

SERUM CHOLESTEROL, BLOOD PRESSURE, AND MORTALITY: IMPLICATIONS FROM A COHORT OF 361 662 MEN

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Summary The risks associated with various levels of serum cholesterol were determined by analysis of 6-year mortality in 361 662 men aged 35–57. Above the 20th percentile for serum cholesterol (>181 mg/dl, >4.68 mmol/l), coronary heart disease (CHD) mortality increased progressively; the relative risk was large (3.8) in the men with cholesterol levels above the 85th percentile (>253 mg/dl, >6.54 mmol/l). When men below the 20th cholesterol percentile were used as the baseline risk group, half of all CHD deaths were associated with raised serum cholesterol concentrations; half of these excess deaths were in men with cholesterol levels above the 85th percentile. For both CHD and total mortality, serum cholesterol was similar to diastolic blood pressure in the shape of the risk curve and in the size of the high-risk group. This new evidence supports the policy of a moderate fat intake for the general population and intensive treatment for those at high risk. There is a striking analogy between serum cholesterol and blood pressure in the epidemiological basis for identifying a large segment of the population (10–15%) for intensive treatment.

Introduction

THERE is now good evidence from clinical trials and other observations that reduction of serum cholesterol in men with high concentrations can reduce the incidence of coronary heart disease (CHD).^{1–4} At what levels should intensive treatment and hypolipidaemic drugs be advised? To answer this question we must look to cohort studies that examine the risk relation between serum cholesterol levels

and heart disease. Several prospective cohort studies have provided information on this risk relation,⁵ but none has had sufficient power to determine its exact pattern.

We analysed the 6-year mortality data for the 361 662 men screened as part of the Multiple Risk Factor Intervention Trial (MRFIT). This group is thirty times larger than the randomised MRFIT study group and seventy times larger than the Framingham cohort. Its large size allows us to examine the precise pattern of risk relation between serum cholesterol and CHD, and to compare it with the pattern observed for blood pressure. The findings have important implications for clinical and public health policy directed at these two risk factors.

Materials and Methods

The methods have been reported in detail elsewhere.^{6–9} MRFIT was a multicentre study of the effect of coronary risk factor reduction in middle-aged men at high risk of coronary artery disease. To select the MRFIT participants, 361 662 men aged 35–57 were screened during a 2-year period beginning in 1973. The screening records included birthdate, social security number, and smoking status, blood pressure, and serum cholesterol. Three measurements of systolic and diastolic blood pressure were made with a mercury sphygmomanometer, the participant being seated; the average of the second and third readings was recorded. Serum cholesterol was determined in one of fourteen laboratories under the supervision of the MRFIT Central Laboratory in San Francisco and the Lipid Standardization Laboratory of the Centers for Disease Control in Atlanta.

In 1982, the vital status of each member of this cohort was determined by matching last name and social security number against Social Security Administration mortality files. Death certificates were then obtained from state health departments, and cause of death was coded by a nosologist according to the 9th revision of the International Classification of Diseases (ICD 9).¹⁰ The CHD death category included those with ICD 9 codes 410 to 414. Death certificates were obtained for 94% of the decedents.

The cohort was divided into approximate twentieths (ie, 5% of the total sample per group) by serum cholesterol and by diastolic blood pressure. Thus there were about 18 000 men, with more than 100 000 person-years of follow-up, in each of the subgroups. The 6-year age-adjusted mortality rates per 1000 men were calculated for death due to CHD and all causes. The 95% confidence intervals for these rates were estimated.¹¹ Relative risks for various subgroups were determined, the lowest 20% of the sample being used as the baseline risk group. Excess risks and attributable risks were calculated by standard methods.¹²

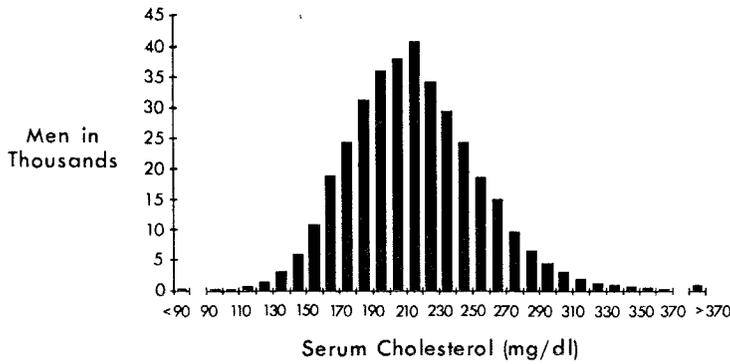


Fig 1—Distribution of serum cholesterol concentrations in 361 662 men screened for MRFIT (1973–75).

