Ischaemic heart disease and cholesterol

There's more to heart disease than cholesterol

EDITOR,—We are impressed by the "cholesterol papers."[1-3] M R Law and colleagues prove that it is highly probable that lowering the serum cholesterol concentration in the population will reduce the risk of ischaemic heart disease without increasing the risk of other disease. The jump from epidemiological evidence to conclusions regarding public health is not, however, as evident as they suggest.

Law and colleagues state that lowering serum cholesterol concentration is critical in reducing ischaemic heart disease. It certainly was not so in the past; why should it be in the future? Several Western populations have seen a steeply decreasing mortality from ischaemic heart disease in association with constant or even increasing cholesterol concentrations.[4] If we compare the cohort of the British United Provident Association (BUPA), which was recruited in 1975-82, with the Whitehall cohort, which was recruited one decade earlier, we observe higher serum cholesterol concentrations in all the fifths of the BUPA population (fig 1[2]). Despite this, the incidence of ischaemic heart disease was at least three times lower in the BUPA cohort. As far as we can see—the y axis varies tremendously—the incidence of ischaemic heart disease in the patients with the lowest fifth of serum cholesterol concentration in the Whitehall study was still higher than that in the patients with the highest fifth of cholesterol concentration in the BUPA cohort. In the Whitehall study serum cholesterol concentrations were lower in the lower classes, but the risk of ischaemic heart disease was four times higher than that in the highest.[5] Differences in cholesterol concentrations may explain the international variation in mortality from ischaemic heart disease but do not explain the variation in middle aged employed men in London.

Before it is concluded that cholesterol concentrations must be reduced we suggest that the costs and benefits of any health programme must be weighed carefully. There is more to ischaemic heart disease than just cholesterol. To reach the target of a 10% reduction in serum cholesterol concentration, drastic changes in the diet of a whole nation are needed. The material and immaterial costs may be far from negligible: people value their food habits highly. A subsequent decline in mortality from ischaemic heart disease of 27% seems high, but, expressed in terms of individual life expectancy gained, this represents only 2·5 to 5·0 months (depending on the assumptions of the decline in mortality in the older age groups). People do not prefer "health at all costs"; few do not know that a meal of a hamburger and chips is unhealthy, but, still, fast food chains fare better than restaurants providing more wholesome Japanese food. Health programmes addressing smoking, hypertension, or a reduction in the tremendous socioeconomic differences may be far more efficient means of reaching the same goals.

LUC BONNEUX
JAN J BARENDREGT

Department of Public Health,
Erasmus University Rotterdam,
PO Box 1738,
3000 DR-Rotterdam,
Netherlands

1 Law MR, Wald NJ, Wu T, Hackshaw A, Bailey A. Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies: data from the BUPA study. *BMJ* 1994;308:363-6. (5 February.)
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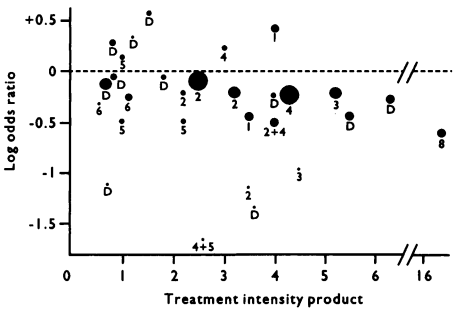
Optimism about drug treatment is unjustified

EDITOR,—M R Law and colleagues' optimistic view on cholesterol lowering is not supported by their evidence.[1,2] Firstly, they belittled the significantly increased mortality from non-coronary causes in the drug trials with the argument that no specific cause of death except haemorrhagic stroke was increased significantly. But death may have been induced by the drugs directly and not by a low cholesterol concentration; and, as eight different drugs with various side effects were used, the time needed for any specific cause of death to appear significantly may simply have been too short.

The excess of deaths from haemorrhagic stroke was said to be balanced by a deficit of deaths from coronary causes. Stroke is a rare disease in the age groups studied in the trials but certainly not in older people. An increased death rate from stroke may therefore outweigh any benefit of lowering cholesterol because in old people high cholesterol is a weak risk factor for death from coronary causes, if it is a factor at all.

Law and colleagues claimed that the effect of cholesterol lowering increased with time.[1] Using the data from their table IV I have calculated the mean differences in fatal and non-fatal infarcts between treatment and control groups in trials where the outcome was known for three time intervals. The mean (SE) decrease of coronary heart disease per 0·6 mmol/ml cholesterol in the intervals was 0·51 (0·26)%, 1·6 (0·60)%, and 0·75 (0·25)% and thus highest in the second period, in disagreement with Law and colleagues' allegation. To reach their conclusion they included results from many trials that contributed data in one or two periods only. Because of the heterogeneity of trials a fair comparison of risk reductions in separate periods is possible only if the outcome is known for all three periods of the trials that are included in this calculation. Law and colleagues also excluded two large, unsupportive trial branches for women,[3,4] which seems irrational because three of the trials they accepted included women.



