Lack of Association Between Cholesterol and Coronary Heart Disease Mortality and Morbidity and All-Cause Mortality in Persons Older Than 70 Years

Harlan M. Krumholz, MD; Teresa E. Seeman, PhD; Susan S. Merrill, PhD; Carlos F. Mendes de Leon, PhD; Viola Vaccarino, MD; David I. Silverman, MD; Reiko Tsukahara, MD; Adrian M. Ostfeld, MD; Lisa F. Berkman, PhD

Objectives.—To determine whether elevated serum cholesterol level is associated with all-cause mortality, mortality from coronary heart disease, or hospitalization for acute myocardial infarction and unstable angina in persons older than 70 years. Also, to evaluate the association between low levels of high-density lipoprotein cholesterol (HDL-C) and elevated ratio of serum cholesterol to HDL-C with these outcomes.

Design.—Prospective, community-based cohort study with yearly interviews.

Participants.—A total of 997 subjects who were interviewed in 1988 as part of the New Haven, Conn, cohort of the Established Population for the Epidemiologic Study of the Elderly (EPESE) and consented to have blood drawn.

Main Outcome Measures.—The risk factor–adjusted odds ratios of the 4-year incidence of all-cause mortality, mortality from coronary heart disease, and hospitalization for myocardial infarction or unstable angina were calculated for the following: subjects with total serum cholesterol levels greater than or equal to 6.20 mmol/L (≥240 mg/dL) compared with subjects with cholesterol levels less than 5.20 mmol/L (<200 mg/dL); subjects in the lowest tertile of HDL-C level compared with those in the highest tertile; and subjects in the highest tertile of the ratio of total serum cholesterol to HDL-C level compared with those in the lowest tertile.

Results.—Elevated total serum cholesterol level, low HDL-C, and high total serum cholesterol to HDL-C ratio were not associated with a significantly higher rate of all-cause mortality, coronary heart disease mortality, or hospitalization for myocardial infarction or unstable angina after adjustment for cardiovascular risk factors. The risk factor–adjusted odds ratio for all-cause mortality was 0.99 (95% confidence interval [CI], 0.56 to 2.69) for the group who had cholesterol levels greater than or equal to 6.20 mmol/L (≥240 mg/dL) compared with the group that had levels less than 5.20 mmol/L (<200 mg/dL); 1.00 (95% CI, 0.59 to 1.70) for the group in the lowest tertile of HDL-C compared with those in the highest tertile; and 1.03 (95% CI, 0.62 to 1.71) for subjects in the highest tertile of the ratio of total serum cholesterol to HDL-C compared with those in the lowest tertile.

Conclusions.—Our findings do not support the hypothesis that hypercholesterolemia or low HDL-C are important risk factors for all-cause mortality, coronary heart disease mortality, or hospitalization for myocardial infarction or unstable angina in this cohort of persons older than 70 years.

(*JAMA*. 1994;272:1335-1340)

From the Section of Cardiovascular Medicine, Department of Internal Medicine (Dr Krumholz), and the Section of Chronic Disease Epidemiology, Department of Epidemiology and Public Health (Drs Krumholz, Seeman, Merrill, Mendes de Leon, Vaccarino, Tsukahara, Ostfeld, and Berkman), Yale University School of Medicine, New Haven, Conn, and the Division of Cardiology, University of Connecticut Medical School, Farmington (Dr Silverman).

Reprint requests to the Section of Cardiovascular Medicine, Yale University School of Medicine, 333 Cedar St, PO Box 208017, New Haven, CT 06520-8017 (Dr Krumholz).

ALTHOUGH cholesterol levels are slightly lower in older age groups compared with younger,[1-3] the prevalence of hypercholesterolemia in the elderly is substantial.[4,5] Treatment of the large number of older patients with elevated cholesterol levels is often advocated to prevent heart disease,[6] which is the leading cause of mortality and morbidity in this group.[7] Even a small reduction in incidence of heart disease in this age group would benefit a large number of people.[8] In addition, the National Cholesterol Education Program (NCEP) Expert Panel has suggested that data from the clinical trials of middle-aged patients should be extrapolated to the elderly population.[9]

For editorial comment see p 1372.