RELATIVE AND EXCESS RISK OF CHD DEATH ASSOCIATED WITH PERCENTILES OF SERUM CHOLESTEROL AMONG MRFIT SCREENEES

Percentiles	Cholesterol (mg/dl)*	Relative risk compared with bottom quintile	Relative risk compared with next lower quintile	Percentage excess risk†
<i>Quintiles</i>				
0–20	≤ 181	1.0	—	—
20–40	182–202	1.3‡	1.3‡	6.8
40–60	203–221	1.7‡	1.3‡	15.2
60–80	222–245	2.2‡	1.3‡	25.8
80–100	≥ 246	3.4‡	1.6‡	52.2
<i>Other intervals</i>				
80–90	246–263	2.8‡		19.7
90–100	≥ 264	4.0‡		32.6

*1 mg/dl = 0.026 mmol/l.

†The excess risk of CHD death attributable to raised serum cholesterol was computed by standard statistical methods¹² and amounted to 48% of all CHD deaths, on the assumption of a baseline risk equal to that in the lowest quintile. The figures in this table are the proportion of that excess risk attributable to various cholesterol percentiles.

‡p < 0.01.

Results

The distribution of serum cholesterol concentrations in the 361 662 screened men is shown in fig 1. The pattern closely resembles a normal distribution.

There were 7840 deaths in this cohort, 2626 of these being from CHD and 2365 from cancer. The CHD mortality rate by serum cholesterol percentile is shown in fig 2. Above the 20th percentile (> 181 mg/dl, > 4.68 mmol/l) the risk of CHD increased as the cholesterol increased. If those with a serum cholesterol below the 20th percentile are considered to be at baseline risk (3.7 CHD deaths/1000 per 6 yr), then about half (48%) of all the CHD deaths were associated with raised serum cholesterol concentrations. About half (54%) of this excess risk occurred in men with concentrations between the 20th and the 85th percentiles, and the other half occurred in the 15% of men with cholesterol levels above the 85th percentile (> 253 mg/dl, > 6.54 mmol/l).

When the cholesterol values were grouped by quintiles, there was a statistically significant (p < 0.01) and progressive increase in relative risk (1.3, 1.7, 2.2, 3.4) for each quintile above the first (table). For individuals above the 85th percentile, the relative risk was strikingly increased (3.8). For the top four quintiles, the table also gives the relative risk that is calculated by comparison of each quintile with the quintile immediately below it; this gives an idea of the risk reduction that can be expected if a patient lowers his risk by one quintile. The final column in the table presents the percentage of the excess risk attributable to each serum cholesterol quintile.

In fig 3, CHD mortality data are plotted with serum cholesterol rather than percentile as the x-axis. This graph

