Cholesterol lowering trials in coronary heart disease: frequency of citation and outcome //

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Abstract

Objective—To see if the claim that lowering cholesterol values prevents coronary heart disease is true or if it is based on citation of supportive trials only.

Design—Comparison of frequency of citation with outcome of all controlled cholesterol lowering trials using coronary heart disease or death, or both, as end point.

Subjects—22 controlled cholesterol lowering trials.

Results—Trials considered by their directors as supportive of the contention were cited almost six times more often than others, according to *Science Citation Index*. Apart from trials discontinued because of alleged side effects of treatment, unsupportive trials were not cited after 1970, although their number almost equalled the number considered supportive. In three supportive reviews the outcome of the selected trials was more favourable than the outcome of the excluded and ignored trials. In the 22 controlled cholesterol lowering trials studied total and coronary heart disease mortality was not changed significantly either overall or in any subgroup. A statistically significant 0.32% reduction in non-fatal coronary heart disease seemed to be due to bias as event frequencies were unrelated to trial length and to mean net reduction in cholesterol value; individual changes in cholesterol values were unsystematically or not related to outcome; and after correction for a small but significant increase in non-medical deaths in the intervention groups total mortality remained unchanged (odds ratio 1.02).

Conclusion—Lowering serum cholesterol concentrations does not reduce mortality and is unlikely to prevent coronary heart disease. Claims of the opposite are based on preferential citation of supportive trials.

Introduction

A causal association between dietary fat, serum cholesterol concentration, and coronary heart disease is reportedly proved beyond doubt,¹ and trial reviewers have concluded that the risk of coronary heart disease is reduced substantially when the serum cholesterol concentration is lowered.²⁻⁴

However, counter views⁵⁻⁸ have been presented, and in two reviews of cholesterol lowering trials only a non-significant lowering of coronary mortality⁹ or no evidence at all¹⁰ was found. As all five reviews were incomplete the disagreement may be due either to the proponents having based their idea on preferential citation of supportive trials or to their critics having ignored such trials. This study is an attempt to determine which of these opposing views is true by

analysing all controlled trials and comparing their frequency of citation with their outcome.

Methods

TRIAL SELECTION

The criteria for including a controlled trial were designed and successful lowering of cholesterol concentrations aimed at preventing coronary heart disease, and total mortality or incidence of coronary heart disease reported as end points. Compiling a fair selection of blind trials was not feasible because most cholesterol lowering drugs have typical and frequent side effects and laboratory records may reflect treatment. Both open and blind trials were therefore accepted. Trials using angiography were excluded.

The incidence of coronary heart disease was defined as including fatal myocardial infarctions and sudden deaths and definite, non-fatal myocardial infarctions in patients surviving to the end of the trial. Intention to treat data were used when available.

A total of 22 trials satisfied these criteria (table I). As different drug treatments were used in the five large branches of the coronary drug project^{19 22-24} they were analysed separately, making a total of 26 trials. In the trial of Marmorston *et al*¹² three different oestrogen preparations were used but because of their small size the three groups were treated as one.

In five trials the participants were stratified into intervention and control groups by age, sex, previous coronary heart disease, other diseases, or various laboratory test results^{12 13 25 34 35}; in one trial cluster allocation was used³²; in the rest random allocation was used.

Two trials^{13 26} did not give mortality from coronary heart disease, four^{14 15 20 21} did not give total mortality, and three^{12 13 26} did not give the number of non-fatal cases of coronary heart disease. Five trials included both sexes, but in three^{20 21 34} it was not possible to extract all relevant figures for each sex and event separately. Thus the number of people at risk for each event differed slightly in the subgroup calculations.

CALCULATIONS

For each event odds ratios and 95% confidence intervals for treatment groups versus control groups were calculated. Odds ratios were the ratio between events and non-events in the treatment group and events and non-events in the control group. Confidence intervals were derived by the logit method.

To test whether an odds ratio differed significantly from unity the difference between the observed (O) and expected (E) numbers of each event in each trial was calculated. E was $d \times n/N$, where d was the total number of events, n the number of subjects in the treatment group, and N the number of subjects in both groups together. The Z statistic was derived from

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FIG 1—Mean annual citations of trials or trial branches considered supportive (right) by authors as regards non-fatal coronary heart disease and of trials considered unsupportive (left).
○=Intervention group <200 subjects. ◐=Intervention group 200-1000 subjects. ●=Intervention group >1000 subjects. Open symbols=Primary prevention. Closed symbols=secondary prevention.