Yet, despite considerable evidence that hypercholesterolemia is associated with increased risk for coronary heart disease (CHD) in young and middle-aged individuals,[10,11] the importance of hypercholesterolemia as a risk factor for cardiovascular disease in persons older than 70 years remains controversial. While some observational studies have found that total serum cholesterol remains an important risk factor for cardiovascular disease in the elderly,[12] others have noted that the risk weakens with advancing age.[13-15] Indeed, while one informal meta-analysis reported that elevated total serum cholesterol is associated with increased risk of mortality from CHD in subjects 65 years of age or older,[16] other studies have failed to find any association between cholesterol and cardiovascular events beyond the age of 70 years.[17,18]

In sum, it is not known whether cholesterol is a risk factor for CHD and

Table 1.—Population Studied

	Men, No.	Women, No.	Total, No.
1982 inception cohort	1169	1643	**2812**
Alive in 1988	668	1151	**1819**
Interviewed in 1988	609	1062	**1671**
Blood sample obtained	387	610	**997**

mortality in persons older than 70 years. Therefore, we examined the association of total serum cholesterol level, high-density lipoprotein cholesterol (HDL-C), and the ratio of total serum cholesterol to HDL-C on subsequent survival and hospitalization for CHD in a heterogeneous cohort of men and women older than 70 years. These subjects were participating in a longitudinal, community-based study of elderly persons,[19] established in 1982, and were interviewed and had cholesterol levels measured in 1988.

METHODS

Study Sample

The study sample comprised subjects from the New Haven, Conn, cohort of the Established Populations, for the Epidemiologic Study of the Elderly (EPESE) program. This program was established in 1982 as a longitudinal, community-based cohort study of noninstitutionalized men and women aged 65 years or older living in New Haven. The study design has been published elsewhere.[19] The 2812 subjects in the cohort were drawn from a probability sample that oversampled men and stratified by housing type. Fewer than 1% of the group have been lost to follow-up. Participants have been interviewed yearly about their health status, medical history, medications, functional status, and income. In 1988, subjects were visited in their homes, and they were asked to have blood drawn for analysis. Of the 1617 subjects from the cohort who were interviewed, 997 consented to have blood drawn. All variables in the following analyses were collected during the 1988 interview at the subjects' homes.

Measurement of Standard Risk Factors

Blood Pressure.—The Hypertension Detection and Follow-up Program protocol was used to obtain three seated blood pressure readings.[20] Systolic and diastolic blood pressures were calculated as the average of the second and third readings. The use of antihypertensive medication was determined by self-report and a review of the patient's medications.

Cigarette Smoking.—Cigarette smoking was ascertained by self-report. Smoking status was classified as current, former, or never smoker.

Body Mass Index.—Height and weight were obtained by self-report and were used to determine body mass index, calculated as the weight in kilograms divided by the square of height, in meters. To adjust for body mass, men and women were classified as having a body mass index of 23 or less, 24 to 27, or 28 or more. These cutpoints were based on approximate tertiles of the body mass distribution.

Diabetes Mellitus.—Subjects who reported that they had ever been told that they had diabetes, sugar in the urine, or high blood sugar were classified as having diabetes mellitus. Previous internal analyses of this cohort have demonstrated at least a 90% correspondence between self-reported diabetes status and medical record data.

Cardiac History.—A history of myocardial infarction was determined by self-report. Charts were reviewed for hospitalizations for myocardial infarction or unstable angina in the 5 years prior to the blood draw. Patients who reported a history of pain that occurred when hurrying or walking uphill were classified as having exertional chest pain.

Cholesterol.—A phlebotomist went to each subject's home to draw blood. The subjects were not required to be fasting (only 12% of the sample had fasted 8 or more hours before having their blood drawn). Samples were processed within 8 hours of collection. Blood was allowed to clot and then spun at 1500 relative centrifugal force for 10 minutes in a refrigerated (4°C) centrifuge. The serum samples were sent to a laboratory (Nichols Laboratory, Capistrano, Calif) for measurement of total cholesterol and HDL-C with a chemistry analyzer (Hitachi 704, Mito City, Japan). Total serum cholesterol was measured using enzymatic (cholesterol oxidase) colorimetry, and the HDL-C was measured by dextran sulfate–magnesium chloride precipitation and enzymatic (cholesterol oxidase) colorimetry.

Outcome Events

Since the inception of the cohort, subjects have been monitored regularly for mortality and hospitalizations. The outcome events in this study included all-cause mortality, CHD mortality, and hospitalization for unstable angina or myocardial infarction. Subjects were followed up through December 31, 1992.

Death certificates were obtained for all subjects who died and were coded by a certified nosologist using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*).[21] Deaths with an underlying cause of CHD were defined as *ICD-9-CM* codes 410 to 414, which include acute myocardial infarction, other acute and subacute forms of ischemic heart disease, and angina pectoris.