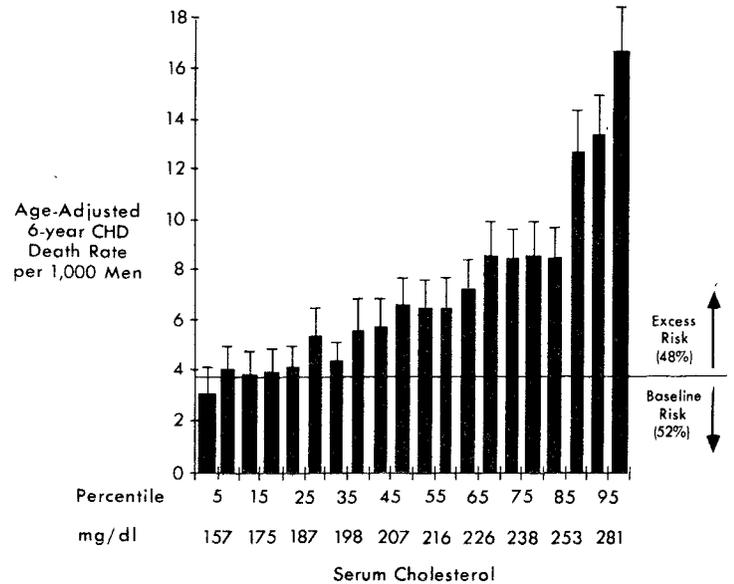


Fig 2—Age-adjusted 6-year CHD death rate per 1000 men screened for MRFIT according to serum cholesterol percentile.

Horizontal line represents expected death rate of 3.7 per 1000 men. Area above the line represents excess risk associated with serum cholesterol. T-bars represent the upper limit of the 95% confidence interval.

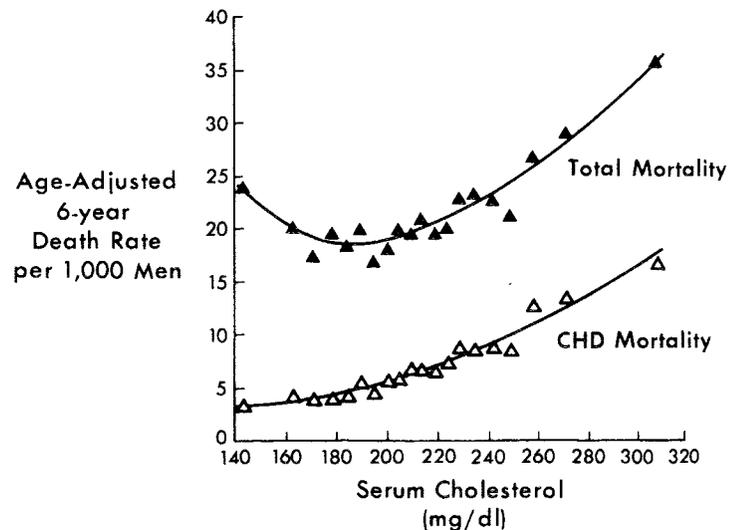


Fig 3—Age-adjusted 6-year CHD and total mortality per 1000 men screened for MRFIT according to serum cholesterol.

Entire cohort of 361 662 men was divided into approximate twentieths, and each point represents the mortality (either CHD or total) and the mean cholesterol level in one of those twentieths. Hand-fitted lines are drawn through the points.

represents the association between CHD and mortality better than fig 2 because plotting by percentiles tends to compress the curve at the higher and lower ends (where the same number of individuals have a wider spread of values).

Fig 3 includes the curve for total mortality by cholesterol level. For both the CHD and total mortality, there was a progressively increasing slope above the 20th cholesterol percentile. For the total mortality curve there was also an increase in mortality below the 10th percentile; this was due to an excess of cancer deaths (see discussion).

When the CHD and total mortality curves by cholesterol percentiles were compared with corresponding curves by diastolic blood pressure (DBP) percentiles (fig 4), there were remarkable similarities in the risk relation. Both risk factors showed a gradual increase in the risk of CHD mortality over most levels, and an accentuation of risk above the 85th percentile (> 253 mg/dl and > 94 mm Hg). The relative risk

