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There is considerable pressure for cholesterol screening of the adult population but programmes have been introduced without sufficient evaluation.

Prescribing costs of cholesterol lowering drugs in primary care totalled £34 million in England in 1992 and are increasing at a rate of over 20% a year.

Blood cholesterol by itself is a poor predictor of individual risk of CHD.

Cholesterol lowering is effective at reducing overall mortality in a small group of patients at high overall risk of CHD death.

Few people identified purely on the basis of cholesterol levels will benefit from treatment.

Cholesterol screening will not make a contribution to the lowering of overall mortality and should be actively discouraged. Therapy should be targeted at those patients at highest overall CHD risk.
A. CORONARY HEART DISEASE

Coronary heart disease is a major cause of premature death and imposes high personal, social and economic costs.

A.1 Coronary heart disease (CHD) is the leading cause of death in the UK 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.

A.2 CHD leads to obstruction of blood flow through the coronary arteries to the heart muscle, due to atherosclerosis (fibro-fatty deposits) and associated blood clots. This may cause sudden death, heart attack (myocardial infarction, which may be fatal), angina, or heart failure.

A.3 CHD imposes high social costs such as impaired quality of life, and reduced economic activity. It also consumes a large share (2.5%) of NHS resources.

A.4 Despite falling mortality from CHD over the last decade, following secular declines in the USA and Australia, CHD remains a major public health problem.

B. CHOLESTEROL AS A RISK FACTOR FOR CORONARY HEART DISEASE

Blood cholesterol is an important risk factor for CHD but should be considered in the context of other risk factors such as smoking, raised blood pressure and inactivity.

B.1 Cholesterol is an important natural fat (lipid) which is manufactured in the body (particularly in the liver) and plays a vital role in cell membranes. Cholesterol is found in several forms in the body, bound to proteins to form lipoproteins.

B.2 Blood cholesterol has a fundamental role in determining the CHD risk of the community as a whole. Naturally occurring variations in cholesterol are strongly associated with CHD mortality. This is demonstrated both in cross country comparisons and in prospective epidemiological studies of individuals, where those with lower levels of cholesterol have lower probability (risk) of CHD. The observed relationship between blood cholesterol and risk of CHD is graded and continuous (see Fig 1).

Figure 1: Age-adjusted 6-year CHD and total mortality per 1,000 men screened for MRFT according to serum cholesterol

B.3 There has been some concern that low levels of cholesterol increase non-CHD deaths from cancer and other causes. This is because cohort studies show an association between naturally occurring low levels of cholesterol and raised non CHD mortality (see Fig 1). Most of this association is likely to be an artefact, due to those people who enter the study with low cholesterol having other characteristics such as respiratory disease, high alcohol consumption and preclinical cancers. When the health status of people at the start of the study is taken into account, the association between low levels of cholesterol and non-CHD deaths is greatly reduced in cohort studies.

B.4 Variations in the average levels of blood cholesterol between whole communities or populations is largely determined by differences in the diets of these communities. Countries with high dietary saturated fat intake and a low ratio of polynsaturated to saturated fatty acids are associated with higher average blood cholesterol levels. However, care should be taken in generalising these results to individuals. There is only a weak relationship between blood cholesterol levels and diet for individuals within societies where people have similar dietary patterns.

B.5 Whilst blood cholesterol is an important and fundamental risk factor, CHD is essentially a multifactorial phenomenon. Other major independent risk factors include cigarette smoking, high blood pressure, diabetes, inactivity and obesity; all of which are to a degree modifiable. Figure 2 shows the importance of considering risk factors together. For example, smokers with high blood pressure have nearly four times the risk of dying from CHD compared to non-smokers with low blood pressure at the same level of cholesterol. A scoring system for estimating overall risk of CHD by considering combinations of risk factors has been developed using data from the British Regional Heart study.
C. EVALUATING SCREENING AND TREATMENT PROGRAMMES

There is considerable pressure for cholesterol screening of the adult population. Cholesterol screening programmes have been introduced without sufficient evaluation.

C.1 One preventive strategy aims to identify individuals at higher risk of CHD and then treat them by the modification of risk factors. For a high risk intervention strategy to be successful those people who are at high risk need to be distinguished from those who are not.

