Cholesterol Fractions and Apolipoproteins as Risk Factors for Heart Disease Mortality in Older Men

Robert Clarke, FRCP; Jonathan R. Emberson, PhD; Sarah Parish, DPhil; Alison Palmer, MSc†; Martin Shipley, MSc; Pamela Linksted, MSc; Paul Sherliker, BSc; Sarah Clark, DPhil; Jane Armitage, FRCP, FFPHM; Astrid Fletcher, PhD; Rory Collins, FRCP

Background: The relevance of blood lipid levels as risk factors for ischemic heart disease (IHD) in older people is uncertain; hence, cholesterol-lowering therapy is not routinely prescribed in older populations.

Methods: We assessed IHD mortality associations with plasma levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein B, and apolipoprotein A1 measured in older men. Ischemic heart disease was assessed in a 7-year follow-up of a cohort of 5344 men (mean age, 76.9 years), including 74.3% without cardiovascular disease (CVD) or statin use and 25.6% with CVD or statin use. Hazard ratios (HRs) for 447 deaths from IHD were estimated for a 2-SD difference in usual plasma lipid levels.

Results: Ischemic heart disease mortality was not significantly associated with total cholesterol levels in all men (HR, 1.05), but a significant positive association in men without CVD and a slight nonsignificant inverse association in men with CVD were observed (HR, 1.47 vs 0.84). The patterns were similar for low-density lipoprotein cholesterol levels (HR, 1.50 vs 0.98) and for apolipoprotein B levels (HR, 1.68 vs 0.93). Ischemic heart disease risks were inversely associated with high-density lipoprotein cholesterol levels and with apolipoprotein A1 levels in men with and without CVD. Ischemic heart disease risks were strongly associated with total–high-density lipoprotein cholesterol levels (HR, 1.37) and apolipoprotein B–apolipoprotein A1 levels (HR, 1.54), and remained strongly related at all ages.

Conclusions: Blood lipid levels other than total cholesterol levels were associated with IHD in older men. Differences in lipid levels that are achievable by statin use were associated with about a one-third lower risk of IHD, irrespective of age.

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Although the associations of ischemic heart disease (IHD) with blood lipid concentrations are strong and graded when measured in middle-aged individuals, there is considerable uncertainty about such associations when measured in old age. Some prospective observational studies have reported positive associations of IHD and all-cause mortality with total cholesterol levels measured in old age, whereas other studies have reported no associations or inverse associations. The discrepant findings of such studies may relate to differences between studies in the age at measurement of cholesterol levels, the duration of follow-up, or the inclusion of individuals with a prior diagnosis of cardiovascular disease (CVD). Total cholesterol is predominantly composed of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), which are positive and negative risk factors for IHD, respectively, as are the surface proteins on LDL-C and HDL-C, apolipoprotein B (Apo B) and apolipoprotein A1 (Apo A1), respectively. Plasma levels of LDL-C and HDL-C tend to decrease longitudinally with age and disease and, hence, in older people. Observational studies have reported that circulating levels of apolipoproteins are better predictors of IHD than total cholesterol levels in middle-aged individuals, but there are no data on their comparative relevance in older people, to our knowledge. The aims of this study were (1) to compare the strength and shape of associations of IHD mortality in relation to total cholesterol, cholesterol fractions, and apolipoproteins in a cohort study of older men and, separately, in men with and without prior CVD at the start of the follow-up period and (2) to assess the extent to which IHD mortality associations with blood lipid levels vary with increasing age in this older population overall and in men with and without prior CVD.
STUDY POPULATION

