Cholesterol and Coronary Heart Disease Mortality

A 23-year Follow-up Study of 9902 Men in Israel

Uri Goldbourt and Shlomit Yaari

A 23-year follow-up study of 10,059 40- to 65-year-old participants in the Israeli Ischemic Heart Disease Study found that of 3473 deaths (34.5%), in 1098 (10.9%) coronary heart disease (CHD) was the underlying cause. Total serum cholesterol (TC) was measured in 9902 individuals. During the study, CHD mortality was elevated primarily in individuals in quintiles 4 and 5 (TC levels ≥217 mg/dl). Although CHD mortality increased marginally with increasing TC at levels below 217 mg/dl, this was entirely explained by age and other correlated risk factors in a multivariate adjustment of the survival curves. The "net" 23-year survival in terms of CHD was 87% in quintile 5 (TC ≥241) versus 93% in quintile 1 (TC <176 mg/dl). CHD mortality was inversely related to the percent of cholesterol in high density lipoprotein (PHDL). All cause mortality increased only when TC was above 240 mg/dl and in the subjects with PHDL levels in the lowest 20%. Lipids appeared to be somewhat less effective in predicting subsequent CHD mortality than did hypertension and smoking and were clearly secondary in assessing risk of all-cause death. The results raise the question whether intensive treatment for hypercholesterolemia is indicated for men at "borderline" levels. We conclude that the association between serum cholesterol and long-term mortality partly reflects the role that levels of co-existing CHD risk factors play in prognosis. At the "borderline-high" cholesterol range, where preventive studies of clinically manifested end points have not been conducted and survival is only marginally jeopardized, the identification and management of nonlipid CHD factors may constitute a primary preventive approach among men in populations with temporal patterns and risk factor-mortality associations similar to the ones in our cohort.

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On the basis of considerable epidemiologic research1–4 and two recent intervention trials,5,6 it has been established that an increased serum level of cholesterol (specifically, low density lipoprotein [LDL] cholesterol) is an etiological risk factor for the incidence of coronary heart disease (CHD) and that pharmacological reduction of LDL cholesterol levels in men with overt hypercholesterolemia5 and possibly a dietary modification in very high risk individuals6 will reduce that incidence. These results have encouraged a number of national or multinational committees and institutions8,9,10 to endorse a policy of aggressive therapy, beginning with dietary intervention, but if this first therapy fails, pursuing pharmacological interventions10 for cholesterol levels that have been hitherto considered too low for drug therapy.

The wisdom of applying drug therapy to "average-high risk" persons (those with LDL cholesterol levels between 130 and 160 mg/dl plus two other risk factors), as advocated by the U.S. National Cholesterol Education Program (NCEP),11 to elderly individuals with elevated cholesterol, or to middle-aged persons with no obvious risk as deduced from family history or risk factors other than high cholesterol has been questioned,12,13,14 and the risks of prolonged drug therapy have been pointed out.15,16 In fact, even dietary management of hyperlipidemia in children17 and in women with moderate cholesterol elevations has been questioned.

The crucial data for establishing the best public health policy in the realm of blood cholesterol is the nature of the long-term association between cholesterol levels and subsequently developing CHD. In the Israeli Ischemic Heart Disease Study (IIHDS), we have studied the association of total serum cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) levels by an evaluation in 1963, measurement of subsequent 5-year incidence of myocardial infarction (MI) and angina pectoris (AP),18 performance of the 23-year follow-up was supported by the Basic Research Foundation, the Israel Academy of Sciences and Humanities, Jerusalem, Israel.

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Methods
This report utilizes the information collected in the IIHD. The IIHD was a prospective study conducted on 10,059 men, who were tenured civil servants and municipal employees and were 40 years old or older in 1963. Concentrations of serum cholesterol were available for 9,902 examinees, while HDL cholesterol measurements were collected for only 6,562 examinees.

The distribution of TC and its association with other variables have been reported. Venous blood was drawn from nonfasting men after electrocardiography and physical examination but before a psychosocial and dietary survey; this was done to avoid the effects of stress from questioning on cholesterol and blood glucose concentrations or blood pressure. Blood was collected in three Vacutainer tubes (one of which was a 20 ml tube to which anticoagulant was not added) for collection of serum. Blood samples were refrigerated and taken daily in ice-cooled containers to a central laboratory, where the tubes were centrifuged, the serum separated, and the cells discarded. Cholesterol was determined by the Anderson and Keys modification of the Abell method. Control procedures for cholesterol determination have been previously reported.

After precipitation of LDL, very low density lipoprotein (VLDL) cholesterol by the method of Burstein and Samaille, cholesterol in the HDL fraction was measured directly.

