explanation for any effects seen. It is, of course, also important to seek out data from unpublished trials to avoid potential publication bias.

Ravnskov's report fails in all these respects.¹ Two trials did not allocate individual treatment by a randomisation procedure,^{2,3} and these cannot have ensured avoidance of non-random imbalances of variables prognostically important to outcome between the groups.⁴ Four trials tested multifactorial interventions, and two were not based on an intention to treat analysis.^{5,6} Avoiding analyses that are not intention to treat analyses is critically important since intention to treat analyses of the same data may generate results that are quantitatively and qualitatively different. An intention to treat analysis of each trial should be obtained or these results excluded. Four of the trials were of pharmacological doses of oestrogen in men and one of dextrothyroxine, both of which are long abandoned, and two of these trials were stopped prematurely. These interventions were confounded by cardiotoxic effects and should not be included.

Ravnskov claims that there is no decrease in mortality or morbidity from coronary heart disease with cholesterol reduction; this is in contrast to results of other meta-analyses.⁷⁻⁹ The conclusions are not supported by Ravnskov's data. The author shows a significant 10% reduction in coronary morbidity but dismisses this for several reasons, including allocation to treatment groups by stratification in some trials, suggesting that such allocation implies non-randomisation. But patients were randomised after being stratified by age, sex, and other factors.

The general finding has been of roughly a 20% decrease in morbidity from coronary heart disease and a 10% decrease in mortality from the disease for a 10% reduction in cholesterol concentration within a few years (R Peto, personal communication).⁶ Because most trials have been conducted in middle aged men at low risk of the disease there have collectively been too few deaths for the very small reductions in total mortality that would be expected from the modest effect of a 10% cholesterol reduction on coronary mortality to be reliably detected or excluded. Clear evidence of any effect of cholesterol lowering on total and non-coronary heart disease mortality will require trials with more power than those completed to date and, quite possibly, than those now being carried out.¹⁰

We believe that the balance of currently available evidence supports a policy in clinical practice of considering lipid lowering treatment for patients with hypercholesterolaemia when they are at high risk of premature coronary heart disease as the benefits of cholesterol reduction seem to be greatest in those most at risk.⁷ Unfortunately, many people who might benefit from advances in lipid lowering treatment, such as those with severe genetic hyperlipidaemias or with established coronary heart disease, are frequently undiagnosed and untreated. Let us now move the debate on to the definition and identification of groups who should receive lipid lowering treatment.

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- World Health Organisation European Collaborative Group. European collaborative trial of multifactorial prevention of coronary heart disease: final report on the 6-year results. *Lancet* 1986;i:869-72.
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EDITOR.—It would be regrettable if U Ravnskov's paper on the frequency of citation and outcome of cholesterol lowering trials challenged confidence in the issues that are not disputable—namely, that there is a strong relation between blood cholesterol concentrations and coronary heart disease and that intervention trials that include lowering blood cholesterol concentrations show a benefit in terms of a reduction in non-fatal coronary heart disease. Furthermore, strict dietary control and a reduction in smoking in men with high cholesterol concentrations may halve the rate of fatal heart attacks.² Ravnskov accuses the authors of papers on, and trials of, preventing coronary heart disease of selective citation, bias, and questionable veracity. But Ravnskov's paper is not free of bias: it ignores the weight of evidence that intervention including a reduction in blood cholesterol concentrations by diet and drugs limits progression and can lead to regression of atheroma.^{3,7}

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- Ravnskov U. Cholesterol lowering trials in coronary heart disease: frequency of citation and outcome. *BMJ* 1992;305:15-9. (4 July.)
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EDITOR.—U Ravnskov's conclusions are misleading.¹ Several of the trials unresponsive of cholesterol lowering were of treatment with oestrogens or thyroxine, agents with other actions that preclude their widespread use in preventing coronary heart disease and to study the effects of cholesterol lowering.

We have recalculated the odds ratios after excluding trials of these agents. The pooled odds ratios for all deaths and for fatal and non-fatal coronary disease were 0.83, 0.65, and 0.75 respectively (all highly significant) with a total study group of 114 932, clearly supporting cholesterol lowering. These figures contrast greatly with the odds ratios for the excluded trials of 1.14, 1.12 (both significant at $p < 0.05$), and 1.03

respectively. The numbers studied in the excluded trials were considerably lower at 13 194, accounting for only 10.3% of trial participants yet 20.3% of all deaths; this added considerable bias when Ravnskov pooled all the trials. It is unfortunate that the above data were not included in Ravnskov's subgroup analysis. Furthermore, Ravnskov excluded results from the 11 year follow up of the nicotinic acid branch of the coronary drug project, a major supportive trial,¹ but included the unresponsive early results.

