Cholesterol lowering and mortality

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The risk of CHD death in clinical trials of cholesterol lowering varies greatly between 1.2 and 128 per 1000 person-years across the the various trials. In a meta-analysis of 34 clinical trials, a significant reduction in total mortality consequent on cholesterol lowering therapy is observed in the trials with high CHD death rates in the control group (>50 deaths per 1000 person-years), while a significant increase in mortality is seen in the low CHD risk trials (<10 CHD deaths per 1000 person-years). Increased non-CHD mortality is restricted to trials in which drugs were used to lower cholesterol and there is no dose-response relationship between degree of cholestrol lowering and increased non-CHD mortality. Cholesterol lowering does not itself seem to result in increased non-CHD motality. Pharmacological cholesterol lowering only appears to have an overall benefit in a small subgroup of patients at very high risk of CHD.

In 1990 it was estimated that a minimum of around 60,000 people were taking cholesterol lowering drugs in Great Britain. By 1992 this had doubled *(Fig. 1.)*. It was suggested that the prescription levels in 1990 were «pitifully low», a statement which is challenged both by a consideration of the trends in prescription levels and by a reasoned assessment of the current evidence regarding who might benefit from cholesterol lowering pharmacotherapy.

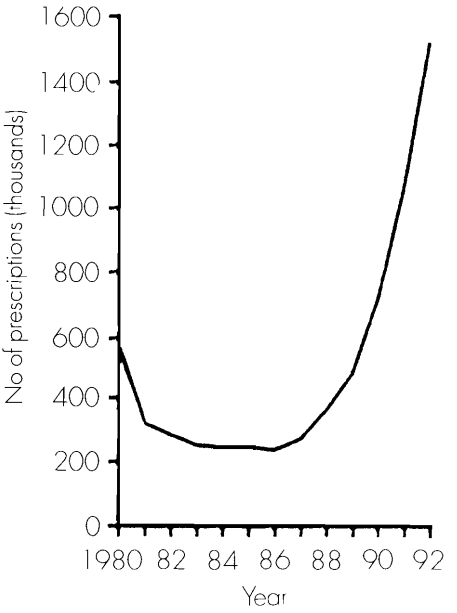
Calculations of the risk/benefit ratio of cholesterol lowering should be based upon the results of randomised trials of cholesterol reduction, not only on predictions from observational data. For this purpose we have performed a meta-analysis of the findings from the clinical trials of cholesterol lowering. Here we will concentrate on the issue of the relationship between the initial level of coronary heart disease (CHD) risk and outcome of cholesterol lowering.

Risks and benefits of cholesterol lowering: what does meta-analysis show?

Included in our meta-analysis were all 34 trials we could find with at least six months follow-up and at least one death. The data which are included were collected up to the termination of the trial; no post-trial data have been included. As far as we could obtain them, they are based upon *intention-to-treat* analysis.

The meta-analysis has been *stratified* according to the rate of coronary heart

Fig. 1: Cholesterol lowering drug prescriptions in England, Wales and Scotland, 1980-1992



disease deaths in the control group of the study. For each trial this reflects the level of CHD risk of the participants included in the study. For example, in a trial in which there was a low rate of death from CHD in the control group, the type of patients randomized into the trial were, on average, at a relatively low level of CHD risk, and vice versa. In performing a meta-analysis stratified on level of risk we are following the recent suggestion of BRAND and colleagues that this should be a standard procedure in meta-analyses.

The CHD death rates per 1000 person years are presented in *Fig. 2*, together with the corresponding odds ratios for total mortality in the trials (it does not include trials in which no deaths occurred in either the treatment or control group).

The rate of coronary heart disease death in the control groups per 1000 person-years in the trials varies from a low of 1.2 per 1000 person-years (i.e. around one death from CHD for each thousand participants over one year of follow-up) to 128 per 1000 person-years. There is, then, a 100-fold difference in risk from the lowest to the highest risk groups included in the trials. As can be seen, this stratification does not directly follow the stratification that has been made previously into «primary» and «secondary» prevention studies, since in some of the trials which are designated to be of «secondary prevention», the actual coronary heart disease mortality rate in the control group has been lower than that in the control group of some of the trials which have been designated «primary prevention».

