High-Density vs Low-Density Lipoprotein Cholesterol as the Risk Factor for Coronary Artery Disease and Stroke in Old Age

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Background: A high total serum cholesterol level does not carry a risk of cardiovascular mortality among people 85 years and older and is related to decreased all-cause mortality. At this old age, there are few data on fractionated lipoprotein levels in the determination of cardiovascular disease risk. The aim of this study was to evaluate the relationships between low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels and mortality from specific causes among people in the oldest age categories.

Methods: Between September 1, 1997, and September 1, 1999, a total of 705 inhabitants in the community of Leiden, the Netherlands, reached the age of 85 years. Among these old people, we initiated a prospective follow-up study to investigate determinants of successful aging. A total of 599 subjects participated (response rate, 87%) and all were followed up to September 2001. Serum levels of total, LDL, and HDL cholesterol were assessed at baseline along with detailed information on comorbid conditions. The main outcome measure was all-cause and specific mortality risk.

Results: During 4 years of follow-up, 152 subjects died. The leading cause of death was cardiovascular disease, with similar mortality risks in all tertiles of LDL cholesterol level. In contrast, low HDL cholesterol level was associated with a 2.0-fold higher risk of fatal cardiovascular disease (95% confidence interval [CI], 1.2-3.2). The mortality risk of coronary artery disease was 2.0 (95% CI, 1.0-3.9) and for stroke it was 2.6 (95% CI, 1.0-6.6). Both low LDL cholesterol and low HDL cholesterol concentrations were associated with an increased mortality risk of infection: 2.7 (95% CI, 1.2-6.2) and 2.4 (95% CI, 1.1-5.6), respectively. The risks were unaffected by comorbidity.

Conclusion: In contrast to high LDL cholesterol level, low HDL cholesterol level is a risk factor for mortality from coronary artery disease and stroke in old age.

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was subsequently confirmed by the Long-Term Intervention with Pravastatin in Ischemic Disease and the Cholesterol and Recurrent Events Trial.\textsuperscript{10,11} Unfortunately, there are few data on LDL and especially HDL cholesterol levels in relation to risk of coronary artery disease and stroke in old age. These data are of great clinical relevance because cardiovascular disease remains the leading cause of death among people in the oldest age categories. Therefore, we explored the relationships between LDL and HDL cholesterol levels and specific mortality in the oldest old within the second cohort of the Leiden 85-Plus Study.

METHODS

Between September 1, 1997, and September 1, 1999, a total of 705 inhabitants in the community of Leiden, the Netherlands, reached the age of 85 years (second cohort of the Leiden 85-Plus Study). Among these 85-year-old persons, we initiated a follow-up study to investigate determinants of successful aging.\textsuperscript{12} There were no selection criteria on health or demographic characteristics. Fourteen inhabitants died before they could be enrolled. The response rate was 87%; a total of 599 subjects (397 women and 202 men) participated. There were no significant differences in various demographic characteristics between the 599 respondents and the source population. The Medical Ethical Committee of the Leiden University Medical Center approved the study, and informed consent was obtained for all subjects.

At baseline, subjects were visited twice at their place of residence within 1 month after the subject's 85th birthday. Face-to-face interviews were administered (visit 1), blood samples were collected early in the morning, and an electrocardiogram was obtained (visit 2). The medical history of the subjects was obtained from their general practitioner (for subjects living independently) or from their nursing home physician (for subjects living in a nursing home [9%]). Information about drug use was obtained from computerized pharmacy registries. At baseline, subjects were classified as having cardiovascular disease when there was a history of myocardial infarction, angina pectoris, arterial surgery, stroke, or intermittent claudication, or when there were signs of myocardial infarction or myocardial ischemia recorded on the electrocardiogram that was obtained in all subjects. The Mimi-Mental State Examination was administered in all subjects.

For the analyses presented in this article, all subjects were followed up for mortality until September 1, 2001. The date of death was obtained from the civic registries reported the death of a subject, the general practitioner (for subjects living in the Netherlands), or from their nursing home physician (for subjects living in a nursing home [9%]). Information about drug use was obtained from computerized pharmacy registries. At baseline, subjects were classified as having cardiovascular disease when there was a history of myocardial infarction, angina pectoris, arterial surgery, stroke, or intermittent claudication, or when there were signs of myocardial infarction or myocardial ischemia recorded on the electrocardiogram that was obtained in all subjects. The Mimi-Mental State Examination was administered in all subjects.