Hospitalizations for acute myocardial infarction and unstable angina were assessed by weekly monitoring at the two New Haven hospitals (Saint Raphael's and Yale-New Haven). We previously determined that approximately 90% of the hospitalizations for CHD occurred at these two facilities. This surveillance was supplemented by information from the Health Care Financing Administration. Diagnoses of myocardial infarction or unstable angina were confirmed by chart review. Myocardial infarction was defined according to standard criteria.[22] Unstable angina was defined as hospitalization for either the new onset of sudden chest pain that was considered to be ischemic or an exacerbation of previously diagnosed angina.

Statistical Analysis

The study sample was compared with subjects who did not have blood drawn. Continuous and normally distributed variables were compared using the Student t test, and other variables were compared using the χ^2 test.

The study sample was stratified by total serum cholesterol value, based on the recommendations of the NCEP Expert Panel,[9] into the following three groups: cholesterol levels less than 5.20 mmol/L (<200 mg/dL), 5.20 to 6.20 mmol/L (200 to 240 mg/dL), and 6.20 mmol/L or higher (≥240 mg/dL). Subjects with total serum cholesterol levels greater than or equal to 6.20 mmol/L (≥240 mg/dL) and 5.20 to 6.20 mmol/L (200 to 240 mg/dL) were compared with subjects with cholesterol less than 5.20 mmol/L (<200 mg/dL). Kaplan-Meier survival curves were generated to show survival among subjects in the three total serum cholesterol groups. The groups were compared by the log-rank test.[23]

Subjects also were stratified in separate analysis by sex-specific tertiles of HDL-C and the ratio of total serum cholesterol to HDL-C. The tertiles of HDL-C were defined as follows: for men, less than or equal to 0.95 mmol/L (≤37 mg/dL), 1.00 to 1.20 mmol/L (38 to 47 mg/dL), and greater than 1.20 mmol/L (>47 mg/dL); for women, less than or equal to 1.05 mmol/L (≤40 mg/dL), 1.06 to 1.30 mmol/L (41 to 50 mg/dL), and greater than 1.30 mmol/L (>50 mg/dL). The tertiles for the ratio of total serum cholesterol to HDL-C were defined as follows: for men, less than 4.17, 4.17 to 5.46, and greater than 5.46; for women, less than 3.82, 3.82 to 5.09, and greater than 5.09.

We designed multivariable logistic regression models to evaluate the asso-

ciations of total serum cholesterol, HDL-C, and total serum cholesterol to HDL-C ratio with outcomes after adjusting for age, sex, and cardiovascular risk factors. The covariate risk factors were selected based on prior studies of EPESE cohorts.[23-25] In separate models, subjects with total serum cholesterol levels greater than or equal to 6.20 mmol/L (≥240 mg/dL) were compared with subjects with total serum cholesterol levels less than 5.20 mmol/L (<200 mg/dL); subjects in the lowest tertile of HDL-C level were compared with subjects in the highest tertile; and subjects in the highest tertile of the total serum cholesterol to HDL-C ratio were compared with those in the lowest tertile.

Covariates in each multivariate model included age (years), systolic blood pressure (mm Hg), body mass index (using the lowest tertile as reference), presence of chest pain on exertion, antihypertensive medication, history of diabetes mellitus, history of myocardial infarction, past smoking history, and current smoking. Multivariate analyses of total serum cholesterol were repeated after excluding the 55 male subjects (14%) and 40 female subjects (7%) with a total serum cholesterol level less than 4.15 mmol/L (<160 mg/dL) because of concerns that low cholesterol levels are associated with increased mortality.[26]

The Professional Software for Survey Data Analysis (SUDAAN) (SAS Inc, Cary, NC) was used for all analyses to adjust for possible design effects of the stratified sampling design that was used to construct the New Haven EPESE cohort; these design effects include housing strata and an oversampling of men. The SUDAAN software computed sampling variances for parameter estimates using the Taylor series approximation method. Since application of simple random sampling assumptions to design-based data can lead to an underestimation of variances and an overestimation of significance levels, it is important to use design-based variance estimates.[27]

RESULTS

Study Sample

Of the 2812 subjects enrolled in 1982 in the New Haven site of the EPESE program, 1617 were interviewed in 1988, and blood samples were obtained from 997 of them (Table 1). The most common reason that blood was not drawn from these subjects was that they refused. Subjects from whom a blood sample was obtained were significantly younger, less likely to be female, and more likely to have diabetes mellitus than the subjects who did not have a blood sample drawn (Table 2). The 4-year rates of CHD mortality and all-cause mortality in the study sample subjects were not significantly different from those without a blood sample (4% vs 4%, respectively, for CHD mortality, and 24% vs 30%, respectively, for all-cause mortality).