C.2 Because cholesterol is a major risk factor for CHD, it has been recommended that all adults should have their blood cholesterol measured (population screening) and that those with cholesterol levels above certain cut-offs be considered for dietary or drug treatments to lower cholesterol. Another form in which this screening can take place is when doctors routinely measure the cholesterol level of all patients during consultations in an untargeted way (opportunistic screening). In this bulletin the term cholesterol screening is used to refer to both population and opportunistic screening, both of which measure blood cholesterol in people in an untargeted way.

C.3 There is considerable pressure for cholesterol screening and treatment programmes from both commercial and professional sources. For example, a number of guidelines have been issued which recommend routine cholesterol measurement in all adults. In the US, this pressure - in the form of the 'know your number' campaign - has led to high levels of screening and treatment.

C.4 Screening and treatment programmes created under technological, scientific or commercial pressures can seriously distort the allocation of health care resources. They should only be instituted on the basis of sound scientific evidence of net benefit to the health and welfare of the population.

C.5 The increase in cholesterol screening and treatment has occurred despite the "lack of evidence of screening value" and the "need for formal quantitative appraisal using existing evidence..." The rest of this bulletin contributes to such an appraisal.

C.6 The effectiveness of cholesterol screening programmes is dependent upon five factors. Each one of these is examined in the following sections below.

D) is blood cholesterol a good measure of CHD risk?
E) can blood cholesterol be measured accurately?
F) are cholesterol lowering treatments effective at reducing mortality in people identified as having high cholesterol?
G) are there any other effects of cholesterol screening?

D. IS BLOOD CHOLESTEROL A GOOD MEASURE OF CHD RISK?

Blood cholesterol by itself is a poor predictor of individual risk of CHD. Mass screening programmes based on a single risk factor (like cholesterol) are likely to misclassify individuals with regard to their CHD risk.

D.1 The degree to which screening is able to identify people likely to go on to have CHD depends on the degree to which CHD risk is confined to a small group of "diseased" people or is more widely diffused within the population.

D.2 Although blood cholesterol is a significant risk factor for CHD it is not a strong predictor in its own right, poorly discriminating between individuals who will or will not go on to have CHD in the absence of treatment. However for the small groups of people with very high levels (largely with a genetic predisposition eg familial hypercholesterolaemia), cholesterol levels make a clear statement of their risk.

D.3 Data from the Framingham study illustrate the considerable overlap in the distribution of blood cholesterol levels in men aged 30-49 who did/did not go on to have CHD (Fig 3). This overlap is because those people who go on to have a CHD event are not a distinct group of diseased people and the relationship between cholesterol levels and CHD is continuous (Fig 1). The use of labels (eg high cholesterol) and arbitrary cut-off levels provide a way of labelling patients more for the sake of "operational convenience" than as a reflection of the underlying process of CHD.

Figure 3: Distribution of serum cholesterol levels in men aged 30-49 years at entry, who did and did not subsequently develop coronary heart disease in 16 years (Framingham Study)
D.4 Screening policies based purely upon cholesterol levels, such as the ‘know your own number’ campaign in the USA can result therefore, in a substantial percentage of the population being falsely classed as at high CHD risk relative to the population as a whole.

E. CAN BLOOD CHOLESTEROL BE MEASURED ACCURATELY?

Cholesterol measurement is subject to various sources of error which can result in misclassification. This is a particular problem for desk top analyzers often used in primary care or the high street, and in home testing kits. Clinical decisions should be based on the average of repeated measurements using well validated laboratory equipment.

E.1 The main screening test for blood cholesterol is the measurement of total blood cholesterol in blood samples obtained by either venipuncture or finger prick. Cholesterol measurements may not accurately reflect the true cholesterol level due to measurement error and natural biological variation. These sources of error can result in misclassification of individuals leading to the incorrect diagnosis and treatment of people.

Measurement Error
E.2 Measurement error can be the result of bias (the degree to which a reading systematically differs from a gold standard or reference value) or imprecision (where measurements are subject to random measurement error which reduces the precision of the measurements, expressed as the coefficient of variation). In the US, the National Cholesterol Education Program (NCEP) laboratory standardisation panel recommends that equipment should not have a bias exceeding 3% and that imprecision be within ±3%. Inaccuracy above these levels will result in significant misclassification.