For the analyses presented in this article, all subjects were followed up for mortality until September 1, 2001. The date of death was obtained from the civic registries. Shortly after the civic registries reported the death of a subject, the general practitioner or nursing home physician was interviewed to determine the cause of death by means of a standardized questionnaire. Two senior specialists of internal medicine (R.G.J.W. and Paul H. E. M. de Meijer, MD, PhD), unaware of the outcomes of the analyses, reviewed the causes of death and classified each death into primary and, if applicable, secondary causes of death according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).\textsuperscript{13} Disagreement between the 2 was solved by consensus. Cardiovascular disease, coronary artery disease, and stroke were classified as ICD-10 codes I00-I09, I20-I25, and I60-I69, respectively. Infection, pneumonia, sepsis, and cancer were classified as A00-B99 or J12-J18, J12-J18, A40-A41, and C00-D48, respectively. Suicide was not reported. A secondary cause of death was defined as a disease that also directly contributed to the death of the subject.

Lipoproteins were determined in blood samples obtained at the second baseline visit at age 85 years. Total cholesterol, triglyceride, and HDL cholesterol levels were analyzed on fully automated computerized analyzers (Hitachi 747 and 911; Hitachi, Ltd, Tokyo, Japan). The level of LDL cholesterol was estimated by the Friedewald equation (LDL cholesterol [millimoles per liter] = total cholesterol – HDL cholesterol – [triglycerides/2.2]), whereby subjects with a triglyceride concentration higher than 443 mg/dL (5.0 mmol/L) were excluded (n = 5). Subjects with a nonfasting serum glucose concentration greater than 200 mg/dL (11.1 mmol/L), a medical history of diabetes, or use of anti-diabetic drugs were classified as having diabetes mellitus. Thyroid dysfunction was defined as a thyrotropin concentration less than 0.3 mIU/L or greater than 4.8 mIU/L. Eighteen (3%) of the 561 subjects with available data reported alcohol consumption of more than 2 U/d, and 6 (1%) of the 561 subjects used lipid-lowering drugs. Exclusion of the subjects with high alcohol intake or use of lipid-lowering drugs did not change the results.

Continuous variables are expressed as medians and interquartile ranges (IQRs) and compared with nonparametric tests that do not assume an underlying distribution of the data. Concentrations of lipoproteins measured at baseline were divided in 3 equal strata representing low, intermediate, and high lipoprotein concentrations. This was done separately for women and men, since women have higher lipoprotein concentrations than men. The advantage of this stratification is that it intrinsically adjusts for sex. As all subjects were aged 85 years on entry into the study, adjustment for age was not required.

In most cases, primary and secondary causes of death were strongly entangled. Therefore, analyses of specific causes of death were based on the primary and the secondary cause of death. Restricting analyses to only primary causes of death did not influence the results. Survival time for subjects was defined as the period from the date of birth to either the date of death or September 1, 2001. Cumulative all-cause and specific mortality were calculated by means of the Kaplan-Meier method and compared with the log-rank test. Mortality risks and 95% confidence intervals (CIs) for the 3 strata of lipoproteins, with the highest tertile being the reference category, were estimated with a Cox proportional hazards model. Covariates were entered as continuous variables into the model. SPSS for Windows (release 10.0; SPSS Inc, Chicago, Ill) was used for data analysis.

RESULTS

Data on lipoproteins were available for 561 of the 599 subjects enrolled. In 38 subjects lipid and lipoprotein levels could not be determined; 7 subjects died before a blood sample could be obtained, 30 subjects refused to give a blood sample, and in 1 subject there was a technical failure. The median follow-up for the 561 subjects was 2.6 years (IQR, 2.1-3.2 years). Baseline characteristics of the subjects are shown in Table 1. During the 4-year follow-up period, 152 of the 561 subjects died. The leading cause of death among these subjects was cardiovascular disease (Table 2). Compared with the 705 subjects who were eligible for the study, the cumulative 4-year mortality risk of the 561 subjects was 0.9 (95% CI, 0.7-1.1; P = .33).