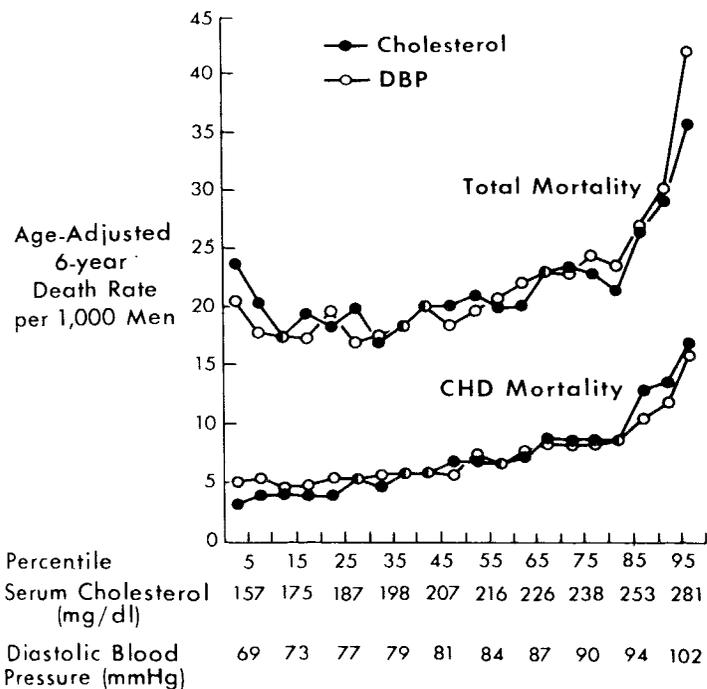


Fig 4—Age-adjusted CHD and total 6-year death rate per 1000 men screened for MRFIT according to serum cholesterol or diastolic blood pressure percentiles.

in this top 15% of the population, by comparison with the bottom quintile, was 3.8 for cholesterol and 2.5 for blood pressure.

Discussion

Our findings support the recommendations of the National Institutes of Health Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease.¹ The Conference called for aggressive treatment of patients with cholesterol concentrations above the 90th percentile. Two-step treatment was recommended—first, intensive dietary therapy under the guidance of a health counsellor, then drugs, if necessary to secure the desired reduction. The Consensus Conference also called for intensive dietary treatment, and occasionally drug therapy, for those with cholesterol levels between the 75th and 90th percentiles.

The data presented here show that the relative risk for CHD mortality rises at an ever-increasing rate beginning at about the 20th percentile. When we consider the data by quintiles, there is a significantly higher relative risk of CHD death for each quintile above the first. It is thus appropriate to use those in the first quintile as the baseline risk group for calculating excess risks. When this is done, half of the observed CHD mortality can be attributed to a raised serum cholesterol (> 181 mg/dl, > 4.68 mmol/l); and half of these excess deaths are in those with cholesterol concentrations above the 85th percentile (> 253 mg/dl, > 6.54 mmol/l). The relative risk in the top 15% of the population is surprisingly large (3.8). From a therapeutic standpoint, therefore, it seems appropriate that the most intensive effort to reduce cholesterol levels and the risk of CHD should be focused on the group with the highest cholesterol levels.

The Consensus Development Conference also called for a general effort to reduce the cholesterol levels in the whole population. This was recommended despite the fact that some investigators have suggested that the cholesterol-CHD association is largely restricted to the upper ranges of serum cholesterol.¹³⁻¹⁵ The data presented here have the precision to reveal the true shape of the risk relation. Half of

the excess CHD deaths were found in men with cholesterol levels between the 20th and 85th percentile. Moreover, the risk increased steadily over this whole range. This supports the Consensus Conference recommendation for a population-wide effort to reduce cholesterol levels through dietary alterations, since four-fifths of the population is likely to benefit.

Comparisons of Curves for CHD and Total Mortality

The total mortality curve by cholesterol percentiles resembles the CHD mortality curve in that the greatest accentuation of risk occurs in the top 10–15% of cholesterol levels. Below the 85th percentile the total mortality curve shows a general decline until the 10th percentile, below which a J-shaped pattern with higher death rates is observed.

The increased total mortality at the lowest cholesterol levels has been noted before.^{16,17} It is primarily due to an increased risk of cancer death in those with the lowest cholesterol concentrations and is probably explained by a cholesterol-lowering effect of cancer.¹⁶ The most recent evidence for this explanation is an analysis of the MRFIT screening cohort which showed that the association between low serum cholesterol and cancer incidence does not persist beyond 5 years of follow-up, whereas that between high serum cholesterol and CHD incidence remains after 5 years.¹⁸

Comparison of Cholesterol and Blood Pressure Curves

The magnitude of the risk associated with hypercholesterolaemia is similar to the magnitude of risk associated with hypertension. Although both of these conditions are recognised as important risk factors for CHD,⁵ there are major differences in the approach to screening and treatment.^{19,20} A survey of the United States population revealed that 98% of adults recall having a blood pressure measurement, for example, while only 35% recall having a serum cholesterol test.²¹ Some of the differences in the approach to hypertension and hypercholesterolaemia might be attributed to a lack of awareness in the medical profession of data concerning the comparable magnitude of the risks associated with these two risk factors. Fig 4 shows that the risks associated with hypercholesterolaemia are similar to those associated with hypertension and that a similar proportion of the population is affected.

