the normal range. While clinical liver disease is rare *(80),* monitoring serum liver enzymes is recommended every 4 to 6 weeks for 15 months after starting lovastatin. Periodic eye examinations are recommended because of a possible association with cataracts (80). Because the drug is new, the side effects of long-term therapy, if any, have yet to be identified.

Fibric Acid Derivatives

Two fibric acid derivatives are currently used in the United States to treat hyperlipidemia. The first, clofibrate, was initially hailed as an important drug, but the indications for its use have narrowed as the results of randomized trials have become known. In the Coronary Drug Project, clofibrate reduced serum cholesterol by only 6 percent (26). In at least one large clinical trial, clofibrate significantly increased overall mortality and did not reduce coronary heart disease (CHD) mortality (24,25).

Clofibrate is generally well-tolerated, although it produces a variety of side effects in a small proportion of patients. Increased appetite (5 percent), decreased libido (14 percent), and breast tenderness (9 percent) are significantly more frequent among clofibrate-treated patients than in subjects given a placebo (26). Some patients get a flu-like syndrome with severe muscle cramps whenever they take the drug. Clofibrate is also associated with an increased incidence of gallstones (3.5 percent over 5 years) (26). Because clofibrate causes significant side effects, does not appear to reduce cardiovascular mortality, and may increase overall mortality, most experts no longer recommend it as a first-line drug for treating hypercholesterolemia.

Gemfibrozil, a newer fibric acid derivative, primarily lowers triglyceride levels. It also lowers LDL and raises HDL levels. In

one multicenter, placebo-controlled, randomized trial, total cholesterol decreased by 10 percent, non-HDL cholesterol fell 11 percent, and HDL cholesterol rose 11 percent (84). In this study, patients on gemfibrozil had a lower incidence of coronary heart disease than patients on placebo.

Gemfibrozil is generally well-tolerated. Gastrointestinal distress is the principal side effect. In the Helsinki Heart Study, moderate to severe upper gastrointestinal symptoms occurred in 11 percent of patients on gemfibrozil and 7 percent of patients on placebo, a highly significant difference (36). These symptoms were much less frequent after the first year of the study. Although gemfibrozil may promote gallstone formation, this complication appears to be less frequent than with clofibrate (17).

Other fibric acid derivatives, such as fenofibrate, bezafibrate, and ciprofibrate, are available in Europe but not in the United States. Experience overseas suggests that these drugs may have somewhat more favorable effects on the lipid profile than gemfibrozil or clofibrate and may be better tolerated. In a short-term randomized trial in the United States, fenofibrate decreased total cholesterol levels by 17.5 percent, lowered LDL-cholesterol levels by 20.3 percent, and raised HDL-cholesterol levels by 11.1 percent among individuals with hypercholesterolemia and normal triglyceride levels. In individuals who had elevations of triglycerides as well as cholesterol, fenofibrate cut total and LDL cholesterol by 16 and 6 percent, respectively, and raised HDL cholesterol by 15.3 percent (68).

Probucol

Probucol reduces serum LDL cholesterol by 10 to 15 percent. However, it also lowers serum HDL cholesterol, often to a greater degree than LDL cholesterol. There are no studies of its effect on survival or primary coronary heart disease events. The mechanism of action of probucol is unknown. Probucol is well-tolerated, with gastrointestinal symptoms occurring in about 10 percent of patients (17). Because of its adverse effect on HDL levels, probucol is not widely used.

Costs of Treatment

Table 4 details the annual cost of using the currently approved medications. Total costs per year of treatment include both retail drug prices, the costs of diagnostic procedures and physician services associated with monitoring the potential side-effects of treatment, and the costs of semiannual lipoprotein analysis to monitor the effectiveness of the treatment. These cost figures assume that:

- doctors prescribe the recommended dose to achieve maximal cholesterol-lowering effect,
- patients are compliant,
- laboratory monitoring as described in the manufacturers' package insert is performed regularly, and
- physicians' fees average $200 per patient per year for monitoring and adjusting therapy.

In order to estimate the retail cost of each prescription drug, OTA obtained average allowed charges from a New Jersey State pharmaceutical reimbursement program available to all non institutionalized persons over age 65 (60,81). For niacin and slow-released niacin, which are available without a physician's prescription, OTA obtained retail prices for generic versions of the compound from a Washington, DC retail drugstore chain (38).

