Effectiveness Bulletin

Cholesterol screening and cholesterol lowering treatment

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Coronary heart disease (CHD) is the leading cause of death in the United Kingdom in men and women. It is also a major cause of premature death, accounting for 40% of deaths in men between the ages of 45 and 64 years. CHD imposes high social costs in terms of impaired quality of life and reduced economic activity and consumes a large share (2.5%) of NHS resources.1 Cholesterol screening and cholesterol lowering programmes are promoted as a way of reducing mortality rates. This paper summarises a review of this strategy.2

Blood cholesterol concentration has a fundamental role in determining the community risk of CHD. Naturally occurring variations in cholesterol concentration are strongly associated with mortality from CHD between countries3 4 and individuals.5 6 The observed relation between serum cholesterol concentration and CHD is graded and continuous, with no apparent threshold.7

Although cholesterol concentration is an important risk factor, CHD is essentially a multifactorial phenomenon. Other major independent risk factors include cigarette smoking, hypertension, diabetes, inactivity, and obesity, all of which are to a degree modifiable. Other characteristics such as lower social class and family history of CHD are risk markers of death from CHD.

Approaches to prevention
Two main approaches to preventing CHD have been identified: those aimed at the whole population (population approach) and those aimed at individuals who are judged to be at highest risk of developing the disease (high risk approach).

Most clinical efforts have been directed at the high risk approach, which uses cholesterol concentration as the key measure in risk factor screening in order to identify those subjects to be treated. In mass risk factor screening all adults have their blood cholesterol concentration measured, and those subjects with high concentrations (according to criteria laid down by guidelines) are then considered to be at higher risk. Alternatively, doctors may routinely measure cholesterol concentration when patients consult for conditions unrelated to any known risk factors—that is, they may perform opportunistic screening.

Cholesterol screening and cholesterol lowering interventions are being strongly promoted, and both the public and doctors are coming under increasing pressure to measure blood cholesterol concentration. In order to evaluate the likely benefits of such a policy four areas will be examined: the ability of cholesterol measurements to predict the risk of CHD accurately; the accuracy of the measurements; the likely effectiveness of cholesterol lowering interventions in reducing mortality from CHD; and, lastly, the other effects of screening.

USE OF CHOLESTEROL CONCENTRATION IN PREDICTING INDIVIDUAL RISK
Even though serum total cholesterol concentration is an important risk factor for CHD in populations, it is poor at discriminating between individual subjects who will or will not progress to CHD without treatment. Data from the Framingham study illustrate the considerable overlap in the distribution of cholesterol concentration in men aged 30–49 who subsequently had different histories of CHD (fig 1).8

This overlap illustrates that those people who progress to a CHD event are not a distinct group, and the relation between cholesterol concentration and CHD is not dichotomous but continuous. The use of labels (for example, high cholesterol concentration) and cut off cholesterol concentrations provide a way of labelling patients more for the sake of “operational convenience” than as a reflection of the underlying process of CHD.9

Therefore the predictive accuracy of cholesterol measurement is very low. For example, of the men aged 35–57 with the highest 20% of the distribution of cholesterol concentration less than 1% will die of a heart attack in the next six years. This proportion rises to only about 2% in men with high blood pressure who also smoke.1 In other words, cholesterol concentration alone is a poor predictor of death from CHD. As the cut off value for cholesterol screening is lowered so a greater proportion of people will be wrongly categorised as at high risk.

ACCURACY OF MEASUREMENT
The main screening test is the measurement of total serum cholesterol concentration in blood
samples obtained by either venepuncture or finger prick. These measurements often do not reflect the true cholesterol concentration, owing to measurement error and natural biological variation. These sources of error can result in misclassification of subjects, leading to incorrect diagnosis and treatment.

**Technical errors**—One problem of cholesterol measurement is that instruments may be recording cholesterol values which systematically differ from the “true” value as measured by standard laboratory equipment (bias), and it is important that each instrument is correctly and regularly calibrated against a standard reference to reduce this bias. A national initiative on cholesterol accuracy, methods, and standardisation has been launched whose aim is to improve the standardisation of cholesterol measurement.

The increasing availability of desktop analysers (such as Reflotron) for use in general practitioners’ surgeries and their spread to high street sites such as chemist and health food shops is particularly worrying because of the reported high levels of bias, which may result in high rates of misclassification of subjects. In addition to systematic bias between machines, measurements of cholesterol concentration are subject to random measurement error which reduces their precision. This is a particular problem of desktop machines, which British studies have shown to have low levels of precision, possibly reflecting poor care of this equipment and inadequate attention to measurement technique.

**Biological variation**—In any individual subject serum cholesterol concentration varies over time. This random variation is quite large and may contribute more to variations between consecutive readings than technical error. It cannot be reduced by improvements to the measuring equipment, it results in considerable misclassification, and it can significantly decrease the potential cost effectiveness of any detection and treatment programme. Increasing the number of measurements on an individual subject and calculating the average serum total cholesterol concentration reduces the degree of misclassification. Thus treatment should be based not on a single measurement but on several measurements made over time, in accordance with a sequential testing protocol which should be established for use in primary and secondary care.