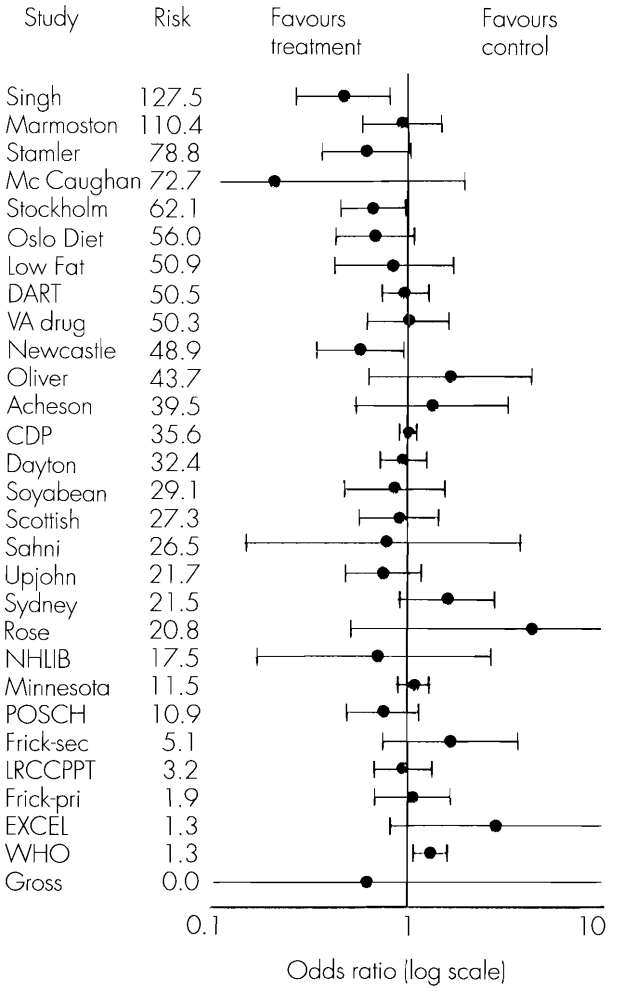


Fig. 2: Effect of treatment on total mortality in studies ranked by risk of CHD death

It can be seen that there is a tendency for net benefits, in terms of reductions in total mortality, in the trials where there is a high CHD death rate in the control group. In the trials in which there was a lower CHD death rate in the control group there is a tendency for there to be either no effect on overall mortality or even increased mortality. This is not because of bias arising from the fact that if, by chance, the death rates in the control group are low one would be likely to see apparently unfavourable effects of the treatment on mortality. First, there is such a wide range of death rates from coronary heart disease that such an effect would not influence the ranking to any great extent. Second, if stratification is made according to combined death rate from coronary heart disease in the control and the treatment groups, it makes little difference to the results.

The reason for using death rate from coronary heart disease in the control group is that this is the CHD risk of patients without treatment, i.e. the risk level which the clinician would want to use for deciding whether or not patients will benefit from therapeutic cholesterol lowering. Reducing the data into three strata, defined according to level of CHD risk in the control group, highlights the importance of considering level of risk when weighing up the risks and benefits of cholesterol lowering. *Fig. 3* shows the effect of cholesterol lowering on total mortality in a stratified meta-analysis.

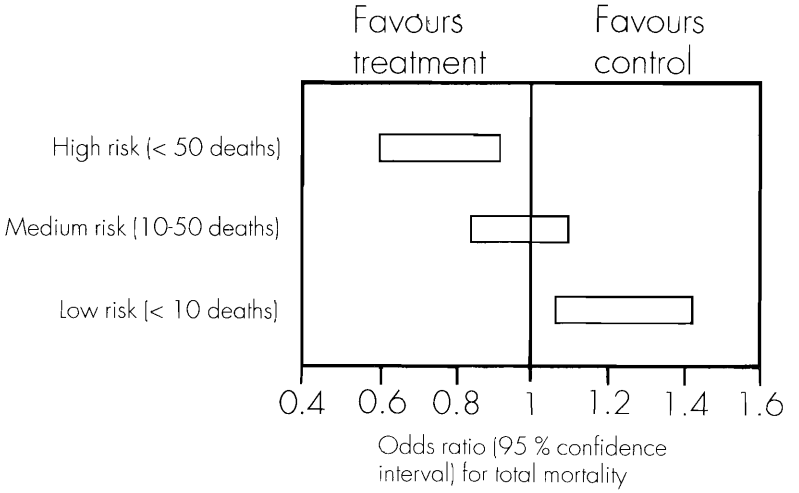


Fig. 3: Meta-analysis of the effect of cholesterol lowering on total mortality stratified by initial risk of death

A weighted regression analysis of the log odds ratio for mortality against the death rate from coronary heart disease in the control group allows a formal examination of the mortality effects of cholesterol lowering in relation to the risk of coronary heart disease death in the control group and reveals a statistically significant association between total mortality outcome and CHD risk (p = 0.001).The reason for the association between benefit from cholesterol lowering and initial level of coronary heart disease risk is that there is a tendency for the reduction in coronary heart disease mortality achieved by treatment to be offset by an increase in mortality from other causes (non-CHD mortality). In this situation the effect on overall mortality depends upon the proportion of total mortality which is due to coronary heart disease, being favourable among individuals at very high risk of death from coronary heart disease and unfavourable among patients at lower risks of dying of coronary heart disease, as *Fig. 3* shows.

The analysis indicates that a positive net benefit, i.e. a reduction in mortality, can be expected when the CHD mortality risk for the untreated individuals is *over 30 per 1000 person-years*. Conversely, at CHD mortality risk below this, the best estimate of the effect of therapeutic cholesterol lowering is that an *increase in overall mortality* is seen in the treatment group. What are the characteristics which place groups at a risk of CHD mortality above 30 per 1000 person-years?

