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ORIGINAL ARTICLE

Serum total cholesterol levels and all-cause mortality in a home-dwelling elderly population: a six-year follow-up

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Abstract

Objective. To investigate the association between serum total cholesterol and all-cause mortality in elderly individuals aged ≥ 75 years. *Design.* A prospective cohort study with a six-year follow-up. *Setting and subjects.* A random sample (n = 700) of all persons aged ≥ 75 years living in Kuopio, Finland. After exclusion of participants living in institutional care and participants using lipid-modifying agents or missing data on blood pressure and cholesterol levels, the final study population consisted of 490 home-dwelling elderly persons with clinical examination. We used the Cox proportional hazard model and the propensity score (PS) method. *Main outcome measure.* All-cause mortality. *Results.* In an age- and sex-adjusted analysis, participants with S-TC ≥ 6mmol/l had the lowest risk of death (hazard ratio, HR = 0.48, 95% CI 0.33–0.70) compared with those with S-TC < 5 mmol/l. HR of death for a 1 mmol increase in S-TC was 0.78. In multivariate analyses, the HR of death for a 1 mmol increase in S-TC was 0.82 and using S-TC < 5 mmol/l as a reference, the HR of death for S-TC ≥ 6 mmol/l was 0.59 (95% CI 0.39–0.89) and for S-TC 5.0–5.9 mmol/l, the HR was 0.62 (95% CI 0.42–0.93). In a PS-adjusted model using S-TC < 5 mmol/l as a reference, the HR of death for S-TC ≥ 6 mmol/l was 0.42 (95% CI 0.28–0.62) and for S-TC 5.0–5.9 mmol/l, the HR was 0.57 (95% CI 0.38–0.84). *Conclusions.* Participants with low serum total cholesterol seem to have a lower survival rate than participants with an elevated cholesterol level, irrespective of concomitant diseases or health status.

Key Words: *Aged, all-cause mortality, cholesterol, cohort, elderly*

It is well established that high serum total cholesterol (S-TC) is associated with greater all-cause and cardiovascular mortality in middle-aged adults [1,2]. A recent meta-analysis of 61 prospective observational studies involving almost 12 million person-years at risk at ages between 40 and 89 years confirmed that S-TC is a strong risk factor of mortality from ischaemic heart disease (IHD) [3]. Age, however, seemed to attenuate the relative effect of total cholesterol on IHD mortality. Interestingly, the association between total cholesterol and total stroke mortality was inverse in the age group 70–89 years and among those with systolic blood pressure above 145 mmHg. In addition, some observational studies of persons aged 65 years or older suggest that cholesterol might be inversely associated with total mortality [4–13]. In the European guideline, in general, the optimal goal for S-TC is < 5.0 mmol/l, and for patients with clinically established cardiovascular disease and patients with diabetes, the optimal treatment goal is < 4.5 mmol/l [14].

Cholesterol levels seem to decrease with age [5,7,15]. Low S-TC in the elderly has often been seen as a marker of frailty [12]. The inverse association between S-TC and mortality has also been interpreted to be due to confounding by chronic diseases

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In the European guideline, in general, the optimal goal for total cholesterol is < 5.0 mmol/l, and for patients with clinically established cardiovascular disease and patients with diabetes, the goal is < 4.5 mmol/l. Age, however, seemed to attenuate the relative effect of total cholesterol on mortality; in elderly populations, low serum total cholesterol has been associated with an increased risk of death.

- High cholesterol did not predict mortality in our study population.
- An inverse association between S-TC and mortality remained clear and significant when adjusted for comorbid diseases.
- There is a need for randomized controlled trials of the use of cholesterol-lowering medication in the elderly population, not only among fit old persons, but also in the elderly population with disabilities and several diseases.

such as dementia or malnutrition [16,17]. However, some epidemiological studies have shown that the inverse association remains obvious among the oldest old, even when adjusted for comorbid diseases [7,10,18].

The aim of this population-based cohort study was to examine the relationship between S-TC and six-year all-cause mortality in home-dwelling elderly aged 75 years or older with concomitant diseases.