Table 3 presents risks of specific causes of death dependent on total serum cholesterol levels at baseline. The median total serum cholesterol concentration was 204 mg/dL (5.27 mmol/L) (IQR, 177-232 mg/dL [4.59-5.99 mmol/L]) for men and 227 mg/dL (5.86 mmol/L) (IQR, 201-256 mg/dL [5.21-6.63 mmol/L]) for women (P < .001). Subjects with a low total serum cholesterol level had a 1.6-fold increased mortality risk (95% CI, 1.1-
2.3) compared with those with a high total serum cholesterol level. This increased all-cause mortality risk with low total cholesterol level resulted from a 2.4-fold increased mortality risk of infection (95% CI, 1.1-5.2), whereas mortality risk of cardiovascular disease and cancer was not increased (Table 3).

Table 4 presents mortality risks according to fractionated cholesterol levels at baseline. The median serum LDL cholesterol concentration was 132 mg/dL (3.42 mmol/L) (IQR, 111-156 mg/dL [2.86-4.03 mmol/L]) for men and 145 mg/dL (3.74 mmol/L) (IQR, 119-172 mg/dL [3.08-4.45 mmol/L]) for women (P<.001). A low LDL cholesterol level was associated with a 1.4-fold higher all-cause mortality risk (95% CI, 1.0-2.1). Again, this was due to a 2.7-fold increased mortality risk of infection (95% CI, 1.2-6.2). Cardiovascular disease mortality, both coronary artery disease and stroke, were independent of LDL cholesterol levels (Table 4). To ascertain that the relationship between low LDL cholesterol levels and mortality from infection was not distorted by comorbidity, we entered serum albumin concentration, score on the Mini-Mental State Examination, and body mass index into the regression model as markers for biochemical, cognitive, and physical frailty, respectively. The adjusted mortality risk of the lowest LDL cholesterol category was 1.2 (95% CI, 0.8-1.8) for death from all causes and 2.1 (95% CI, 1.2-3.9) for infection mortality, respectively. Further adjustment for diabetes mellitus, body mass index, use of β-blocking agents, and thyroid dysfunction, which are all associated with low HDL cholesterol levels as well as increased mortality, did not alter the risk estimates (data not shown).

The median serum HDL cholesterol concentration was 43 mg/dL (1.10 mmol/L) (IQR, 36-52 mg/dL [0.92-1.34 mmol/L]) for men and 52 mg/dL (1.35 mmol/L) (IQR, 42-62 mg/dL [1.08-1.60 mmol/L]) for women (P<.001). A low HDL cholesterol level was associated with a 1.7-fold increased all-cause mortality risk (95% CI, 1.2-2.5), determined by a 2.0-fold increased mortality risk of cardiovascular disease (95% CI, 1.2-3.2) and a 2.4-fold increased mortality risk of infection (95% CI, 1.1-5.6) (Table 4, Figure). The increased cardiovascular disease mortality risk in the lowest HDL cholesterol category was present for both mortality from coronary artery disease (2.0; 95% CI, 1.0-3.9) and stroke (2.6; 95% CI, 1.0-6.6). This increased mortality risk of cardiovascular disease associated with low HDL cholesterol level was similar among men and women (1.6; 95% CI, 0.8-3.4; and 2.2; 95% CI, 1.1-4.4, respectively).

In a final analysis, to exclude that the association between HDL cholesterol level and mortality was distorted by frailty, we adjusted for levels of LDL cholesterol by means of multivariable regression. The reasoning is that subjects who have comorbidity that decreases serum HDL cholesterol levels and increases mortality risk, and can thus explain the associations found, are also identified by low levels of LDL cholesterol. This was not the case, as the adjusted mortality risks for subjects with low compared with high HDL cholesterol levels were unaffected, ie, 1.8 (95% CI, 1.2-2.6) for all-cause mortality, 2.0 (95% CI, 1.2-3.3) for cardiovascular mortality, 2.0 (95% CI, 1.0-3.9) for coronary artery disease mortality, 2.6 (95% CI, 1.0-6.9) for fatal stroke, and 2.6 (95% CI, 1.1-5.9) for infection mortality, respectively. Further adjustment for diabetes mellitus, body mass index, use of β-blocking agents, and thyroid dysfunction, which are all associated with low HDL cholesterol levels as well as increased mortality, did not alter the risk estimates (data not shown).