(O-E)/√V with two tailed p=0.05 corresponding to Z=1.96, and the variance (V) of each finding was derived from E(1-n/N)(N-d)/(N-1).

With the Mantel-Haenszel test as used by Yusuf *et al*¹⁶ mean weighted odds ratios with 95% confidence intervals and Z scores were calculated for all trials together and for various constellations of trials—that is, unifactorial and multifactorial, drug and dietary, primary and secondary preventive trials, and trials of varying length.

The mean annual number of citations of the trials according to *Science Citation Index* was calculated when possible up to five years after their publication. The number of mutual citations between the trials was also recorded and analysed. Only citations which appeared in the main report of the trial were considered. The mean weighted odds ratio was calculated for the trials selected for the mentioned reviews^{2-4 9 10} and for those excluded or overlooked.

Results

CITATION ANALYSIS

To study the influence of trial outcome on frequency of citation the trials were divided into two groups—those (n=14) regarded by the authors as supportive and those (n=10) considered unsupportive. (Most regarded by the authors as trials supportive were not supportive by conventional statistics (table I)). The multiple risk factors intervention trial²⁹ was excluded from this analysis as owing to its small effect on serum cholesterol concentration it was considered inconclusive (fig 1).

The mean annual number of citations of the suppor-

tive trials was 40 and of the unsupportive trials 7.4. Frequent citation of a paper was not correlated with trial size (fig 1), nor was it due to its having been published in a major journal—that is, the *New England Journal of Medicine*, *Lancet*, *BMJ*, or *JAMA*. Supportive trials published in major journals (n=8) were cited on average 61 times a year and unsupportive trials (n=10) eight times a year. This difference was also evident when comparing papers published in the same journal. Thus in the first four years after its publication the supportive Lipid Research Clinics trial³⁰ was cited 109, 121, 202, and 180 times each year whereas the unsupportive trial of Miettinen *et al*³¹ was cited six, five, three times, and once each year.

Even minor differences in outcome were reflected in citation frequency. The Newcastle trial²¹ with an odds ratio of 0.58 (morbidity and mortality from coronary heart disease combined) was cited 12 times a year whereas the Scottish trial²⁰ with an odds ratio of 0.82, published in the same issue of the journal, was cited only nine times each year.

The total number of mutual citations was 72:49 to supportive or inconclusive (multiple risk factor intervention) trials, 23 to unsupportive ones (fig 2). Nine of the citations to unsupportive trials concerned the discontinued branches of the coronary drug project.^{19 22 23} As these trials were considered as choice failures by the investigators (wrong drug) and not real treatment failures only 14 citations concerned trials which were considered unsupportive.

Only four supportive trial reports cited unsupportive trials.^{12 13 16 18} Thus 10^{20 21 24 25 27 28 30 32-34} of 14 reports of trials considered supportive or inconclusive did not mention any unsupportive trial.