Material and methods

This study is part of a larger population-based, multidisciplinary Kuopio 75+ health study focusing on the clinical epidemiology of diseases, medication, and functional capacity in elderly persons aged 75 years or older. The target population was a random sample (n = 700) of all the inhabitants of the City of Kuopio, Finland, who were aged 75 years or more on 1 January 1998 (n = 4518). The final cohort included 601 participants (86% of random sample). These participants attended a structured clinical examination and an interview conducted by a geriatrician and a trained nurse. Of these, 78 lived in an institution and 30 used lipid-modifying agents. Of the remaining 493 participants, three missed data on cholesterol and blood pressure measurements. Our final study population consisted of 490 home-dwelling elderly who were examined in 1998 and who did not use any serum lipid modifying agents and whose blood pressure and serum total cholesterol were measured.

The data were collected by means of interviews, clinical examinations, and clinical tests. A trained nurse at the outpatient clinic of a municipal hospital interviewed the participants regarding their use of medicines and recorded the medicines they were currently taking. The participants were also asked to bring their prescriptions and medicine containers. A geriatrician reviewed the medication and examined the subjects' overall physical and mental health. Medical records from the municipal health centre, home nursing service, local hospitals, and the Kuopio University Hospital were also available. The structured interview and examination also included items concerning sociodemographic factors, living conditions, and health status. In assessing self-rated health, for the analyses, the participants were classified as having good, moderate, or poor health.

Blood pressure was measured twice after 10 minutes of rest in a sitting position by the trained nurse using a calibrated mercury column sphygmomanometer, according to the international guidelines [19]. Serum total cholesterol was measured once in Kuopio University Hospital after 12 hours of fasting. All the serum total cholesterol assays were analysed in the Kuopio University Hospital laboratory using standard enzymatic techniques. The clinical criteria for dementia were those of DSM-IV [20]. Blood-pressure-lowering medication includes regular use of diuretics (loop diuretics excluded), beta-blocking agents, calcium-channel blockers, or agents acting on the renin-angiotensin system. The history of stroke, diabetes mellitus, cancer, hypertension, myocardial infarction, valvular insufficiency, coronary angioplasty, and bypass operation were defined as history at any time during life based on medical records or a geriatrician examination.

Mortality data were obtained from Statistics Finland, which is the National Health Register Authority in Finland. Life span was calculated from the date of examination in 1998 to 31 December 2003. There was no loss to follow-up. Written informed consent was obtained from the study participants or their relatives.

The data were analysed using SPSS 14.0 for Windows (Statistical Package for Social Sciences 14.0). Statistical significances of differences between exposure groups were tested using the chi-squared test and Kruskal–Wallis test. The participants were divided into thirds according to their serum total cholesterol (S-TC) level. Survival curves were estimated with the Kaplan–Meier method and compared using the log-rank test. The association between S-TC and mortality was analysed using the Cox proportional hazards model. The confounders in the initial multivariable model were age (continuous variable), sex, systolic blood pressure (continuous variable), self-reported

Table I. Baseline characteristics of 490 home-dwelling participants aged 75 years or more by serum total cholesterol level.

Characteristic	Serum total cholesterol level				
	< 5 mmol/l (n = 159)	5–5.9 mmol/l (n = 157)	≥ 6 mmol/l (n = 174)	Total (n = 490)	*P*-value
Age, years (SD)	82 (± 4.8)	81 (± 4.5)	80 (± 3.7)	81.4 (± 4.4)	< .001
Sex					
Male (%)	61 (38)	47 (30)	27 (16)	135 (28)	< .001
Mean SBP, mmHg (SD)	142 (± 24.6)	152 (± 23.2)	156 (± 23.4)	150 (± 24.4)	< .001
Mean S-TC, mmol/l (SD)	4.33 (± 0.5)	5.48 (± 0.3)	6.94 (± 0.8)	5.6 (± 1.2)	< .001
S-HDLC	1.24 (± 0.3)	1.48 (± 0.4)	1.63 (± 0.4)	1.5 (± 0.4)	
S-LDLC	1.86 (± 0.5)	2.64 (± 0.5)	3.62 (± 0.8)	2.7 (± 0.9)	
Self-reported health* (%)					
Good	42 (28)	57 (37)	73 (42)	172 (36)	.089
Moderate	78 (50)	69 (45)	75 (43)	222 (46)	
Poor	33 (22)	29 (19)	26 (15)	88 (18)	
MMSE, mean (SD)	23.3 (± 7)	25.3 (± 5)	25.4 (± 4)	24.7 (± 5)	.017
Use of medications (%)					
Blood pressure lowering medication†	101 (64)	104 (66)	118 (68)	323 (66)	.707
Long-acting nitrates	56 (35)	44 (28)	54 (31)	154 (31)	.383
Loop diuretics	40 (25)	11 (7)	15 (9)	66 (14)	< .001
Diseases (%)					
Dementia	35 (22)	21 (13)	19 (11)	75 (15)	.014
Diabetes mellitus	41 (26)	32 (20)	23 (13)	96 (20)	.015
Cancer	39 (25)	30 (19)	33 (19)	102 (21)	.363
Atrial fibrillation*	43 (27)	24 (15)	13 (8)	80 (17)	< .001
Valvular insufficiency*	48 (32)	40 (28)	51 (31)	139 (30)	.673
Coronary disease‡*	58 (37)	43 (28)	62 (36)	163 (34)	.189
Stroke	21 (13)	17 (11)	15 (9)	53 (11)	.404
NYHA‖ classification*					< .001
1	41 (30)	60 (39)	50 (30)	151 (33)	
2	46 (33)	64 (42)	81 (49)	191 (42)	
3 or 4	52 (37)	30 (20)	34 (21)	116 (25)	
Obstructive pulmonary disease	28 (18)	17 (11)	16 (9)	61 (13)	.048
Parkinson's disease	6 (4)	2 (1)	2 (1)	10 (2)	.167

