The Relation Of Serum Cholesterol To Risk Of Coronary Heart Disease: Implications For The Elderly

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***Abstract*: Elevated cholesterol is a known risk factor for coronary heart disease (CHD) in young and middle-aged persons. Because of the high prevalence of CHD in a growing elderly population, physicians must decide whether to devote clinical attention to this condition in older patients. Longitudinal cohort studies show that while the association between serum cholesterol and CHD decreases after age 55 years, it still persists. Primary prevention trials performed mostly on middle-aged men have reduced the incidence rate of CHD through cholesterol lowering but they have yet to show a reduction in overall mortality. Secondary prevention studies of lipid alteration have reported decreased mortality and slowed progression of coronary stenoses, again in predominantly male subjects aged less than 60 years. Implications of these findings for care of older patients are discussed along with recommendations for clinical management and future research. (J Am Board Fam Pract 1990; 3:271-82.)**

Coronary heart disease (CHD) is overwhelmingly the leading cause of death for persons aged 65 years and greater in the United States.[1] A large body of research has established several risk factors for CHD, one of which is elevated serum cholesterol.[2] Surveillance of several large elderly cohorts shows a high prevalence of hypercholesterolemia and other risk factors.[3-7]

Much of the research leading to the identification of cardiac risk factors was performed on middle-aged persons, raising a question of applicability to older adults. Clinicians now face a dilemma about treatment of hypercholesterolemia in the elderly. Treatment of this common condition in an ever-expanding population segment would incur considerable time commitment and cost. Health care workers need to be informed of the risk that cholesterol confers to older adults before making decisions about management.

This report reviews the current epidemiologic evidence regarding hypercholesterolemia as a risk factor for CHD in the elderly. Two types of research constitute the majority of epidemiologic studies in this field: (1) nonexperimental cohort studies examining the association between cholesterol levels and CHD, and (2) experimental trials of cholesterol modification in an effort to reduce CHD risk. Because so few experimental trials have involved persons aged greater than 65 years, this review describes trials involving younger persons as well. Implications for risk reduction in the elderly are also discussed.

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Methods

Using the key words "hyperlipidemia," "hypercholesterolemia," "cholesterol," "elderly," "aged," and "old," the MEDLINE files were searched through the CD ROM system from 1982 to the present. Articles dating before 1982 were accessed from cross-reference of the more recent articles. Longitudinal studies were considered for review if they contained participants aged > 55 years. Experimental trials were included if the sample size was greater than 20.

Literature Review

Nonexperimental Research

Numerous investigations in risk factor research have taken the form of longitudinal cohort studies in which potential risk factors for CHD are analyzed for an association with heart disease endpoints. These outcomes usually include cardiac mortality (fatal myocardial infarction [MI] or sudden death) and first episode of CHD (nonfatal MI or angina); all-cause mortality is often

considered as well. In the 1970s, data from the Framingham Study indicated that the association of serum cholesterol and CHD no longer held for older men.[8] Over the next several years, results from other aging cohorts became available, which, taken as a whole, offer a reasonably accurate picture of the association between serum cholesterol and CHD in the elderly.

Framingham Data

A random sample of men and women living in Framingham, Massachusetts, aged 30–62 years at entry, has been followed biennially since 1948. In 1970, the investigators initiated measurement of the following serum lipid components at each biennial examination: high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low density lipoprotein (VLDL), in addition to total cholesterol (TC) and triglycerides (TG). Analysis of cholesterol subfractions began to show a positive association between LDL and CHD, with an observed negative correlation between HDL and CHD.[9]

The relation between serum cholesterol and CHD in an older cohort was reexamined by Gordon, et al.[10] They looked at 1025 men and 1445 women aged 49–82 years at the time of the 11th biennial examination. Approximately 4 years later, 79 men and 63 women had experienced their first coronary event. Using logistic regression analysis and controlling for age, both HDL (negative) and LDL (positive) were found to be significant predictors of CHD incidence. These results suggested that TC was less predictive of CHD in older persons because of the opposing effects of LDL and HDL, with the corollary that VLDL loses its association with CHD in the elderly.