The most important differences between these two risk factors are in the drugs used to treat hypertension and those used to treat hypercholesterolaemia. In general, these differences make the treatment of hypertension simpler and more effective. With the development of better methods for treating hypercholesterolaemia, including better cholesterol-lowering drugs and more palatable diets, the approaches to screening and treating of hypertension and hypercholesterolaemia should become more similar.¹⁹

Other Considerations

One concern with interpreting these risk relations is that some of these men were already receiving treatment at the time of the screening and that others received risk factor intervention subsequent to screening. This would tend to flatten out the curves. Because only a small percentage of those with very high serum cholesterol are treated, this bias is likely to be more important for hypertensive than for hypercholesterolaemic men. However, we believe that this

bias is not likely to have qualitatively altered our conclusions.

The current data deal with men aged 35–57. The mean serum cholesterol is lower in younger age groups, and in general varies by the age, sex, and race of the population. Until information on these other groups becomes available, however, it seems reasonable to follow the Consensus Conference recommendation of determining cutpoints by applying percentiles to the age-specific distributions reported by the Lipid Research Clinics (LRC) prevalence study.^{1,22}

Since serum cholesterol concentrations vary considerably from one measurement to another in a given individual (SD 18 mg/dl, 0.47 mmol/l),²³ clinical decisions to begin or modify drug treatment should be based on the mean of readings obtained on several occasions. The best total cholesterol value as a cutpoint for clinical decisions will be influenced by the concentration of high-density lipoprotein cholesterol. Clinical decisions should also be influenced by the presence of other risk factors, which accentuate the absolute level of risk and thereby increase the benefit associated with a given decrement in serum cholesterol.^{8,14,24} Clinical management guidelines that address all of these issues are being prepared in the United States as part of the new National Cholesterol Education Program.²¹

We have not reviewed here the broad spectrum of evidence justifying the desirability of efforts to lower serum cholesterol and blood pressure; this has already been done by groups established for the purpose of making health policy.^{1,2,22,25} Our goal has been to report on a set of epidemiological data that is much larger than its predecessors and that can help in guiding how, specifically, this policy should be implemented.

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EFFECTS OF SYNVINOLIN (MK-733) ON PLASMA LIPIDS IN FAMILIAL HYPERCHOLESTEROLAEMIA

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Summary The effects of synvinolin (MK-733), a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, were investigated in 43 patients with heterozygous familial hypercholesterolaemia in a double-blind, placebo-controlled, dose-finding study. Synvinolin was given in doses ranging from 2.5 mg to 80 mg per day for 4 weeks. 8 patients received placebo. Low-density-lipoprotein cholesterol fell on average by 18% on 2.5 mg/day and 42% on 80 mg/day. The drug was as effective whether it was given once or twice daily. Serum high-density-lipoprotein cholesterol tended to increase and serum triglycerides to decrease on the higher doses. The drug was tolerated well. Except for a slight rise in alanine aminotransferase in 3 patients no objective side-effects were observed.

Introduction

A HIGH serum cholesterol level is a major risk in coronary heart disease.¹ Intervention studies with diet and drugs have shown that lowering the concentrations of total and low-density-lipoprotein (LDL) cholesterol in the blood can reduce the risk of coronary heart disease² and arrest the progression of atherosclerotic lesions.³ Patients with familial hypercholesterolaemia are at especially high risk of premature atherosclerosis.⁴ Heterozygous subjects with this disorder have only half the normal amount of high-affinity receptors for LDL on cell membranes, and LDL levels are two to three times higher than normal; cholesterol-lowering diets have only a limited effect, which makes drug therapy

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