Notes: *Variables with some missing values.
†Including: diuretics except loop diuretics, beta blocking agents, calcium channel blockers, or agents acting on the rennin-angiotensin system.
‡Including: myocardial infarction, bypass operation, or coronary angioplasty.
‖New York Heart Association functional classification

health, history of cancer, dementia, diabetes mellitus, atrial fibrillation, valvular insufficiency, stroke, use of loop diuretics, use of long-acting nitrates, use of blood-pressure-lowering medication, coronary disease (including myocardial infarction, bypass operation, or coronary angioplasty), obstructive pulmonary disease, and NYHA classification. Exclusion of a variable from this initial model was based on a change of less than 10% in the hazard ratio (HR) of serum total cholesterol. The variable was deleted unless it contributed to model fit ($p < 0.10$ in the likelihood ratio test). In a supplementary analysis, instead of individual confounders, a propensity score (PS) for each participant was included in the Cox model. The PS was estimated with a multinomial logistic regression model that included the original confounders listed above and the following variables: Mini-Mental State examination score, history of hypertension, myocardial infarction, bypass operation, coronary angioplasty, Parkinson's disease, and heart failure (Boston criteria). In the PS-adjusted model, coronary disease variables were included individually.

In addition, we examined the association between S-TC and mortality among the elderly with and without certain concomitant diseases. We classified participants as having heart disease if he/she had a history of myocardial infarction, atrial fibrillation, valvular insufficiency, bypass operation, pacemaker, coronary angioplasty or NYHA classification stage 3 or 4. Obstructive pulmonary disease refers to asthma and chronic obstructive pulmonary disease. Finally, the participants were divided into two groups according to their systolic blood pressure level.

Results

At the baseline, the mean age of the home-dwelling participants was 81.4 years (SD±4.4) and 72% (n = 355)