TABLE 1—Pertinent data from trials

Trials	Type of study	Duration (years)	Mean annual citations	No of investigated individuals intervention group/controls	All deaths		Fatal coronary heart disease		Non-fatal coronary heart disease		Mean initial serum cholesterol (mmol/l)	Mean cholesterol difference (%)
					No (intervention group/controls)	Odds ratio	No (intervention group/controls)	Odds ratio	No (intervention group/controls)	Odds ratio		
Oliver and Boyd ¹¹	SUDr	5	12	50/50	17/12	1.63	13/10	1.41	5/8	0.58	6.19	9.5
Marmorston <i>et al</i> ¹⁵	SUDr	5	6†	285/147	71/32	1.19	63/29	1.15				
Stamler <i>et al</i> ¹¹	SUDr	5	8†	156/119	37/40	0.61						
Research committee ¹⁴	SUDi	3	7	123/129			20/24	0.85	26/24‡	1.17	6.76	8.3
Rose <i>et al</i> ¹⁵	SUDi	2	7	28/52			5/4	2.60	3/7	0.77	6.84	8.8
Leren ¹⁶	SUDi	5	15†	206/206	41/56	0.67	37/50	0.68	24/31	0.74	7.70	13.9
MRC soyabean ¹⁷	SUDi	4	9	199/194	28/31	0.86	25/25	0.97	20/26	0.72	7.07	13.5
Dayton <i>et al</i> ¹⁸	PUDi	7	15†	424/422	174/177	0.96	41/50	0.80			6.06	12.7
Coronary drug project, 5 mg oestrogen ¹⁹	SUDr	1.5	12	1119/2789	91/193	1.19	67/133	1.27	56/76	1.88**	7.10	
Scottish Society ²⁰	SUDr	5	9†	350/367			34/35	1.02	20/37	0.54		16
	Men			288/305								
Newcastle ²¹	Women			62/62								
	SUDr	3-6	12†	244/253			23/38	0.61	27/37	0.73	6.71	11
Coronary drug project, dextrothyroxine ²²	Men			192/208			2/6	0.26			6.37	10
	Women			52/45							7.02	15
Coronary drug project, 2.5 mg oestrogen ²³	SUDr	3	11	1083/2789	160/339	1.25*	119/274	1.13	78/175	1.16	6.50	12
Coronary drug project, nicotinic acid ²⁴	SUDr	4.7	8	1101/2789	219/525	1.07	162/410	1.00	94/242	0.98		
Coronary drug project, clofibrate ²⁴	SUDr	6.2	78†	1119/2789	273/709	0.95	203/535	0.93	84/304	0.66**	6.55	9.9
Dorr <i>et al</i> ²⁵	SUDr	6.2	78	1103/2789	281/709	1.00	195/535	0.90	114/304	0.94	6.55	6.5
	PUDr (men)	2	8†	548/546	17/27	0.62	9/22	0.40	13/24	0.53	8.14	9.8
Woodhill <i>et al</i> ²⁶	PUDr (women)	2		601/583	20/21	0.92	10/9	1.08	22/19	1.13	8.40	9.8
	SUDi	5	<1	221/237	39/28	1.60					7.31	4.3
Committee of Principal Investigators, clofibrate ²⁷	PUDr	5.3	20†	5331/5296	128/87	1.47**	36/34	1.05	131/174	0.74*	6.47	8.5
Oslo Study Group ²⁸	PMDi	5	55†	604/628	16/24	0.68	6/14	0.44	13/22	0.61	7.54	9.1
Multiple risk factor intervention trial ²⁹	PMDi	7	185	6428/6438	265/260	1.02	115/124	0.93	162/156	1.04	6.19	2.9
Lipid Research Clinics ³⁰	PUDr	7.4	153†	1906/1900	68/71	0.95	30/38	0.78	125/149	0.82	7.28	9
Miettinen <i>et al</i> ³¹	PMDiDr	5	4	612/610	10/5	2.01	4/1	4.01	7/5	1.40	7.46	6.3
WHO Collaborative Group ³²	PMDi	6	9†	30489/26971	1325/1186	0.99	428/398	0.95	499/475	0.93		1
Helsinki heart study ³³	PUDr	5	164†	2051/2030	45/42	1.06	14/19	0.73	42/65	0.63*	7.02	9.9
Stockholm secondary prevention study ³⁴	SUDr	5	8†	279/276	61/82	0.66*	47/73	0.56	25/27	0.91	6.84	13
	Men			219/223								
Frantz <i>et al</i> ³⁵	Women			60/53								
	PUDi (men)	1.1	6	2197/2196	158/153	1.03	39/34	1.15	30/40	0.75	5.46	13.8
	PUDi (women)			2344/2320	111/95	1.16	22/20	1.09	40/27	1.47	5.46	13.8

S=Secondary prevention. P=Primary prevention. U=Unifactorial. M=Multifactorial.
Dr=Drug. Di=Diet.
*p<0.05; **p<0.01 (two tailed p=0.05 and p=0.01 correspond to Z=±1.96 and ±2.58).
†Trials considered supportive by their directors.

‡Including possible infarcts.

§Deaths from non-coronary causes were "equally distributed."

||Mean duration of trial for intervention group was 4.2 years, for the control group 5.3 years.