Nineteen thousand nineteen male civil servants working in London aged 40 to 69 years were recruited between 1967 and 1970 into the Whitehall Study,\textsuperscript{16,17} details of which have been previously reported. Following the success of a pilot study of the feasibility of recontacting surviving participants in 1995, all 8448 surviving participants were sought for resurvey in 1997-1998.\textsuperscript{18} A postal questionnaire asked about smoking status, medications taken in the last month, last known civil service employment grade, and diagnoses of prior heart attack, angina, or stroke.\textsuperscript{19} The 7044 participants (83.4%) who responded to the resurvey were subsequently sent a blood collection kit and were asked to attend their local clinic to have a blood sample collected and measurements taken of height, weight, and blood pressure. Nonfasting blood samples were obtained from 5434 men (77.1% of respondents), from which blood lipid levels were successfully measured for 5355 men (98.3%). Medical history, medication use, smoking status, and mortality follow-up status were recorded for 5344 (99.8%) of these men. The nonrespondents were older and had a lower previous employment grade, but response rates were not associated with total cholesterol levels recorded from 1967 to 1970.\textsuperscript{19} Among 5344 men with complete data, 1337 (25.0%) reported a prior diagnosis of heart attack, angina, or stroke; 93 reported taking statins. Thirty-two of those without prior CVD also reported taking statins and were included in the group with prior CVD (to minimize the risk of reverse causality). Therefore, the chief comparisons involve the 3975 men (74.4%) without prior CVD or statin use vs the 1369 men (25.6%) with prior CVD or statin use. The repeatability of a self-reported history of prior CVD after an interval of 2 years was high, with k scores of 0.91 for angina and 0.78 for heart attack. The resurvey was approved by the ethics committees of the participating institutions.

LABORATORY ANALYSIS

Blood was collected into a 10-mL vacuum-sealed tube (Vacutainer; Becton Dickinson, Franklin Lakes, NJ) containing potassium EDTA with 0.34 mmol/L of aprotinin and was mailed at room temperature to the laboratory in Oxford, United Kingdom. The mean time in the mail was 1.3 days (range, 0-7 days), with 78% arriving within 24 hours and 96% arriving within 48 hours of collection. On arrival in the laboratory, the blood was centrifuged, and the plasma was aliquoted for storage at −40°C. All lipid analyses were performed on autoanalyzers (Beckman Synchrotron CX4 and CX3; Beckman Coulter UK Limited, High Wycombe, England), which were programmed to subtract a sample blank absorbance reading from the final reaction absorbance to correct for any interference from hemolysis, which can rarely arise when samples are transported for a prolonged period.\textsuperscript{20-21} Apolipoprotein A1 and Apo B levels were measured by immunoturbidimetric assays (Immuno Reagents, Vienna, Austria). HDL-C and LDL-C levels were measured directly (N-Genic reagents; Bio-Stat Limited, Stockport, England), and total cholesterol level was measured enzymatically (reagent, Beckman Coulter UK Limited). The intra-assay coefficients of variation, based on successive assays of laboratory control material, were 4% for Apo A1 and Apo B, 5% for HDL-C and LDL-C, and 2% for total cholesterol. Previous studies\textsuperscript{22,23} indicated that minor changes in blood lipid levels arose due to delayed separation of mailed blood samples; therefore, wherever possible (>99% of samples), lipid level analyses were adjusted for duration of time spent in the mail before separation of plasma and for date of assay to avoid assay drift.

MORTALITY FOLLOW-UP

Participants were flagged for mortality at the Office for National Statistics, which provided the date and cause (including codes for the International Classification of Diseases [ICD], Ninth and Tenth Revisions) of all deaths occurring until the end of September 2005. The mean follow-up period was 6.8 years (maximum, 8.4 years). Cause-specific mortality was coded using ICD-9 up to August 2002 and ICD-10 subsequently. Ischemic heart disease deaths were predefined as those allocated ICD-9 codes 410 to 414 and ICD-10 codes I20 to I25 as the underlying cause of death.

