

Screening for and Treatment of Hypercholesterolaemia-A Review

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Abstract

The screening for and treatment of hypercholesterolaemia is still a complex and controversial issue. As hypercholesterolaemia is a major risk factor for coronary heart disease (CHD), there was initially much enthusiasm for mass screening with intervention recommended for persons with serum cholesterol levels ≥ 6.5 mmol/L. However, trials of treatment of hypercholesterolaemia using lipid lowering drugs showed overall benefit (i.e. reduced all-cause mortality) only for persons with pre-existing CHD (secondary prevention) or other major risk factors. For this and other reasons (e.g. cost effectiveness) screening for hypercholesterolaemia has been recommended for persons with CHD or major risk factors (family history of premature coronary heart disease, cigarette smoking, hypertension, and diabetes mellitus). Recent trials with statins have shown greater benefit than with other lipid lowering drugs, confirming the benefits of secondary prevention. In addition, one trial has shown overall benefit after 5 years for middle-aged hypercholesterolaemic males without a previous myocardial infarction, raising the possibility of mass screening. However, longer follow-up of a number of trials of primary prevention including on persons without risk factors together with a full assessment of the local situation with regards to hypercholesterolaemia is needed before mass screening can be recommended.

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Introduction

Cardiovascular diseases are major health problems in developed countries including Singapore. In particular, coronary heart disease (CHD) has been increasing in Singapore though it has recently declined¹ and is now the commonest single cause of death.² CHD is a major cause of premature death and results in high social costs such as impaired quality of life and reduced economic activity. Furthermore, it directly imparts high economic costs both on the individual and the government.

There is much effort going into the prevention of CHD. Primary prevention includes "population" and "high-risk" strategies³ which can be complementary. The "population" strategy seeks to improve health-oriented behaviour of the whole population so as to reduce its risk of CHD. The "high-risk" strategy seeks to identify by screening persons within the population who are at high risk of CHD, in particular those with hypercholesterolaemia and hypertension. Health education on lifestyles and possibly the use of drugs are then directed at these individuals so as to reduce the levels of the risk factor(s).

Despite its importance and the object of much research, screening for and treatment of hypercholesterolaemia remains a complex and controversial

issue. Screening, whether "high-risk" or "mass", is a major undertaking and serious consideration needs to be given before it is embarked upon. This paper reviews the screening and treatment of hypercholesterolaemia.

Ethical Principal of Screening

Screening programmes, in which doctors approach apparently healthy individuals to make them patients for a lifetime, should only be introduced when they are sure that, treatment facilities are available, treatment is of proven efficacy, and treatment does more good than harm.

Approaches to Screening

- 1) Active screening of all adults (mass approach).
- 2) Active screening of persons at high risk (high-risk approach). For hypercholesterolaemia this would be the presence of CHD or ischaemic changes on electrocardiogram (ECG) or other risk factors.
- 3) Opportunistic screening where doctors measure the risk factors during consultation. This can be mass or high-risk or a combination of the two approaches.

Other Effects of Screening

The Labelling Phenomenon

Persons classified as being hypercholesterolaemic and

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at increased risk of heart disease may develop anxiety and even develop “the sick role”.⁴ To reduce this, screening programmes should incorporate participant follow-up, counselling, and treatment by health professionals.

Costs

These include the laboratory cholesterol measurement, cost of the drug therapy, and cost of the follow-up and monitoring. The cost-effectiveness of cholesterol lowering drug treatment compared to other methods of prevention has still to be evaluated.

Cholesterol as a Risk Factor

That cholesterol is a major risk factor for CHD has been established from descriptive regional comparison studies (e.g. the Seven Countries Study⁵) and analytical cohort studies (e.g. the Whitehall Study⁶). Some cohort studies showed a relationship between low cholesterol levels and raised non-CHD mortality.⁷ However, more research is needed to decide how much of this is causal and how much is due to confounding.⁸ Serum cholesterol as a causal risk factor is shown by randomised trials in which lowering cholesterol has been shown to be effective at reducing CHD.

Diet (mainly high saturated fat) is the main determinant of cholesterol levels at the population level, though much less so at the individual level.

Cholesterol as a Predictor

CHD is a multifactorial disease with risk factors other than hypercholesterolaemia being cigarette smoking, hypertension, diabetes, physical inactivity, and obesity. Furthermore, factors are multiplicative for risk of CHD⁹ and moderate hypercholesterolaemia accounts for more cases of CHD than severe hypercholesterolaemia because the former is much more common. Also the relationship is continuous,¹⁰ so that any cut-off point for hypercholesterolaemia is purely arbitrary.