E.3 Different laboratory analyzers can give different readings for the same blood sample.1 A recent study in Scotland and Northern Ireland found that laboratory equipment systematically overestimated cholesterol levels by over 4% at the cut off of 7.8mmol/l. This would result in a 50% increase in the numbers of people screened being recommended for treatment.10 Bias can be reduced in laboratory equipment by regular calibration against a standard, and precision increased by using good equipment and repeat analyses.11 A National Initiative on Cholesterol Accuracy, Methods and Standardisation has been launched which aims to improve the standardisation of cholesterol measurement.

E.4 The increasing use of compact measuring devices - ‘desk top’ analyzers (such as Reflotron) - in GP surgeries and their spread to high street chemist and health food stores is particularly worrying in this context because they are less accurate and are less amenable to national initiatives for quality control. There is significant bias and variation between machines in these sort of analyzers, even under strict laboratory conditions. In one UK general practitioner based study, Reflotron showed a bias of +8%.12 British GP studies have also shown levels of imprecision as high as 5.5%13 and 7.5%,14 possibly reflecting the poor care of equipment and inadequate attention to measurement technique. GPs using machines under these conditions will not be able to confidently distinguish between people with cholesterol levels of 7.1mm/l (raised) and 5.3mm/l (not raised). A recent review of five devices commonly used in public cholesterol screening environments concluded that none of the methods met the NCEP performance recommendations for cholesterol measurement.15 Home cholesterol testing kits are likely to be even less accurate.

Biological Variability
E.5 In any individual the blood cholesterol concentration is not constant over time. This random biological variation is quite large and results in considerable misclassification.16-21 This source of error cannot be reduced by improvements to the measuring equipment. In order to reduce misclassification several measurements should be made over time and clinical decisions should be based upon the average of several readings rather than a single measurement.16

F. ARE CHOLESTEROL LOWERING TREATMENTS EFFECTIVE?

Cholesterol lowering is effective at reducing overall mortality in a small group of patients at high overall risk of CHD death. Few people identified purely on the basis of cholesterol levels will benefit from treatment. People at lower overall risk treated with drug therapy may experience a small increase in total death rate. Dietary interventions are only likely to have much impact if they are very strict and applied to high risk individuals.

F.1 “Screening programmes in which doctors approach apparently healthy individuals to make them patients for a lifetime, ethically must ensure that .. treatment is of proven efficacy, and that it does more good than harm.”22

F.2 Although blood cholesterol is a risk factor for CHD it cannot be assumed that reduction in a person with high levels is beneficial. It may not automatically confer upon that person the same reduced risk of death experienced by others, naturally at that lower cholesterol level. This could be because people with different cholesterol levels are different in other ways which affect CHD risk; the effect of raised cholesterol may be long term and not easily reversible; changing cholesterol level may have negative biological side effects or the pharmacological agents used to lower cholesterol may have adverse effects.

F.3 To reliably assess the effectiveness of intervening to reduce blood cholesterol on total mortality randomised controlled trials (RCTs) of cholesterol lowering must be examined. This is because in well designed RCTs patients receiving treatment are compared with similar people who do not receive the treatment (control group). In this way differences in the outcome between the groups can be more confidently attributed to the difference in treatment received, rather than other differences between the individuals.

F.4 Most of the RCTs of cholesterol lowering interventions are too small to be able to estimate with any reliability the effects of treatment on deaths due to CHD, other causes of death and total mortality. In the absence of sufficiently large trials the results of available trials need to be pooled together in a quantitative overview (meta-analysis) in order to get estimates of the likely effectiveness of treatment.
F.5 Because previous meta-analyses have not taken into account the large variations in risk of CHD between study populations they have not presented a clear picture of the likely benefits consequent on cholesterol lowering. A new meta-analysis was carried out as part of the research for this bulletin which included all randomised controlled single factor trials of cholesterol lowering treatment with at least 6 months of follow up in which at least one death occurred. These studies were stratified by risk of CHD death in the control group (See Appendix). The results of this analysis have recently been reported elsewhere and are only summarised here.

F.6 These results are based on evidence from reviewing existing therapies which will have to be reconsidered in the light of the results of new studies as they become available. Several trials of the newer cholesterol lowering agents (the 'statins') are due to report over the next 5 years.