Table 2.—Characteristics of the Study Subjects and Subjects Not Included Because No Blood Sample Obtained*

Characteristic	Study Sample			Not Included in Study Sample
	Men	Women	Total	
No.	387	610	997	674
Mean (±SD) age, y	77.8 (±5.4)	79.4 (±6.1)	78.8 (±5.9)	80.2 (±6.3)†
Sex, % female	. . .	. . .	64	71†
Race, % white	83	81	82	82
Housing stratum, %				
Public	5	8	8	8
Private	7	16	13	14
Community	88	75	80	78
Mean (±SD) blood pressure, mm Hg				
Systolic	137.3 (±17.7)	139.2 (±21.0)	139.6 (±19.8)	138.8 (±17.8)
Diastolic	76.6 (±10.5)	75.6 (±11.3)	75.9 (±11.0)	75.2 (±10.6)
Antihypertensive treatment, %	49	50	50	47
Diabetes, %	17	18	17	13†
History of myocardial infarction, %	20	13	15	17
Exertional chest pain, %	12	10	10	7
Current smoker, %	15	11	12	10
Mean (±SD) body mass index‡	25.8 (±4.2)	25.8 (±5.0)	25.2 (±4.7)	25.3 (±4.6)

*All numbers are weighted for the sampling design.
†$P<.05$ in comparison with study sample.
‡Weight in kilograms divided by the square of height in meters.

The characteristics of the study sample are reported in Table 2. The mean age was 78 years for men and 79 years for women; ages ranged from 71 years to 104 years. Cardiac risk factors were common in the cohort, but a history of a prior myocardial infarction was reported by fewer than 20% of the subjects. There were only 53 subjects who had a confirmed hospitalization for acute myocardial infarction or unstable angina in the 5 years prior to the blood draw.

The prevalence of a total serum cholesterol level greater than or equal to 6.20 mmol/L (≥240 mg/dL) was higher for women than for men. Only 63 (16%) of the 387 male subjects had a total cholesterol level greater than or equal to 6.20 mmol/L (≥240 mg/dL) compared with 206 (34%) of the 610 female subjects. In contrast, the prevalence of low HDL-C levels (<0.90 mmol/L [<35 mg/dL]) was lower for women than men. Low HDL-C was measured in 102 male subjects (26%) compared with 53 female subjects (9%).

Outcome Event Analysis

There was no significant association between total serum cholesterol levels and incidence of myocardial infarction and unstable angina for either sex (Table 3). The highest rates of myocardial infarction or unstable angina were in the groups with the lowest serum cholesterol levels. After adjustment for sex and cardiovascular risk factors, the odds ratio for myocardial infarction or unstable angina for the highest total serum cholesterol group compared with the lowest was 0.59 (95% confidence interval [CI], 0.29 to 2.60) (Table 4). There were also no significant differences for CHD mortality among the total serum cholesterol groups for either sex (Table 3). The adjusted odds ratio of CHD mortality associated with a cholesterol level greater than or equal to 6.20 mmol/L (≥240 mg/dL) compared with a cholesterol level less than 5.20 mmol/L (<200 mg/dL) was 0.60 (95% CI, 0.18 to 1.98).

Finally, there was no association between cholesterol group and all-cause mortality (Table 3). In men, the survival curves of the three total serum cholesterol groups intertwined (Figure 1) and were not significantly different. In women, the highest mortality was in the group with total serum cholesterol level less than 5.20 mmol/L (<200 mg/dL), followed by the group with total serum cholesterol levels between 5.20 and 6.20 mmol/L (200 mg/dL and 240 mg/dL), and then the group with total serum cholesterol level greater than or equal to 6.20 mmol/L (≥240 mg/dL). The survival curves did not cross, as shown in Figure 2, and were significantly different ($P<.001$). For men and women combined, the odds ratio associated with an elevated cholesterol level was 0.99 (95% CI, 0.56 to 2.69). The multivariate analyses with total serum cholesterol were repeated after excluding subjects with cholesterol levels less than 4.15 mmol/L (<160 mg/dL) and the odds ratios did not change substantially (data available on request). Multivariate analyses were also

Table 3.—Four-Year Incidence of Outcome Events Stratified by Serum Cholesterol Level, HDL-C Level, and Serum Cholesterol to HDL-C Ratio*