Hence, while at the population level blood cholesterol is the most important predictor of CHD, it is by itself a poor predictor of individual risk of CHD. Mass screening programmes based on just cholesterol are likely to misclassify individuals with regard to their CHD risk.

Measurement of Cholesterol

While it is low density lipoprotein (LDL) cholesterol that is the risk factor for CHD, it is total cholesterol that is used for screening, because measurement of the former requires either the fasting state (to use the Friedewald formula) or ultracentrifugation, neither of which are needed for total cholesterol. Serum cholesterol is measured in blood samples (non-fasting) obtained by venipuncture or finger prick. There are two sources of error which can result in misclassification

(both false-positive and false-negative):

Measurement Error

There are two types:

- i) Systematic error (bias) where the reading systematically differs from a reference value (gold standard). This is reduced by regular calibration against a standard.
- ii) Random error (imprecision) which reduces the precision of the measurements, expressed as the coefficient of variation (standard deviation divided by the mean). Precision is increased by using good equipment and repeat analyses.

The US National Cholesterol Education Program (NCEP) recommends that bias should not exceed 3% and imprecision should be within $\pm 3\%$. Desk top analysers (often used in primary care and the high street) and home testing kits are not likely to achieve this level of accuracy. One study found that none of five methods (Reflotron, Vision, Ektachem DT-60, QuickRead, and Liposcan) met the NCEP performance recommendations.”

Biological Variability

In any individual the blood cholesterol concentration is not constant over time and this random biological variation can be quite large. To reduce misclassification the average of several readings should be used rather than a single measurement.

Hence cholesterol measurement can result in misclassification. Clinical decisions should be based on the average of repeated measurements using well-calibrated laboratory equipment.

Effects of Treating Hypercholesterolaemia

The ability to reduce risk of CHD depends on two factors: Whether there is effective advice or treatment and whether or not that advice or treatment is acceptable to people (i.e. compliance is satisfactory).

There have been a number of randomised controlled trials on the reduction of blood cholesterol by diet and/or drugs at both primary (in persons without CHD) and secondary (in persons with CHD) levels. There have been meta-analyses of the earlier trials.¹²⁻¹⁴ The general conclusions drawn were:

- 1) Lowering cholesterol is effective at reducing myocardial infarction and CHD deaths.
- 2) Dietary changes (mainly a reduction in saturated fat) have no adverse effects. However, the change needed for a significant effect on blood cholesterol and mortality from CHD is major; a step 2 diet (with very low levels of saturated fat and cholesterol) rather than a step 1 diet. This dietary change is only likely to be widely accepted by those at high risk of CHD. Step 1 and 2 diets have been described.¹⁵

3) Drug treatment might increase mortality from other causes. For persons at high risk of CHD (with ischaemia or other risk factors) the reduction in deaths from CHD outweighs deaths from other causes, so that all-cause mortality is reduced. However, for persons at low risk (sole hypercholesterolaemia) the reduction in deaths from CHD is counter-balanced by the increase in deaths from other causes, so that all-cause mortality is not reduced. Deaths from other causes have concerned cancers and external causes (accidents, suicide, or homicide). The effect of lowered cholesterol on psychological mood has been reviewed.¹⁶

It was therefore concluded that treatment of hypercholesterolaemia is justified only within high-risk groups (i.e. persons with CHD and/or other risk factors).

However, there are a number of trials, either recently completed or still underway, of the newer cholesterol lowering agents, the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors (statins), which block endogenous synthesis of cholesterol. These are summarised in Table I.

Results are confirming benefit with regard to secondary prevention. The Scandinavian Simvastatin Survival Study (4S) trial demonstrated benefits with regard to both CHD and all-cause mortality in patients with clinical CHD and moderately to severely elevated cholesterol levels (Table I).¹⁷ The Pravastatin Atherosclerosis Intervention Program pooled data for a predetermined analysis from 4 atherosclerosis regression trials namely: 1) Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I); 2) Pravastatin, Lipids and Atherosclerosis in the Carotid Arteries (PLAC-II); 3) Regression Growth Evaluation Statin Study (REGRESS); and 4) Kuopio Atherosclerosis Prevention Study (KAPS).¹⁸ The pooled data analysis provided support for the clinical benefits of pravastatin in reducing cardiovascular morbidity and mortality (all-cause mortality was also reduced though not at a statistically significant level) in mild-to-moderate hypercholesterolaemic patients with established atherosclerotic cardiovascular disease (Table I).¹⁸ The Cholesterol and Recurrent Events (CARE) trial investigated the effects of pravastatin in patients with CHD and average serum cholesterol levels and results showed that for males and females there was a reduction in