Wilson, et al. further analyzed the role of HDL in older adults.[11] Data were collected from essentially the same cohort described above (men and women aged 50–79 years in 1970–1972) over a much longer follow-up period (12 years). After adjusting for age, TC, blood pressure, body mass index, and cigarette use, low HDL was highly correlated with CHD mortality. The relative risk of CHD death for men with HDL levels in the lowest quintile compared with the highest was 4.1; for women the corresponding figure was 3.1. The risk of death from any cause was 1.9 times greater for men in the lowest quintile compared with the highest; for women in the lowest quintile, the relative risk was 1.5, but unlike the other results, this value was not statistically significant.

Recently, the Framingham data were analyzed for cardiac risk factors in an exclusively elderly population.[12] Members of the Framingham cohort who survived to age 65 free of CHD were entered in the study. The sample of 2501 was followed for an average of 9.6 years. Using proportional hazards modelling, TC was found to be an independent correlate of CHD incidence. Persons with total cholesterols at or above the 90th percentile, i.e., ≥ 275 mg/dL (7.11 mmol/L) for men and ≥ 306 mg/dL (7.91 mmol/L) for women, exhibited a relative risk of 1.8 for CHD compared with those with TC less than 200 mg/dL (5.17 mmol/L).

MRFIT Data

For the Multiple Risk Factor Intervention Trial (MRFIT) study, a sample of 356,222 men aged 35–57 years and free of CHD were screened and followed for 6 years. Stamler, et al. stratified the sample by age and analyzed the relation of TC to CHD incidence.[13] The eldest stratum consisted of 36,704 men aged 55–57 years. Dividing the sample into quintiles by TC and controlling for other risk factors, a relative risk of 2.4 for CHD mortality was found for the highest quintile (TC ≥ 245 mg/dL or 6.33 mmol/L) compared with the lowest (TC ≤ 181 mg/dL or 4.68 mmol/L). Furthermore, the risk of CHD mortality rose with each increasing quintile of TC.

Pooling Project Data

Combining data from five different longitudinal studies, the Pooling Project studied cardiac risk factors for men aged 40–64 years.[14] Similar to the above studies, the sample was divided into quintiles of serum cholesterol. The investigators calculated risk ratios of CHD incidence for the highest quintile compared with a combination of the lowest two quintiles. The relative risk decreased as age increased, from 3.6 for ages 45–49 years to 1.5 for ages 60–64 years. Incidence rates were also found to increase with age, however, and the risk difference between the highest and lowest TC quintiles was found to be constant for each age group.

Other Studies

Numerous other longitudinal studies have attempted to describe relations between TC and

CHD in older adults. Agner and Hansen assembled a cohort of men and women aged 70 years in Sweden and restudied them 10 years later.[15] The highest quartile for serum cholesterol had a significant increase in cardiovascular mortality in men; a similar trend was observed in women but was not statistically significant. In the Whitehall Study, Rose and Shipley followed 17,718 male civil servants in London for 10 years.[16] The 60–64-year-old segment of the sample at entry showed a CHD risk increase for each rise of 38.7 mg/dL (1.00 mmol/L) in TC. The Elderly Program Pilot Project examined 551 hypertensive men and women aged > 60 years (mean = 72 years).[17] At 34 months of follow-up, multivariate analysis showed a relative risk for first CHD event of 1.3 for persons with cholesterol levels in the upper third of the sample distribution versus those in the lower third. Barrett-Connor, et al. studied 1407 men and 1780 women aged 50–79 years enrolled in the Lipid Research Clinics Prevalence Study, with 9-year follow-up.[18] Total cholesterol was a significant predictor of CHD, conferring a relative risk of 1.4–1.8, with a TC rise of one standard deviation (36.8 mg/dL or 0.95 mmol/L), depending on age and sex. As part of the Donolo-Tel Aviv prospective study, 826 persons aged 55–64 years at entry were restudied after 20 years.[19] Persons with TC greater than 264 mg/dL (6.82 mmol/L) were found to be at twice the risk of CHD compared with those with TC less than 200 mg/dL (5.17 mmol/L).

