Is a high serum cholesterol level associated with longer survival in elderly hypertensives?*

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The relationship between serum total cholesterol, measured at randomization, and mortality was investigated in 822 patients, who were followed for an average of 3.1 years in a double-blind trial, conducted by the European Working Party on High Blood Pressure in the Elderly. Serum cholesterol, measured at randomization, was 0.54 mmol/l higher in women than in men, and declined with increasing age in both men (0.028 mmol/l per year) and women (0.036 mmol/l per year). During follow-up on randomized treatment, cholesterol fell by a similar amount with placebo (0.11 mmol/l per year) and with active treatment (0.14 mmol/l per year). Active treatment consisted of hydrochlorothiazide (25–50 mg/day) plus triamterene (50–100 mg/day) with the addition of α-methyldopa (0.5–2.0 g/day) in one-third of the patients. Serum total cholesterol, measured at randomization, was independently and inversely correlated with total ($P = 0.03$), non-cardiovascular ($P = 0.03$) and cancer ($P = 0.04$) mortality during follow-up on double-blind treatment. Total and non-cardiovascular mortality were also negatively correlated with haemoglobin and body weight at randomization.

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All factors being equal, an increase in serum total cholesterol by 2.3 mmol/l was associated with a 1-year prolongation of survival. However, after adjustment for gender, age, cardiovascular complications and systolic blood pressure at randomization, the correlations between serum cholesterol and cardiovascular and cardiac mortality were not significant. In conclusion, a high serum total cholesterol level is associated with longer survival in elderly hypertensives. This can be explained by the association of lower non-cardiovascular mortality with high serum cholesterol, and by the absence of a positive relationship in this population between cholesterol and cardiovascular mortality. However, recommendations for disease prevention must not be changed in the light of the present findings.

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Introduction

In both normotensive [1–3] and hypertensive [4–6] middle-aged subjects, serum total cholesterol is a major risk factor for cardiovascular disease, in particular coronary heart disease. However, in older people cardiovascular disease is the most frequently recorded single cause of death [7]. In a cohort of hypertensive patients with an average age of 50 years at entry, Bulpitt *et al.* [8] found that serum total cholesterol was not related to cardiovascular death when age, impairment of renal function, smoking habit and systolic blood pressure before treatment were accounted for.

The present article is based on the results of the trial conducted by the European Working Party on High Blood Pressure in the Elderly (EWPHE) [9–11], and examines whether serum total cholesterol in elderly hypertensives is associated with elevated risk, and therefore with a poorer prognosis.

Methods

Study protocol

The entry criteria for subjects included: (1) age of at least 60 years and (2) sitting blood pressure of 160–239/90–119 mmHg on placebo during a run-in period. After stratification by gender, age and the presence or absence of cardiovascular complications, the patients (n = 840) were randomized to active treatment (hydrochlorothiazide plus triamterene) or the placebo. If blood pressure remained elevated, α-methyldopa was added to the active regimen and a matching placebo was given in the control group. Full details of the trial protocol have been published elsewhere [10].

Quality control

Blood samples for the determination of serum total cholesterol were taken at randomization and thereafter at yearly intervals. Serum total cholesterol was measured in 20 different laboratories. Nine centres, which recruited a total of 432 patients, participated in a quality-control programme. They received two lyophilized control sera, containing a known low or high concentration of cholesterol (Precilip E.L.; Boehringer Pharma, Brussels, Belgium), from the central laboratory in Ghent, Belgium (Professor De Schaepdryver). In each of the nine centres the two sera were included three times, at weekly intervals, in routine cholesterol measurements, and on each occasion the control determinations were repeated four times. Thus, for each of the nine laboratories, and for each of the two control sera, a total of 12 measurements were available for comparison with the standard.

For the control serum with the low cholesterol concentration (3.5 mmol/l), the deviations from the standard value averaged −1% in the nine laboratories, and ranged from −8 to +8%. For the control serum with the high cholesterol level (7.5 mmol/l), the deviations averaged +6% with a range from −16 to +12%. However, in seven of the nine centres, the average deviations for the high cholesterol control sera were within 5% of the standard. In view of the small deviations from the standard in the laboratories which took part in the quality control programme, cholesterol measurements in the present analysis were not adjusted for possible differences between centres.