TABLE I: RANDOMISED TRIALS OF CHOLESTEROL LOWERING TREATMENT WITH STATINS

Study	Drug	Population	Mean follow-up	Outcome
Scandinavian Simvastatin Survival Study (4S)	Simvastatin	Persons aged 35 to 70 years, with CHD (angina or previous MI) and cholesterol 5.5 to 8.0 mmol/L (212 to 310 mg/dl)	5+ years	1. Fatal CHD and non-fatal MI reduced by 32% ($P < 0.01$) 2. All-cause mortality reduced by 33% ($P < 0.01$)
Pravastatin Atherosclerosis Intervention Program*	Pravastatin	Persons with atherosclerotic vascular disease and cholesterol 4.0 to 8.0 mmol/L (155 to 310 mg/dl)	2 to 3 years	1. Fatal CHD and non-fatal MI reduced by 62% ($P < 0.01$) 2. Stroke reduced by 62% ($P = 0.05$) 3. All-cause mortality reduced by 46% (not statistically significant, $P = 0.17$)
Cholesterol and Recurrent Events (CARE)	Pravastatin	Persons aged 21 to 75 years, with previous MI and cholesterol < 6.2 mmol/L (240 mg/dl)	5 years	1. Fatal CHD and non-fatal MI reduced by 24% ($P < 0.01$), with benefit down to LDL-cholesterol 3.2 mmol/L (125 mg/dl) 2. Stroke reduced by 31% ($P = 0.03$) 3. All-cause mortality reduced by 9% (not statistically significant, $P = 0.37$)
Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	Pravastatin	Persons aged 31 to 75 years, with CHD (unstable angina or previous MI) and cholesterol 4.0 to 7.0 mmol/L (155 to 270 mg/dl)	5+ years	1. Not yet completed 2. End point will be fatal CHD
West of Scotland Coronary Prevention Study (WOSCOPS)	Pravastatin	Men aged 45 to 64 years, without a history of MI and cholesterol ≥ 6.5 mmol/L (250 mg/dl)	5 years	1. Fatal CHD and non-fatal MI reduced by 31% ($P < 0.01$) 2. All-cause mortality reduced by 22% ($P = 0.05$)
Prospective Pravastatin Pooling Project (PPP)**	Pravastatin	Persons aged 21 to 75 years, with and without CHD and a full range of cholesterol levels	5+ years	1. Not yet completed 2. End points will be CHD events and total mortality both overall and in subgroups (including women and the elderly)

CHD: coronary heart disease; MI: myocardial infarction; LDL: low density lipoprotein

* Pooled data from PLAC-I, PLAC-II, REGRESS and KAPS

** Pooled data from CARE, LIPID and WOSCOPS

cardiovascular events, both CHD and stroke, with benefit going down to a LDL-cholesterol level of 125 mg/dl (3.2 mmol/L), though overall mortality was not reduced at a statistically significant level (Table I).¹⁹ The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial is also investigating the effects of pravastatin in patients with CHD and average serum cholesterol levels²⁰ but is not yet completed (Table I). It has been concluded that aggressive lipid lowering treatment is clinically indicated for both males and females with proven CHD across a wide range of LDL-cholesterol concentrations.²¹

Of more significance with regard to screening for hypercholesterolaemia are primary prevention trials. The West of Scotland Coronary Prevention Study (WOSCOPS) investigated the effects of pravastatin on middle-aged men without a history of myocardial infarction and plasma cholesterol 26.5 mmol/L (250 mg/dl).²² The drug significantly reduced the risk of myocardial infarction and death from CHD without increasing death from other causes so that all-cause mortality was also reduced (Table I).²² However, it was not established that all-cause mortality was reduced in persons with one or none of the risk factors of cigarette smoking, hypertension or diabetes.

The Prospective Pravastatin Pooling (PPP) project has already been set up as a pooled evaluation of the LIPID, CARE and WOSCOPS trials of pravastatin and its baseline characteristics and methodology described.²³ Over the coming years PPP will provide important information on total mortality and CHD events both overall and in subgroups, such as women and the elderly (Table I).

Hence, the results of trials with the statins are very encouraging. However, the follow-up period has only been around 5 years and a longer time may be needed to fully evaluate their efficacy, particularly with regard to all-cause mortality.