A summary of studies measuring the relative risk of CHD with increased total cholesterol in cohorts exclusively greater than age 55 is shown in Table 1.

Several other long-term projects have used similar designs with slightly younger samples. Three studies yielded a positive relation between CHD and TC in men aged 40–65 years when controlling for age.[20-22] Results of individual age strata were not published. Another investigation reported the waning, yet persistent, association of TC and CHD with age.[23]

Additional studies have focused on subfractions of total cholesterol. The Israeli Ischemic Heart Study, involving 5952 men aged 40–64 years monitored for 5 years, showed an inverse association between HDL and MI for men greater than 50 years.[24] In a cross-sectional study, HDL was a significant predictor of coronary artery occlusion in 5216 adults (mean age = 56

Table 1. Relative Risk of CHD in Cohorts Exclusively Greater than Age 55 Years.*

Author–Year	Source of Data	Size of Cohort	Age at Entry	Follow-Up Years (Mean)	Population Subgroups Used in Calculation of Relative Risk	Relative Risk for CHD	CHD Endpoint Studied
Harris, et al. 1988[12]	Framingham Study	998 M 1,503 W	65	2–26 (9.6)	> 90th Percentile for TC / TC < 200 mg/dL (5.17 mmol/L)	1.5 M† 2.3 W	Incidence
Stamler, et al. 1986[13]	MRFIT Study	36,704 M	55–57	6	Highest quintile for TC / Lowest quintile for TC	1.7 M	Mortality
Pooling Project 1978[14]	Pooling Project	822 M	55–59	5–10	Highest quintile for TC / Lowest quintile for TC	1.7 M	Incidence
Agner and Hansen 1983[15]	Ambulatory Danish Elders	230 M 210 W	70	10	Highest quintile for TC / Lowest quintile for TC	2.2 M NA W†	Mortality
Rose and Shipley 1986[16]	Whitehall Study	NA	60–64	10	Given TC value plus 38.7 mg/dL / Given TC value	1.2 M	Mortality
Siegel, et al. 1987[17]	HTN in Elderly Pilot Project	201 M 350 W	> 60	(2.8)	Highest third for TC / Lowest third for TC	1.3 M,W	Incidence
Barrett-Connor, et al. 1984[18]	LRC Prevalence Study	873 M 890 W	65–79	(9)	Given TC value plus 36.8 mg/dL / Given TC value	1.4 M 1.5 W	Incidence
Brunner, et al. 1987[19]	Donolo-Tel Aviv Study	435 M 391 W	55–64	20	TC > 264 mg/dL (6.82 mmol/L) / TC < 200 mg/dL (5.17 mmol/L)	2.6 M	Incidence

*M = Men, W = Women, NA = Not Available.
†Result is not statistically significant at $P < 0.05$ level.

years) referred for cardiac catheterization.[25] An analysis of 113 elderly residents of a rural Japanese community known for longevity showed extremely high HDL levels and very low CHD compared with urban controls.[26] A study involving 62 men with noninsulin-dependent diabetes mellitus aged 40–79 years found LDL to be a significant predictor of CHD mortality over 12 years of follow-up.[27]

Given the nature of cohort research, the results of the studies outlined in this section are in considerable agreement. The relatively mild inconsistencies are most probably due to differences in research design and inherent weaknesses of cohort studies in general. As seen in Table 1, the studies exhibit modest differences in age group, gender mix, outcome type, and follow-up time. Like all cohort studies, control of extraneous factors affecting the tested outcome may be deficient, creating further variance in results between studies.