	Men†				Women			
Outcomes (%)	No.	MI or Unstable Angina, %	CHD Mortality, %	All-Cause Mortality, %	No.	MI or Unstable Angina, %	CHD Mortality, %	All-Cause Mortality, %
Total cholesterol, mmol/L (mg/dL)								
<5.20 (<200)	185	7.6	5.1	24.7	183	5.1	5.0	19.5
5.20 to 6.20 (200 to 239)	139	4.3	5.2	15.5	221	2.6	4.5	15.6
≥6.20 (≥240)	63	4.6	2.4	31.6	206	3.3	2.1	13.1
HDL-C‡								
Lowest tertile	126	8.7	4.6	17.3	155	3.4	3.3	18.8
Middle tertile	129	5.2	5.7	22.6	184	2.7	5.6	17.0
Highest tertile	130	3.5	4.0	25.1	171	4.5	2.1	11.7
Total cholesterol to HDL-C ratio§								
Lowest tertile	125	6.2	5.7	27.9	158	2.8	3.4	15.4
Middle tertile	131	6.2	5.2	16.0	178	4.4	3.8	12.0
Highest tertile	129	4.9	1.4	21.5	174	3.2	4.2	19.7

*Percentages are weighted for the sampling design. MI indicates myocardial infarction; CHD, coronary heart disease; and HDL-C, high-density lipoprotein cholesterol.
†Two men did not have values for HDL-C.
‡Tertiles for HDL-C: men, ≤0.95 mmol/L (≤37 mg/dL), 1.00 to 1.20 mmol/L (38 to 47 mg/dL), and >1.20 mmol/L (>47 mg/dL); women, ≤1.05 mmol/L (≤40 mg/dL), 1.06 to 1.30 mmol/L (41 to 50 mg/dL), and >1.30 mmol/L (>50 mg/dL).
§Tertiles for total cholesterol to HDL-C ratio: men, <4.17, 4.17 to 5.46, and >5.46; women, <3.82, 3.82 to 5.09, and >5.09.

Table 4.—Odds Ratios (and 95% Confidence Intervals) of Outcome Events, Adjusted for Age, Sex, and Risk Factors*

	MI or Unstable Angina		CHD Mortality		All-Cause Mortality	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Subjects with TC ≥6.20 mmol/L (≥240 mg/dL) compared with subjects with TC <5.20 mmol/L (<200 mg/dL)	0.55 (0.20-1.49)	0.59 (0.29-2.60)	0.41 (0.13-1.27)	0.60 (0.18-1.98)	0.75 (0.45-1.25)	0.99 (0.56-2.69)
Subjects in lowest tertile of HDL-C compared with subjects in the highest tertile	1.39 (0.54-3.56)	1.28 (0.47-3.48)	1.26 (0.46-3.42)	1.18 (0.43-3.22)	1.06 (0.64-1.77)	1.00 (0.59-1.70)
Subjects in highest tertile of TC/HDL-C compared with subjects in the lowest tertile	0.94 (0.34-2.61)	0.87 (0.29-2.60)	0.66 (0.24-1.82)	0.74 (0.29-1.60)	0.61 (0.37-1.02)	1.03 (0.62-1.71)

*Odds ratios calculated for the 867 men and women with complete risk factor information. Covariates for the adjusted logistic regression models include age, sex, systolic blood pressure (mm Hg), diabetes (no/yes), body mass index (coded as ≤23 [no/yes] and >27 [no/yes]), antihypertensive use (no/yes), current smoking (no/yes), past smoking history (no/yes), history of myocardial infarction (no/yes), and chest pain on exertion (no/yes). HDL-C indicates high-density lipoprotein cholesterol; MI, myocardial infarction; CHD, coronary heart disease; and TC, total cholesterol.

repeated without weighting for design effects. The odds ratios were similar, but the CIs were smaller (data available on request).

The outcomes by tertiles of HDL-C and the ratio of total serum cholesterol to HDL-C are shown in Tables 3 and 4. There were no significant differences in outcomes between either low HDL-C levels or elevated total serum cholesterol to HDL-C ratio. The adjusted odds ratios of low HDL-C compared with high HDL-C for the incidence of myocardial infarction or unstable angina and for CHD mortality were greater than 1.0; however, confidence intervals were wide and included 1.0.

COMMENT

Hypercholesterolemia in the very elderly population is attractive as a potentially modifiable risk factor for cardiovascular disease because it is prevalent and has been shown to be strongly associated with adverse outcomes in younger cohorts.[10,11] The reduction of cholesterol in clinical trials of middle-aged subjects has been associated with a reduction in cardiovascular disease,[28] and experts have suggested that these results may be extrapolated to older subjects.[9] The principal finding of our investigation, however, was that elevated total serum cholesterol levels, low HDL-C levels, and the total serum cholesterol to HDL-C ratio were not strongly associated with increased all-cause mortality, CHD mortality, or hospitalizations for cardiovascular disease in a cohort of men and women older than 70 years with 4 years of follow-up.