The smaller number of readings of the lipoprotein fractions (only 6,547 of both total and HDL cholesterol) was the result of the late introduction of this test into the study protocol. The entry of examinees into the study was not correlated with any health criteria and was dictated merely by administrative convenience. The age-specific mean values for cholesterol in the subjects in whom the HDL fraction was measured was almost identical with those of the 9,902 men in whom total cholesterol was measured, and the association between cholesterol values at entry and subsequent development of MI was also similar in both study groups.

Mortality Follow-up
Over a period of 23 years (1963 to 1986) a total of 3,473 deaths were recorded, including 1,098 deaths attributed to CHD. Of the latter, 1,083 men had their cholesterol levels assessed. Information on death was derived from the Israeli Mortality Registry. The cause of death was documented as CHD on the basis of individual determination during 1970 and of the International Classification of Disease, version 9 (ICD-9) thereafter. Details for the 15-year mortality follow-up have been published and the present analysis essentially adds 8 more years of follow-up, a person-year analysis, and the life-table aspect of the analysis.

Statistical Methods
Age-adjusted total mortality and CHD mortality rates were calculated in deciles of lipid levels by using the person-year method. In computing the mortality rates, subjects were classified into five 10-year age groups.

Results
The distribution of the main causes of death over 23 years is presented in Table 1. Deaths attributed to CHD accounted for slightly less than one-third of the total. Deaths occurred under "other" included 148 deaths due to "other heart disease" and less than 80 for any other single cause over the follow-up period.

Table 2 presents the age-adjusted all-cause mortality rates in deciles of TC and HDL expressed as percent of cholesterol (PHDL). Meaningful elevations in all-cause mortality were seen only in the two top TC deciles (TC>241 mg/dl) and in the two bottom deciles of PHDL.
Table 2. 23-year All-Cause Mortality in Deciles of Lipid Levels

<table>
<thead>
<tr>
<th>Total serum cholesterol</th>
<th>Rate/10000</th>
<th>Percentage of HDL cholesterol</th>
<th>Rate/10000</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;161</td>
<td>149 (271)</td>
<td>&lt;11.7</td>
<td>228 (266)</td>
</tr>
<tr>
<td>161-176</td>
<td>150 (316)</td>
<td>11.7-13.5</td>
<td>199 (266)</td>
</tr>
<tr>
<td>177-187</td>
<td>149 (282)</td>
<td>13.5-14.9</td>
<td>177 (235)</td>
</tr>
<tr>
<td>188-197</td>
<td>166 (317)</td>
<td>14.9-16.1</td>
<td>168 (215)</td>
</tr>
<tr>
<td>198-206</td>
<td>142 (278)</td>
<td>16.1-17.3</td>
<td>166 (231)</td>
</tr>
<tr>
<td>207-216</td>
<td>156 (339)</td>
<td>17.3-18.7</td>
<td>145 (212)</td>
</tr>
<tr>
<td>217-227</td>
<td>173 (374)</td>
<td>18.7-20.2</td>
<td>155 (203)</td>
</tr>
<tr>
<td>228-241</td>
<td>178 (380)</td>
<td>20.2-22.3</td>
<td>156 (215)</td>
</tr>
<tr>
<td>242-260</td>
<td>204 (376)</td>
<td>22.3-25.5</td>
<td>141 (201)</td>
</tr>
<tr>
<td>&gt;260</td>
<td>233 (472)</td>
<td>&gt;25.5</td>
<td>142 (189)</td>
</tr>
<tr>
<td>Total</td>
<td>170 (3405)</td>
<td></td>
<td>167 (2233)*</td>
</tr>
</tbody>
</table>

The values are age-adjusted rates per 10,000 person years. The number of deaths are given in parentheses.

*Only 2233 subjects who subsequently died had both total cholesterol and high density lipoprotein (HDL) cholesterol levels assessed.

(PhDL<13.5%), with slight elevations at deciles 3 to 5 of the latter variable.

Figure 1 demonstrates a curvilinear association between TC levels and subsequent CHD mortality. A continuous rise in death rates beyond the sixth decile of TC (levels between 207 and 216 mg/dl) can be observed. CHD death rates were inversely related to PhDL (Figure 2).