F.7 The analysis shows that cholesterol lowering achieves a significant reduction in total mortality only among patients with very high initial overall risk of CHD death. In people with very high risk about 17 deaths are avoided per 1000 person years [Odds Ratio = 0.74 (95% CI: 0.60-0.92)]. In a medium risk group there is no benefit from treatment. Treated patients with lower CHD risk experience an increase of about 1.2 deaths per 1000 person years [Odds Ratio=1.22 (95% CI: 1.06-1.42)] see Fig 4.

Figure 4: Effect of cholesterol lowering and total mortality stratified by number of CHD deaths per 1000 person-years in control subjects

F.8 It is estimated that cholesterol lowering treatment results in net benefit in people with over a 3% (95% CI 2.7% - 3.8%) chance of dying from CHD over the next year. This means that only a subgroup of people at high overall risk of CHD death are likely to derive a net benefit from cholesterol lowering treatments. These people will have combinations of risk factors, eg men with ischaemic changes, who smoke, have high blood pressure and high blood cholesterol.

F.9 High cholesterol alone (except in small groups of genetically predisposed individuals) does not indicate sufficient risk for individuals to benefit from treatment.

F.10 Using data from the Whitehall Study and the British Regional Heart Study, the group of people with sufficiently high overall risk likely to benefit from cholesterol lowering treatments represents around 2% of middle aged men (Martin Shipley and Professor Shaper, personal communications). This is a smaller percentage of the population than is suggested by some existing guidelines sent to doctors such as the European Atherosclerosis Society recommendations. Several guidelines, if implemented literally, can lead to up to 25% of middle aged men being regarded as candidates for treatment.

F.11 The reason for these findings is that although lowering cholesterol is highly effective at reducing death from CHD, drug treatments may also increase mortality from other causes [Odds Ratio=1.21 (95% CI: 1.05 - 1.39)]. When people are at very high risk of CHD death, the benefit from lowering CHD death rates overwhelms any adverse effects. However, when people are at lower risk, any CHD benefit may be counter-balanced by the increase in total mortality due to the adverse effects of treatment.

F.12 The increase in adverse effects associated with drug therapy appears to be induced by the drugs used rather than cholesterol lowering in and of itself. There does not appear to be any adverse effect of non-drug treatments on other causes of death [Odds Ratio=1.02 (95% CI: 0.88 - 1.19)].

F.13 'Non-drug' (mainly diet) therapies are also only associated with a significant reduction in total mortality in people with markedly elevated overall risk. However, they do not appear to have adverse effects.

F.14 The sorts of diets in the trials which show a beneficial effect on cholesterol lowering and mortality are very restrictive and are unlikely to be widely acceptable except to those at very high absolute risk of CHD. Less restrictive (step 1) diets are less effective at reducing cholesterol and are unlikely to have any great impact on individual mortality risk. A recent randomised controlled trial of a step 2 diet (with very low levels of saturated fat and cholesterol) in people with moderately raised cholesterol also showed only a small (average 5%) reduction in blood cholesterol levels.

G. ARE THERE OTHER EFFECTS OF SCREENING?

Mass population screening and the labelling of asymptomatic people as 'high risk' may result in a reduction in quality of life and the adoption of a sick role in those people. Measurement of blood cholesterol without proper medical supervision and counselling should be actively discouraged.

G.1 Mass cholesterol screening and treatment programmes intervene in the lives of asymptomatic individuals. Often screening is seen simplistically in terms of groups of people who will benefit (those detected at high risk or reassured) and those who are not affected. The situation is more complex and significant personal adverse effects may result from screening.

G.2 Categorisation of people with 'high' cholesterol as hyperlipidaemic, and therefore at high risk of heart disease, may have adverse effects such as increased anxiety and the possible adoption of a 'sick role' seen in studies of hypertensives - the labelling phenomenon. Clinical case studies have highlighted the way in which some asymptomatic patients who previously felt themselves to be well began to perceive themselves as unhealthy (and developed somatic symptoms) as a result of the diagnosis of raised cholesterol. Application of the diagnosis 'hypercholesterolaemia' should be avoided in order to reduce the labelling phenomenon.
G3 There is evidence that many of the negative effects of labelling may be avoided if the screening programmes incorporate appropriate treatment by health professionals, consistent participant follow-up and deliver care in a reassuring manner. This requires considerable investment of time involving possibly individual instruction programmes to teach patients what to expect, stressing the ability to lead normal lives. This is a further reason why supermarket, pharmacy or home testing should be discouraged.