Several conclusions can be drawn based on the enormous amount of nonexperimental data that have been produced. First, the association between total serum cholesterol and CHD risk decreases with age but nonetheless remains a risk factor. This concept is particularly supported by studies with large cohorts and lengthy follow-up. Elderly persons in the upper third to upper fifth of the TC distribution appear to be at approximately 1.5–2.5 times the risk of CHD for the next 5–15 years compared with those with lower serum cholesterols. The risk of all-cause mortality also appears to be higher in elderly persons with hypercholesterolemia, though this is a less consistent finding. Second, it is quite clear that the inverse relation between HDL and CHD persists and is possibly strengthened with increasing age. The relative risk of CHD associated with an unfavorable HDL level in older persons is approximately 3.0–4.0 times greater than the risk for persons with a favorable HDL level. Third, the positive correlation between LDL and CHD in the elderly is also firmly established. Finally, whereas the relative CHD risk of persons with unfavorable lipids compared with those with desirable levels declines with age, the corresponding risk difference remains constant across age groups.

Experimental Research

The nonexperimental studies showed that the association of serum cholesterol and CHD persists with age. What now remains a question for practitioners is whether lowering of cholesterol in the elderly will result in reduction of CHD. Ever since cholesterol was first suspected as a cardiac risk factor, trials of lipid-lowering interventions have been conducted. Demonstrating a risk-reducing effect of cholesterol modification has proved to be a formidable, expensive, and time-consuming task. The existence of numerous risk factors for CHD and the long-term nature of atherogenesis require trials to have huge samples and lengthy follow-up. Trials of primary prevention are directed at reducing risk in disease-free persons. Secondary prevention trials test the effects of lipid alteration in persons who already have CHD.

Unfortunately, there have been no large-scale studies to date that involve strictly older persons, and many involve only men. Geriatric clinicians are forced to evaluate these studies for their applicability to the predominantly female, elderly population.

Primary Prevention Trials

Many of these studies have used similar methods. Usually, a large, at-risk cohort is assembled through a screening procedure. Subjects are then randomly assigned to experimental and control groups. Intervention directed at the experimental group usually consists of dietary and pharmacologic modifications of serum lipids, often under a double-blinded design. Endpoints generally include net changes in serum lipids, CHD incidence and mortality, and overall mortality. The results of several large-scale trials are summarized in Table 2. Whereas several trials have included participants aged 50 years and greater, only one[38] had persons who were more than 70 years of age.

Three major studies tested the effects of lipid-lowering drugs in middle-aged men. The Helsinki Heart Study[28] and the Lipid Research Clinics Primary Prevention Trial[29,30] reported decreases in CHD through cholesterol reduction, although overall mortality was not significantly different in experimental and control groups. In contrast, the World Health Organization (WHO) Cooperative Trial on Primary Prevention initially showed a significant reduction in nonfatal MI in the experimental group, no difference in fatal MI, and a significant *increase* in overall mortality in

men receiving clofibrate.[31] Excess mortality in the treated group disappeared on long-term follow-up after cessation of the trial. Numerous reasons have been proposed for the increased mortality seen in the clofibrate group, but a definitive explanation is lacking.[32,33]

Additional trials used interventions designed to lower several risk factors simultaneously, again using middle-aged men as subjects. Lipid alteration was generally sought through dietary modification. Many of these trials were characterized by small risk factor reduction differential between experimental participants and controls at follow-up. Examples of this included the MRFIT study[34] and the Göteburg Trial in Sweden.[35] Both studies achieved significant reduction of TC in the study group, but they also showed substantial cholesterol lowering in the controls. Neither found significant change between groups in cardiac endpoints. The WHO European Collaborative Trial only produced a net TC reduction of 1.2 percent, and there was no significant difference in CHD incidence or mortality after 6 years.[36] The Oslo Study reported significant TC reduction in markedly hyperlipidemic men during a 5-year period and found a 47 percent risk reduction in CHD.[37]

Other studies have differed in design, producing interesting results despite possible flaws. An early, combined primary and secondary preventive trial of a diet high in unsaturated fat was performed on men veterans in the Los Angeles Domicile.[38] The average age of the 846 participants was 65.5 years (range 50–89 years). After 8 years of follow-up, the experimental group showed lower TC and a decreased number of CHD endpoints. However, no difference was seen in all-cause mortality, and the statistical