To examine the time pattern of the association between baseline serum cholesterol and CHD mortality, we calculated Kaplan-Meier survival curves (Figure 3). Individuals who originally had TC of more than 240 mg/dl (quintile 5 at baseline) showed a clear-cut increased risk, which appeared to be augmented over time. At about 10 years into the follow-up period, a slowly growing CHD mortality excess was noticed in study subjects at the 4th quintile (217 ≤ TC ≤ 241). There is little evidence (apparent only for quintile 3 and at the very late stage of the follow-up) that the bottom three quintiles differed in terms of CHD mortality risk. Age-adjustment of the above curve according to the Cox model (not shown) failed to change the pattern observed in the Kaplan-Meier curves. When corrected for age differences between individuals with varying cholesterol levels, survival lost very little of its dependency on cholesterol.

To illustrate the association between TC and CHD mortality in subgroups at obvious risk differences, such as hypertensive, normotensive, smoking, and nonsmok-
ing men, we examined these associations by quintiles of TC and levels of the other risk factor. Figure 4 shows clearly that in the three groups of men with SBP<140, 140≤SBP≤159, and SBP≥160 mm Hg, the patterns of TC-CHD mortality associations were similar. Hypertension without hypercholesterolemia appeared to confer a worse prognosis than elevated TC in “normotensives” (SBP<140). The results for diastolic blood pressure and cigarette smoking (not shown) suggested that, in different categories of these variables, the TC-CHD mortality association followed a similar pattern. Thus, it did not appear that TC interacted with blood pressure or smoking in a way that would alter the association of TC with CHD mortality, depending on smoking habits or on the presence or absence of hypertension.

Proceeding to a multivariate analysis of the 23-year CHD follow-up (Table 3), the following variables were adjusted for: age, cigarette smoking, TC, HDLC, SBP, diabetes, AP at baseline, and HHA. Quetelet Index was unrelated to CHD mortality (standardized risk ratio=1.03, p=0.50) and fell out in a stepwise analysis. Our estimates of the covariate-adjusted increased risk associated with either increased TC or reduced HDLC imply that the risk of CHD mortality increases, on average, by about one-third among men in whom TC is increased (or HDLC is reduced) by one standard deviation. The effect of the lipids on 23-year CHD mortality appeared to be smaller than that of elevated SBP.

All-cause mortality (Table 3) was successfully predicted not only by age, diabetes, and AP, but also by SBP and smoking habits. A very limited excess risk of long-term all-cause mortality was observed for dyslipidemia expressed by "undesirable" levels of TC or HDLC. All the estimates of relative risk (RR), associated with each of the predictive variables presented, were statistically significant with p (the probability that no excess risk really exists of 0.002 or less).

We repeated the multivariate analysis with the following two alternative modifications: first, we ran the analysis on the 5990 men who began the study without HHA, AP, or diabetes. In this group, only 550 CHD deaths occurred, as compared to 723 CHD deaths in men for whom the analysis was given in Table 3. The RR of CHD mortality was 1.31 for TC and 1.41 for HDLC as compared to 1.29 and 1.36 when all subjects were included. The RRs for age, SBP, and cigarette smoking also increased slightly, and the overall risk profile emerged grossly similar to that shown in Table 3. In another analysis, we eliminated the information with respect to HHA, AP, and diabetes. In that way, the part mediated by the latter diseases in the relationship of TC to death (if such mediation has indeed occurred) is "fully credited" to TC. In this kind of analysis, we obtained an adjusted RR of 1.36 (95% confidence interval, 1.27 to 1.46) for TC and 1.38 (1.26 to 1.50) for HDLC.

The time pattern of CHD mortality, according to baseline TC adjusted for covariates, is reflected by the adjusted survival curves in Figure 5. We used the revised PHGLM program to "block" the curves by cholesterol quintiles and model on the above-mentioned covariates. In comparison with the Kaplan-Meier curves, these latter adjusted life-table curves indicated that: 1) in the evaluation of the net effect of cholesterol on risk, only quintiles 4 and 5 implied survival patterns that showed a non-negligible difference from those of the rest of the sample; 2) about one-third of the worsened survival associated with elevated cholesterol in the univariate (Kaplan-Meier) life-tables was eliminated. The eventual predicted mean net survival rates for men at quintile 5 was near 87%, compared to 93% in quintile 1 (Figure 5), whereas the crude (unadjusted) survival rates (Figure 3) were 82% and 93%, respectively, in quintiles 5 and 1; 3) the departure of the curve for quintile 4 became apparent much later during the study than for quintile 5. The R index for predictive ability was 0.238, indicating that CHD mortality over the 23-year period was far from being fully predictable by the "established risk factors" we measured a single time and included in the prediction model.

Discussion

The present report focuses on the patterns of association between serum cholesterol and CHD mortality, in a long-term 23-year follow-up of 9902 middle-aged and elderly individuals from a healthy, working population. Because levels of TC were measured for men in the preretirement age range, the discussion is essentially related to the predictive role of cholesterol measured at ages 65 and below.

