Papers

Cholesterol reduction and non-illness mortality: meta-analysis of randomised clinical trials

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Abstract

Objective To investigate the association between cholesterol lowering interventions and risk of death from suicide, accident, or trauma (non-illness mortality).

Design Meta-analysis of the non-illness mortality outcomes of large, randomised clinical trials of cholesterol lowering treatments.

Studies reviewed 19 out of 21 eligible trials that had data available on non-illness mortality.

Interventions reviewed Dietary modification, drug treatment, or partial ileal bypass surgery for 1-10 years

Main outcome measure Deaths from suicides, accidents, and violence in treatment groups compared with control groups.

Results Across all trials, the odds ratio of non-illness mortality in the treated groups, relative to control groups, was 1.18 (95% confidence interval 0.91 to 1.52; P = 0.20). The odds ratios were 1.28 (0.94 to 1.74; P = 0.12) for primary prevention trials and 1.00 (0.65 to 1.55; P = 0.98) for secondary prevention trials. Randomised clinical trials using statins did not show a treatment related rise in non-illness mortality (0.84, 0.50 to 1.41; P = 0.50), whereas a trend toward increased deaths from suicide and violence was observed in trials of dietary interventions and non-statin drugs (1.32, 0.98 to 1.77; P = 0.06). No relation was found between the magnitude of cholesterol reduction and non-illness mortality (P = 0.23).

Conclusion Currently available evidence does not indicate that non-illness mortality is increased significantly by cholesterol lowering treatments. A modest increase may occur with dietary interventions and non-statin drugs.

Introduction

Many people are now trying to lower their serum cholesterol concentrations in order to prevent coronary heart disease. Modification of diet is the first line intervention for hypercholesterolaemia, but as it has limited efficacy,[1][2] a rapidly growing number of people are taking cholesterol lowering drugs.[3] As with all broadly prescribed, preventive treatments, it is important to establish that long term cholesterol reduction does not have severe adverse effects. Ten years ago, evidence supporting the efficacy of lowering cholesterol concentrations in prevention of coronary heart disease was just beginning to accumulate. At that time, data from randomised clinical trials raised concerns that reducing cholesterol concentrations might increase cancer mortality and deaths from suicides, accidents, and violence (non-illness mortality).[4–6]

A powerful class of cholesterol lowering drugs has been introduced in the past decade—hydroxymethylglutaryl coenzyme A reductase inhibitors, or statins. Several large clinical trials have shown that these drugs reduce major cardiovascular events by 20-30%.[7] The trials also indicated that treatment with a statin for five to six years does not affect mortality from cancer. Nevertheless, the carcinogenic properties of cholesterol lowering drugs have been noted in some laboratory research,[8] and the potential effect of statins on rates of cancer in humans requires further study and longer follow up.

Whether non-illness mortality increases with cholesterol reduction also remains unclear.[9–11] Associations have been reported between low serum cholesterol concentrations and non-illness mortality,[12] suicidal behaviour,[13–15] violent crime,[16] and impulsive aggression and personality disorders.[17–19] However, a recent case-control study found that neither fatal nor non-fatal injuries were related to use of cholesterol lowering drugs.[20] Although suicides, accidents, and trauma are a leading cause of premature death, they are relatively uncommon among participants in clinical trials. This hinders the study of treatment effects and may be due to underrepresentation of people at risk of death from these causes (by exclusion of people with a history of mood disorder, other psychiatric illness, substance misuse, or antisocial behaviour). A 1990 meta-analysis of 103 deaths due to suicide or violence among men participating in large primary prevention trials found that non-illness mortality was increased significantly by cholesterol lowering diets and drugs.[4] This quantitative review re-evaluates the potential effects of cholesterol interventions on non-illness mortality, adding outcomes reported among women, data from secondary prevention trials, and the findings of recent clinical trials of statins. We included intervention specific analyses because statins and other treatments have been found to differ significantly in their effects on non-coronary heart disease mortality.[21]