Our study sample was drawn from the survivors of a representative sample of New Haven residents who were 65 years of age or older in 1982. Therefore, the subjects in this analysis were at least 71 years of age and were a heterogeneous group representing the diversity of urban society. Within this cohort, there was a substantial prevalence of elevated cholesterol, with 34% of the women and 16% of the men having a cholesterol level greater than or equal to 6.20 mmol/L (≥240 mg/dL). Other studies have also reported a high prevalence of elevated cholesterol in the elderly population. For example, in the third National Health and Nutrition Examination Survey (NHANES III), 39% of the subjects aged 65 to 74 years and 32% of subjects aged 75 years and older had cholesterol levels greater than or equal to 6.20 mmol/L (≥240 mg/dL).[29] Also, in the Cardiovascular Health Study, a community-based study of individuals 65 years of age or older who were recruited from May 1989 to May 1990, 24% had cholesterol levels greater than or equal to 6.20 mmol/L (≥240 mg/dL).[5]

Unexpectedly, the gradient of the survival curves in women showed the best survival occurring in the group with total serum cholesterol levels greater than or equal to 6.20 mmol/L (≥240 mg/dL), followed by the group with total serum cholesterol levels between 5.20 and 6.20 mmol/L (200 and 240 mg/dL) and, fi-

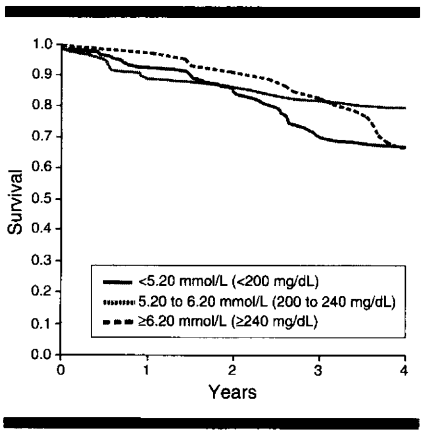

Figure 1.—Kaplan-Meier survival curves for men in the study sample, stratified by total serum cholesterol level.

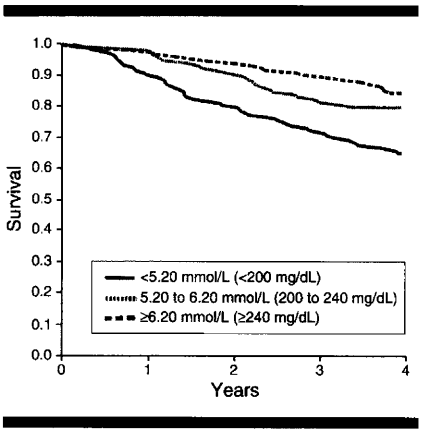

Figure 2.—Kaplan-Meier survival curves for women in the study sample, stratified by total serum cholesterol level.

nally, by the group with cholesterol levels less than 5.20 mmol/L (<200 mg/dL). These findings strongly suggest that elevated cholesterol alone should not be considered an important risk factor for mortality for very elderly women.

Our findings contrast with previously published reports. Barrett-Connor et al,[15] in a study of a white, upper-middle-class community, found that elevated cholesterol levels were associated with increased ischemic heart disease events in men and women aged 65 to 79 years. Benfante and Reed[13] from the Honolulu Heart Program, a study of cardiovascular disease among men of Japanese ancestry, reported that total serum cholesterol was significantly associated with incident CHD among subjects aged 65 to 74 years after adjusting for age, blood pressure, cigarettes smoked per day, and history of diabetes. Rubin and colleagues,[12] in a study of white men aged 60 to 79 years who were members of a health maintenance organization, also found that elevated total serum cholesterol was associated with increased mortality from CHD after adjusting for age, blood pressure, and smoking status. Aronow and colleagues,[30] in a study of very elderly nursing home residents, reported that total serum cholesterol was associated with coronary events in men and women after adjusting for age, smoking status, presence of hypertension, presence of diabetes mellitus, obesity, and antecedent coronary artery disease.

The difference in our study sample compared with other studies may explain why our findings contrast with these reports. The mean age of our study sample was greater than the upper age limit of the studies of Barrett-Connor et al,[15] Benfante and Reed,[13] and Rubin et al.[12] The sample in the study by Barrett-Connor et al[15] was restricted to white men and women, the study by Benfante and Reed was from the Honolulu Heart Program[13] and was restricted to men of Japanese ancestry, and the study by Rubin et al[12] was restricted to white men. The study by Rubin et al[12] and the study by Barrett-Connor et al[15] did not include patients of low socioeconomic status. The study by Aronow et al[30] was conducted among residents of a long-term care facility. Our sample, by comparison, began as a representative sample of subjects living in New Haven and was heterogeneous with respect to sex, race, and socioeconomic status. The most important difference may be that our sample was substantially older than most of the other cohorts.