Statistical methods

Means were compared by Student's t-test. Death rates were age- and sex-adjusted using the direct method [12], and compared with two-tailed tests by computing the standardized normal deviate. Mortality was correlated with serum total cholesterol and other risk factors by Cox's regression. A stratified Cox's model [13] was used to account for the differences between placebo and active treatment. Both the Cox's regression [13] and the multiple linear regression [14] were effected by a stepwise procedure, terminating when all regression coefficients included in the model were statistically significant at the 5% level. However, in the first step of Cox's regression, cholesterol was forced into the model.

Results

Patient characteristics at randomization

At randomization, measurements of serum total cholesterol were not available in 10 of the 424 patients subsequently treated with the placebo and in eight of the 416 patients allocated to active treatment, leaving a total of 822 subjects for analysis. The patient-years of observation in the placebo and active treatment groups were 1228 and 1347, respectively. The two treatment groups were similar at randomization in sex distribution (70% women), age (72 ± 8 years, mean ± s.d.), sitting blood pressure (182 ± 17/101 ± 7 mmHg), body weight (67 ± 12 kg), serum total cholesterol (6.36 ± 1.34 mmol/l; 246 ± 52 mg/dl), and in the percentage of patients with cardiovascular complications (36%).

Cholesterol at randomization

Serum cholesterol at randomization was higher in women than in men (6.46 versus 6.07 mmol/l; $P < 0.001$). In the two sexes, serum cholesterol was inversely correlated with age in single regression (Fig. 1), but was not related to body weight, body mass index, fasting blood glucose, or serum uric acid. However, in the multiple regression analysis, 6% of the variance in serum total cholesterol was independently explained by gender, age and a significant positive partial correlation with serum uric acid.

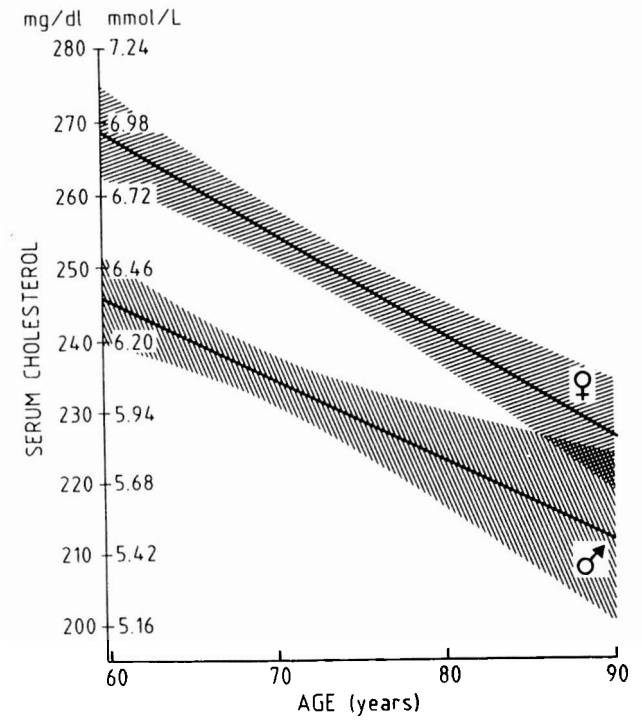

Fig. 1. Relationship between serum total cholesterol at randomization and age in 250 male and 572 female patients. Males: y (mmol/l) = 8.07 − 0.028 x (years), r = −0.14, $P = 0.03$; females: y = 9.10 −0.036 x, r = −0.23, $P < 0.001$. The shaded area represents the 95% confidence interval for the prediction of the population mean along the regression line.

Cholesterol during the follow-up period

Follow-up measurements of serum cholesterol were available from 300 patients on placebo and 313 patients on active treatment.

During the first 3 years of follow-up, serum total cholesterol fell significantly in the two treatment groups (Fig. 2). However, the rates of decline, 0.11 ± 0.08 mmol/l per year on placebo and 0.14 ± 0.09 mmol/l per year on active treatment, were similar, so that throughout the follow-up period cholesterol levels were not significantly different in the two groups.