A number of limitations are inherent in such a long-term prospective study that relates, over nearly a quarter of a century, single baseline measurements to prognosis, which is restricted to fatal outcome as coded in death certificates (albeit under a central system of correction and possible recoding). We suspect that these limitations are typical of the majority of such reports from studies inaugurated in the 1950s and 1960s. A single casual determination of cholesterol (or another physiological or biochemical variable) to predict long-term outcome encapsulates a possible error in measurement and a possible effect of regression to the mean. The remoteress of the end of the follow-up period implies that changes of level may have occurred either "spontane-
Figure 3. Kaplan-Meier survival curves for cholesterol quintiles: 23-year coronary heart disease mortality.

Figure 4. Age-adjusted coronary heart disease mortality in quintiles of cholesterol. Quintiles are divided according to "normal" (<140), borderline (140 to 159), and elevated (>160 mm Hg) levels of systolic blood pressure at entry.

Ously," because of a disease process or as a result of therapy. Clearly, we cannot assume that the quantitative effect of risk factors does not vary over time. The results also reflect a composite effect of serum cholesterol on incidence and case fatality; without details on long-term incidence, the effects on nonfatal and fatal outcomes cannot be separated. Since the above is also true for other risk factors (notably for a casual blood pressure reading, where intra-individual variation is large and regression to the mean constitutes a severe hindrance), we hypothesize that the comparison between different risk factors in determining long-term mortality will not place cholesterol at disfavor. However, in terms of the magnitude of the association between cholesterol and the probability of mortality, it is quite likely that this analysis, as well as parallel ones from long-term observational studies, underestimate the effect of risk factors on disease.

Other caveats relate to the "healthy worker effect" or to the specific nature of the participating population. Not surprisingly, the short-term prognosis of our study participants was favorable, mortality being 80% of parallel ages...
in the Israeli Jewish population, at the mid-1960s. This was accentuated to an extreme in the MRFIT volunteer screenee cohort of over 300,000 individuals where mortality was “approximately one-half of that expected with the use of U.S. life tables, and even after adjustment for the incomplete death ascertainment based on the Social Security Administration file, the number of deaths is substantially lower than we would expect on the basis of U.S. life tables.” The latter group is often viewed as providing the rationale for defining the nature of risk factor-disease associations (Reference 11, page 39) and as a “scientific underpinning for these (the NCEP’s) goals and endeavors.” Finally, generalization from one specific population, be it Israeli or British civil servants, men of Japanese ancestry in Hawaii, or (those consenting to participate in) community studies such as families in Tecumseh or individuals in Framingham, may also be open to criticism. It has, if somewhat implicitly, been assumed that risk functions derived from such study samples are relevant to general populations, especially in the broad application of the “Framingham risk scores.”

We have identified only one other published report of a nature comparable to ours that involves a life-table analysis of long-term mortality by baseline cholesterol. In that study, Anderson et al. reported that an increased 30-year overall and cardiovascular mortality was associ-

Table 3. Multivariate Analysis. 23-year All-Cause and Coronary Heart Disease Mortality

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Increment</th>
<th>CHD mortality (723 deaths)</th>
<th>All-cause mortality (2233 deaths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 10 years</td>
<td></td>
<td>2.02 (1.80, 2.26)</td>
<td>2.31 (2.07, 2.35)</td>
</tr>
<tr>
<td>TC 40 mg/dl</td>
<td></td>
<td>1.29 (1.20, 1.39)</td>
<td>1.07 (1.03, 1.12)</td>
</tr>
<tr>
<td>HDL-C 10 mg/dl (decrease)</td>
<td></td>
<td>1.36 (1.25, 1.49)</td>
<td>1.09 (1.04, 1.14)</td>
</tr>
<tr>
<td>Angina pectoris present</td>
<td></td>
<td>1.48 (1.11, 1.98)</td>
<td>1.44 (1.19, 1.73)</td>
</tr>
<tr>
<td>History of heart attack</td>
<td>verified</td>
<td>5.26 (3.94, 7.01)</td>
<td>2.61 (2.08, 3.27)</td>
</tr>
<tr>
<td>Diabetes present</td>
<td></td>
<td>2.73 (2.16, 3.44)</td>
<td>2.16 (1.86, 2.50)</td>
</tr>
<tr>
<td>Smoking 0 to 11-20 clgs/day</td>
<td></td>
<td>1.35 (1.22, 1.50)</td>
<td>1.42 (1.34, 1.51)</td>
</tr>
<tr>
<td>SBP 20 mm Hg</td>
<td></td>
<td>1.50 (1.42, 1.59)</td>
<td>1.40 (1.35, 1.45)</td>
</tr>
<tr>
<td>Diagnosis of malignant disease before study</td>
<td></td>
<td>9.26 (5.46, 15.77)</td>
<td></td>
</tr>
</tbody>
</table>

All the risk factors in the table are significantly associated with all-cause and coronary heart disease (CHD) mortality with \( p < 0.0002 \), except for angina pectoris with CHD mortality \( (p = 0.007) \) and total cholesterol with total mortality \( (p = 0.0019) \).