Studies of very elderly cohorts that have included men and women support our findings. Kronmal and colleagues,[18] using data from the Framingham Heart Study, reported no evidence that all-cause mortality or CHD mortality was associated with elevated cholesterol in subjects older than 70 years. Zimetbaum and colleagues,[17] in a report of volunteers with a mean age of 79 years from the Bronx Aging Study, also found that elevated total serum cholesterol was not an independent risk factor for cardiovascular disease or mortality.

There are many possible explanations for the observation that cholesterol is not a risk factor for cardiovascular disease in the very elderly. The cholesterol level of elderly individuals may not represent their lifetime exposure and, thus, not effectively stratify their risk. Also, as a result of selective survival, hypercholesterolemic individuals who remain in the cohort may be relatively resistant to the effects of lipids. In addition, aging may cause changes in the arterial wall that decrease its susceptibility to cholesterol concentrations in the blood.

We also investigated whether HDL-C levels could confound the association between total serum cholesterol and outcome. We did not detect an association between the ratio of total serum cholesterol to HDL-C and outcomes. We did find an increased risk for CHD events with low HDL-C levels, but the results were not significant. Thus, these results cannot strongly support low HDL-C as an important risk factor in elderly subjects. In addition, a low HDL-C level was not associated with an increased risk of all-cause mortality.

Our study has some important limitations. The most important issue in a negative study concerns sample size and power. Our study is one of the largest to investigate the association of cholesterol and mortality in the very elderly, with almost 1000 subjects in our sample. This sample size and the high event rate allowed us to analyze the data at 4 years of follow-up. Prior to our analysis, we estimated that we had more than an 80% power to detect a relative risk of 1.6 in all-cause mortality for the highest serum cholesterol group compared with the lowest. That power calculation was based on one tail since we were testing the hypothesis that an elevated total serum cholesterol would confer an increased risk.

Second, since some subjects refused to have blood drawn, our study sample did not include the entire cohort. Nevertheless, our sample was heterogeneous and there were only minor differences between participants and those who did not have blood drawn.

Third, this study focused on persons who were older than 70 years; the mean age of the cohort at the time that a cholesterol level was drawn was approximately 79 years. These results are important since the very elderly represent a rapidly increasing segment of the population with a high prevalence of hypercholesterolemia, and information about its importance in the very elderly is lacking. However, our results are not generalizable to younger subjects.

Fourth, the relevance of this study for patients who have had a myocardial infarction is not clear. Data from the Framingham Heart Study[31] suggest that hypercholesterolemia is an important risk factor after a myocardial infarction. In our sample, however, there were relatively few individuals with a recent myocardial infarction. Thus, our study cannot provide information about the importance of hypercholesterolemia as a risk factor after an individual survives a myocardial infarction.

Finally, our CHD mortality end point was derived from death certificates. Although some deaths may have been misclassified, this is unlikely to have introduced a bias into the study since there is no reason to believe that individuals

with a high cholesterol level would be less likely to be coded with a death from CHD. Nevertheless, concerns about this end point prompted us to focus also on morbidity from confirmed myocardial infarction and unstable angina, and on all-cause mortality.

In summary, our findings do not support cholesterol as a risk factor with a graded and continuous association with all-cause mortality, CHD mortality, or hospitalization for an acute ischemic event among very elderly subjects. Our findings will need to be corroborated in other large studies of very elderly populations, with and without prior manifestations of coronary artery disease.

This study was supported in part by grants 1T-32-AG-0-0153 and R01-AG-1-1042 from the National Institutes of Health, Bethesda, Md.