Table 2. Summary of Primary Prevention Trials of Lipid Alteration.*

Name	Sample Composition	Duration (Yrs.)	Lipid Intervention	Lipid Change in Experimental Group TC(↓)	HDL(↑)	LDL(↓)	Decrease in CHD Incidence and Mortality	Comments
Helsinki[28]	4,081 M, age 40–50 Non-HDL-C ≥ 200 mg/dL (≥ 5.17 mmol/L)	5	Gemfibrozil 1.2 g/d	11%	10%	11%	Incidence 34% Mortality NS	No change in overall mortality; no age strata presented
Lipid Research Clinics[29,30]	3,806 M, age 35–59 TC > 265 mg/dL (> 6.85 mmol/L)	7–10	Cholestyramine 24 g/d	13%	NS	13%	Incidence 19% Mortality NS	No change in overall mortality; no age strata presented
WHO[31,32,33]	15,745 M, age 30–59 Mean TC 249 mg/dL (6.43 mmol/L)	5.3	Clofibrate 1.6 g/d	9%	NA	NA	Nonfatal MI 25% Mortality NS	25% increase in overall mortality in clofibrate group
MRFIT[34]	12,866 M, age 35–57 Mean TC 253 mg/dL (6.54 mmol/L)	5–6	Low-fat diet	7%	NS	7%	Mortality 7%†	Modest differences between experimental and control groups' risk factors
Göteburg[35]	30,000 M, age 47–54 Mean TC 250 mg/dL (6.46 mmol/L)	10	Low-fat diet	7%	NA	NA	Incidence NS Mortality NS	No difference between experimental and control groups' TC reduction
WHO European Collaborative[36]	49,781 M, age 40–59 Mean TC 217 mg/dL (5.61 mmol/L)	6	Low-fat diet	1%†	NA	NA	Incidence NS Mortality NS	Slight difference between experimental and control groups' risk factors
Oslo[37]	1,232 M, age 40–49 TC 290–379 mg/dL (7.49–9.79 mmol/L)	5	Low-fat diet	13%	NA	NA	Incidence 47% Mortality 38%†	Fewer, but NS overall deaths in experimental groups
LA VA Domicilary[38]	846 M, age 50–89 Mean TC 234 mg/dL (6.05 mmol/L)	8.5	Low-fat diet	20%	NA	NA	Mortality 32%	No change in overall mortality; some men had pre-existing CHD
Colestipol[40]	757 M, 936 W, Mean age 54; TC ≥ 250 mg/dL (≥ 6.46 mmol/L)	3	Colestipol 15 g/d	10%	NA	NA	Mortality NS	Randomization did not consider EKG, smoking status

*M = Men, W = Women, NS = Not Significant, NA = Not Available.
†Result is not statistically significant at $P < 0.05$ level.

power of the study was hampered by its small sample size. Another dietary trial on men volunteers aged 40–59 years achieved lowering of TC and CHD in the experimental group, but smoking status and EKG abnormalities were not included in tests of randomization, and there was a high dropout rate.[39] A randomized, single-blind trial of colestipol treatment was performed in 2278 hypercholesterolemic persons (mean age was 50.5 years for men, 57.0 years for women), some of whom had pre-existing coronary disease.[40] TC was significantly reduced in the experimental group, but CHD mortality was unchanged for men who were free of CHD at the start of the study. Women also exhibited no change in CHD with treatment, and the randomization process did not consider CHD history, smoking status, and EKG abnormalities.

Secondary Prevention Trials

The high prevalence of CHD in the elderly necessitates careful scrutiny of secondary prevention trials. These studies generally have used a shorter follow-up period and smaller sample size to observe an effect. A summary of prominent secondary prevention trials that included sample participants aged > 50 years appears in Tables 3 and 4. Results of these investigations are more consistent than was seen for the primary prevention studies.