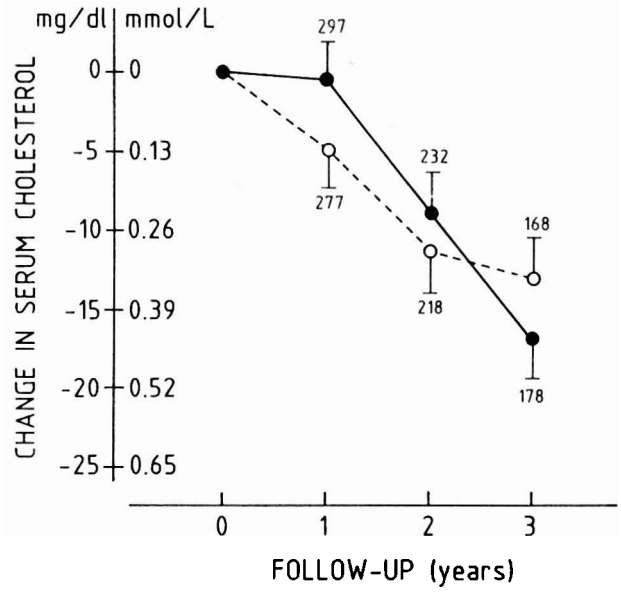

Fig. 2. Changes in serum total cholesterol after randomization in patients on placebo (○) and on active treatment (●). Values are means ± s.d.

Cholesterol as a risk indicator

Of the 822 patients included in the present analysis, 160 died while being followed on double-blind treatment. The cause of death was cardiovascular in 103 patients and non-cardiovascular in 57. Cardiovascular mortality included 46 deaths from cardiac causes (International Classification of Diseases, 8th revision, pp 410–414 and 425–429) and 31 cerebrovascular events. Non-cardiovascular mortality included seven deaths from gastrointestinal cancer (four deaths from stomach cancer), five deaths from lung cancer, five from urogenital neoplasms, and one from a malignant eye tumour.

Age- and sex-adjusted mortality in quintiles of serum cholesterol

On a first analysis, the total study population was stratified by quintiles of serum total cholesterol at randomization. The characteristics of the patients by quintiles of serum cholesterol are presented in Table 1. As shown in Fig. 3, total ($P < 0.001$), cardiovascular ($P < 0.01$), non-cardiovascular ($P < 0.001$) and cardiac ($P < 0.01$) mortality, adjusted for age and gender, decreased with increasing serum total cholesterol. A similar trend was also ob-

Table 1. Characteristics of patients in quintiles of serum cholesterol at randomization.

	Range of serum total cholesterol (mmol/l)				
	3.10–5.09	5.10–5.89	5.90–5.19	5.20–6.49	6.50–12.8
Number	164	159	166	168	165
Age (years)*	74 ± 9	73 ± 9	70 ± 7	71 ± 8	70 ± 7
Systolic pressure (mmHg)*	183 ± 16	182 ± 17	183 ± 17	182 ± 17	183 ± 16
Diastolic pressure (mmHg)*	101 ± 7	100 ± 7	100 ± 7	101 ± 7	101 ± 7
Body weight (kg)*	65.4 ± 12.8	65.9 ± 13.1	67.1 ± 12.4	67.8 ± 13.2	67.8 ± 10.7
Body mass index (kg/m²)*	26.0 ± 4.9	26.0 ± 4.7	26.7 ± 4.8	26.7 ± 4.3	26.6 ± 4.0
Haemoglobin (mmol/l)†	8.72 ± 1.03 (150)	8.75 ± 0.88 (139)	8.79 ± 0.79 (144)	8.89 ± 0.85 (146)	8.96 ± 0.86 (139)
Men (%)	27	21	19	17	16
Cardiovascular complications (%)	25	17	22	20	17
Current smokers (%)	22	17	22	21	18

*Values are means ± s.d. †Haemoglobin was measured in all subjects (number of measurements is given in parentheses).

served for cancer mortality, but not for cerebrovascular death (Fig. 3).