We do not dispute the fact that frequent citation of reports tends to propagate a particular view. Twenty or so years ago, when many of the unresponsive studies were reported, however, there were fewer similar reports on lipid lowering with, consequently, a lower citation rate in the first four years after publication. Additionally, a report is more likely to cite another to support its conclusions. Indeed, this may be one reason why Ravnskov fails to mention the findings of the six studies of the regression of atheroma, none of which support Ravnskov's conclusions.

The poor relation between outcome and the degree of cholesterol lowering is not surprising as participants with higher concentrations are more likely to have a greater reduction with treatment but will also have worse pre-existing vascular disease.

Ravnskov's report shows how trials often bear little relation to clinical practice. The mean initial cholesterol concentrations in the trials given in table 1 show that, based on current recommendations,¹ most patients studied would not have received treatment other than dietary advice. We hope that clinical practice will not be swayed by the erroneous conclusions of this report.

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EDITOR.—One of the problems with meta-analyses of controlled trials is that if the array of trials studied encompasses primary prevention studies, secondary prevention studies, studies of various drugs, studies of dietary intervention, and unifactorial and multifactorial interventions then the data analysed are so heterogeneous as to be without meaning. U Ravnskov's meta-analysis of cholesterol lowering trials fits this description.¹

What many clinicians want to know is whether long term drug treatment in a young or middle aged patient whose cholesterol concentration remains raised despite dietary changes will reduce his or her chances of a cardiovascular event or premature death. Unfortunately, none of the primary intervention trials to date have been large enough to have the statistical power to have a reasonable chance of detecting a significant effect on mortality. Trials with more than 1500 subjects in the treatment and control groups have a fair chance of showing an effect of cholesterol lowering on cardiovascular risk if the follow up is over five years.

Only three primary prevention drug trials fit these criteria. All showed a reduction in cardiovascular events. The clofibrate trial showed a 20% lower incidence of ischaemic heart disease in the treated group compared with the controls, but the incidence of gall stones and total mortality were

1 Ravnskov U. Cholesterol lowering trials in coronary heart disease: frequency of citation and outcome. *BMJ* 1992;305:15-9. (4 July.)

2 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.

higher in the treated group²; for these two reasons the use of this particular drug has waned. The two other trials each showed a significant benefit in reduction of coronary risk with two very different drugs.^{3,4} This is strong evidence that use of carefully selected drugs to lower cholesterol concentration has an important clinical benefit. I do not believe that the meta-analysis alters this view.

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EDITOR,—U Ravnskov's paper is an impressive demonstration of the citation bias that favours references to supportive rather than unsupportive trials.¹ Ravnskov unintentionally illustrates this thesis by not mentioning the cholesterol lowering arm of our diet and reinfarction trial, the results of which were unsupportive or inconclusive, depending on the expectations, given a net cholesterol reduction of 3.6%.²

Similar analyses of trials in other topics of research would be illuminating. Publication bias is well recognised; citation bias must also be considered in the evaluation of medical evidence of all kinds.

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- 2 Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PL, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;ii:757-61.

EDITOR,—In most human endeavours winners get cited more often than losers because people are most interested in winners. Yet this citation bias does not negate the fact that winners usually win because they are better. So also with prevention trials: the successful ones get cited more often, but only if they are perceived to be better. For example, in U Ravnskov's table I, strikingly positive trials such as that of Dorr *et al* and the Stockholm secondary prevention study (odds ratio for fatal coronary heart disease 0.40 (men) and 0.56 respectively) each accumulated only eight citations a year, presumably because their designs were flawed.¹ In contrast, the less positive but larger and better designed Lipid Research Clinics trial and Helsinki heart study (odds ratio for fatal coronary heart disease 0.78 and 0.73 respectively) collected 153 and 164 citations a year respectively.

Ravnskov should realise that preferential citation reflects the perceived quality of the evidence rather than the outcome.

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- 1 Ravnskov U. Cholesterol lowering trials in coronary heart disease: frequency of citation and outcome. *BMJ* 1992;305:15-9. (4 July.)

AUTHOR'S REPLY,—P N Durrington and colleagues still think that lowering cholesterol is useful as my unsupportive results are due to bias. According to them, I should have excluded multifactorial trials, non-randomised trials, and two trials that allegedly did not use the intention to treat principle. They have obviously not made any calculations because if these trials had been excluded the overall results would have been even more unfavourable. They find support in Holme's meta-analysis, although his review included four of the trials that I should have excluded; and also in a seven year old abstract by Peto *et al*. Let us discuss the matter again when Peto *et al* have published their results in detail.

Trials of oestrogens and thyroxine should also have been excluded; these drugs "do not simply reduce cholesterol," as F L Game and R H Neary put it. No drug simply reduces cholesterol concentration; most of them have several diverse side effects, but trial directors make things easy for themselves if they claim their drug to be cardioprotective when the number of coronary events is lowered but cardiotoxic when the number is increased.