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Details of the trials included in the meta-analysis and their full references are available on the BMJ's website

Methods

Selection and description of studies

We included clinical trials of cholesterol lowering treatments in which participants were randomly assigned to a cholesterol lowering intervention or a control group, the mean serum cholesterol concentration in the control group remained relatively stable ($\leqslant 5\%$ variation) during the trial, and other interventions (such as antihypertensive drugs or advice on stopping smoking or stress reduction) were not administered preferentially to participants in the treatment group. We included only trials that were designed to measure effects of treatment on clinical events and mortality. Trials intended to study treatment effects on serum lipid concentrations and tolerability and those examining preclinical outcomes (angiographic findings) typically lack procedures for following subjects who withdraw from the study and independent monitors to adjudicate cause of death.

We identified studies by using the ancestry approach (locating previous studies cited in reference lists of already identified studies and published review articles) and computer based literature searches of Medline from 1966 to March 2000. The search strategy paired the term "controlled clinical trial" with each of the following: "cholesterol," "diet (fat restricted)," and "anticholesterolemic drugs."

The computerised literature searches identified 275 references, but only a few were clinical trials of cholesterol reduction. Together with trials accumulated by the ancestry approach, we had a total of 64 trials for consideration. Twenty one met our inclusion criteria (see *BMJ*'s website for list of trials and details). The most common reasons for exclusion were the use of multifactorial risk interventions and studies not designed to monitor clinical events and cause specific mortality. The Veterans Administration high density lipoprotein cholesterol trial was not included because it did not study the effects of cholesterol lowering. We extracted data from the primary publication, supplemented by subsequent reports when available.[22 23]

The reports of 15 of the 21 eligible trials contained data on non-illness mortality. We sought data from the authors for the other six trials[w9 w11 w13 w14 w20 w21] and for two trials for which non-illness mortality data were incomplete.[w1 w3] Investigators provided previously unpublished non-illness mortality data for four trials.[w9 w11 w13 w14] Therefore, we were able to include data from 19 of the 21 trials meeting the meta-analysis selection criteria. The two trials for which non-illness mortality was not available (both secondary prevention trials of clofibrate) and the two with incomplete results were comparatively small, together accounting for only 3% of the trial data in terms of patient years of observation.

Analysis of data

For each trial, we constructed 2×2 contingency tables enumerating the number of non-illness related deaths (accidents, violence, and suicide) and the number of participants not dying of non-illness causes separately for the intervention and control groups. These tables were combined according to the Mantel-Haenszel procedure,[24] as modified by Yusuf and Peto[25] and

previously described by us.[4] This analysis generates a summary odds ratio and associated 95% confidence interval for non-illness mortality in the treated participants relative to controls.

We assessed the association of non-illness mortality with the average amount of cholesterol reduction through a weighted regression model. The dependent variable in the regression analyses was the log odds ratio of non-illness mortality for the intervention group versus the control group across the individual studies. To include studies containing groups with no deaths from non-illness causes, we assigned a value of 0.5 for the number of deaths in these groups. We performed a sensitivity analysis to examine the degree to which the results changed when a value of 0.01 or 0.1 was assigned as the number of deaths for these groups. Additionally, we fitted a model excluding the five studies that contained groups with no deaths from non-illness causes. These changes did not substantially affect the results. Analysis of the residuals found no evidence of any violation of the assumptions in the regression model.