STATISTICAL ANALYSIS

Hazard Ratios and Floating Absolute Risks

Age- and smoking-adjusted hazard ratios (HRs) of IHD mortality associated with blood lipid levels were estimated using Cox proportional hazards regression models. Hazard ratios and 95% confidence intervals (CIs) were estimated for each third of the lipid distributions and were presented as “floating absolute risks” (which allows CIs to be compared between all exposure categories rather than comparing exposure groups with some arbitrarily chosen reference category with no CI\textsuperscript{26}). Subsequently, HRs associated with 2-SD differences in measured levels were estimated. A 2-SD difference in lipid levels is approximately equivalent to the mean difference between the top and bottom thirds of a normal distribution and for LDL-C levels (51.4 mg/dL [to convert to millimoles per liter, multiply by 0.0259]) is approximately equivalent to the changes that can be achieved with statin therapy.\textsuperscript{27} Estimates of the SD were derived from all men and were also adjusted for age and smoking status (for consistency with the main age- and smoking-adjusted analyses). Tests for linearity were performed by assessing the statistical significance of quadratic lipid terms, while the proportional hazards assumption was assessed by including interactions between the lipid level and logarithm of follow-up time.

Correction for Regression Dilution Bias

The combined effects of measurement error and within-person variability mean that the standard analyses of associations of single measurements of baseline levels with risk can lead to substantial underestimation of the importance of blood lipid levels to risk.\textsuperscript{26} Therefore, HRs were corrected for this “regression dilution bias” by dividing the logarithm of HR associated with baseline levels (and its standard error) by the correlation coefficient (r) of the lipid values measured in individuals at different times. The correlation coefficients between successive lipid values were obtained from samples collected on 2 occasions at an interval of 2 to 3 years from 1042 participants in a separate study,\textsuperscript{28} which used identical methods for blood collection and lipid analysis in the same laboratory during the same period (a previous study\textsuperscript{29} showed that such correlation coefficients are independent of age and sex). Associations between the usual levels of lipids (Apo A1, Apo B, total cholesterol, total cholesterol/HDL-C ratio, and Apo B/Apo A1 ratio) and IHD mortality risk were estimated separately among men younger than 75 years, 75 to 79 years, and 80 years or older at resurvey. Tests for linear trend in the lipid effects by age were performed by including interaction terms between age group and lipid level in the Cox proportional hazards regression model.


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Characteristics of Study Participants

Table 1 gives selected characteristics of all men in the study and of those without prior CVD (74.4%) and with prior CVD (25.6%). Among 1369 men with prior CVD, 125 (9.1%) reported statin use (93 with and 32 without reported CVD). The mean ± SD age at resurvey was 76.9 ± 4.9 years and was higher among men with prior CVD (77.6 years) than among those without prior CVD (76.6 years). Previous myocardial infarction was reported by 11.3% of all men, stroke by 7.2%, angina by 14.2%, and cancer by 7.8%. The differences in the mean levels of lipids between men with and without prior CVD were statistically significant (except for Apo B levels), although clinically small. Overall, Apo B levels were strongly and positively correlated with LDL-C levels (r = 0.73, P < .001), and Apo A1 levels were strongly and positively correlated with HDL-C levels (r = 0.84, P < .001). Apo B levels were inversely correlated with Apo A1 levels (r = −0.11, P < .001), and LDL-C levels were inversely correlated with HDL-C levels (r = −0.09, P < .001). Although ApoA1 levels were only weakly correlated with LDL-C levels (r = 0.03, P = .021), Apo B levels displayed a strong inverse correlation with HDL-C levels (r = −0.41, P < .001).

Association Between Different Lipid Levels and IHD Mortality

Among 5344 men, 447 (8.4%) were certified as having died of IHD within the following 7 years (rate, 12.3 per 1000 person-years). Death from IHD was recorded in 215 (5.4%) of 3975 men without prior CVD or statin use (7.7 per 1000 person-years) and in 232 (16.9%) of 1369 men with prior CVD (27.8 per 1000 person-years). The overall mortality rate was also higher in men with prior CVD compared with those without prior CVD (84.3 vs 44.3 per 1000 person-years). Table 2 gives the mean ± SD values for each of the different lipid measurements in the overall population, as well as the age- and smoking-adjusted HRs associated with 2-SD differences in usual levels of each lipid in all men and in men with and without prior CVD. Figure 1 shows these associations graphically by thirds of the lipid distributions.