**EFFECTIVENESS OF CHOLESTEROL LOWERING INTERVENTIONS**

Though serum total cholesterol concentration is a risk factor for CHD it cannot be assumed that intervening to reduce the concentration in people with raised serum cholesterol concentration is beneficial since the effects may be irreversible and the treatments may have adverse side effects which attenuate any other benefit. As has been stated: “Screening programmes in which doctors approach apparently healthy individuals to make them patients for a lifetime, ethically must ensure that treatment facilities are available, that treatment is of proven efficacy, and that it does more good than harm.”

To assess reliably the effectiveness of intervening to reduce serum cholesterol concentration the results of randomised controlled trials must be examined. Most of these are too small to allow any reliable estimate of the effects of treatment on deaths due to CHD, other causes of death, and total mortality. Therefore the results of these trials need to be pooled in a quantitative overview (meta-analysis).

Previous meta-analyses have not taken into account the large variations in risk of CHD between study populations and therefore have not presented a clear picture of the likely benefits consequent on lowering serum cholesterol concentration. Recently, as part of the research for the Effective Health Care Bulletin, a new meta-analysis was carried out which stratified studies by risk of death from CHD. Published and unpublished data from all identified randomised controlled trials of cholesterol lowering with six months’ follow up or more and with at least one death were included in the meta-analysis, the results of which are reported in detail elsewhere. The meta-analysis shows that the magnitude, and even existence, of net benefit is strongly dependent on the initial level of risk of CHD. Net benefit from cholesterol lowering in terms of total mortality was seen only for trials which included patients with considerably raised initial risks of CHD (odds ratio 0.78 [95% confidence interval 0.63 to 0.95]). In the medium risk group there is no benefit from treatment and in the low risk group the total mortality among those treated was significantly raised (odds ratio 1.22 [1.05 to 1.42]) (see fig 2).

Weighted linear regression analysis shows that there is a linear trend of greater reduction in total mortality as the risk of death from CHD increases. It is estimated that cholesterol lowering treatment results in net benefit only in people with a risk of death from CHD of over about 3% (2.7% to 3.8%) a year. The analysis also shows a significant increase in non-CHD mortality in trials of drug treatment (odds ratio 1.21 [1.05 to 1.39]) but not in
non-drug trials (odds ratio 1.02 (0.88 to 1.9)). The increase in adverse effects associated with drug treatment therefore seems to be induced by the drugs used rather than by cholesterol lowering. These results are based on existing evidence and must be reviewed in the light of the results of new studies. For example, several trials of the newer cholesterol lowering agents ("statins") are due to report over the next five years.

The meta-analysis identifies a small subgroup of people who are likely to benefit from treatment with cholesterol lowering drugs – for example, people with high global risk of CHD due to a combination of risk factors, such as men who have ischaemic changes in their cardiovascular system, who smoke and who have high blood pressure and high blood cholesterol concentrations. From data from the Whitehall study and the British regional heart study this represents around 2% of men aged 50–59 (M Shiple, G Shaper, personal communication). People with high global risk sufficiently high to benefit from cholesterol lowering treatments constitute a much smaller percentage of the population than is suggested by existing guidelines sent to doctors, such as the new British Hyperlipidaemia Association’s guidelines on detection and management of hyperlipaemia or the European Atherosclerosis Society’s recommendations, which could lead to up to a quarter of middle aged men being regarded as candidates for treatment.

OTHER EFFECTS OF SCREENING

Population cholesterol screening and treatment programmes intervene in the lives of symptomless individuals. Often screening is seen simplistically in terms of groups of people who will benefit (those who are detected subjects at high risk or those not, who will be reassured) and those who are not affected. The situation is more complex and there may be significant personal adverse effects which result from screening.

Categorisation of people with “high” serum cholesterol concentration as hyperlipidaemic, and therefore at high risk of heart disease, is likely to have deleterious effects such as increased anxiety and possible adoption of a sick role seen in studies of hypertensive patients – the labelling phenomenon. Clinical case studies have highlighted the way in which some symptomless patients who previously felt themselves to be well began to perceive themselves as unhealthy as a result of having had a raised cholesterol concentration detected.

Application of the medical diagnosis “hypercholesterolaemia” should be avoided in order to reduce the labelling phenomenon associated with screening. There is evidence that many of the negative effects associated with screening programmes may be avoided if they incorporate appropriate treatment by health professionals and consistent participant follow up and they deliver care in a reassuring manner. This is one of the reasons why supermarket, pharmacy, shop, or home screening should be deprecated and, when possible, stopped.

Conclusion

Screening and treatment programmes created under technological or scientific and commercial pressures, or both, can seriously distort the allocation of health care resources. They should be instituted only on the basis of sound scientific medical evidence of the benefit to the health and welfare of the population. By this criterion untargeted screening of the population for cholesterol concentration is not justified and may indeed result in large numbers of people being treated for whom there are no benefits, or even net adverse effects. Serum cholesterol concentration should not remain the principal focus of clinical guidelines aimed at preventing CHD; instead, for individual subjects the global risk of CHD should be the criterion. Only subjects at greatly raised risk of death from CHD should be considered for treatment with currently available cholesterol lowering drugs.

Fig 2 Effect of cholesterol lowering and total mortality stratified by number of deaths from coronary heart disease per 1000 person years in control subjects.

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4 Simons LA. Inter-relation of lipids and lipoproteins with coronary artery disease mortality in 19 countries. Am J Cardiol 1986;57:3-G-10G.
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