Odds ratio for fatal and non-fatal coronary heart disease against treatment intensity product (net cholesterol lowering (mmol/l) ×years of treatment) in cholesterol lowering trials. The diameter of the symbols is given by $\sqrt{n/v}$ where n is the number of events in the trial. One trial with only one event is not shown. Intervention: 1=gemfibrozil; 2=clofibrate; 3=cholestyramine; 4=niacin; 5=colestipol; 6=lovastatin; 7=probucol; 8=ileal bypass; d=diet.

Law and colleagues did not explain how they calculated the dose-response relation. No correlation is present between odds ratio for coronary disease and the treatment intensity product for each trial (figure). The treatment intensity product is the mean net decrease of cholesterol multiplied by the number of years in treatment. In weighting with a factor that reflects the strength of each trial—for instance, the reciprocal of the variance of the log odds ratio—a weak, negative correlation may appear owing to the large number of observations in some of the trials. This is misuse of statistics, however, because it demands a dose-response relation for the individual observations in each study to be present, and there was none; individual outcome and degree of cholesterol lowering was sought in 14 trials and found to be unsystematically related in four and unrelated in the rest.[5]

The lack of dose-response relation is crucial because it indicates that the diet-heart idea is fundamentally wrong.

UFFE RAVNSKOV
Specialist in internal medicine

S-233 61 Lund,
Sweden

1 Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994;308:367-72. (5 February.)
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Effective diets are unpalatable

EDITOR,—M R Law and colleagues report that reduction of serum cholesterol by 10% will reduce coronary events by 25-30%, and that reduction of cholesterol by change in diet does not increase non-coronary mortality.[1-3] We are in broad agreement with these conclusions, but the recommendations

for action proposed by these authors and by Michael Marmot[4] give us concern. Beyond good intentions and strong rhetoric lies the unforgiving world of therapeutics. The assertion of Law and colleagues that reduction in total dietary fat from 42% to 35% of total energy intake will reduce total cholesterol by 10%.[2] is completely unfounded. Marmot should know better than to cite an analysis based largely on short term experimental data to support his assertion that a reduction of 10% in saturated fatty acids will lower cholesterol by 0·5 mmol/l.[4] He should also recognise the difference between scepticism about diet, which he attributes to us, and realism. All we did was draw together the findings of all long term controlled trials of dietary fat reduction to lower cholesterol.[5] Recent evidence leaves little doubt that our conclusions were correct.

The step 1 diet recommended by the national cholesterol education programme in the United States involves reducing total dietary fat to 30% of total energy intake (lower than the 35% Law and colleagues mention) and an increase in the ratio of polyunsaturated to saturated fat to 1·0. In all controlled trials of individual intervention this diet has lowered total cholesterol by only 2%, and in population interventions the cholesterol response has been even smaller.[5] Recently the OXCHECK and the family heart group studies have reported falls in cholesterol of only 2%.[8] The step 2 diet[6] also aims for total dietary fat of 30% but with a further increase in polyunsaturated:saturated ratio to 1·4. This has been tested in only one short term controlled trial in highly motivated subjects (reference 66[2]). Total cholesterol was reduced by 5%, but a 5% fall in low density lipoprotein cholesterol was paralleled by a similar reduction in high density lipoprotein cholesterol, so that the low density cholesterol:high density lipoprotein ratio was unaltered. What effect this will have on coronary risk is a matter of speculation, but epidemiological data predict no change. A 10% reduction in total cholesterol can be achieved, but only by much more rigorous (which might be considered "step 3") diets with total dietary fat below 30%.[5] In trials of these diets total fat has been reduced to between 20% (Oslo study; reference 58[2]) and 27% (St Thomas's atherosclerosis regression study; reference 43[2]), and serum cholesterol has fallen by an average of 13%.[5] Law and colleagues say correctly that we should not repeat research that has already been performed, but should disseminate the results.[3] It has been shown repeatedly that step 3 diets are unpalatable, and they require intensive supervision and even (as in the St Thomas's study) provision of special foodstuffs. The diets used in the trials cited as successful have generally been abandoned and do not appear in any of the current guidelines.

These studies have included many thousands of subjects in several countries and were conducted by investigators who aimed to show that changes in diet were successful. We agree entirely that reduction in population cholesterol concentrations is highly desirable and likely to reduce substantially the incidence of ischaemic heart disease. However, the authors should apply the same rigour to assessing the effectiveness of interventions as they have to their analyses of the epidemiological and clinical trial data. They do no one a service by overstating the efficacy of the step 1 diet, which has been shown repeatedly not to work, or by pretending that step 3 diets, which do work, are feasible or palatable.