The apparent lack of an association of IHD mortality with total cholesterol levels in all men (HR, 1.05; 95% CI, 0.85-1.30) masked a positive association in men without prior CVD and a nonsignificant inverse association in men with CVD (HR, 1.47 vs 0.84; P = .01 for heterogeneity) (Table 2). There were also strong positive associations of IHD mortality in men without prior CVD but not in those with prior CVD for LDL-C levels (HR, 1.50 vs 0.98; P = .06) and for Apo B levels (HR, 1.68 vs 0.93; P = .01). In contrast, IHD mortality was inversely associated with HDL-C levels (HR, 0.60; 95% CI, 0.48-0.75) and with Apo A1 levels (HR, 0.61; 95% CI, 0.48-0.78) in all men, and these associations were similar in men with vs without CVD for HDL-C levels (HR, 0.69 vs 0.74; P = .71) and for Apo A1 (HR, 0.62 vs 0.87; P = .16).

The ratios of total cholesterol:HDLC or Apo B:Apo A1 combined the opposing positive effects on IHD risk of increasing levels of total cholesterol or Apo B with the inverse effects on IHD risk of increasing levels of HDL-C or Apo A1. These ratios were strong predictors of IHD mortality in all men, with HRs of IHD of 1.57 (95% CI, 1.32-1.86) for total cholesterol:HDLC and 1.54 (95% CI, 1.27-1.87) for Apo B:Apo A1. These 2 lipid ratios were the strongest lipid predictors of IHD risk in men without CVD, as reflected by the most extreme HRs in Figure 1B and the numerical results in Table 2. Although not apparent from the data in Figure 1, the strength of the association of usual levels of HDL-C or Apo A1 with IHD mortality risk in all men was marginally attenuated as the lipid level increased (P < .01 for tests of quadratic components in continuous analyses). However, this was not the
Table 2. Predictive Strengths of Different Lipid Level Indexes for Ischemic Heart Disease Mortality

<table>
<thead>
<tr>
<th>Lipid Level Index</th>
<th>All Men, Mean</th>
<th>Measured SD</th>
<th>Correlation Coefficient at 2 y</th>
<th>2 × Usual SD</th>
<th>Hazard Ratio (95% Confidence Interval) per 2-SD Higher Usual Level in All Cases</th>
<th>P Value for Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>213.0</td>
<td>38.0</td>
<td>0.76</td>
<td>1.70</td>
<td>1.05 (0.85-1.30) 1.47 (1.08-1.98) 0.84 (0.63-1.13)</td>
<td>0.01</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>130.0</td>
<td>30.0</td>
<td>0.73</td>
<td>1.33</td>
<td>1.19 (0.96-1.47) 1.50 (1.10-2.03) 0.98 (0.73-1.31)</td>
<td>0.06</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>42.0</td>
<td>15.0</td>
<td>0.79</td>
<td>0.67</td>
<td>0.60 (0.48-0.75) 0.74 (0.54-1.01) 0.69 (0.50-0.95)</td>
<td>0.71</td>
</tr>
<tr>
<td>Total/HDL cholesterol ratio</td>
<td>5.69</td>
<td>2.54</td>
<td>0.73</td>
<td>4.34</td>
<td>1.57 (1.32-1.86) 1.71 (1.31-2.23) 1.21 (0.94-1.54)</td>
<td>0.08</td>
</tr>
<tr>
<td>Apo B, mg/dL</td>
<td>87.0</td>
<td>23.0</td>
<td>0.74</td>
<td>0.39</td>
<td>1.34 (1.08-1.65) 1.68 (1.26-2.26) 0.93 (0.68-1.26)</td>
<td>0.01</td>
</tr>
<tr>
<td>Apo A1, mg/dL</td>
<td>95.0</td>
<td>14.0</td>
<td>0.68</td>
<td>0.24</td>
<td>0.61 (0.48-0.78) 0.87 (0.62-1.21) 0.62 (0.44-0.88)</td>
<td>0.16</td>
</tr>
<tr>
<td>Apo B/Apo A1 ratio</td>
<td>0.93</td>
<td>0.29</td>
<td>0.82</td>
<td>0.52</td>
<td>1.54 (1.27-1.87) 1.70 (1.29-2.24) 1.11 (0.84-1.47)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Abbreviations: Apo, apolipoprotein; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

*In all men and adjusted for age and smoking (for consistency with the estimates of the hazard ratios).