Results

The table gives the non-illness mortality for the included trials. Trials were classified as primary prevention if criteria for participants' eligibility did not include a history of coronary heart disease; all or most participants in these studies were free of heart disease at entry. Secondary prevention trials were those consisting exclusively of people with clinically evident coronary heart disease. Most participants were men aged between 40 and 70 years. The primary prevention trials had a total of 42 500 participants and secondary prevention trials enrolled 28 204 participants. All but one trial assigned an equal number of participants to the intervention and control groups. The cholesterol lowering intervention was dietary in five trials, pharmacological in 13 trials, and surgical in one trial. Five of six trials published after 1990 used a statin as the cholesterol lowering intervention. Each treatment successfully lowered the average serum cholesterol concentration in the intervention group, relative to corresponding control conditions, although
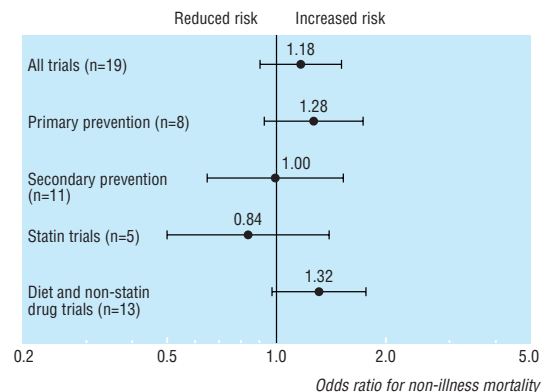
Odds ratios and 95% confidence intervals of non-illness mortality in treated groups, relative to controls, in randomised clinical trials of cholesterol reduction. Statins were used in two primary prevention and four secondary prevention trials

Mean cholesterol reduction and non-illness mortality in randomised clinical trials of cholesterol reduction

Trial (year published)	Primary or secondary prevention	Treatment	No of subjects randomised		Median follow up (years)	Mean cholesterol reduction (%)*	Non-illness mortality		Odds ratio† (95%CI)
			Treated	Control			Treated	Control	
Los Angeles Veterans Administration study (1969)‡	Primary	Diet	424	422	8.0	12.7	4	0	—
World Health Organization cooperative trial (1978)§	Primary	Clofibrate	5331	5296	5.3	9.0	24	25	0.95 (0.54 to 1.67)
Colestipol-Upjohn study (1978)¶	Primary	Colestipol	548	546	1.9	9.6	2	0	—
Lipid Research Clinics coronary primary prevention trial (1984)	Primary	Choletyramine	1906	1900	7.4	8.5	11	4	2.75 (0.92 to 8.26)
Helsinki heart study (1987)	Primary	Gemfibrozil	2051	2030	5.0	9.6	10	4	2.48 (0.81 to 7.63)
Minnesota coronary study (1989)	Primary	Diet	4541	4516	1.1	13.6	33	28	1.17 (0.71 to 1.94)
West of Scotland coronary prevention study (1995)	Primary	Pravastatin	3302	3293	4.9	20.0	5	6	0.83 (0.25 to 2.72)
Air Force/Texas coronary atherosclerosis prevention study (1998)	Primary	Lovastatin	3304	3301	5.2	19.3	1	3	0.33 (0.04 to 2.87)
Oslo diet-heart study (1966)**	Secondary	Diet	206	206	5.0	13.9	0	0	—
MRC soybean oil trial (1968)	Secondary	Diet	199	194	4.0	16	0	0	—
Scottish Society of Physicians clofibrate trial (1971)**	Secondary	Clofibrate	350	367	1.7	16	1	1	1.05 (0.07 to 16.86)
Coronary drug project (niacin, clofibrate) (1975)	Secondary	Niacin, clofibrate	1119, 1103	2789	6.2	9.9, 6.5	8,5	15	1.09 (0.52 to 2.29)
Stockholm ischaemic heart disease study (1988)**	Secondary	Clofibrate and niacin	279	276	5.0	13	1	0	—
Diet and reinfarction trial (1989)**	Secondary	Diet	1018	1015	2.0	3.5	1	1	1.00 (0.06 to 15.97)
Partial ileal bypass surgery (1990)	Secondary	Surgery	421	417	9.7	23.3	3	3	0.99 (0.2 to 4.94)
Helsinki heart study—ancillary study (1993)	Secondary	Gemfibrozil	311	317	5.0	8.5	1	1	1.02 (0.06 to 16.41)
Scandinavian simvastatin survival study (1994)	Secondary	Simvastatin	2221	2223	5.4	26	6	7	0.86 (0.29 to 2.55)
Cholesterol and recurrent events trial (1996)	Secondary	Pravastatin	2081	2078	5.0	20	8	4	2.00 (0.62 to 6.50)
Long term intervention with pravastatin in ischaemic disease (1998)	Secondary	Pravastatin	4512	4502	6.1	18	6	11	0.54 (0.2 to 1.45)