L E RAMSAY
Professor of clinical pharmacology and therapeutics
W W YEO
Lecturer in medicine and pharmacology
P R JACKSON
Senior lecturer in clinical pharmacology and therapeutics
Royal Hallamshire Hospital,
University of Sheffield,
Sheffield S10 2JF

1 Law MR, Wald MJ, Wu T, Hackshaw A, Bailey A. Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies: data from the BUPA study. *BMJ* 1994;308:363-6.
2 Law MR, Wald MJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994;308:367-72.
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Drug trial deaths cannot be dismissed

EDITOR,—M R Law and colleagues' report of their meta-analyses of cholesterol lowering trials[1] is misleading as it underplays two important results which agree with results of our work[2]: the increase in mortality from causes other than coronary heart disease in people given drug treatment and the importance of the level of the risk of coronary heart disease in the effect of treatment on overall mortality.

According to table V in their paper, mortality from causes other than coronary heart disease is significantly increased in the drug trials (odds ratio 1·20 (95% confidence interval 1·02 to 1·40)); this finding is unlikely to be due to chance. But the authors attempt to dismiss this finding by selective discussion and dismissal of a few individual trials. For example, they assert that the only significant cause of the increased mortality from causes other than coronary heart disease is the six deaths due to clofibrate. When they report the longer term follow up of some trials (table I), however, they choose to ignore, for example, the widely known results of the longer term (8·5 year) follow up of the Helsinki primary prevention study, which showed a nearly significant 20% increase in total mortality in those receiving gemfibrozil.[3] As with the beneficial effects on mortality from coronary heart disease, any effects on mortality from causes other than coronary heart disease are likely to become more pronounced with longer follow up and therefore be underestimated in the existing trials. Table I shows this trial as having 10 deaths in the treatment group compared with 21 in the control group whereas Frick *et al* reported 19 deaths in the treatment group and only 12 in the control group.[4]

The results also confirm our finding that the benefit of cholesterol lowering treatment is greater for those at higher risk of death from coronary heart disease. This result can also be observed in trials that include subjects with and without evidence of coronary heart disease. In the Upjohn colestipol trial, for example, those with pre-existing disease (mortality from coronary heart disease in the control group 50/1000 person years) showed a clear benefit in terms of reduced total mortality (odds ratio 0·30 (0·1 to 0·8)), whereas those with coronary heart disease at baseline, who had one fifth of the risk of mortality from coronary heart disease, showed no benefit (odds ratio 1·14 (0·5 to 2·9)). Adverse effects of drugs on mortality from causes other than coronary heart disease have to be considered in this context. For example, though the authors point to the well established adverse effects of clofibrate, they fail to point out that in several trials in which clofibrate alone was given to people at high risk of death from coronary heart disease an overall reduction in total mortality was observed.[5-7] Thus the fact that a drug has adverse effects does not necessarily imply that it should not be used; rather, care has to be taken to identify those patients who are at sufficiently high risk of coronary heart disease to benefit from the treatment. Unfortunately, the manner in which the analysis is conducted and interpreted does not contribute to this important aim of all good clinical and public health decision making.

TREVOR A SHELDON
Senior research fellow
FUJIAN SONG
Research fellow
Centre for Health Economics,
University of York,
York YO1 5DD

1 Law MR, Thompson SG, Wald NJ. Assessing possible hazards of reducing serum cholesterol. *BMJ* 1994;308:373-9. (5 February.)
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Hidden bias in observational study

EDITOR,—M R Law and colleagues argue that regression dilution bias and the surrogate dilution effect underestimate the association of serum cholesterol concentration and ischaemic heart disease in observational studies.[1] Their method of correcting for this may, however, introduce bias of another kind.

Many of their 21 515 subjects attending for medicals were likely to have been told that their cholesterol concentration was too high and to modify their diet accordingly. If the repeat measurements of total cholesterol concentration differed solely by random variation then the mean would not be expected to change. In fact, the mean total cholesterol concentration is 0·15 mmol/l lower in the 5696 subjects who underwent repeat measurement—and this reduction is likely to be greater in those subjects with higher initial concentrations. This could have introduced a skew into their correction, and therefore their conclusion—that a reduction in total or low density lipoprotein cholesterol concentration of 0·6 mmol/l corresponds to a reduction in the risk of ischaemic heart disease of 25-30%—must be interpreted with caution.

JULIAN MILLO
Barnet General Hospital,
Barnet,
Hertfordshire EN5 3DJ

1 Law MR, Wald NJ, Wu T, Hackshaw A, Bailey A. Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies; data from the BUPA study. *BMJ* 1994;308:363-6. (5 February.)

"Cholesterol papers" add to the confusion...

EDITOR,—We believe that the adjustment for the so called "surrogate dilution effect" in M R Law and colleagues' re-estimation of the magnitude of the association between serum cholesterol concentration and mortality from ischaemic heart disease is not justified.[1] Stopping smoking reduces the risk of ischaemic heart disease, but not to the level of someone who has never smoked. Law and colleagues confuse the risks associated with various serum cholesterol concentrations in observational studies with alterations in risk consequent on