†Adjusted for age and smoking and corrected for regression dilution bias. The corrected logarithm of the hazard ratio \( r \) (corresponding to a 2-SD difference in usual levels) is obtained from the uncorrected logarithm of the hazard ratio \( \beta^* \) (corresponding to a 2-SD difference in measured levels) through the equation \( r = (\beta^*/r) \). Multiplication by \( r \) is needed because the usual SD equals \( r \) times the measured SD.

‡The hazard ratios in all men need not necessarily lie between the estimates among men with and without prior CVD because they are not adjusted for prior CVD.

Figure 1. Associations of ischemic heart disease mortality vs usual plasma lipid measurements in all men (A) and in subsets with and without prior cardiovascular disease (CVD) (B). Estimates are adjusted for age and smoking. The “prior CVD” group includes 32 men without prior CVD but who are taking statins. The same distance on each horizontal axis denotes the same proportional difference in lipid measurement. The area of each plotting symbol is proportional to the amount of statistical information (i.e., it is inversely proportional to the variance of the logarithm of absolute risk), and the fitted lines through the points show the inverse variance–weighted linear fits. The relative risk differences associated with 2-SD differences in usual levels of each lipid measure are given in Table 2. Similarly, adjustment for other CVD risk factors had little material effect on IHD risk estimates (data not shown). Exclusion of 125 men who were taking statins at baseline also had little effect on the IHD risk estimates associated with any of the blood lipid levels among the remaining individuals with CVD (data not shown). Hazard ratios in all men did not vary during the follow-up period for any of the blood lipid measurements \((P > .10\) for all tests of proportionality).
ASSOCIATIONS WITH IHD MORTALITY WITH INCREASING AGE

**Figure 2** shows the age-specific strength of the associations in all men, after adjustment for age (within each age group) and smoking, with 2 SD differences in usual levels of total cholesterol, Apo B, Apo A1, total cholesterol: HDL-C ratio, and Apo B/Apo A1 ratio. There was no apparent attenuation in the strength of these associations with increasing age: for example, a 2 SD higher usual level of the Apo B/Apo A1 ratio was associated with an HR of 1.58 (95% CI, 1.09-2.28) at younger than 75 years, 1.47 (95% CI, 1.06-2.04) at 75 to 79 years, and 1.57 (95% CI, 1.14-2.16) at 80 years or older. Further adjustment for other CVD risk factors did not materially alter these associations (data not shown).

**COMMENT**

In this prospective study of 5344 older men, there was no significant association of IHD mortality with total cholesterol levels in all men. However, this apparent lack of an association masked a positive association of IHD risk with total cholesterol levels in men without prior CVD (or statin use) and a nonsignificant inverse association in men with prior CVD (or statin use). A similar pattern was observed for LDL-C and for Apo B levels, with strong positive associations in those without CVD and nonsignificant inverse associations among those with CVD. In contrast, IHD mortality was inversely associated with HDL-C levels and with Apo A1 levels, irrespective of the presence or absence of CVD. The absence of associations of IHD mortality with LDL-C, Apo B, and total cholesterol levels in men with prior CVD may reflect “reverse causality bias” (from high-risk individuals being treated, resulting in a low LDL-C level and a lower risk, but not as low as those who always had a low LDL-C level), because LDL-lowering therapy has been shown to be strongly protective of IHD mortality in older people. It is possible that changes in diet or drug use after the onset of CVD may have different effects on LDL-C levels than on HDL-C levels. Alternatively, perhaps some cytokine-mediated reduction in hepatic synthesis or secretion of lipoproteins may account for the age-related changes in the proportions with low levels of LDL-C and HDL-C in older populations.