Under these assumptions, the least expensive regimen, nicotinic acid, costs over $500 per year. Cholestyramine, often described as the agent of first choice, costs $1,200 per year when purchased in bulk and over $2, 100 annually when the more convenient pre-measured packets are employed. Gemfibrozil costs $850 per year including monitoring costs. The newest, and possibly most effective, agent is lovastatin. It costs

Table 4--Costs of Treating Hypercholesterolemia (in 1988 dollars)

Drug	Lipids[a] No.	Lipids[a] Cost	Chemistries[b] No.	Chemistries[b] Cost	CBC No.	CBC Cost	ECG No.	ECG Cost	Eye exam[c] No.	Eye exam[c] Cost	Annual cost of physician services	Annual monitoring cost[d]	Size	Daily dose[e]	Annual retail cost[f]	Total annual treament cost (includes monitoring)
Lovastatin	3	$58	12	$203	NA	NA	NA	NA	1	$86	$200	$547	20mg tablet	40mg	$1,141	$1,687
Colestipol	3	$58	NA	NA	NA	NA	NA	NA	NA	NA	$200	$258	5g packet	30g	$1,309	$1,567
													500g can		1,000	1,258
Niacin (nicotonic acid)	1	$19	6	$101	NA	NA	NA	NA	NA	NA	$200	$321	50mg tablet	3g	$194	$515
													100mg tablet		104	425
Niacin (nicotonic acid, slow release)	1	$19	6	$101	NA	NA	NA	NA	NA	NA	$200	$321	125mg tablet	3g	$312	$633
													250mg tablet		205	525
estyramine	3	$58	3	$51	NA	NA	NA	NA	NA	NA	$200	$309	9g packet	54g	$2,150	$2,459
													378g can		1,198	1,507
Gemfibrozil	3	$58	3	$51	3	$35	NA	NA	NA	NA	$200	$343	300mg capsule	1,200mg	$506	$850
Probucol	3	$58	NA	NA	NA	NA	2	$67	NA	NA	$200	$325	250mg tablet	1,000mg	$554	$879
													500mg tablet		534	859

[a]Lipid panel [illegible] and calculated low density lipoprotein.

[b]Chemistries are blood chemistry panel including three or more tests: glucose, liver function tests including transaminases, and total cholesterol.

[c]Eye Exam is a limited consultation for slit lamp exam by ophthalmologist.

[d]Recommended monitoring procedures were taken from the manufacturers' package inserts. "Periodically" was taken to mean three times per year and "frequently" was taken to mean six times per year. Monitoring costs include average allowed Medicare charges from a Northern California group practice laboratory.

[e]Daily doses are taken from Adult Treatment Panel; National Cholesterol Education Program; National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services, "Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults," Arch. Intern. Med. 148:36-69, 1988.

[f]Annual retail costs are average allowed costs from the New Jersey Pharmaceutical Assistance to the Aged and Disabled Program (S. Luger, Chief Pharmaceutical Consultant, New Jersey Pharmaceutical Assistance to the Aged and Disabled Program, Trenton, NJ, personal communication, Dec. 5, 1988; and D. Iozzia, Drug Reimbursement Analyst, Blue Cross/Blue Shield of New Jersey, Newark, NJ, personal communication, Feb. 10, 1989), except for niacin for which costs were estimated from retail prices in a District of Columbia chain pharmacy (D. Fukuzawa, Foer's Pharmacy, Washington, DC, personal communication, Dec. 5, 1988). Cost assumes full patient compliance.

ABBREVIATIONS: CBC = complete blood count; ECG = resting electrocardiogram; NA = Not applicable; No. = number of tests recommended per year.

SOURCE: Office of Technology Assessment, 1989.

over $1,600 per year, including monitoring Costs . Even purchasing at wholesale and using the lowest cost laboratory available, as might be the case for a public clinic or health maintenance organization, these regimens are expensive. Only nicotinic acid, available as a generic product, costs less than several hundred dollars per year.

As more products become available (new HMG CoA reductase inhibitors are in the preliminary phases of approval by the Food and Drug Administration) and as alternative agents (psyllium or oat bran, for instance) are evaluated, price competition may lower the costs of treatment.