TABLE II—Mean weighted odds ratios of selected trials and of excluded and ignored trials in six trial reviews

Reviews	Selected criteria	Selected trials	Mean weighted odds ratio* (95% confidence interval) for selected trials†	Exclusion criteria	Excluded trials	Ignored trials	Mean weighted odds ratio† for excluded and ignored trials	Mean weighted odds ratio† (95% confidence interval) for all trials
Lipid Research Clinics ¹	U, P, S, Di, Dr	14, 16-18, 22, 24, 27, 30	$\left\{ \begin{array}{l} 1.04 (0.95 \text{ to } 1.13) \\ 0.92 (0.84 \text{ to } 1.01) \\ 0.80 (0.71 \text{ to } 0.89) \end{array} \right.$	Total mortality as only end point, sex hormones, <200 participants, <3 years	11-13, 15, 19, 23, 26	25	$\left\{ \begin{array}{l} 1.11 \\ 1.06 \\ 1.10 \end{array} \right.$	$\left\{ \begin{array}{l} 1.06 (0.98 \text{ to } 1.13) \\ 0.96 (0.88 \text{ to } 1.04) \\ 0.87 (0.79 \text{ to } 0.95) \end{array} \right.$
Holme ¹	U, M, P, S, Di, Dr	14-18, 20, 21, 24-30, 32-35	$\left\{ \begin{array}{l} 1.00 (0.95 \text{ to } 1.05) \\ 0.89 (0.83 \text{ to } 0.96) \\ 0.86 (0.80 \text{ to } 0.92) \end{array} \right.$	Diet and drugs in same trial, discontinued trials	19, 22, 23, 31	11, 12, 13	$\left\{ \begin{array}{l} 1.14 \\ 1.11 \\ 1.18 \end{array} \right.$	$\left\{ \begin{array}{l} 1.02 (0.98 \text{ to } 1.07) \\ 0.94 (0.88 \text{ to } 1.00) \\ 0.90 (0.84 \text{ to } 0.96) \end{array} \right.$
Rossouw <i>et al</i> ⁴	U, S, Di, Dr	14, 16, 17, 20, 21, 24, 34	$\left\{ \begin{array}{l} 0.92 (0.83 \text{ to } 1.03) \\ 0.88 (0.79 \text{ to } 0.98) \\ 0.85 (0.73 \text{ to } 1.00) \end{array} \right.$	<100 participants, <3 years, thyroxine, oestrogen	11-13, 19, 22, 23	15, 26	$\left\{ \begin{array}{l} 1.15 \\ 1.11 \\ 1.17 \end{array} \right.$	$\left\{ \begin{array}{l} 1.02 (0.95 \text{ to } 1.10) \\ 0.97 (0.89 \text{ to } 1.05) \\ 0.93 (0.83 \text{ to } 1.03) \end{array} \right.$
McCormick and Skrabanek ¹⁰	U, M, P, S, Di, Dr	27-33	$\left\{ \begin{array}{l} 1.02 (0.95 \text{ to } 1.09) \\ 0.93 (0.83 \text{ to } 1.04) \\ 0.88 (0.80 \text{ to } 0.96) \end{array} \right.$	Minor trials	11-18, 20-21, 26	19, 22-25	$\left\{ \begin{array}{l} 1.03 \\ 0.96 \\ 0.92 \end{array} \right.$	$\left\{ \begin{array}{l} 1.02 (0.97 \text{ to } 1.07) \\ 0.95 (0.89 \text{ to } 1.01) \\ 0.89 (0.84 \text{ to } 0.96) \end{array} \right.$
Muldoon <i>et al</i> ⁶	U, P, Di, Dr	18, 25, 27, 30, 33, 35	$\left\{ \begin{array}{l} 1.08 (0.96 \text{ to } 1.20) \\ 0.86 (0.70 \text{ to } 1.05) \\ 0.80 (0.70 \text{ to } 0.91) \end{array} \right.$	No	No	?		
Present review	U, M, P, S, Di, Dr	1-35	$\left\{ \begin{array}{l} 1.02 (0.97 \text{ to } 1.07) \\ 0.94 (0.88 \text{ to } 1.00) \\ 0.90 (0.84 \text{ to } 0.96) \end{array} \right.$	No	No	?		

U=Unifactorial. P=Primary prevention. S=Secondary prevention. M=Multifactorial. Di=Diet. Dr=Drug.
*Minor deviations from ratios given in reviews are due to other definitions of myocardial infarction.
†Upper line of figures=total mortality; middle line=coronary mortality; lower line=non-fatal coronary heart disease.

