SCREENING RELATIVES OF PATIENTS WITH PREMATURE CORONARY HEART DISEASE

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Used properly, screening detects metabolic time bombs before they wreak havoc; used inappropriately, screening may transform an asymptomatic individual into a modern semblance of Damocles, perpetually anxious about the future. Hence, before undertaking screening it is important to first answer the question as to whether the results are likely to influence the future management of the person screened. If the answer is no or uncertain, then it might be better to desist.

Familial occurrence of risk factors such as a raised low density lipoprotein (LDL) cholesterol is sometimes caused by a dominantly inherited disorder—for example, familial hypercholesterolaemia (FH)—but more often reflects interaction between weaker genetic traits and shared environmental influences, especially a poor diet. This review focuses mainly on metabolic risk factors causally related to the premature onset of coronary heart disease (CHD) and modifiable by alterations in diet and lifestyle or by drug treatment. Increasing evidence that certain agents, notably statins, can prevent or delay the onset of CHD makes it imperative to screen for dyslipidaemia the relatives of all patients developing or dying from CHD before the age of 55 if male or 65 if female.

CATEGORIES OF RISK FACTOR

The essential criteria of a risk factor are that it shows an independent and quantitative relation with the disease in question, there is evidence of a causal mechanism and, most importantly, there is reversibility of risk. Depending on the strength of the supporting evidence risk factors can be divided into various categories, as discussed below. Factors associated with a disease which lack any of these three criteria, except age, should be regarded as risk markers rather than as true risk factors.

LDL: AN OBLIGATORY RISK FACTOR

Numerous prospective surveys have shown a positive correlation between serum cholesterol over a wide range of concentrations and the risk of developing CHD. The correlation between total cholesterol and CHD is almost entirely due to the correlation between the latter and the concentration of LDL in plasma, whether expressed as the mass of LDL particles or the concentration of LDL cholesterol. LDL has been shown to be atherogenic in experimental animals and also in man, best exemplified by FH. Furthermore, the risk of CHD can be decreased by therapeutic reduction of LDL cholesterol concentrations. Thus, LDL not only has all the criteria of a true risk factor but its presence in plasma is obligatory for other risk factors to exert their effects.

The minimum concentration of LDL cholesterol required for coronary atherogenesis in man appears to be approximately 2 mmol/l, judging from postmortem studies showing fatty streaks¹—precursors of raised plaques²—in the aorta and coronary arteries of children and young adults dying suddenly from unrelated causes (fig 1). As with total cholesterol the relation between LDL cholesterol and CHD risk is curvilinear, relative risk ranging from < 2 at concentrations below 4.1 mmol/l to 35 in patients with FH³ with concentrations above 6 mmol/l throughout life.

The primacy of LDL cholesterol as a risk factor and therapeutic target was stressed in the most recent US guidelines on CHD prevention,⁴ which classified risk factors other than LDL as major, life habit, and emerging. Diabetes was given a higher priority than other major risk factors and was regarded as conferring a degree of risk equivalent to the presence of pre-existing CHD.

OTHER MAJOR RISK FACTORS

Major risk factors other than LDL cholesterol and diabetes are listed in table 1. Age, blood pressure, and high density lipoprotein (HDL) cholesterol, as well as total cholesterol, are used as continuous variables to calculate CHD risk in the current Joint British Societies' guidelines, together with cigarette smoking and diabetes as categorical variables.⁵ Alternatively age, hypertension, low HDL cholesterol, and family history of premature CHD can all be used as categorical variables to calculate risk.⁴ A family history of death from CHD in either parent before age 55 conferred a relative risk

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Figure 1 Fatty streak involvement of aorta and coronary arteries, expressed as per cent of intimal surface, in children and young adults according to quartiles of LDL cholesterol. Reproduced from Berenson *et al.*¹

of 1.3 in their progeny in the Framingham study,⁶ whereas in the US nurses health study the relative risks of manifesting non-fatal or fatal CHD were 2.8 and 5.0, respectively, if one or other parent had developed CHD before the age of 60.⁷ The effect of family history is largely independent of other major risk factors, implying the existence of a separate mechanism.

LIFESTYLE OR HABITUAL RISK FACTORS

These risk factors tend to be interdependent and are permissive in that they exert at least some of their effects via one or other of the major risk factors alluded to above.

Obesity

Obesity commonly precedes the development of hypertension, glucose intolerance, and dyslipidaemia. Several studies have shown a strong positive correlation between the degree of adiposity and fasting triglycerides, even after correcting for other variables. Plasma cholesterol is also positively correlated with body mass index, although less strongly than triglyceride, whereas HDL cholesterol is inversely correlated.