J F Goodwin, and also Game and Neary, think that I have biased my results by excluding the trials of regression of atheroma. These trials, however, used angiographic changes as the primary end point. They did record cardiac morbidity and mortality also, but, owing to the few events that occurred, their inclusion should not have changed the overall results. Furthermore, regression of atheroma was not proved by these studies. What they recorded is a trivial, generalised widening of the coronary vessels and this is also what is seen in the rare published angiographs.¹ But atheromatosis is a localised disease, and its rate of progression is independent of the cholesterol concentration; this has been shown by at least six angiographic studies that have never been cited.²

Game and Neary suggest that the expected correlation between outcome and degree of cholesterol lowering was neutralised by a greater lowering in those at greater risk. Their idea cannot be tested from published data, but it seems unlikely because a high serum cholesterol concentration is not a risk factor after one or more myocardial infarctions,³ and nine of the 13 trials that had analysed the relation were secondary preventive trials.

I excluded the unsupportive trial of Burr *et al* because some of the controls were advised to eat more fish.⁴ But it must be unintentional that my critics, by citing mainly favourable reports, have illustrated the point of my paper.

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- 1 Brown G, Albers JJ, Fisher LD, Schaeser SM, Lin J-T, Kaplan C, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 1990;323:1289-98.
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Adenosine and cardiac arrhythmias

EDITOR,—Having seen the common reluctance of doctors to diagnose ventricular tachycardia, we agree with Clifford J Garratt and colleagues that "both accident and emergency departments and cardiac care units would be safer places for patients

with arrhythmias if the first instinct of the doctor on the spot was to reach for adenosine rather than verapamil."¹ We wish, however, to sound a note of caution.

Torsades de pointes developed in a 24 year old woman who had narrow complex tachycardia of 160 beats/min with a prolonged QT interval when 6 mg adenosine was given intravenously to establish the diagnosis.² This led the authors to suggest that adenosine should not be used in the presence of the prolonged QT syndrome. Another woman with a narrow complex tachycardia and a systolic blood pressure of 62 mmHg became briefly unresponsive with fixed dilated pupils after being given 12 mg adenosine; sinus rhythm resumed after some minutes.² A woman with supraventricular tachycardia of 176 beats/min went into asystole for 17 seconds and became unconscious, but the rhythm ultimately reverted to normal sinus rhythm.³

As with many other drugs initially declared safe, problems like those described above may occur; more importantly, adenosine may be used inappropriately, as in the woman with a systolic blood pressure of 62 mmHg, in whom cardioversion should have been used.

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- 1 Garratt CJ, Malcolm AD, Camm AJ. Adenosine and cardiac arrhythmias. *BMJ* 1992;305:3-4. (4 July.)
- 2 Wesley RC, Turnquest P. Torsades de pointes after intravenous adenosine in the presence of QT syndrome. *Am Heart J* 1992;123:794-6.
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Cardiopulmonary resuscitation in British hospitals

EDITOR,—Hugh Tunstall-Pedoe and colleagues' survey of cardiopulmonary resuscitation in British hospitals provides a baseline against which other results can be measured.¹ We have been auditing the outcome of cardiopulmonary resuscitation at the City Hospital, Nottingham, since September 1991 with the aim of determining whether the in house resuscitation training programme is adequate and well directed. The hospital had 1208 admissions to the coronary care unit during 1991.

Data on cardiac arrests were recorded on an audit form by the team leader. Completion of data collection was measured by cross checking with "arrest calls" put out from the hospital switchboard and showed that over 95% of calls were audited. Our results to April this year are in good agreement with those of Tunstall-Pedoe and colleagues' study. One hundred and forty three forms were collected in seven months (about 245 a year). Sixty (43%) out of 141 patients (two arrests were repeat arrests and excluded) survived resuscitation, of whom 42 (70%) were alive at 24 hours. At a median follow up of six weeks 29 patients (69% of survivors at 24 hours) were still alive. Survival data for one year are not yet available. Similarly, our figures for the type of arrest (cardiac 49% (70/143), respiratory 17% (25/143), and mixed cardiac and respiratory 24% (35/143)) and immediate survival related to age (age <50, 68% (13/19); 50-70, 60% (24/40); and >70, 38% (25/65); data on age incomplete) agree with those of Tunstall-Pedoe and colleagues' survey.

The authors comment that the paper is an initial publication and will be followed by subgroup analyses including analysis of specific rhythms. Unfortunately, this means that they have not presented data on the outcomes related to the initial cardiac rhythm observed by the team leader, which we have found is of major importance. We observed that immediate survival was 71%