The results of the present study show that, in elderly people aged 85 years, HDL cholesterol, but not total or LDL cholesterol, is associated with mortality from coronary artery disease and stroke. Subjects with low HDL cholesterol level were at increased risk of all-cause, cardiovascular, and infection mortality.
cholesterol levels carry a 2- to 3-fold increased mortality risk of coronary artery disease and stroke. Furthermore, LDL and HDL cholesterol concentrations are inversely correlated with all-cause mortality mainly because of lower mortality from infection.

Among the oldest old, cardiovascular disease is, as in middle-aged people, the leading cause of death. However, in contrast to observations in middle-aged people, our present and previous studies show that total serum cholesterol is not a risk factor for fatal cardiovascular disease in old age.2 It has been argued that the 2 main cholesterol lipoprotein fractions, ie, LDL and HDL cholesterol, have opposite effects on cardiovascular disease risk and account for this finding.14 This reasoning appears to be only partly true, as we show here that fatal cardiovascular disease is independent of LDL cholesterol levels.

In contrast, it has been suggested that, at age greater than 80 years, HDL cholesterol is the most important lipid component that determines mortality risk.13 The EPESE (Established Populations for Epidemiological Studies of the Elderly) investigators presented the first line of evidence that HDL cholesterol is relevant in cardiovascular mortality. They demonstrated that, in persons older than 70 years, HDL cholesterol level had a strong inverse relationship with coronary heart disease mortality, and that this risk persisted among men and women older than 80 years.16 The present prospective follow-up study confirms the relationship between low serum HDL cholesterol level and mortality from coronary heart disease in old age and extends this relationship to fatal stroke.

Stroke is a disabling disorder, more than 80% of the strokes in patients older than 65 years being of ischemic

Table 3. All-Cause and Specific Mortality Risks According to Strata of Serum Total Cholesterol*<sup>a</sup>

<table>
<thead>
<tr>
<th>Mortality Risk</th>
<th>Strata of Total Cholesterol, mg/dL</th>
<th></th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low 179 (163-195) (n = 187)</td>
<td>Intermediate 222 (208-231) (n = 187)</td>
<td>High 263 (248-280) (n = 187)</td>
</tr>
<tr>
<td>All cause</td>
<td>1.6 (1.1-2.3)</td>
<td>0.8 (0.5-1.3)</td>
<td>1.01</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1.3 (0.8-2.2)</td>
<td>0.8 (0.5-1.4)</td>
<td>.28</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.2 (0.6-2.2)</td>
<td>0.8 (0.4-1.6)</td>
<td>.64</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.4 (0.6-3.4)</td>
<td>0.9 (0.3-2.3)</td>
<td>.44</td>
</tr>
<tr>
<td>Infection</td>
<td>2.4 (1.1-5.2)</td>
<td>1.1 (0.4-2.7)</td>
<td>.03</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.0 (0.4-2.4)</td>
<td>0.6 (0.2-1.6)</td>
<td>.90</td>
</tr>
</tbody>
</table>

*SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

Mortality risks (95% confidence intervals) were obtained from a Cox regression model. Total cholesterol levels were divided into 3 equal strata for women and men separately and are expressed as median (interquartile range).

Table 4. All-Cause and Specific Mortality Risks According to Strata of Fractionated Cholesterol*<sup>b</sup>

<table>
<thead>
<tr>
<th>Mortality Risk</th>
<th>Strata of LDL Cholesterol, mg/dL</th>
<th></th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low 106 (94-116) (n = 185)</td>
<td>Intermediate 141 (132-148) (n = 186)</td>
<td>High 177 (165-196) (n = 185)</td>
</tr>
<tr>
<td>All cause</td>
<td>1.4 (1.0-2.1)</td>
<td>0.8 (0.5-1.2)</td>
<td>1.05</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1.2 (0.8-2.1)</td>
<td>0.7 (0.4-1.3)</td>
<td>.38</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.1 (0.6-2.1)</td>
<td>0.7 (0.3-1.3)</td>
<td>.74</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.3 (0.5-3.2)</td>
<td>1.0 (0.4-2.5)</td>
<td>.56</td>
</tr>
<tr>
<td>Infection</td>
<td>2.7 (1.2-6.2)</td>
<td>1.3 (0.5-3.3)</td>
<td>.01</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.0 (0.4-2.4)</td>
<td>0.6 (0.2-1.6)</td>
<td>.92</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mortality Risk</th>
<th>Strata of HDL Cholesterol, mg/dL</th>
<th></th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low 36 (32-40) (n = 188)</td>
<td>Intermediate 49 (46-54) (n = 185)</td>
<td>High 64 (60-73) (n = 188)</td>
</tr>
<tr>
<td>All Cause</td>
<td>1.7 (1.2-2.5)</td>
<td>1.3 (0.7-1.6)</td>
<td>1.01</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2.0 (1.2-3.2)</td>
<td>1.0 (0.6-1.8)</td>
<td>1.01</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.0 (1.0-3.9)</td>
<td>1.2 (0.6-2.5)</td>
<td>.04</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.6 (1.0-6.6)</td>
<td>1.4 (0.5-4.0)</td>
<td>.05</td>
</tr>
<tr>
<td>Infection</td>
<td>2.4 (1.1-5.6)</td>
<td>1.6 (0.6-3.8)</td>
<td>.03</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.7 (0.3-2.0)</td>
<td>0.8 (0.2-2.1)</td>
<td>.54</td>
</tr>
</tbody>
</table>