The pattern of obesity is also important in that the metabolic effects of excess fat on the abdomen differ from its effects when deposited on the thighs. Abdominal obesity and the accompanying glucose intolerance, hypertension, hypertriglyceridaemia, and low HDL cholesterol has been termed the “metabolic syndrome”⁴; additional features are hyperinsulinaemia and small, dense LDL particles.

Physical inactivity

A comparison of sedentary and highly active individuals showed that their relative risk for CHD death was 1.6. Risk was particularly increased in the lowest quintile of fitness, suggesting that even mild-to-moderate fitness may be protective. The main effect of aerobic exercise is to enhance physical fitness, but it has potentially beneficial effects also on blood pressure and serum lipids.

Atherogenic diet

An atherogenic diet exerts adverse effects on other CHD risk factors. Caloric excess promotes obesity and a sedentary state, both of which lead to hypertriglyceridaemia and a low HDL cholesterol and, eventually, to diabetes. Excessive intake of saturated fat increases LDL cholesterol whereas trans fatty acids both raise LDL and lower HDL. Excess cholesterol in the diet is hypercholesterolaemic in individuals who are efficient absorbers and blunts their response to statin treatment.⁸

EMERGING RISK FACTORS

These risk factors include Lp(a) lipoprotein, homocysteine, prothrombotic factors, impaired glucose tolerance, pro-inflammatory factors, and subclinical atherosclerosis.

Impaired glucose tolerance

Impaired glucose tolerance predicts cardiovascular events whether or not this is manifested as overt diabetes. Hyperinsulinaemia is a common accompaniment of impaired glucose tolerance and, as mentioned earlier, the two are

Table 1 Major risk factors for CHD, other than LDL cholesterol and diabetes.⁴

- ▶ Cigarette smoking
- ▶ Hypertension ($\geq 140/90$ mm Hg or on antihypertensive medication)
- ▶ Low HDL cholesterol (< 1 mmol/l; HDL > 1.55 mmol/l acts as a “negative” risk factor)
- ▶ Family history of premature CHD (CHD in male first degree relative < 55 years of age, in female first degree relative < 65 years of age)
- ▶ Age (men ≥ 45 years; women ≥ 55 years)

Abbreviations

CHD: coronary heart disease
CRP: C reactive protein
CT: computed tomography
FH: familial hypercholesterolaemia
HDL: high density lipoprotein
LDL: low density lipoprotein
NCEP: US National Cholesterol Education Program
PAI-1: plasminogen activator inhibitor

Table 2 Causes of increased homocysteine concentrations³**► Aging**

- Smoking: greater effect in women
- High alcohol intake
- High coffee intake
- Poor nutrition: deficiency of folate, B6, B12
- Endocrine: diabetes, hypothyroidism, postmenopausal
- Renal failure
- Autoimmune: rheumatoid arthritis
- Enzyme mutations: methylenetetrahydrofolate reductase, cystathionine β synthase
- Iatrogenic: methotrexate, phenytoin, metformin, fibrates

Figure 2 Relative risks of myocardial infarction in apparently healthy men according to tertiles of total: HDL cholesterol ratio (high, > 5.01; middle, 3.78–5.01; low, < 3.78) and C reactive protein (high, > 1.69 mg/l; middle, 0.72–1.69 mg/l; low, < 0.72 mg/l). Reproduced from Ridker *et al.*⁹ with permission.

frequently associated with other risk factors such as hypertension, obesity, and dyslipidaemia in the metabolic syndrome.

Prothrombotic factors

Several prospective studies have demonstrated an association between fibrinogen and CHD. Increased concentrations are associated with glucose intolerance, cigarette smoking, and hypercholesterolaemia. A fibrinogen concentration of > 3.1 g/l is associated with relative risks of CHD of 1.6 in men and 2.9 in women.

Case control studies have shown an association between increased concentrations of tissue plasminogen activator inhibitor (PAI-1) and CHD although prospective data are lacking. Concentrations of PAI-1, like those of factor VII, are strongly correlated with serum triglycerides, which may explain the known association between hypertriglyceridaemia and hypercoagulability. An increased frequency of factor V Leiden has been reported in patients with premature myocardial infarction but normal coronary arteries.

Lp(a) lipoprotein

Lp(a) lipoprotein consists of an LDL particle covalently linked to a molecule of apolipoprotein(a). The importance of Lp(a) as a risk factor for cardiovascular disease remains controversial. Case control studies have suggested that risk increases with Lp(a) concentrations above 30 mg/dl whereas in a large prospective study the risk of future myocardial infarction increased steeply only at concentrations above 60 mg/dl. No studies have been done which show therapeutic benefit from lowering Lp(a) per se, but reduction of concomitantly raised LDL cholesterol mitigates the risk associated with an increased concentration of Lp(a).