*The relative risk is that associated with an increment, or decrement for high density lipoprotein cholesterol (HDL-C) as stated, and adjusted for age, total cholesterol (TC), HDL-C, smoking, systolic blood pressure (SBP), angina pectoris, verified history of a heart attack, diagnosis of malignant disease, and diabetes.

Figure 5. Adjusted life-table curves by cholesterol quintiles: 23-year coronary heart disease mortality adjusted by age, systolic blood pressure, high density lipoprotein cholesterol, smoking habits, diabetes, and angina.
ated with increased cholesterol in those younger than 50 and an estimated 5% overall and 9% cardiovascular mortality increase per 10 mg/dl in a “smoothed” exponential model. Our results are consistent with a curvilinear association between TC and CHD mortality, where the risk was seen mainly at quintiles 4 and 5 (in the present study, levels above 216 mg/dl) and was augmented over time. When adjusted for other CHD risk factors, the effect of cholesterol on CHD mortality (Figure 5) appeared to be fully restricted to the top two quintiles. The survival differences in the bottom three quintiles were removed by the adjustment. This is important, as it would suggest that an increasing CHD risk associated with increases of TC in “normal” or moderately high levels (below 220) represents correlations with other risk factors. This could be significantly illuminated if large cohorts, such as that of the MRFIT screenees in particular, were analyzed with similar adjustments. We conclude that some of the excess CHD mortality risk in the upper two quintiles and probably most of the risk differences at lower levels reflected confounding by co-acting risk factors.

The low R value of 0.239 indicates a relatively low predictability of CHD mortality over 23 years. Given the limitations discussed above, the actual association between the risk factors and CHD mortality might be stronger than that indicated in this, or any other, longitudinal study of an observational nature, in which a single measurement of every risk factor is used to predict outcome.

Although the use of a long-term observational study based on a single cholesterol measurement to draw inferences regarding the potential effects of intervention may be limited, several points can be made. First, the question arises whether at levels of cholesterol previously regarded as normal (200 to 220 mg/dl) and possibly up to 239 mg/dl (the upper limit for “borderline-high blood cholesterol” according to the report of the NCEP Expert Panel11), correction of co-existing risk factors may be tantamount to dealing with the excess cardiovascular mortality risk statistically implied by having a total cholesterol in the 200 to 239 mg/dl range. If this is true (and bearing in mind that intervention studies have so far been restricted to considerably higher levels of TC), our observation may have ramifications for health policy.

If our findings can be duplicated in long-term analyses of other cohorts, perhaps more emphasis should be placed on individual cases and individual treatment, which are commonly viewed as the “high risk” component of a scheme emphasizing a “population strategy.” Differences of opinion abound with respect to how important each intervention component is in an overall strategy of cholesterol lowering.14,16

Our analysis, both on the univariate and multivariate levels, indicates that cholesterol is not a major factor in all-cause mortality, at least below extreme elevations, which are relatively rare in the population. These observational findings are in line with the results—as far as overall mortality goes—of the Lipid Research Clinics Coronary Primary Prevention Trial and the Helsinki Trials.5,6 The combined set of results from observational5,11-44 and experimental studies indicates that across a sizeable portion of the cholesterol range, all-cause mortality does not change. Therefore, where the risk of nonfatal heart attacks is not high, the case for cholesterol reduction may not be strong.45

In summary, this long-term observational study indicates that serum cholesterol predicts long-term CHD mortality, that the association between the two entities at levels considered “borderline hyperlipidemia” may reflect the correlation of cholesterol with other risk factors, and that cholesterol is not a major factor in all-cause mortality over most of its range. We suggest that identification and management of co-existing CHD risk factors may, at least in 40- to 65-year-old men and in settings similar to those of our population, constitute a primary preventive approach when cholesterol is in the “borderline-high” range.

Acknowledgments

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References

Index Terms: serum cholesterol  • long-term mortality  • preventive strategies  • epidemiology  • survival analysis

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