Although total cholesterol level is the most widely used blood test for prediction of IHD risk in the overall population, this study demonstrated that it had the least extreme HR for IHD mortality when used alone. In contrast, the ratios of total cholesterol/HDL-C or Apo B/Apo A1 were strong predictors of IHD mortality in all men, irrespective of the age at which plasma lipid levels were measured.

The IHD risk associations observed in this study may not be generalizable to other populations (or to women), not least because trends in the uptake of treatments may vary between populations and within populations over time. However, similar results have been observed in postmenopausal women living in the United States, where the total cholesterol/HDL-C ratio was identified as the strongest overall predictor of IHD risk. When all men were considered together in the present study, there was no significant attenuation in the strength of the association of IHD mortality with increasing age for any of the lipid markers considered (Figure 2). Further studies involving a larger number of IHD cases are required to provide greater precision about the variation in IHD risk estimates associated with lipid levels in people older than 80 years. While there may have been errors in the classification of causes of death in this study, any such errors would be likely to result in conservative estimates of HRs.

There is considerable uncertainty about the importance of blood lipid levels for prediction of IHD risk in older people, and cholesterol-lowering therapy is not routinely prescribed in older populations. In the present study, only 2% of all participants (8% of those with prior CVD) were taking statins at the time of the survey in 1997. A more recent survey of older people in the United Kingdom reported that 13% of those without prior CVD and 38% with prior CVD were taking statins. A Canadian survey of 77 000 older people with CVD reported that only 19% were prescribed statins. Findings from the present study suggest that differences in LDL-C levels that are achievable by statin therapy may be associated with reductions in IHD risk in this older population (although this will clearly depend on the extent that risk is reversible in this older population). A meta-analysis of the randomized trials of statin therapy indicated that lowering LDL-C levels by about 38.6 mg/dl during 5 years reduced the risk of major vascular events by about 20% in people 75 years or older (relative risk, 0.82; 95% CI, 0.72-0.93; P <.001), and the differences in vascular risk...
were directly proportional to the difference in lipid levels achieved by drug therapy. Moreover, because the ratios of total cholesterol/HDL-C and Apo B/Apo A1 were directly proportional to the difference in lipid levels, benefits than those achieved by solely lowering Apo B levels.

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Correspondence: Robert Clarke, FRCP, Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, England (robert.clarke@cts.uox.ac.uk).

Author Contributions: Study concept and design: Clarke, Fletcher, and Collins. Acquisition of data: Clarke, Linksted, Sherliker, and Clark. Analysis and interpretation of data: Clarke, Emberson, Parish, Palmer, Shipley, Armitage, and Collins. Drafting of the manuscript: Clarke, Parish, and Shipley. Critical revision of the manuscript for important intellectual content: Emberson, Parish, Shipley, Sherliker, Clark, Armitage, Fletcher, and Collins. Statistical analysis: Clarke, Emberson, Parish, Shipley, and Collins. Obtained funding: Clarke, Fletcher, and Collins. Administrative, technical, and material support: Clarke, Parish, Linksted, Sherliker and Clark. Study supervision: Clarke, Parish, and Collins.

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REFERENCES


**Correction**

**Errors in Notations and Values.** In the article titled “Cholesterol Fractions and Apolipoproteins as Risk Factors for Heart Disease Mortality in Older Men” by Clarke et al, published in the July 9th issue of the Archives (2007; 167[13]:1373-1378), several errors were reported. On page 1373, “Results” section of the structured abstract, right-hand column, lines 9 and 10 the hyphen between “total” and “high-density lipoprotein cholesterol levels” and the en-dash between “apolipoprotein B” and “apolipoprotein A1” should have been virgules. In Table 1, page 1373, “Prior CVD*” column, last entry for “Apo B/Apo A1 ratio”, should have been 0.97±0.30. In Table 2, page 1376, all of the entries for the “2×Usual SD” column should have read from top to bottom as follows: 66, 51, 26, 4.34, 39, 24, and 0.52. On page 1337, Figure 2, a typographical error occurred in the notation for Apo A1 in the “Blood Lipid/Age of Baseline” column.