TABLE III—Mean weighted odds ratios and confidence intervals for three events; all trials and subgroups of trials

	All deaths		Fatal coronary heart disease		Non-fatal coronary heart disease	
	No*	Odds ratio (95% confidence interval)	No*	Odds ratio (95% confidence interval)	No*	Odds ratio (95% confidence interval)
All trials	24	1.02 (0.97 to 1.07)	27	0.94 (0.88 to 1.00)	24	0.90 (0.84 to 0.96)
Men only	21	1.02 (0.97 to 1.07)	22	0.95 (0.89 to 1.02)	19	0.90 (0.84 to 0.96)
Women only†	2	1.12 (0.87 to 1.44)	3	0.94 (0.58 to 1.51)	2	1.33 (0.91 to 1.95)
Unifactorial	20	1.04 (0.98 to 1.11)	23	0.94 (0.88 to 1.02)	20	0.87 (0.81 to 0.95)
Multifactorial	4	0.99 (0.92 to 1.07)	4	0.94 (0.83 to 1.06)	4	0.95 (0.85 to 1.05)
Primary prevention	12	1.02 (0.95 to 1.08)	12	0.92 (0.83 to 1.02)	11	0.83 (0.75 to 0.92)
Secondary prevention	12	1.02 (0.95 to 1.10)	15	0.96 (0.88 to 1.04)	13	0.96 (0.89 to 1.04)
Drugs‡	14	1.04 (0.97 to 1.12)	16	0.95 (0.87 to 1.03)	14	0.87 (0.79 to 0.95)
Diet‡	9	1.00 (0.94 to 1.06)	10	0.93 (0.84 to 1.03)	9	0.94 (0.85 to 1.04)
Duration:						
<5 years§	5	1.01 (0.87 to 1.19)	9	0.86 (0.69 to 1.08)	8	0.90 (0.73 to 1.10)
5 years	7	0.91 (0.76 to 1.09)	6	0.81 (0.65 to 1.00)	5	0.68 (0.53 to 0.86)
>5 years	7	1.00 (0.95 to 1.06)	7	0.93 (0.85 to 1.01)	6	0.87 (0.81 to 0.95)

*Number of trials or trial branches; men and women are recorded as separate trials when possible.
†Data from two trials^{19,21} with more favourable results from women could not be used.
‡Except trial of Miettinen *et al*¹⁹ which used both diet and drugs.
§Exclusive of three trials^{19,22,23} discontinued because of excess of events.
||Z score > ±2.58 (p<0.01).

Table II gives the selection criteria and mean weighted odds ratios for the selected trials in six trial reviews and also those of the excluded and ignored trials. Odds ratios for all three events (total mortality, coronary mortality, non-fatal coronary heart disease) were considerably lower for the selected trials in the three supportive reviews²⁻⁴ than for the excluded and ignored trials whereas there was no such difference in the unsupportive review of McCormick and Skrabanek.¹⁰ Even so, total mortality was unchanged in all reviews and coronary mortality only marginally reduced in two reviews.

EVENT FREQUENCIES

Table I gives pertinent data from the trials arranged chronologically. Figure 3 shows all odds ratios and 95% confidence intervals. The trials are arranged according to their odds ratios. The most supportive and most unsupportive trials were mostly small with large confidence intervals whereas most of the trials with odds ratios around unity were large with narrow confidence intervals, giving the whole display the shape of a sandglass with its waist against the line of unity. Thus with increasing precision of a trial its odds ratio approached unity.

Table III shows that odds ratios for total and coronary mortality did not differ significantly from unity, either overall or in any subgroup.

Non-fatal coronary heart disease events occurred in

2.76% of subjects in the intervention groups as against 3.08% of subjects in the control groups. Owing to the great number of subjects studied this difference of only 0.32% was statistically significant. A significant reduction was also found in the unifactorial, primary prevention, and drug trial subgroups.

The small percentage differences were overestimated because the three branches of the coronary drug project were discontinued after 1.5-4.5 years whereas the control group continued for more than six years. Odds ratios were not influenced as each trial was a unit when estimating the weighted means.

Odds ratios estimated for groups in trials of three different lengths showed that total mortality was unchanged and that mortality from coronary heart disease was higher in the long trials than in the short ones.

Mean unweighted odds ratio for all deaths in trials which did not use random allocation was 1.14 versus 0.89 in trials which did. For coronary mortality the mean odds ratio was 1.11 versus 0.91 whereas for non-fatal coronary heart disease it was almost the same (0.90 versus 0.96).