*Change in cholesterol concentration in intervention group during trial relative to control group.
†Not reported for trials with zero deaths in either the treatment or control group.
‡Data on non-illness mortality available for years 6-8 only: 318 intervention and 317 control subjects during that time.
§Mortality data by "intention to treat" reported in 1992.[23]
¶Only data for men available for inclusion in analyses.
**Unpublished non-illness mortality data obtained from trial investigators in early 2000.

the mean reduction varied appreciably across studies (3.5% to 26%). Together, these studies generated about 338 000 patient years of randomised clinical trial data.

The figure shows the odds ratios for non-illness mortality across trials in the treated groups compared with control subjects. The χ^2 test of heterogeneity among trial findings was not significant (P > 0.05). The overall odds ratio across trials was not significantly different from 1 (1.18, 95% confidence interval 0.91 to 1.52; P = 0.20). Subgroup analyses were conducted on primary and secondary prevention trials separately, and on the basis of previous meta-analyses, clinical trials using statins were separated from those using other cholesterol lowering interventions. These analyses also found no significant increases in the odds of non-illness mortality associated with cholesterol reduction. In the 13 trials of dietary therapy or non-statin drugs there was an increase in death from suicide and trauma in the treatment group compared with the control group, although this finding was not significant (odds ratio 1.32, 0.98 to 1.77; P = 0.06). Finally, in a weighted regression model, the odds ratio of non-illness mortality in the treatment group versus the control group in each of the trials was not related to the mean cholesterol reduction ($\beta = -0.04$ (SE 0.03), P = 0.23).

Discussion

In this updated meta-analysis we found that deaths from suicides, accident, and violence were not significantly increased among participants randomised to a cholesterol lowering intervention compared with those in the control groups. This was true for both primary and secondary prevention trials when they were analysed separately. Additionally, we found no association between the size of the magnitude of cholesterol reduction and the likelihood of death from suicide, accident, or trauma.

Although this analysis included a total of 215 people who died of non-illness causes, deaths from suicide, accidents and trauma are uncommon in randomised clinical trials of cholesterol reduction, and were less common than would be expected from population data. Among control participants in the two large American trials conducted in the 1990s,[w8 w18] mortality from suicide and other injuries was 25 per 100 000 person years compared with an age and sex specific normative population rate of about 68 per 100 000.[26] Therefore, we should consider whether selection of participants may have influenced the results of these studies. Clinical trials use rigorous eligibility criteria that either explicitly or indirectly exclude people with histories of mental disorder or substance

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What is already known on this topic

Cholesterol lowering treatments reduce cardiovascular mortality and morbidity

These treatments may affect mortality from other causes

What this study adds

Overall, cholesterol lowering treatments do not affect risk of death from suicide, accident, or trauma

Statins did not adversely affect non-illness mortality, but the effect of other treatments is less clear

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misuse.[w17] As a result, the trials exclude many people who may be particularly susceptible to the psychological effects of medical treatments. Whether selection bias influences reported treatment effects on non-illness mortality is difficult to determine, but the small number of deaths per trial may affect interpretation of our results. The confidence interval for the odds ratio across all 19 studies, for instance, straddles 1 and includes, at the upper boundary, a potential 50% increase in non-illness mortality.