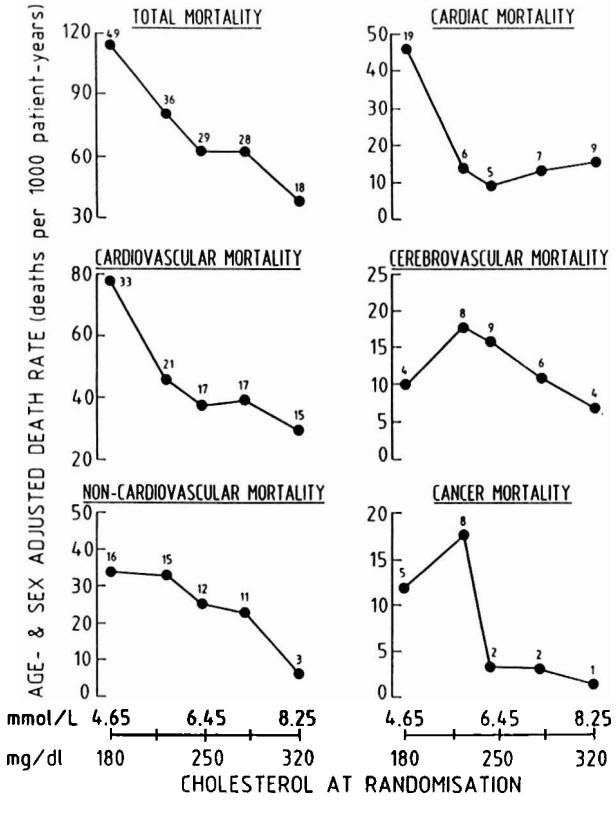

Fig. 3. Age- and sex-adjusted mortality rates in quintiles of the cholesterol distribution at randomization. For each quintile, the number of deaths is given along the plotted line.

The relationship between mortality and serum cholesterol adjusted for multiple risk factors

Independently of the effects of active versus placebo treatment, total mortality was inversely correlated with serum cholesterol, and also with body weight and haemoglobin measured at randomization (Table 2). In addition, total mortality was higher in men and in patients with cardiovascular complications at randomization, and increased with age and with systolic blood pressure. The relative hazard rate shown in Table 2 indicates that, independent of other risk factors and treatment, total mortality was 14% lower [95% confidence interval (CI) 1–25%] for each 1 mmol/l (39 mg/dl) increase in serum total cholesterol at randomization. Alternatively, all factors being equal, an increase in serum total cholesterol by 2.3 mmol/l (90 mg/dl) was associated with a prolongation of survival by approximately 1 year.

Non-cardiovascular ($P = 0.02$) and cancer ($P = 0.04$) mortality were inversely correlated with serum total cholesterol at randomization, while a similar tendency ($P = 0.08$) was also observed for cardiovascular mortality (Table 2). In contrast, the relationships between serum cholesterol and cardiac and cerebrovascular mortality (Table 2), and the incidence of fatal and non-fatal myocardial infarction combined (54 events) were not statistically significant. For myocardial infarction, the 95% CI of the relative hazard rate was 0.855–1.279.

The following risk factors determined at randomization were not significantly related to mortality or the incidence of myocardial infarction: diastolic blood pressure, smoking habits, fasting blood glucose, and serum uric acid, potassium and creatinine. Changes in cholesterol and in other biochemical measurements during the first year of follow-up also did not improve the prediction of mortality by serum total cholesterol measured at randomization.

Discussion

This article reports on the prognostic significance of serum total cholesterol in a selected population of elderly hypertensive patients. Cholesterol subfractions were not measured 20 years ago since, when the present trial was

Table 2. Relationship between serum cholesterol and other risk indicators at randomization with subsequent mortality.

	Cause of death					
	Total*	Cardiovascular	Cerebrovascular	Cardiac*	Non-cardiovascular	Cancer*
Included in analysis	706	822	822	718	810	810
Patients (n)	150	103	31	44	57	18
Events (n)						
Relative hazard rates						
Cholesterol (mmol/l)						
Hazard rate	0.862	0.867	1.007	0.898	0.776	0.638
95% confidence interval	0.751–0.989	0.740–1.106	0.622–1.325	0.693–1.165	0.625–0.964	0.418–0.974
P	0.03	0.08	0.96	0.42	0.02	0.04
Other risk indicators						
Being male	2.569	2.154	NS (0.17)	4.428	3.171	5.082
Age (years)	1.095	1.108	1.062	1.112	1.120	NS (0.19)
Presence of cardiovascular complications	1.824	1.582	NS (0.27)	NS (0.10)	2.193	NS (0.14)
Systolic blood pressure (mmHg)	1.014	1.022	1.043	NS (0.44)	NS (0.93)	NS (0.97)
Body weight (kg)	0.979	NS (0.20)	NS (0.29)	NS (0.78)	0.962	0.937
Haemoglobin (mmol/l)	0.823	NS (0.10)	NS (0.80)	0.731	NS (0.59)	NS (0.53)

*Models include all subjects for whom body weight and/or haemoglobin data were available. NS, not significant (*P* value given in parentheses).

planned by EWPHE, the prognostic significance of these subfractions was still largely unknown.