While the reduction in coronary heart disease mortality is proportional to the reduction in cholesterol levels achieved in the trials, there is no such relationship with non-CHD mortality. Moreover, separation of the trials into those in which drugs were used to lower cholesterol from other (mainly diet) trials reveals that elevated non-CHD mortality is confined to trials using drug treatment. This suggests that increased non-CHD mortality is a side-effect of drug treatment, rather than of cholesterol lowering itself.

The observed adverse effects which have been seen with pharmacological lowering of cholesterol in certain groups of patients makes it important to determine the characteristics which place groups in the high-risk categories who receive benefit from this treatment.

Who might benefit from cholesterol lowering?

It is necessary to use data from prospective population based epidemiological studies to identify the characteristics of a group with a risk of CHD death of 30 per 1000 person-years, above which the best available current evidence suggests therapeutic benefit from pharmacological cholesterol lowering (and vice versa).

The *Renfrew and Paisley study* involved a community sample (80% response) from the *Renfrew* and *Paisley* districts of the West of Scotland. An analysis of this study shows that *even for participants with many coexisting risk factors* (high blood pressure, smoking, angina, ECG ischaemia) together with high cholesterol levels ($\geq$ 7.8 mmol/l) the CHD mortality rates are *lower* than the 30 per 1000 person-years threshold (28.9 per 1000 men-years). This is particularly marked for women (15.6 per 1000 women-years). The general conclusion is that a risk of CHD death of 30 per 1000 person-years is going to relate to a very small proportion of the population. In the *Paisley and Renfrew sample*, only 3% of men had cholesterol concentrations $\geq$7.8 mmol/l, and much smaller proportions had both such high levels of cholesterol and other risk factors. Moreover, the *Renfrew* and *Paisley* population come from an area with very high rates of CHD mortality: at the same level of risk factors, the average people in Great Britain will tend to suffer lower rates of CHD.

The data presented here will, to a certain degree, underestimate the risk of coronary death at these high cholesterol levels, because of the well known phenomenon of attenuation, through which measurement imprecision consequent on the use of single measures of plasma cholestrol leads to reductions in the strength of associations between predictor and outcome variables. Thus a group defined with cholesterol concentrations consistently above a certain level will have higher coronary heart disease risk than a group defined simply by a single measurement of cholesterol. Working aganst this, however, is the fact that the *Renfrew* and *Paisley* population come from an area with very high rates of coronary mortality; at the same level of risk factors, most people in Great Britain will tend to suffer lower rates of coronary mortality.

On the basis of the best available current evidence, clinical guidelines should suggest that pharmacological cholesterol lowering treatment be reserved for patients at markedly elevated risk of CHD - a 3% per year risk of death from CHD.

Clinical guidelines currently available tend to be internally inconsistent, considering some groups of patients to be candidates for pharmacological lowering of cholesterol even though they are at considerably lower risk of coronary heart disease mortality than other groups of patients, who are not considered candidates for such treatment. Guidelines also tend to recommend the use of cholesterol lowering drugs at levels of risk well below that at which benefit has been seen to outweigh risk. For example, the new *British Hyperlipidaemia Association* guidelines on the detection and management of hyperlipidaemia appear to consider male smokers with a cholesterol level over 6.5 mmol/l to be a high priority for lipid lowering drug therapy in «diet resistant» cases (which most are likely to be). In Scotland this would suggest that more than a quarter of middle-aged men should be candidates for drug treatment. The CHD mortality risk of 12 per 1000 men-years in such a group, however, is well below the level at which treatment has been shown to be beneficial. In the USA, doctors were asked in 1983, 1986 and 1990 to report the serum cholesterol concentrations at which they would commence pharmacotherapy in male patients *with no evidence* of cardiovascular disease. The median range fell from 8.8 - 9.3 mmol/l in 1983 to 7.8 - 8.3 mmol/l in 1986 and to 6.2 - 6.7 mmol/l in 1990. Apparently, many individuals are treated at a level of CHD risk for which current evidence suggests that there are no benefits, and even possible harm, consequent upon the use of cholesterol lowering drugs. The high (and rapidly rising) prescription rates for cholesterol lowering drugs in the USA show that changes in the reported behaviour of these US doctors translate into actual practice.

Starting patients on cholesterol lowering drugs is often a lifetime venture. It is

clear, therefore, that the long-term safety of such treatment should be established before its use becomes widespread. Unfortunately, this has not been the case in practice. Possible reasons for this irrational kind of medicine are discussed in other parts of this book. A degree of caution sometimes maintained in professional guidelines and statements is clearly not seen in pharmaceutical company advertisements or their disguised promotional activities. Physicians should learn to resist inducements to perform what is essentially promotional activity when it may well prove to be detrimental to the interests of their patients in the long run.

From the best available evidence it can be *concluded* that cholesterol lowering will benefit a group at markedly elevated risk of coronary heart disease, but will not benefit (or may even be associated with adverse consequences) patients at low risk. The degree of risk above which benefit is seen includes only a small minority of the population.

Further reading

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