References

1. Ettinger WH, Wahl PW, Kuller LH, et al. Lipoprotein lipids in older people: results from the Cardiovascular Health Study. *Circulation.* 1992;86:858-869.
2. The Lipids Research Clinic Program Epidemiology Committee. Plasma lipid populations in selected North American populations. *Circulation.* 1979;60:427-439.
3. Curb JD, Reed DM, Yano K, Kautz JA, Albers JJ. Plasma lipids and lipoproteins in elderly Japanese-American men. *J Am Geriatr Soc.* 1986;34:773-780.
4. Johnson CL, Rifkind BM, Sempos CT, et al. Declining serum total cholesterol levels among US adults. *JAMA.* 1993;269:3002-3008.
5. Manolio TT, Furberg CD, Wahl PW, et al. Eligibility for cholesterol referral in community-dwelling older adults. *Ann Intern Med.* 1992;116:641-649.
6. Kafonek S, Kwiterovich P. Treatment of hypercholesterolemia in the elderly. *Ann Intern Med.* 1990;112:723-725.
7. US Senate Subcommittee on Aging. *Aging America.* Washington, DC: US Dept of Health and Human Services; 1991:273.
8. Denke MA, Grundy SM. Hypercholesterolemia in elderly persons: resolving the treatment dilemma. *Ann Intern Med.* 1990;112:780-792.
9. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA.* 1993;269:3015-3023.
10. Castelli WP. Epidemiology of coronary heart disease. *Am J Med.* 1984;76:4-12.
11. Stamler J, Wentworth DN, Neaton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous or graded? findings in 356 222 primary screenees of the Multiple Risk Factor Intervention Trail (MRFIT). *JAMA.* 1986;256:2823-2828.
12. Rubin SM, Sidney S, Black DM, Browner WS, Hulley SB, Cummings SR. High blood cholesterol in elderly men and the excess risk for coronary heart disease. *Ann Intern Med.* 1990;113:916-920.
13. Benfante R, Reed D. Is elevated serum cholesterol a risk factor for coronary heart disease in the elderly? *JAMA.* 1990;263:393-396.
14. Castelli WP, Wilson PW, Levy D, Anderson K. Cardiovascular risk factors in the elderly. *Am J Cardiol.* 1989;63(suppl):12H-19H.
15. Barrett-Connor E, Suarez L, Khaw K, Criqui MH, Wingard DL. Ischemic heart disease risk factors after age 50. *J Chronic Dis.* 1984;37:903-908.
16. Manolio TA, Pearson TA, Wenger NK, Barrett-Connor E, Payne GH, Harlan WR. Cholesterol and heart disease in older persons and women: review of an NHBLI workshop. *Ann Epidemiol.* 1992;2:161-176.
17. Zimetbaum P, Frishman WH, Ooi WL, et al. Plasma lipids and lipoproteins and the incidence of cardiovascular disease in the very elderly. *Arterioscler Thromb.* 1992;12:416-423.
18. Kronmal RA, Cain KC, Ye ZS, Omenn G. Total serum cholesterol levels and mortality risk as a function of age. *Arch Intern Med.* 1993;153:1065-1073.
19. Cornoni-Huntley J, Ostfeld AM, Taylor J, et al. Established populations for epidemiologic studies of the elderly: study design and methodology. *Aging Clin Exp Res.* 1993;5:27-37.
20. Hypertension Detection and Follow-up Program Cooperative Group. Blood pressure studies in 14 communities: a two-stage screen for hypertension. *JAMA.* 1977;237:2385-2391.
21. *International Classification of Diseases, Ninth Revision, Clinical Modification.* Washington, DC: Public Health Service, US Dept of Health and Human Services; 1988.
22. Ischemic Heart Disease Registers. *Report of the Fifth Working Group on Ischemic Heart Disease Registers.* Copenhagen, Denmark: World Health Organization; 1971.
23. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient, part 2: analysis and examples. *Br J Cancer.* 1977;35:1-39.
24. Seeman TS, Mendes de Leon CF, Berkman LF, Ostfeld AM. Risk factors for coronary heart disease among older men and women: a prospective study of community-dwelling elderly. *Am J Epidemiol.* 1993;138:1037-1049.
25. LaCroix AZ, Guralnick JM, Curb JO, Wallace RB, Ostfeld AM, Hennekens CH. Chest pain and coronary heart disease mortality among older men and women in three communities. *Circulation.* 1990;81:437-446.
26. Hulley SB, Walsh JM, Newman TB. Health policy on blood cholesterol. *Circulation.* 1992;86:1026-1029.
27. Freeman DH, Livingston MM, Leaf PJ, Berkman LF. Sampling strategies for studying older populations. In: Wallace R, Woolson R, eds. *The Epidemiologic Study of the Elderly.* New York, NY: Oxford University Press; 1992:46-59.
28. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Drug Project Trial results: reduction in the incidence of coronary heart disease. *JAMA.* 1984;251:351-364.
29. Sempos CT, Cleeman JI, Carroll MD, et al. Prevalence of high blood cholesterol among US adults. *JAMA.* 1993;269:3009-3014.
30. Aronow WS, Herzig AH, Etinenne F, D'Alba P, Ronquillo J. 41-month follow-up of risk factors correlated with new coronary events in 708 elderly patients. *J Am Geriatr Soc.* 1989;37:501-506.
31. Wong ND, Wilson PWF, Kannel WB. Serum cholesterol as a prognostic factor after myocardial infarction: the Framingham study. *Ann Intern Med.* 1991;115:687-693.