Hyperhomocysteinaemia

Homocysteine is a sulphur containing amino acid produced during the metabolism of methionine. Men with homocysteine concentrations in the upper 5% of the reference range (5–15 μ mol/l) have a threefold increase in risk of myocardial infarction when compared with the lower 90%. Folic acid supplements have been shown to reduce raised homocysteine concentrations, whatever the cause (table 2). The place of homocysteine measurement in cardiovascular disease prevention should become clearer when the results of intervention trials using folate supplementation of the diet are available.

C reactive protein

C reactive protein (CRP) is a non-specific marker of inflammation and concentrations are raised in a wide variety of inflammatory disorders. High sensitivity assay methods

allow accurate measurement of small increases in CRP and there is evidence that raised concentrations are an independent risk factor for myocardial infarction, peripheral vascular disease, and stroke. The reference range for CRP is 0–2.5 mg/l and, although assay of CRP is not yet an established part of routine cardiovascular risk assessment, recent research suggests that it adds to the predictive value of the total:HDL cholesterol ratio⁹ (fig 2).

Subclinical atherosclerosis

Non-invasive methods for detecting subclinical atherosclerosis either identify abnormalities of vascular structure or provide evidence of vascular or myocardial dysfunction. The former includes ultrasound examination of the carotid and femoral arteries, and electron beam computed tomographic (CT) scanning for coronary calcification. Electron beam CT has been claimed to detect coronary calcification in over 90% of patients with angiographically proven coronary artery disease, but the prognostic significance of this finding for clinical events is disputed. Non-invasive methods used to detect myocardial ischaemia or vascular dysfunction include electrocardiography, measurement of the ankle:arm blood pressure ratio, and flow mediated arterial dilatation. Evidence that the presence of pre-clinical disease predicts an increased risk of CHD has come from the cardiovascular health study in which asymptomatic individuals over the age of 65 years with an abnormal carotid ultrasound examination, reduced ankle:arm pressure ratio or major electrocardiographic abnormality had a relative risk of developing coronary events double that of individuals without these abnormalities.¹⁰

The ϵ 4 allele

Inheritance of an ϵ 4 allele (that is, having an apoE3/4 or 4/4 genotype or phenotype) occurs in approximately 25% of the population and is associated with a relative risk of CHD of 1.5 (table 3). The increased risk of CHD is caused in part by an accompanying increase in LDL cholesterol, although the severity of coronary atherosclerosis is greater than can be accounted for on this basis alone. Individuals with an ϵ 4 allele tend to hyperabsorb cholesterol and hence respond poorly to statin treatment.⁸

Table 3 Prevalence of lipid risk factors, relative odds, and population attributable risk (PAR) for CHD³

Factor	Prevalence (%)	Relative odds for CHD	PAR for CHD (%)
Familial hypercholesterolaemia	0.2	35	6.4
ε4 allele	24	1.53	11
HDL cholesterol <0.90 mmol/l	23	2.39	24
LDL cholesterol >3.4 mmol/l	67	1.34	18
LDL cholesterol >4.1 mmol/l	30	1.41	11

PREVALENCE OF RISK FACTORS IN PATIENTS WITH PREMATURE CHD

A large study of the prevalence of modifiable risk factors in US men with angiographically documented coronary artery disease before the age of 60 showed that virtually all had one or more risk factors.¹¹ Compared with controls, the frequency of hypertension was 41% *v* 19%, of diabetes 12% *v* 1%, of cigarette smoking 67% *v* 28%, and of a low HDL cholesterol 63% *v* 19%. However, the frequency of a raised LDL cholesterol was similar in the two groups, 26% *v* 26%, reflecting the high prevalence of hypercholesterolaemia in the general population.

A subsequent study¹² revealed that more than 50% of such patients had a familial dyslipidaemia, the most common being a low HDL cholesterol accompanied by either hypertriglyceridaemia or mixed dyslipidaemia; next came a raised Lp(a), which evinced greater heritability than other familial dyslipidaemias, apart from FH.

Premature CHD is especially common in Asians in whom low HDL cholesterol, raised Lp(a), and hyperinsulinism appear to be more important risk factors than raised cholesterol or triglyceride.

PREVALENCE OF RISK FACTORS IN ASYMPTOMATIC RELATIVES OF PATIENTS WITH PREMATURE CHD

A large US study of persons developing CHD before the age of 60 showed that an LDL cholesterol concentration of ≥ 4.1 mmol/l was more than twice as common in their asymptomatic siblings below the age of 60 as in the population at large (38% *v* 16%).¹³ Analogous but much less pronounced differences were observed in the European atherosclerosis research study (EARS) which investigated young adults with a paternal history of myocardial infarction before the age of 55.¹⁴ In this study the best lipoprotein discriminants were plasma apoB and triglyceride concentrations, which were higher in those with a positive family history of premature CHD than in age and sex matched controls. This study also confirmed the importance of hypertension as a familial risk factor for CHD.