Policy on Hypercholesterolaemia

Initially there was much enthusiasm for mass cholesterol screening and treatment programmes. Concepts in the US were “know your cholesterol number” (i.e. everyone should have their blood cholesterol measured) and “one size fits all” (i.e. the importance of the cholesterol level is irrespective of the presence of CHD or other cardiovascular risk factors) with 6.5 mmol/L defined as the level above which action was needed. Guidelines for treatment were issued by European,²⁴ British²⁵ and US^{26,27} organisations. If serum cholesterol was raised, detailed lipid analysis was recommended for individual assessment and treatment.

Serum cholesterol cut-off points of 7.8 mmol/L (300 mg/dl), 6.5 mmol/L (250 mg/dl), and 5.2 mmol/L (200 mg/dl) were widely recognised as representing consid-

erable, significant, and some increased risk of CHD respectively. If serum cholesterol was 26.5 mmol/L or between 5.2 and 6.4 mmol/L with the presence of CHD or at least two other risk factors (cigarette smoking, hypertension, diabetes mellitus, family history of premature CHD), nutritional advice and dieting if overweight were recommended and if no response lipid-lowering drugs were recommended. If serum cholesterol levels were 27.8 mmol/L, then lipid-lowering drugs were recommended from the beginning.

However, as the results of trials on lipid lowering drugs came in, the second look was more cautious. The importance of multifactorial assessment was stressed and it was considered more cost-effective to limit screening for high serum cholesterol to persons with CHD or other risk factors.²⁸ In other words the “high-risk” approach was favoured.

At this point in time the arguments for and against mass screening could be summarised as follows:

In favour of mass screening:

- 1) It identifies persons with familial hypercholesterolaemia.
- 2) Knowledge of their hypercholesterolaemia motivates individuals to change their lifestyles.

Against mass screening:

- 1) Familial hypercholesterolaemia can be identified from a family history of premature CHD.
- 2) It is not established that knowledge of hypercholesterolaemia acts as a motivator.
- 3) Cholesterol levels vary between individuals.
- 4) Measurement of cholesterol has inaccuracies.
- 5) Hypercholesterolaemia on its own is a poor predictor of CHD.
- 6) Treatment of sole hypercholesterolaemia does not reduce total mortality.
- 7) Cost-effectiveness of mass screening is in doubt.

The argument against mass screening was generally accepted and the “high-risk” approach was recommended. Screening for hypercholesterolaemia was recommended for those with:

- 1) A family history of premature CHD,
- 2) A family history of hypercholesterolaemia,
- 3) A history of CHD,
- 4) Presence of other risk factors especially cigarette smoking, hypertension and diabetes mellitus,
- 5) Maybe clinical evidence of high cholesterol i.e. xanthelasmata or xanthomas and corneal arcus in persons under 50 years.

The statins have been found to be more effective than other lipid lowering drugs. Trials have established their effectiveness with CHD. However, if the effectiveness of the statins also becomes established in hypercholesterolaemic persons without CHD and with or without other risk factors, then a third look at screening

will be indicated. There will be a stronger argument for mass screening with a view to treatment of hypercholesterolaemia in persons with or without CHD or other risk factors.

In the mid-1980s, serum cholesterol levels in Singapore were shown by the Thyroid and Heart Study to be high²⁹ and comparable to Western countries.³⁰ However, there is evidence from the recently completed National University of Singapore Heart Study that levels have fallen by about 10% by the mid-1990s probably largely resulting from government health education programmes i.e. from the population approach to primary prevention (unpublished data). The first priority must be for these programmes to be continued and indeed strengthened. In addition there should be screening for hypercholesterolaemia in persons over 40 years with CHD or at least two major risk factors (family history of premature CHD, cigarette smoking, hypertension and diabetes), probably on an opportunistic basis. For persons with serum cholesterol 26.5 mmol/L (after 2 or 3 measurements with calibrated equipment) dietary advice should be given and if this fails to lower cholesterol sufficiently then a lipid lowering drug (probably a statin) should be prescribed.

There is as yet insufficient evidence to justify mass screening for hypercholesterolaemia. The Ministry of Health in Singapore has recently warned against mass screening for a number of conditions including hypercholesterolaemia and stressed the importance of a healthy lifestyle.³¹ Longer follow up of a number of trials of primary prevention of CHD is needed, particularly in persons without any or with not more than one major risk factor. Even if the findings are favourable, problems such as errors in measurement, poor compliance to treatment, and cost-effectiveness will still remain. With regard to cost benefit/effectiveness, the costs of drug therapy have to be compared with the costs of CHD to individuals, society, and the health services. It is recognised that cost benefit/effectiveness of drug therapy depends on level of risk and that further economic analyses are required.²¹ Furthermore, before mass screening is embarked upon a full assessment of the local situation with regards to hypercholesterolaemia is needed.

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