The numbers of deaths due to non-medical causes were given in 12 trials^{11 12 16-18 25 27 28 30 31 33 35} with a mean weighted odds ratio of 1.55 (95% confidence interval 1.11 to 2.16; p<0.05). Mean weighted odds ratio for all deaths in the same trials was 1.05 (95% confidence interval 0.95 to 1.17); with the exclusion of violent death it was 1.02 (0.91 to 1.13). The numbers of deaths from cancer were given in 14 trials^{11 16-19 24 25 27 28 30 31 33-35} with a mean weighted odds ratio of 1.15 (0.91 to 1.45).

No relation was found between the net mean cholesterol reduction in each trial and any of the end points

FIG 2—Mutual citations among trials.

($r=0.35$ for total mortality, 0.31 for coronary mortality, and 0.26 for incidence of non-fatal coronary heart disease; $p>0.1$ in all three). Net mean cholesterol reduction was taken as the percentage difference of serum cholesterol during the entire trial if available or possible to calculate or estimate graphically or, if not, the difference at the end of the trial. Consideration was

given both to the mean cholesterol concentration and to the number of participants at various times in the trial.

In 14 trials a relation between individual cholesterol changes and outcome had been sought by the investigators and found to be unsystematic^{16 18 27 28} or totally absent.^{12 17 20 22 24 26 29 34}

Discussion

In the diet-heart hypothesis faulty composition of the diet may increase the serum cholesterol concentration, and a high cholesterol concentration is a major cause of atherosclerosis and coronary heart disease. This notion has come from epidemiological studies and animal experiments, the results of which are only suggestive. To prove causality cholesterol lowering experiments on human beings are mandatory. Many such trials have been published, leaving a general impression that lowering the cholesterol concentration is beneficial.

My findings, however, show that the preventive effect of such treatment has been exaggerated by tendency in trial reports, reviews, and other papers cite supportive results only. Most striking was that in 16 trial reports published after 1970 a total of 48 supportive or inconclusive trials were cited but, with the exception mentioned above, not a single unsupportive one.

The question therefore remains: does lowering the blood cholesterol concentration prevent coronary heart disease and does it reduce mortality?

Combining all controlled trials known to me disclosed no effect on mortality, though there was a 0.32% reduction in non-fatal coronary heart disease. This effect was significant, but its veracity is questionable.

Firstly, outcome was unrelated to the degree of cholesterol lowering, either among trials or among participants. The lack of a relation among participants had been reported by Marmorston *et al*¹² in 1962 and was confirmed by many others but, although detrimental to the cholesterol hypothesis, it received little attention.

As further strong evidence against causality coronary mortality was only marginally and non-significantly improved. Total mortality was not improved at all, even after correction for excess mortality induced by the intervention. Any reduction in non-fatal coronary heart disease should reduce coronary mortality and also total mortality because coronary heart disease is the major cause of death in middle aged men in most affluent countries.

It is often said that most trials have been of too short duration. The argument rests on the favourable results from the 11 year follow up study of the nicotinic acid branch of the coronary drug project³⁷ (annual citation frequency 56). The clofibrate branch of the same trial, however, did not reduce mortality, and in the 9.6 year follow up study of the World Health Organisation's clofibrate study³⁸ (annual citation frequency 18) both total mortality and coronary mortality were significantly increased.

My findings also fail to support the argument for longer trials: long trials were rather worse off than short ones. Including the discontinued branches of the coronary drug project should have worsened the result for short trials and given an impression of long trials being more favourable—though it would have been necessary to explain why the number of events increased during the first years of intervention. All three events were more frequent in subjects treated for more than five years than in those treated for five years only.

Diagnosing myocardial infarction is difficult, and in the absence of necropsy evidence cases may be

FIG 3—Odds ratios and 95% confidence intervals for all events and all trials, and weighted mean. Odds ratio <1.0 indicates that intervention reduced number of events; odds ratio >1.0 indicates that intervention increased it. Narrow confidence intervals in some trials indicate great statistical strength and vice versa. ○=Primary prevention. ●=Secondary prevention.

missed.³⁹ In addition, this potential inaccuracy may have been skewed because many trials were open or drugs were used that have frequent and easily recognisable side effects. That the investigators were immune to the risks of unblindedness was contradicted by their reference lists: for two decades authors cited supportive trials only.