Health Outcomes of Treatment

There is little information about the effects of treating hypercholesterolemia in the elderly. None of the randomized controlled clinical trials of the treatment of hypercholesterolemia included significant numbers of the elderly. Virtually all that is known about the effects of treatment is based on studies of middle- aged men. Several large randomized trials have addressed the effects of pharmacologic treatment in this population. Several other trials have assessed dietary therapy.

Several lines of evidence suggest that treatment might be effective. For example, animal (83) and human studies (16,76) have found that cholesterol reduction can slow or even reverse the progression of atherosclerosis. Clinical trials have shown that treatment can impede the development of heart disease in hypercholesterolemic individuals. At least two studies found that reducing cholesterol levels that start above 260 mg/dl can diminish cardiovascular mortality, and one study has shown that a cholesterol-lowering medication reduces 15-year all-cause mortality among survivors of myocardial infarction.

Table 5 displays key findings from several major studies of interventions to reduce mortality by lowering cholesterol. Asymptomatic, hypercholesterolemic individuals, such as those who would be identified in a screening program, were the subjects of several primary prevention trials. These trials have shown that moderate cholesterol reduction lowers both the incidence of and mortality from CHD among individuals who have no clinical evidence of CHD. However, the interventions did not significantly affect all-cause mortality. The Lipid Research Clinics-Coronary Primary Prevention Trial (LRC-CPPT) is widely cited as the first randomized trial to show that drug therapy of hypercholesterolemia in asymptomatic subjects reduces coronary disease morbidity and mortal it y. The LRC-CPPT enrolled 3,806 men aged 35 to 59 whose serum cholesterol, after an attempt at dietary management, was at least 265. Both the intervention and control groups continued to receive a dietary intervention after the start of the trial. At an average of 7 years of followup, the choles - tyramine-treated group suffered less morbidity and mortality from ischemic heart disease than the control group. There was a statistically significant ($p<0.01$) reduction in the incidence of angina, which was experienced by 15 percent of the control group and 12 percent of the treatment group. CHD mortality was also reduced by the intervention; 2.3 percent of the control group died from definite or suspected CHD death, compared with 1.7 percent of the cholestyramine group. However, all-cause mortality was 3.7 percent and 3.6 percent in the control and cholestyramine-treated groups, respectively, a difference that was not statistically significant (78). Analysis of the cholestyramine-treated patients showed that an 8-percent reduction in serum total cholesterol was associated with a 19-percent reduction in CHD incidence. The magnitude of the reduction in the incidence of CHD corresponded to the degree of reduction in total cholesterol levels. Thus, the individuals who adhered closely to the intervention tended to have larger declines in cholesterol and a lower incidence of CHD (79). However, CHD incidence in the control group did not show a statistically significant

Table 5.--Randomized Trials of Cholesterol Reduction and Mortality

Study	Number of patients	Characteristics[a]	Intervention	Mean followup (in years)	Mean change[b]	Mortality[c]			
						Coronary heart disease		All causes	
						Intervention	Control	Intervention	Control
Lipid Research Clinics[d]	1,906	Age 35-59 plasma cholesterol ≥ 265 (mean 279)	Cholestyramine	7.4	8.5%	1.6	2.0[e]	3.6	3.7
Helsinki Heart Study[f]	2,051	Age 40-55, non-HDL cholesterol >200 (mean total cholesterol 289)	Gemfibrozil	5	1%	0.7	0.9	2.2	2.1
Coronary Drug Project:	1,119	Age 30-64, survivors of myocardial infarction (mean cholesterol 253)	Niacin	6	10.1%	18.8	18.9	21.2	20.9
■ Coronary Drug Project Research Group, 1975[g]									
■ Canner et al., 1986[h]				15		36.5	41.3[e]	52	58.2[e]
World Health Organization:	5,331	Age 30-59 upper one-third of cholesterol distribution (mean cholesterol 249)	Clofibrate	5.3	9%	0.13	0.12	0.62	0.52[j]
■ Committee of Principal Investigators, 1984[i]									
■ Committee of Principal Investigators, 1984[k]				13.2		0.36	0.35	0.86	0.79
Multiple Risk Factor Intervention Trial[l]	6,428	Age 35-57, high-risk (mean cholesterol 254)	Diet, smoking reduction, blood pressure control	7	2%	1.8	1.9	4.1	4
Wadsworth Veterans Administration Hospital[m]	424	Age 55-89, residing in Veterans domicile (mean cholesterol 233)	Diet	8[n]	12.7%	9.6	14.2[o]	41	41.9
Oslo Study[p]	604	Age 40-49 cholesterol 290-380, high risk (mean cholesterol 323)	Diet, smoking reduction	5	13%	1	2.2[e]	2.6	3.8

(footnotes found on next page)

[a]Cholesterol are levels reported in units of mg/dl.