Several studies have used recurrence of CHD events or mortality as endpoints (Table 3). Perhaps the most significant of these was a trial of niacin therapy on MI survivors, which was part of a larger study conducted by the Coronary Drug Project Research Group (CDPRG).[41,42] Using a randomized, double-blind design, 1119 men aged 30–64 years received 3.0 grams of niacin per day for 6.2 years. Results showed significant reduction of TC and reinfarction in the niacin group, but no change in overall mortality. Reanalysis at 15 years of follow-up, however, showed a significant decrease in overall mortality in the treated group, which held for participants aged > 55 years. Two studies of clofibrate therapy on patients with angina or previous MI were conducted during the late 1960s in Great Britain.[43,44] Researchers examined relatively small samples of both men and women aged 40–69 years and followed them for at least 5 years. Randomization did not succeed in significantly matching placebo and control groups for smoking habit and prior CHD in one of the projects,[43] and there were significantly higher TC values in the male placebo group on entry in the others.[44] Both studies recorded significant decreases in sudden death and overall mortality in clofibrate-treated persons with a history of angina; only one study found an overall reduction in mortality among all

Table 3. Summary of Secondary Prevention Trials of Lipid Alteration Using CHD Incidence and Mortality as Endpoints.*

Name	Sample Composition	Duration (Yrs.)	Lipid Intervention	Lipid Change in Experimental Group TC(↓)	HDL(↑)	LDL(↓)	Decrease in CHD Incidence and Mortality	Comments
Coronary Drug Project Research Group[41,42]	1119 M, age 30–64 in study group, MI survivors	6.2	Niacin 3.0 g/d	10%	NA	NA	Nonfatal MI 26% Overall mortality 11%	Mortality reduction noted after 15-year follow-up
Newcastle[43,45]	400 M, 97 W, mean age = 53, with prior MI, angina, or both	5	Clofibrate 1.5–2.0 g/d	12%	NA	NA	Fewer nonfatal MI†, Overall mortality 43%	Significant differences in smoking, EKG patterns between experimental group and controls
Scottish[44,45]	583 M, 124 W, mean age = 53, (range 40-69), with prior MI, angina, or both	6	Clofibrate 1.6–2.0 g/d	13%	NA	NA	Fewer nonfatal MI†, Lower CHD mortality†	No change in overall mortality
Colestipol[40]	337 M, 248 W, mean age = 54, with prior MI, angina, or both	3	Colestipol 15 g/d	10%	NA	NA	Overall mortality 69% in men	No reduction in mortality in women

*M = Men, W = Women, NS = Not Significant, NA = Not Available.
†Result is not statistically significant at $P < 0.05$ level.

Table 4. Summary of Secondary Prevention Trials of Lipid Alteration Using Coronary Angiographic Endpoints.*

Name	Sample Composition	Duration (Yrs.)	Lipid Intervention	Lipid Change in Experimental Group TC(↓)	HDL(↑)	LDL(↓)	Observed Change in Coronary Stenotic Lesions	Comments
NHLBI Type II[47]	116 M, age 21–55 years with hypercholesterolemia and CHD on angiography	5	Cholestyramine 24 g/d	17%	8%	26%	Significantly less definite or probable progression in cholestyramine group	All NS trends in favor of cholestyramine group
CLAS[48]	162 M, age 40–59 years, with prior coronary bypass	2	Colestipol 30 g/d, niacin 3–12 g/d	26%	37%	43%	Significantly less progression in treated group for all measures	Significantly more regression in experimental group
Nikkila, et al.[49]	26 M, 2 W under 57 years as experimental group; 20 controls; all with 2- or 3-vessel CHD	7	Clofibrate 2 g/d, niacin 2 g/d, or both	18%	10%	19%	Significantly less progression, lower CHD mortality in treated group	Progression related to TC/HDL ratio
Leiden Intervention Trial[50]	35 M, 4W age 33–59 years with ≥ 50% stenosis of at least one coronary vessel	2	Vegetarian diet	10%	NA	NS	No progression of lesions in 18 of the participants	Progression related to TC/HDL ratio; uncontrolled study

*M = Men, W = Women, NS = Not Significant, NA = Not Available.