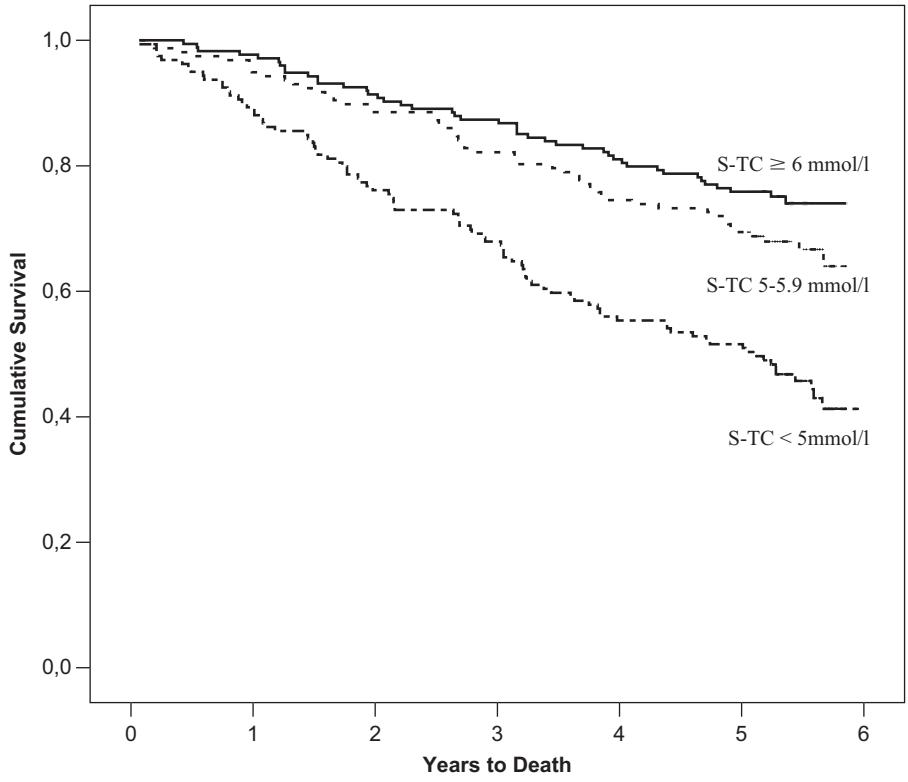

Figure 1. Serum total cholesterol (S-TC) and mortality using Kaplan–Meier survival analysis (Log rank $p < 0.001$).

of them were female. The mean S-TC was 5.6 mmol/l (SD ± 1.2 mmol/l, range 2.4–9.5 mmol/l). S-TC declined with age in women ($p < 0.05$), and at any age women had higher S-TC levels than had men ($p < 0.001$). The participants were divided into thirds based on serum total cholesterol levels (Table I). Compared with the upper thirds, the participants in the lowest third tended to be older, male, had lower systolic blood pressure, and more commonly used loop diuretics and suffered more commonly from diseases/morbid conditions such as dementia, diabetes mellitus, obstructive pulmonary diseases, and heart diseases.

During the six-year follow-up, 185 participants (38%) died. The participants with S-TC<5 mmol/l had the highest risk of death (Figure 1). The mean survival time among the participants with S-TC <5 mmol/l was 4.1 years, while among those with S-TC ≥ 6 mmol/l it was 5.1 years. When S-TC was treated as a continuous variable, the age- and sex-adjusted HR of death for each 1 mmol increase in S-TC was 0.78 (95% CI 0.68–0.89). In the multivariable analyses, the HR of death for a 1 mmol increase in S-TC was 0.82 (95% CI 0.70–0.95, $p = 0.008$). In addition, age (HR = 1.12, 95% CI

Table II. Hazard ratios (HR) of death among participants according to serum total cholesterol (S-TC) thirds calculated from multivariate Cox proportional hazards models.

S-TC	HR Model 1[1]	HR Model 2[2]	HR Model 3[3]
< 5 mmol/l	1 (ref)	1 (ref)	1 (ref)
5–5.9 mmol/l	0.57 (95% CI 0.40–0.80)	0.62 (95% CI 0.42–0.93)	0.57 (95% CI 0.38–0.84)
≥ 6 mmol/ll	0.48 (95% CI 0.33–0.70)	0.59 (95% CI 0.39–0.89)	0.42 (95% CI 0.28–0.62)

Notes: Cox proportional hazard model. [1]Adjusted for age and sex.
[2]Adjusted for age, atrial fibrillation, dementia, use of loop diuretics, stroke. Variables in the initial model: systolic blood pressure (continuous variable), sex, self-reported health, diabetes mellitus, history of cancer, valvular insufficiency, coronary disease (including myocardial infarction, bypass operation, or coronary angioplasty), use of long-acting nitrates, use of blood-pressure-lowering medication, obstructive pulmonary disease, NYHA classification (New York Heart Association functional classification).
[3]Propensity-score-adjusted model. Variables in the model: age (continuous variable), atrial fibrillation, dementia, NYHA classification, systolic blood pressure (continuous variable), use of loop diuretics, Mini-Mental State examination score, sex, self-reported health, diabetes mellitus, history of cancer, valvular insufficiency, history of hypertension, myocardial infarction, bypass operation, use of long-acting nitrates, use of blood-pressure-lowering medication, obstructive pulmonary disease, Parkinson's disease, heart failure (Boston criteria).