Supportive results are not only cited more often: they are also published more often. In a recent investigation⁴⁰ 44% of studies with null results, but only 15% of studies with statistically significant results, remained unpublished. Although randomised clinical trials are less prone to publication bias than uncontrolled studies,⁴⁰ a few unsupportive trials being withheld from publication could alone have introduced the trivial reduction in non-fatal coronary heart disease.

Some workers may have had valid reasons for excluding certain trials from citation, but the reasons in the supportive reviews in table II may be questioned.

To exclude a trial²⁶ because only total mortality was used as an end point is illogical as death is the only outcome which is absolutely free of bias. To exclude trials because they had been discontinued due to unforeseen side effects does not seem justified as the main "side effect" in two of them^{19,22} was coronary heart disease. The increased incidence of coronary heart disease in the hormone branches of the coronary drug project may rather have been a chance result of an unsuccessful randomisation because in one of the intervention groups in the trial of Marmorston *et al*¹² and in the double blind trial of Stamler *et al*,¹³ both of which used hormones, mortality was lowered.

Nor is there reason to exclude small or short trials. Although small trials may be inconclusive, they may be better designed and conducted than large ones. And if cholesterol lowering had effect who's to say whether a long trial with a modest degree of cholesterol lowering is more informative than a short one with more pronounced lowering?

Conclusion

Authors of papers on preventing coronary heart disease by lowering blood cholesterol values tend to cite only trials with positive results. The impression of success presented to doctors is false because the numbers of controlled cholesterol lowering trials in which total mortality and coronary mortality were reduced equal the numbers in which they were increased. This is due not to the trials having been too short or to the introduction of other causes of death but to ineffective treatment. Methods subject to bias, such as open trials or the use of drugs with characteristic side effects, or stratification instead of random allocation of participants, probably explain the overall 0.32% reduction recorded in non-fatal coronary heart disease.

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- 1 Gotto AM, LaRosa JC, Hunninghake D, Grundy SM, Wilson PW, Clarkson TB, *et al*. The cholesterol facts. A summary of the evidence relating dietary fats, serum cholesterol, and coronary heart disease. *Circulation* 1990;81:1721-33.
- 2 Lipid Research Clinics Program. The lipid research clinics coronary primary prevention trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA* 1984;251:365-74.
- 3 Holme I. An analysis of randomized trials evaluating the effect of cholesterol reduction on total mortality and coronary heart disease incidence. *Circulation* 1990;82:1916-24.
- 4 Rossouw JE, Lewis B, Rifkind BM. The value of lowering cholesterol after myocardial infarction. *N Engl J Med* 1990;323:1112-9.
- 5 Smith RL. Dietary lipids and heart disease. The contriving of a relationship. *American Clinical Laboratory* 1989;Nov:26-33.