participants.[45] A very early study of dietary modification in MI survivors reported no improvement in the treated group, but the results were severely flawed by small sample size (264), brief duration (3 years), and a randomization design that lacked baseline assessment of group comparability for smoking status, blood pressure, and EKG patterns.[46] Among men participants with prior CHD in the previously mentioned colestipol trial, the treated group had highly significant reduction in CHD mortality.[40]

More recent trials of secondary prevention have used coronary angiography to monitor endpoints of coronary stenosis, permitting higher statistical analytic power with smaller samples (Table 4). Two of the more prominent studies of this type modified lipids through pharmacologic means in middle-aged men.[47,48] On repeat angiography, the experimental persons had significantly less progression of atherosclerotic plaques than controls and exhibited more regression of plaques in one of the trials.[48] Two smaller studies documented similar findings and found that favorable endpoints were related to successful lowering of the TC/HDL ratio.[49,50]

In contrast to the cohort studies, experimental research exhibits some conflicting findings. Many of the trials contained features that make their results difficult to evaluate. Some resulted in substantial cholesterol lowering in both experimental and control groups and subsequently failed to show a difference in CHD risk.[34,35] Another was not able to achieve significant reduction of TC.[36] Several trials reported reduction of CHD in the experimental group, but no significant overall decrease in mortality.[28,29,37,44] The angiographic studies must be viewed with some caution, because it is uncertain whether an endpoint of "less progression" translates clinically to a lowering of CHD risk. Catheterization studies also have potential problems with inter- and intra-observer variability, but this was controlled for somewhat in two of the studies by blinding the physicians who evaluated the angiograms.[47,48]

Despite these points of issue, the experimental studies have established several concepts regarding risk reduction through lipid modification. Taken as a whole, the primary prevention trials have shown a definite reduction in the CHD incidence with modification of cholesterol through pharmacologic means, excluding the use of clofibrate. Dietary trials that successfully lowered TC have also reported decreases in CHD. The effi-

cacy of primary prevention in reducing overall mortality has yet to be established. Secondary prevention of CHD mortality through cholesterol modification has consistently been found. All-cause mortality reduction has also been shown in secondary preventive trials, but further data are required to establish this finding firmly. It is clear that reduction of the TC/HDL ratio through diet or drug intervention inhibits progression of coronary atherosclerosis and may in fact cause regression of plaques.

Application of these results to the elderly population can only be indirectly supported because of the lack of studies involving persons greater than 55 years, let alone those more than 65 years. There is no evidence that cholesterol lowering would *not* reduce CHD risk in older adults. Because heart disease is so widespread in the aged, even mild CHD risk reduction through lipid alteration would potentially have a large overall preventive effect.

Discussion

This review has shown that total cholesterol, and especially its HDL and LDL subfractions, remains associated with CHD in the elderly. Although the risk of CHD with abnormal cholesterol decreases with age, the risk difference between persons with high cholesterols compared with those with desirable levels stays constant. Randomized controlled trials show that while primary prevention of CHD incidence can be achieved through lipid modification in predominantly middle-aged, male cohorts, reduction in CHD and overall mortality through cholesterol lowering has not yet been adequately demonstrated. Experimental research, again in largely middle-aged populations, offers convincing evidence that secondary prevention of CHD is attainable. Lowering of the TC/HDL ratio results in less progression of coronary lesions and may cause regression of atherosclerotic plaques.

Further research should focus on three issues. First, experimental studies are needed to determine whether primary prevention of CHD through cholesterol reduction is effective and safe in the elderly. Second, studies examining the functional outcomes of lipid modification should be performed. Third, the costs of case finding and treatment of dyslipidemia in the older population as a whole need to be explored.

To define precisely the relation of cholesterol and CHD risk in the elderly, a large randomized trial of lipid modification in a geriatric population with long-term follow-up would be required. Given the cost as well as associated feasibility issues, it is unlikely that such a study would be funded in this country. Smaller studies of the antilipemia agent lovastatin in older adults are in progress and should provide valuable information regarding drug therapy in the elderly. Very little research has been performed concerning dietary alteration of blood lipids in older age groups. Because physicians are often reticent about drug treatment of dyslipidemia, more work examining both the benefits and hazards of dietary therapy in the elderly needs to be performed.