Studies aimed at detecting subclinical atherosclerosis have shown associations between a family history of premature CHD and coronary calcification on electron beam CT, increased frequency of carotid plaques on ultrasound, and impaired endothelium dependent dilatation of the brachial artery. The precise mechanism whereby family history exerts its effect remains to be determined.

In actual practice family screening for risk factors is undertaken in less than 20% of patients who sustain a CHD event before the age of 55.¹⁵ Hopefully this will improve in the light of the results of a survey of over 130 000 families in the USA, where families with a history of premature CHD represented only 14% of the general population but accounted for over 70%

of reported cases of CHD in men and women before the ages of 55 and 65, respectively.¹⁶

PRACTICAL RECOMMENDATIONS FOR SCREENING

Screening individuals with a family history of premature CHD is encouraged by all the current guidelines on CHD prevention, namely the Joint British Societies,⁵ the Joint European Societies,¹⁷ and the US National Cholesterol Education Program (NCEP).⁴ Each advocates using risk factors to calculate the 10 years absolute risk of a CHD event although they differ in the methodology used and the level of risk above which drug treatment should be commenced. The Joint European Societies guidelines are flawed by omitting HDL cholesterol from the risk calculation, whereas the NCEP's Framingham based point scoring system is more laborious than the Joint British Societies', which is also Framingham derived but computerised. Levels of risk above which lipid lowering drugs are advocated range from 15%⁵ to 20% per 10 years,^{4, 17} the latter value being the more realistic in current circumstances.

The National Service Framework for CHD recommends screening all those under the age of 75 with a family history of hyperlipidaemia or premature CHD,¹⁸ as illustrated in fig 3. However, the level of risk above which drug treatment is advocated in those whose total cholesterol is 5–7.9 mmol/l, 30% per 10 years, is too high and based on economic constraints rather than on scientific evidence. As stated previously, 20% per 10 years is currently regarded as an appropriate criterion for primary prevention with statins. Risk factors not mentioned by the National Service Framework for CHD which can contribute to the overall assessment of risk are measurement of Lp(a), CRP, and fibrinogen, the latter especially in subjects found to be hypertriglyceridaemic. This has therapeutic relevance in that most fibrates lower both triglyceride and fibrinogen concentrations. Also, in dyslipidaemic subjects whose risk is borderline, detection or exclusion of subclinical atherosclerosis may influence decisions on whether to treat.

Figure 3 Recommendations of the National Service Framework on CHD for screening lipids in subjects with a family history of premature CHD.¹⁸

Screening relatives of patients with premature CHD: key points

- ▶ Early lesions of atherosclerosis are apparent in childhood, their extent and severity reflecting plasma lipid concentrations
- ▶ The premature onset of CHD in adults is usually associated with the presence of one or more underlying risk factors
- ▶ A family history of premature CHD is a risk factor in its own right and a marker for other risk factors, genetic and environmental
- ▶ Dyslipidaemia, especially raised LDL, is an important risk factor, detectable on family screening and reversible by life-style modification or drug treatment
- ▶ The National Service Framework for CHD recommends screening the lipids of relatives under the age of 75 of men who have developed CHD before 55 or women before 65

Screening in childhood

A family history of premature CHD or dyslipidaemia, or both, is generally accepted as valid grounds for paediatric screening, although there are some who consider it unjustified even then. The most common indication is FH, where there is a 50:50 chance that the child will be affected if one of the parents is a known heterozygote. A provisional diagnosis can be made at birth by demonstrating an LDL cholesterol concentration of > 1.1 mmol/l in cord blood, although this must be confirmed by further testing, preferably in a lipid clinic. Values of total and LDL cholesterol of > 6.7 mmol/l and > 4.0 mmol/l, respectively, in at least two fasting blood samples taken between the ages of 1–16 are regarded as diagnostic of FH.¹⁹

Other inherited disorders include familial hypertriglyceridaemia and familial combined hyperlipidaemia, both of which carry an increased risk of CHD,²⁰ as does type III hyperlipoproteinaemia, which is commonly caused by homozygous inheritance of the $\epsilon 2$ allele. These three disorders show delayed penetrance and are best screened for after puberty. Family screening of children for inherited dyslipidaemias is more cost effective than population screening but is often neglected, despite its relevance to the prevention of premature CHD.

CONCLUSION

The potential yield from family screening in identifying high risk individuals is considerable but increased resources are needed to carry this out properly. Although the recommendations of the National Service Framework for CHD are aimed at general practitioners, the initial identification by cardiologists of risk factors in a patient with premature CHD is crucial, not least because it provides a powerful incentive to primary health care teams to screen the rest of the family.

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Additional references appear on the Heart website