H. COSTS

Prescribing of cholesterol lowering drugs in primary care costs a total of £34 million in England in 1992 and the volume is increasing at a rate of about 20% a year.

H.1 The weighted average cost of cholesterol lowering treatment for one year including both drug and monitoring costs is currently around £400 per person. The cost of a laboratory cholesterol measurement is £4 - £10.

H.2 Despite the evidence above that indications for their use are limited, prescriptions of cholesterol lowering drugs have been increasing rapidly over the last 5 years (Fig 5). Data from the Prescription Pricing Authority (PPA) for the last year shows an annual growth rate of GP prescribing of cholesterol lowering drugs in England of around 20%, with costs increasing by over 22% per annum. This is mainly due to the rapid growth of the newer HMG CoA reductase inhibitor drugs (statins) at around 40% pa and the fibrates growing at around 15% pa (Fig 6).

Figure 5: Cholesterol lowering drug prescriptions England, Wales and Scotland, 1986-1992

Source: Department of Health; NHS Common Services Agency; Welsh Common Services Agency.

H.3 It is estimated that the number of people receiving treatment with lipid lowering drugs is about between 100,000 and 120,000 in England at a total drug cost of £34 million. If current trends continue an estimated extra 27,000 people will receive therapy this year at an additional cost of around £7 million. A shift of all fibrate prescribing to the statins (which have yet to be fully evaluated) would cost an additional £17 million.

H.4 Information is not available on who is prescribed cholesterol lowering drugs, and therefore it is not possible to make a judgement about the degree to which current treatment is appropriate. However, if the rapid growth in prescribing of cholesterol lowering drugs continues, the number of people receiving therapy is likely to exceed the total number who can be expected to derive significant benefit.

Figure 6: Trends in costs of FHSA prescribing of lipid lowering drugs in England. (Quarterly total costs by class)

*Data for October 1992 are unavailable.

H.5 The cost-effectiveness of cholesterol lowering drug treatment in the high risk groups has still to be evaluated.

H.6 The role of cholesterol lowering treatments needs to be considered in the context of the costs and effectiveness of alternative interventions for preventing CHD. For example, stopping smoking and the taking of aspirin are each likely to result in a greater reduction in mortality than cholesterol lowering treatments, possibly at less cost.

I. IMPLICATIONS FOR HEALTH CARE

Cholesterol screening will not make a contribution to the lowering of overall mortality rates and should be actively discouraged. Therapy should be targeted at those patients at highest overall CHD risk.

I.1 The Health of the Nation sets a target for the reduction of CHD by at least 40% by the year 2000. “Effectiveness and cost effectiveness are becoming vital issues” for decision-makers in the National Health Service.

I.2 Whilst cholesterol screening and treatment may help lower CHD mortality rates, on current evidence, it is unlikely to make a contribution to the reduction of total mortality and will result in a considerable increase in prescribing cost. Rather than increase the amount of prescribing, a more rational policy would be to ensure that treatment is better targeted at people most likely to derive net benefit ie. those with high enough overall risk (see sections F.8 - F.10). Therefore health and other authorities and GPs should discourage cholesterol screening and ensure that cholesterol measurement is targeted only on those people likely to be at high risk.

I.3 A key area for future work is to develop a risk factor score which will assist clinicians in identifying those patients who fall into the high risk group.

I.4 Because a large number of people are at slightly elevated risk of CHD, they make a quantitatively greater contribution to the population burden of disease than the small number of people at greatly increased risk. Significant additional reductions in the national CHD mortality rate may possibly be achieved by focusing on population approaches to prevention such as changing national food and agricultural policy, national action on the availability and price of tobacco etc.
References


Appendix

Randomized clinical trials on cholesterol lowering included in the meta-analysis

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*MA: male; F: female; age: range of age or average age of subjects; TC: treatment/control. NA: not available; FH: familial hypercholesterolemia.

References of trials used in the meta-analysis

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