Much emphasis is placed on the efficacy of cholesterol modification in lowering CHD or overall mortality. As Fried and Bush appropriately point out, it may be more beneficial from a geriatric perspective to consider the ability of lipid therapy to prevent morbidity rather than mortality.[51] Not only does cholesterol lowering have the potential to reduce morbidity in the elderly through prevention of CHD, it may also do so through prevention of other cardiovascular disorders. Several studies suggest that this may be the case for stroke and peripheral vascular disease.[52-56] Additional research should focus on the relation between abnormal serum cholesterol and morbidity, which would include testing the efficacy of lipid modification in the prevention of functional decline in the elderly.

Because of the high prevalence of lipid disorders, the cost-benefit issues of treatment must be considered as an important research topic. Health services researchers have come to contrasting conclusions about the overall utility of cholesterol treatment.[57-59] Most of the analyses performed have not included older adults. Obviously, it will be important to assess the costs of treating dyslipidemia in the elderly as more information is gathered about its beneficial effects.

Clinicians need to evaluate the current evidence about screening and treatment of hypercholesterolemia in older patients. Recently, much has been written on how the existing data should be interpreted, citing issues of language use when study findings are reported, the difference between treatment of manifest disease and modifi-

cation of risk factors, and the translation of epidemiologic data to individual cases.[60] There is strong evidence that an elevated serum cholesterol is associated with CHD in older adults. In the context of a mass screening, then, a high cholesterol would suggest an increased risk of CHD, even in the elderly, and would warrant further diagnostic investigation. However, it also has been shown that the efficacy of lipid treatment in the elderly is yet unproved, forcing physicians to make management decisions on the available, albeit inadequate, data.

Recommendations about detection and treatment of dyslipidemia in the elderly have differed. Garber, et al. suggested that testing for elevated cholesterol should be optional in persons aged more than 70 years because benefits of treatment in this age group have yet to be proved.[61] In a subsequent report prepared for the federal Office of Technology Assessment, these same authors (plus three others) stated that without beneficial evidence, cholesterol screening and treatment in those more than 65 years old could not be recommended.[62] In contrast, the National Cholesterol Education Program guidelines for classification of serum cholesterol "are uniform for adult men and women of all ages."[63] However, the report later states that treatment of high cholesterol in persons greater than age 60 years is up to the individual discretion of the physician.

As in all areas of geriatric care, treatment of a disorder must be carefully weighed against possible adverse effects of therapy. Some authors do not recommend cholesterol modification after age 70 years, arguing that lipid-lowering agents have potentially serious side effects and that low-fat diets can contribute to malnutrition.[64] Others recommend only dietary treatment in the elderly.[65] Conversely, several reports have called for relatively aggressive treatment of lipid disorders in the elderly, even drug therapy if necessary.[66-70]

When caring for geriatric patients, primary care physicians must consider a complex array of biophysical and psychosocial issues. Cholesterol management in the elderly not only requires evaluation of cardiovascular risk and benefit but also assessment of functional status, risks of malnutrition or adverse drug effects with treatment, ability to pay for treatment, ethnic issues of dietary habits, quality of life, and a variety of other factors. For these reasons, it would be premature to recommend definite guidelines for blanket detection and management of lipid disorders in persons aged > 65 years. Yet, there is compelling evidence that dyslipidemia is a risk factor for CHD in the elderly. Keeping in mind the frequency of CHD in older persons, it seems reasonable to devote clinical attention to detection and treatment of dyslipidemia in elders who have no contraindications to lipid-lowering therapy. Case finding would involve screening for elevated serum cholesterol in healthy elders, with lipoprotein typing of persons with high TC (> 200 mg/dL or 5.20 mmol/L), a history of CHD, or the presence of two other cardiac risk factors. Dietary, exercise, and drug therapies to lower the TC/HDL ratio should be employed if treatment poses no undue risk. In addition, patients should be monitored carefully for signs of malnutrition, adverse drug effects, or functional decline.

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