[b]Percent of change is the difference between intervention group and control group cholesterol levels, expressed as percentage of original cholesterol level.

[c]Mortality figures are the cumulative numbers of deaths per 100 subjects during the followup period, with exception of the World Health Organization trial, where deaths per 100 subjects per annum are reported.

[d]Lipid Research Clinics Program, "The Lipid Research Clinics Coronary Primary Prevention Trial Results: I. Reduction in Incidence of Coronary Heart Disease," J.A.M.A. 251:351-364, 1984; and Lipid Research Clinics Program, "The Lipid Research Clinics Coronary Primary Prevention Trial Results: II. The Relation Of Reduction in Incidence of Coronary Heart Disease to Cholesterol Lowering," J.A.M.A. 251:365-374, 1984.

[e]difference between intervention and control groups is significant at p<0.05. two-tailed test.

[f]M.H. Frick, O. Elo, K. Haapa et al., "Helsinki Heart Study: Primary-Prevention Trial With Gemfibrozil in Middle-Aged Men With Dyslipidemia," N. Engl. J. Med. 317:1237-1245, 1987.

[g]Coronary Drug Project Research Group, "Clofibrate and Niacin in Coronary Heart Disease," J.A.M.A. 231:360-381, 1975.

[h]P.L. Canner, K.G. Berge, N.K. Wenger et al., "Fifteen year Mortality in Coronary Drug Project Patients: Long-Term Benef t With Niacin," J. Am. Coil. Cardiol. 8:1245-1255, 1986.

[i]Committee of Principal Investigators, "A Cooperative Trial in the Primary Prevention of Ischaemic Heart Disease Using Clofibrate: Report From the Committee of Principal Investigators," Brit. Heart. J. 40:1069-1118, 1978.

[j]Difference between intervention and control groups is significant at p<0.05, two-tailed test, but in wrong direction.

[k]Committee of principal Investigators, "WHO Cooperative Trial on Primary prevention of Ischaemic Heart Disease With Clofibrate To Lower Serum Cholesterol: Final Mortality Follow-up, 2:600-604, 1984.

[l]Multiple Risk Factor Intervention Trial Research Group, "Multiple Risk Factor Intervention Trial: Risk Factor Changes and Mortality Results," J.A.M.A. 248:1465-1477, 1982.

[m]S. Dayton, M. Pearce, S. Hashimoto et al., "A Controlled Clinical Trial of a Diet High in Unsaturated Fat in Preventing Complications of Atherosclerosis, " Circulation 40(suppl. 2):II-1--II-63, 1969.

[n]Entire followup period; mean not reported.

[o]Statistical significance not reported in study.

PI. Hjermann, K.V. Byre, 1. Holme et al., "Effect of Diet and Smoking Intervention on the Incidence of Coronary Heart Disease: Report From the Oslo Study Group of a Randomized Trial in Healthy Men," Lancet 2:1303-1310, 1981.

ABBREVIATION: HDL = high-density lipoprotein.

SOURCE: A. Garber, B. Littenberg, and H. Sex, "Screening for Cardiac Risk Factors: Serum Cholesterol and Triglycerides," forthcoming in Ann. Intern. Med.

relation to the degree of cholesterol lowering due to diet (71). In summary, the LRC-CPPT trial showed that cholestyramine given to hypercholesterolemic, asymptomatic men without a prior myocardial infarction diminishes morbidity and mortality from CHD but does not reduce overall 7-year mortality.