Table III. Mortality of participants with and without concomitant diseases or symptoms adjusted by age and sex.

Disease or symptom	n	HR (95% CI)	Disease or symptom	n	HR (95% CI)
History of hypertension	309		No history of hypertension	179	
< 5 mmol/l	89	1 (ref)	< 5 mmol/l	69	1 (ref)
5–5.9 mmol/l	100	0.66 (0.42–1.04)	5–5.9 mmol/l	57	0.46 (0.27–0.81)
≥ 6 mmol/l	120	0.51 (0.32–0.82)	≥ 6 mmol/l	53	0.43 (0.22–0.83)
Current hypertension (SBP ≥ 140 mmHg)	344		No current hypertension (SBP < 140 mmHg)	176	
< 5 mmol/l	84	1 (ref)	< 5 mmol/l	82	1 (ref)
5–5.9 mmol/l	121	0.68 (0.42–1.08)	5–5.9 mmol/l	52	0.54 (0.32–0.93)
≥ 6 mmol/l	139	0.59 (0.36–0.98)	≥ 6 mmol/l	42	0.43 (0.22–0.81)
Heart disease*	316		No heart disease[1]	140	
< 5 mmol/l	113	1 (ref)	< 5 mmol/l	32	1 (ref)
5–5.9 mmol/l	99	0.51 (0.34–0.77)	5–5.9 mmol/l	49	0.81 (0.39–1.71)
≥ 6 mmol/l	104	0.47 (0.30–0.73)	≥ 6 mmol/l	59	0.59 (0.27–1.30)
Stroke	53		No stroke	437	
< 5 mmol/l	21	1 (ref)	< 5 mmol/l	159	1 (ref)
5–5.9 mmol/l	17	0.43 (0.16–1.14)	5–5.9 mmol/l	140	0.58 (0.40–0.84)
≥ 6 mmol/l	15	1.66 (0.25–1.72)	≥ 6 mmol/l	138	0.45 (0.29–0.68)
Obstructive pulmonary disease	61		No obstructive pulmonary disease	428	
< 5 mmol/l	28	1 (ref)	< 5 mmol/l	130	1 (ref)
5–5.9 mmol/l	17	0.30 (0.11–0.83)	5–5.9 mmol/l	140	0.62 (0.43–0.90)
≥ 6 mmol/l	16	0.96 (0.35–2.63)	≥ 6 mmol/l	158	0.46 (0.30–0.69)
History of cancer	102		No history of cancer	386	
< 5 mmol/l	33	1 (ref)	< 5 mmol/l	119	1 (ref)
5–5.9 mmol/l	30	0.52 (0.26–1.05)	5–5.9 mmol/l	126	0.60 (0.40–0.90)
≥ 6 mmol/l	39	0.45 (0.21–0.93)	≥ 6 mmol/l	141	0.50 (0.32–0.79)
Dementia	75		No dementia	415	
< 5 mmol/l	35	1 (ref)	< 5 mmol/l	155	1 (ref)
5–5.9 mmol/l	21	0.51 (0.26–1.02)	5–5.9 mmol/l	136	0.61 (0.41–0.92)
≥ 6 mmol/l	19	0.58 (0.25–1.32)	≥ 6 mmol/l	124	0.51 (0.33–0.79)

Notes: [1]Including myocardial infarction, atrial fibrillation, valvular insufficiency, bypass operation, pacemaker, coronary angioplasty, NYHA classification 3 or 4. S-TC 5-5.9 mmol/l S-TC ⩾ 6 mmol/l S-TC < 5 mmol/l.

1.08–1.16, p < 0.001), dementia (HR = 2.71, 95% CI 1.84–3.98, p < 0.001), use of loop diuretics (HR = 1.98, 95% CI 1.34–2.94, p = 0.001), and atrial fibrillation (HR = 1.60, 95% CI 1.09–2.37, p = 0.018) were significantly associated with the risk of death.

Using S-TC <5 mmol/l as the reference value, the age- and sex-adjusted HR of death for S-TC ≥6 mmol/l was 0.48 (95% CI 0.33–0.70) and for S-TC 5.0–5.9 mmol/l, the HR was 0.57 (95% CI 0.40–0.80) (Table II). In a multivarible analysis using the S-TC < 5 mmol/l as a reference value, the HR of death for S-TC ≥ 6 mmol/l was 0.59 (95% CI 0.39–0.89) and that of S-TC 5.0–5.9 mmol/l was 0.62 (95% CI 0.42–0.93). In the PS-adjusted model, the respective HRs were 0.42 (95% CI 0.28–0.62) and 0.57 (95% CI 0.38–0.84).