The absence of a significant effect of treatment on non-illness mortality alone does not exclude the possibility of cholesterol reduction having any adverse effects on psychological wellbeing or quality of life. Nevertheless, randomised controlled trials suggest that statins do not increase new psychiatric diagnoses and hospital admissions or non-fatal trauma[27 28] and may not adversely affect sleep[29] or self reported quality of life, mood, hostility, or anger expression.[30–32] These findings are clinically important because statins are now the most reliable and widely prescribed cholesterol lowering drugs. Statins have, however, been reported to reduce cognitive performance.[30 33]

Treatments for hypercholesterolaemia have varying effects on lipids and the rest of the body,[34 35] and these treatments may therefore affect the brain or behaviour differently.[36] Interestingly, risk of stroke falls during treatment in high risk patients taking statins but not in patients taking other cholesterol lowering interventions.[37] Earlier meta-analyses of cholesterol lowering diets and non-statin drug treatment found treatment related increases in non-illness mortality.[4 5 9] This effect is only marginally significant when recent trial data are included. Data on other behavioural outcomes during treatment with non-statin interventions are also mixed and incomplete. Studies in primates have found that consumption of low fat and low cholesterol diets potentiates aggressive behaviour and decreases social affiliation.[38 39] In humans, several dietary interventions have been found to be free of adverse effects on mood but, like statins, may induce subtle cognitive decrements.[40 41]

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Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk)

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Abstract

Objective To examine the value of glycated haemoglobin (HbA_{1c}) concentration, a marker of blood glucose concentration, as a predictor of death from cardiovascular and all causes in men.

Design Prospective population study.

Setting Norfolk cohort of European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk).

Subjects 4662 men aged 45-79 years who had had glycated haemoglobin measured at the baseline survey in 1995-7 who were followed up to December 1999.

Main outcome measures Mortality from all causes, cardiovascular disease, ischaemic heart disease, and other causes.

Results Men with known diabetes had increased mortality from all causes, cardiovascular disease, and ischaemic disease (relative risks 2.2, 3.3, and 4.2, respectively, P < 0.001 independent of age and other risk factors) compared with men without known diabetes. The increased risk of death among men with diabetes was largely explained by HbA_{1c} concentration. HbA_{1c} was continuously related to subsequent all cause, cardiovascular, and ischaemic heart disease mortality through the whole population distribution, with lowest rates in those with HbA_{1c} concentrations below 5%. An increase of 1% in HbA_{1c} was associated with a 28% (P < 0.002) increase in risk of death independent of age, blood pressure, serum cholesterol, body mass index, and cigarette smoking habit; this effect remained (relative risk 1.46, P = 0.05 adjusted for age and risk factors) after men with known diabetes, a HbA_{1c} concentration ⩾7%, or history of myocardial infarction or stroke were excluded. 18% of the population excess mortality risk associated with a HbA_{1c} concentration ⩾5% occurred in men with diabetes, but 82% occurred in men with concentrations of 5%-6.9% (the majority of the population).

Conclusions Glycated haemoglobin concentration seems to explain most of the excess mortality risk of diabetes in men and to be a continuous risk factor through the whole population distribution. Preventive efforts need to consider not just those with established diabetes but whether it is possible to reduce the population distribution of HbA_{1c} through behavioural means.

Introduction

The global prevalence of diabetes is predicted to rise from 135 million in 1995 to 300 million by 2025.[1–3] In the United Kingdom, diabetes and associated complications cost the NHS £4.9bn a year, about a tenth of its entire budget.

Various blood glucose threshold concentrations have been proposed for the diagnosis of diabetes,[4–7] based on the relation to risk of microvascular complications of diabetes, particularly retinopathy.[8] However, people with diabetes are also at increased risk of macrovascular diseases such as coronary heart disease and stroke,[9] and it is uncertain whether the relation between blood glucose concentration and such diseases has a threshold or is a continuum.

Glycated haemoglobin (HbA_{1c}) concentration is an indicator of average blood glucose concentration over three months and has been suggested as a diagnostic or screening tool for diabetes.[8 10]

We examined the relation between glycated haemoglobin concentrations, diabetes, and subsequent mortality in men.

Participants and methods

We studied men in the Norfolk cohort of the European Prospective Investigation into Cancer and Nutrition. The cohort comprises 25 623 men and women aged 45-79 years resident in Norfolk, recruited from general practice age-sex registers.[11] Additional data were collected for the Norfolk cohort to enable us to exam-