- 6 Stehbens WE. Diet and atherogenesis. *Nutr Rev* 1989;47:1-12.
- 7 Oliver MF. Doubts about preventing coronary heart disease. Multiple interventions in middle aged men may do more harm than good. *BMJ* 1992;304:393-4.
- 8 Smith GD, Pekkanen J. Should there be a moratorium on the use of cholesterol lowering drugs? *BMJ* 1992;304:421-4.
- 9 Muldoon MF, Manuck SB, Matthews KA. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. *BMJ* 1990;301:309-14.
- 10 McCormick J, Skrabanek P. Coronary heart disease is not preventable by population interventions. *Lancet* 1988;ii:839-41.
- 11 Oliver MF, Boyd GS. Influence of reduction of serum lipids on prognosis of coronary heart-disease. A five-year study using oestrogen. *Lancet* 1961;ii:499-505.
- 12 Marmorston J, Moore FJ, Hopkins CE, Kuzma OT, Weiner J. Clinical studies of long-term estrogen therapy in men with myocardial infarction. *Proc Soc Exp Biol Med* 1962;110:400-8.
- 13 Stamler J, Pick R, Katz LN, Pick A, Kaplan BM, Berkson DM, *et al*. Effectiveness of estrogens for therapy of myocardial infarction in middle-age men. *JAMA* 1963;183:632-8.
- 14 Research Committee. Low-fat diet in myocardial infarction. A controlled trial. *Lancet* 1965;ii:501-4.
- 15 Rose GA, Thomson WB, Williams RT. Corn oil in treatment of ischaemic heart disease. *BMJ* 1965;ii:1531-3.
- 16 Leren P. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial. *Acta Med Scand* 1966; suppl 466:1-92.
- 17 Research Committee to the Medical Research Council. Controlled trial of soyabean oil in myocardial infarction. *Lancet* 1968;ii:693-700.
- 18 Dayton S, Pearce ML, Hashimoto S, Dixon WJ, Tomiyasu U. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. *Circulation* 1969;40:1-63.
- 19 Coronary Drug Project Research Group. The coronary drug project: initial findings leading to modification of its research protocol. *JAMA* 1970;214:1303-13.
- 20 Research Committee of the Scottish Society of Physicians. Ischaemic heart disease: a secondary prevention trial using clofibrate. *BMJ* 1971;iv:775-84.
- 21 Group of Physicians of the Newcastle upon Tyne Region. Trial of clofibrate in the treatment of ischaemic heart disease. *BMJ* 1971;iv:767-75.
- 22 Coronary Drug Project Research Group. The coronary drug project. Findings leading to further modifications of its protocol with respect to dextrothyroxine. *JAMA* 1972;220:996-1008.
- 23 Coronary Drug Project Research Group. The coronary drug project. Findings leading to discontinuation of the 2.5-mg/day estrogen group. *JAMA* 1973;226:652-7.
- 24 Coronary Drug Project Research Group. The coronary drug project. Clofibrate and niacin in coronary heart disease. *JAMA* 1975;231:360-81.
- 25 Dorr AE, Gundersen K, Schneider JC, Spencer TW, Martin WB. Colestipol hydrochloride in hypercholesterolemic patients—effect on serum cholesterol and mortality. *J Chronic Dis* 1978;31:5-14.
- 26 Woodhill JM, Palmer AJ, Leelarthapin B, McGilchrist C, Blacket RB. Low fat, low cholesterol diet in secondary prevention of coronary heart disease. *Adv Exp Med Biol* 1978;109:317-30.
- 27 Report from the Committee of Principal Investigators. A cooperative trial in the primary prevention of ischaemic heart disease using clofibrate. *Br Heart J* 1978;40:1069-103.
- 28 Hjermann I, Byre KV, Holme I, Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of a Randomised Trial in Healthy Men. *Lancet* 1981;ii:1303-10.
- 29 Multiple Risk Factor Intervention Trial Research Group. Multiple risk factor intervention trial. Risk factor changes and mortality results. *JAMA* 1982;248:1465-77.
- 30 Lipid Research Clinics Program. The Lipid Research Clinics coronary primary prevention trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984;251:351-64.
- 31 Miettinen TA, Huttunen JK, Naukkarinen V. Multifactorial primary prevention of cardiovascular diseases in middle-aged men. Risk factor changes, incidence, and mortality. *JAMA* 1985;254:2097-102.
- 32 World Health Organization European Collaborative Group. European collaborative trial of multifactorial prevention of coronary heart disease: final report on the 6-year results. *Lancet* 1986;ii:869-72.
- 33 Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, *et al*. Helsinki heart study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-45.
- 34 Carlson LA, Rosenhamer G. Reduction of mortality in the Stockholm ischaemic heart disease secondary prevention study by combined treatment with clofibrate and nicotinic acid. *Acta Med Scand* 1988;223:405-18.
- 35 Frantz ID, Dawson EA, Ashman PL, Gatewood LC, Bartsch GE, Kuba K, *et al*. Test of effect of lipid lowering by diet on cardiovascular risk. The Minnesota coronary survey. *Arteriosclerosis* 1989;9:129-35.
- 36 Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 1985;27:335-71.
- 37 Canner PJ, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, *et al*. Fifteen year mortality in coronary drug project patients: long-term benefit with niacin. *Journal of the American College of Cardiology* 1986;8:1245-55.
- 38 Committee of Principal Investigators. WHO cooperative trial on primary prevention of ischaemic heart disease using clofibrate to lower serum cholesterol: mortality follow-up. *Lancet* 1980;ii:379-85.
- 39 Zarling EJ, Sexton H, Milnor P. Failure to diagnose acute myocardial infarction. The clinicopathologic experience at a large community hospital. *JAMA* 1983;250:1177-81.
- 40 Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991;ii:867-72.

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