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

Mortality risks (95% confidence intervals) were obtained from a Cox regression model. The LDL and HDL cholesterol levels were divided into 3 equal strata for women and men separately and are expressed as median (interquartile range).
The observed relationship in the present follow-up study between low HDL cholesterol level and stroke at old age is in line with the observed inverse relationship between HDL cholesterol levels and ischemic stroke mortality in middle-aged Israeli men.18 Confirmatory data were presented in the Tromso Study, a cross-sectional study among middle-aged persons, in which low levels of HDL cholesterol were associated with echolucent carotid artery plaques, a major risk factor for stroke.19

Experimental studies with pravastatin sodium and gemfibrozil in middle-aged men showed a reduction in stroke risk concurrent with an increase in HDL cholesterol level.8-11,20 At present, data on the effectiveness of HDL-increasing therapy on stroke risk in the elderly are lacking. This is of importance, as stroke is a very heterogeneous disorder and the determinants at the various age categories are markedly different. Data on efficacy of treatment at a relatively young age therefore cannot be extrapolated to (very) old age. Since stroke is the most prevalent and disabling disorder in the oldest old, a trial among persons of this age category is eagerly awaited.

The present study shows that low total, LDL, and HDL cholesterol levels are all associated with an increased mortality risk, questioning the necessity of cholesterol-lowering therapy in the elderly. This adverse effect of low total and low fractionated cholesterol levels appeared to be related to increased mortality from infectious disease and confirms our finding from an earlier cohort of the Leiden 85-Plus Study that was enrolled more than a decade before. This inverse relationship has also been reported in critical care patients, i.e., patients with low serum lipid and lipoprotein levels had higher risk of nosocomial infections. Animal studies have shown that reconstituted HDL cholesterol can bind bacterial lipopolysaccharide, a causative substance of gram-negative septic shock, and may therefore be beneficial when gram-negative bacteria are present in the circulation.22,23

Total and fractionated cholesterol levels were assessed in standardized morning blood samples that were not drawn with subjects fasting, although they sometimes may have been. It is, however, unlikely that this distorted the results presented in this article, as cholesterol levels are little affected by nonfasting sampling conditions, and as triglyceride levels were shown to be rather low.

We adjusted the relationship between fractionated cholesterol levels for frailty in 3 multivariable models. First, we adjusted for markers of biochemical, cognitive, and physical frailty and observed that the mortality risk estimate of infection for the lowest LDL cholesterol category remained the same. Second, the increased mortality risk related to low serum levels of HDL cholesterol was unaffected after adjustment for serum levels of LDL cholesterol. Third, adjustment for diabetes mellitus, body mass index, use of β-blocking agents, and thyroid dysfunction did not alter the mortality risk.

The present study shows that people aged 85 years with high total or fractionated cholesterol levels have lower risk of mortality, because of their protective effects against death from infectious disease. In addition, low HDL cholesterol level, but not high LDL or high total cholesterol level, is a risk factor for fatal coronary artery disease and stroke. Present strategies in cholesterol intervention are based on lowering LDL cholesterol level in both middle and old age. Although the present observations do not infer causality, it may be argued that increasing HDL cholesterol levels is more advantageous than lowering total cholesterol levels among old people. However, prospective studies in the elderly with HDL-increasing interventions should provide evidence for such a strategy.

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