The effect of S-TC on mortality was studied separately in participants with and without concomitant diseases (Table III). When adjusting for sex and age, an inverse association between S-TC and mortality was seen in elderly persons without the concomitant diseases considered here, i.e. dementia, stroke, obstructive pulmonary disease, and no history of hypertension or cancer. Using S-TC <5 mmol/l as the reference value, high S-TC (≥ 6 mmol/l) was associated with decreased mortality in participants with SBP < 140 mmHg (age- and sex-adjusted HR = 0.43, 95% CI 0.22–0.81). In participants with SBP ≥ 140mmHg, the association was attenuated but was significant.

Discussion

Principal findings

We found that low S-TC was associated with an increased risk of all-cause mortality during a six-year follow-up among home-dwelling elderly aged 75 years and older who did not use serum lipid modifying medication. The inverse association remained clear and significant when adjusted for comorbid diseases. Furthermore, high S-TC and low mortality was consistently seen in elderly persons without concomitant diseases such as dementia, stroke, obstructive pulmonary disease, and in those with no history of hypertension or cancer. This association was even evident in persons with heart disease. On the other

hand, previous studies have established that high levels of cholesterol in midlife are risk factors for many of these diseases [2,21].

Relation to other studies

Our results support previous reports on increased risk of death associated with low total cholesterol [4–13]. Accordingly, the participants with the lowest cholesterol levels had a poorer health status at the baseline. While we were able to control for over 20 different comorbidities and other confounders by means of propensity score adjustment and we observed considerable overlap in the scores among the exposure groups (data not shown), a low total cholesterol level may still be an indicator of unmeasured frailty or poor health in this population.

All our participants were 75 years or older with a mean of over 81 years at the baseline, a value higher than in many other studies [8,10,13]. Therefore, it is possible that our participants compared with those who died before the age of 75 were less susceptible to diseases associated with high cholesterol, either as a result of a lack of additional risk factors (smoking, diabetes, hypertension) or due to some undefined protective factors. However, due to non-comparability of the persons with low and high cholesterol levels in the presence of unmeasured risk factors, the estimates of the effects of total cholesterol on mortality observed here and in other studies among the elderly (i.e. survivors) do not necessarily reflect causal effects [22]. Another important difference compared with the previous studies is that our study consisted of a random sample of the elderly population with wide inclusion criteria, and more than two out of three participants were women. Therefore, the generalizability of the study results to the general elderly population in Finland is presumably good.

Study strengths and weaknesses

The present study has several strengths compared with earlier studies. First, use of a geriatrician in examining the participants' overall physical and mental health increased the quality of data collection and thus decreased misclassification of study variables. Second, by means of propensity score adjustment it was possible to control for more confounders than it would have been using only a traditional multivariable adjustment. On the other hand, S-TC was measured only once; therefore, the observed associations between S-TC and mortality may be weakened by misclassification of the main exposure variables. It is notable that in our study there was no loss to follow-up.

This study is an observational study on the association between untreated cholesterol and mortality. Therefore, it is not possible to make any conclusions about the benefits and harms of lipid-lowering treatment of the elderly, because the effect of total cholesterol level on mortality may be different in those using lipid-lowering medication.

High cholesterol did not predict mortality in our study population. On the contrary, low cholesterol levels were associated with higher mortality. This association seems to be only partly explained by frailty. To find out the effects of cholesterol on survival and incidence of disease in old age, we need randomized controlled trials of statins in the elderly population, not only among fit old persons, but also in the elderly population with disabilities and several diseases.

Although the scientific evidence strongly supports lipid lowering for primary and secondary prevention of coronary heart disease in the general population, trials specifically designed to define the role of such therapy in older patients are limited, and current recommendations are derived mainly from sub-analyses of available data. In the light of our results, only secondary prevention for proven ischaemic heart disease by lipid-lowering interventions seems to be justified in patients aged over 75 years.

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Conflict of interests

None declared.

Ethical approval

The study was approved by the ethics committee of the Hospital District of Northern Savo and Kuopio University Hospital.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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