The Helsinki Heart Study, another medication trial, obtained similar results in 4,081 asymptomatic, hypercholesterolemic men aged 40 to 55 who were randomly assigned to receive either placebo or gemfibrozil (36). Beyond 2 years of followup, gem fibrozil decreased total and LDL cholesterol by about 9 percent each and raised HDL cholesterol levels by 9 percent. At 5 years of followup, compared to the controls, the gemfibrozil group experienced significantly fewer cardiac events but the same overall mortality rate. Most of the excess noncardiac deaths in the treatment groups of both the LRC-CPPT trial and the Helsinki Heart Study were due to accidents and violence.

The Oslo Study (56), which enrolled more than 1,200 men whose cholesterol levels ranged from 290 to 380 mg/dl (average value, 328.9 mg/dl), found that a combined diet and smoking intervention produced a large but statistically insignificant fall in all-cause mortality. By the end of the trial (averaging 5 years of observation), 2.6 percent of the intervention group died, compared with 3.8 percent of the control group (P=0.246). Nearly 80 percent of the men smoked cigarettes at the time of enrollment, and the combined intervention decreased tobacco consumption by 45 percent. In a followup study conducted after the termination of the trial (between 8.5 and 10 years after enrollment), the difference in overall mortality approached statistical significance. By that time, 3.15 percent of the intervention group and 4.94 percent of the control group had died, corresponding to a one-sided p-value of approximately 0.05, not adjusted for multiple comparisons (57). Because the intervention substantially reduced cigarette smoking during the trial, the trend toward a significant decline in overall mortality could not be attributed to cholesterol reduction alone. This trial enrolled men whose cholesterol levels were higher than in the populations included in the LRC-CPPT and Helsinki studies, and its small sample size limited its power to detect clinically significant differences in outcomes.

Other trials that were designed to lower coronary disease and death rates by reducing cholesterol did not show a benefit from the intervention. In at least one case, there may have been no benefit because the intervention did not lower the cholesterol level substantial y. In MRFIT, which tested a multifaceted intervention (designed to alter diet, promote smoking cessation, and control blood pressure), the cholesterol level in the intervention group fell by only 2 percent more than in the control group, and neither CHD nor all-cause mortality was lower in the intervention group.

Evidence from trials of individuals with established CHD complements the findings from primary prevention studies of cholesterol reduction. Established CHD might not seem to be amenable to preventive efforts, so trials targeted toward middle-aged men who have CHD might not seem directly relevant to a screening population of asymptomatic elderly men and women. Despite such concerns, these studies provide important clues to the likely effects of cholesterol reduction in asymptomatic individuals. Men with CHD are at such a high risk of death from CHD and of recurrent cardiac morbidity that secondary prevention might show a benefit from cholesterol reduction in this population, despite a relatively short period of observation. The Coronary Drug Project, a secondary prevention trial that tested several cholesterol-lowering interventions in this population, has provided evidence that cholesterol reduction leads to lower all-cause mortality. This study showed that nicotinic acid, when given to 30 to 64 year-old male

survivors of myocardial infarction, reduced cholesterol levels by about 10 percent (21). It had no effect on mortality at a followup period averaging 6 years. However, at an average of 15 years after the inception of the trial, the men treated with nicotinic acid had an all-cause mortality rate that was 11 percent lower than the placebo group (p=0.0004), even though the Coronary Drug Project regimen only lasted for about 6 years. The mortality reduction was primarily due to a fall in the CHD mortality rate. Larger benefits were reported in another secondary prevention trial, the Stockholm Ischemic Heart Disease Study (1 00), which found a 29 percent reduction in 5-year all-cause mortality among survivors of myocardial infarction treated with a combination of clofibrate and nicotinic acid. However, only limited conclusions can be drawn from this trial, It was small and not double-blinded; the authors did not report whether the all-cause mortality difference was statistically significant; and 24 percent of the intervention group withdrew from the trial (as against only 10 percent of the control group).

In the absence of direct evidence pertinent to the elderly, these studies must serve as the most important basis for inferring the effects of cholesterol reduction in older Americans. Although cholesterol reduction can reduce the incidence of CHD and the rate of CHD death among middle-aged asymptomatic men without clinical evidence of heart disease, it has not been shown to lower overall mortality in this population. These studies may not have had sufficient years of followup or numbers of subjects to detect an overall mortality benefit, but benefits delayed for many years might not be pertinent to the elderly, who have a high rate of death from other causes. If the elderly suffer more side effects from medication or dietary interventions than the subjects of these trials did, the case for treating hypercholesterolemia will be weakened.