Figure 3 shows an unexpected negative association between serum total cholesterol and the sex- and age-adjusted death rates for total, cardiovascular and cardiac mortality. The inverse relationship between total mortality and cholesterol was confirmed in a multivariate model (Table 2), when, in addition to gender and age, treatment and other risk factors were also accounted for. All factors being equal, the model showed that a 2.3 mmol/l (90 mg/dl) higher serum cholesterol at randomization was associated with a 1-year prolongation of survival. The longer survival of these selected elderly hypertensive patients can be explained by two mechanisms: the absence of a positive correlation between serum cholesterol and cardiovascular and cardiac mortality (Table 2), and the presence of a significant negative correlation with non-cardiovascular and cancer mortality (Table 2).

A positive association between serum cholesterol and coronary events has been observed in middle-aged hypertensive patients in the International Primary Prospective Prevention Study in Hypertension (IPPPSH) and the Medical Research Council (MRC) trial [4,5], but not in the Department of Health and Social Security (DHSS) Hypertension Care Computing Project [8,23], where subjects ranged in age from 13–89 years. On balance, many studies confirm that in middle-aged normotensive [1–3] and hypertensive [4–6] subjects, serum total cholesterol is a potent predictor of cardiovascular risk. In contrast, in those aged over 60 years, serum total cholesterol is not [16,17] or is only weakly [19,20] associated with increased cardiovascular morbidity and mortality. In a cohort of patients aged 49–82 years at entry, the incidence of coronary events was positively correlated with the serum concentration of low-density lipoprotein cholesterol, but negatively with the subfraction of high-density lipoprotein cholesterol [18]. Thus, it is possible that in the elderly, in whom the relationship between serum total cholesterol and cardiovascular risk becomes weak, cholesterol subfractions remain associated with cardiovascular risk.

It is unlikely that the present lack of association between serum cholesterol and total mortality was due to the predominant role of blood pressure as a cardiovascular risk factor [11,22], or to the known inverse relationship between serum cholesterol and cerebral haemorrhage in some populations [25]. Whether cholesterol at an older age is less important in causing atheromatosis has not been established. A Swedish intervention study showed that the risk carried by a high serum cholesterol level in middle-aged hypertensive men is reversible [6], but no such intervention study has yet been carried out in the elderly. Furthermore, subjects with a higher serum cholesterol level may have a greater probability of dying from cardiovascular illness in middle-age, so that an initially positive correlation with serum cholesterol weakens in older populations. Finally, a low serum cholesterol may be an expression of poor health, as suggested in the present study by the higher non-cardiovascular and cancer mortalities (Fig. 3), and the lower average haemoglobin and body weight (Table 1) in the two lowest fifths of the cholesterol distribution at randomization. A low serum cholesterol level in subjects in ill health has been suggested to explain the J-shaped relationship between total mortality and serum cholesterol observed in some studies in middle-aged men [24], and more recently in very old women [21].

In agreement with previous studies, which were mainly of middle-aged subjects [26–31], the present analysis in elderly hypertensives confirmed the inverse correlation between serum total cholesterol and non-cardiovascular and cancer mortality. The negative association between serum cholesterol and cancer has been attributed

occurrence of colorectal neoplasms, although lung cancer and leukaemia have also been incriminated [32]. Several speculative mechanisms [33,34] have also been proposed to explain the negative correlation with cancer mortality, such as confounding by the primary anticarcinogenic effects of liposoluble vitamins. Furthermore, in subjects whose liver excretes cholesterol at a faster rate, changes in the intestinal microflora may occur and lead to metaplasia of the epithelium [33,34]. It has also been suggested that the negative correlation between serum cholesterol and cancer mortality is due to the presence of the cancer at the time of the cholesterol measurement [30]. However, the negative correlation between serum cholesterol and cancer mortality may persist for up to 18 years after the cholesterol measurements, and when cases occurring during early follow-up are excluded [31,32].

In the present study, serum total cholesterol decreased with age. In the cross-sectional analysis of the data at randomization, serum cholesterol levels were higher in women than in men. However, the rate of decline with age was similar in both sexes, both in the cross-sectional analysis of all patients (Fig. 1) and in the longitudinal follow-up of the patients on placebo (Fig. 2).

In conclusion, in the elderly hypertensives under study, a longer period of survival was observed with higher serum cholesterol levels. These findings could be explained by the lower non-cardiovascular, and, in particular, cancer mortality in the patients with a high serum cholesterol level, and by the absence of a positive correlation between serum cholesterol and cardiovascular mortality. However, recommendations on the prevention of cardiovascular and non-cardiovascular illness should be based on findings from prospective intervention studies, and must not be changed as a result of the present *post-hoc* analysis in selected patients with hypertension.

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