Prevention of coronary heart disease: putting theory into practice

ABSTRACT—The two main approaches to delivering preventive care for coronary heart disease, ie to reducing its causal risk factors, depend upon an understanding of the major causes of this disorder. One is population based and involves educating the public in healthier behaviour and making changes in the environment to facilitate this. In the other, persons at high risk are identified and provided with individual counselling and ongoing care; the diagnostic and therapeutic components of this approach must proceed in parallel, and resources will be needed to permit this. Both strategies are necessary: they are complementary; they are not competitive either conceptually or for funding. Personal risk varies widely. Hence a system of priorities is required for phasing the provision of care according to need. High risk is most often due to the presence of multiple risk factors but also results from single, pronounced risk factors. Those in greater need include persons with coronary disease, those with multiple sources of risk, and those with severe hypercholesterolaemia, hypertension, or diabetes. So-called selective testing differs little, in practice, from such a prioritised system of comprehensive risk factor control.

Preventive strategies against coronary heart disease (CHD) are based on reducing its modifiable causes. Such an approach has a sound theoretical foundation. The epidemiology of the major risk factors—high serum cholesterol, cigarette smoking and raised blood pressure—shows characteristics which indicate that they are causes of coronary heart disease [1,2]; in the case of cholesterol, even Koch's postulates are fulfilled.

Studies in which risk-factor levels are modified provide supporting findings. Persons who give up cigarette smoking are less likely to develop coronary heart disease than those who continue to smoke. Trials of serum cholesterol reduction show a decrease in coronary heart disease incidence and mortality [2,3] and, in the few in which an extended follow-up has been reported, in total mortality [4,5]; a favourable effect is seen on the rate of progression of atherosclerosis in man [6,7] and in several animal models [8,9]. These trials establish that it is possible at least partially to reverse the risk of coronary heart disease.

Since a causal role for these risk factors has been established, efforts are being made to translate theory into preventive practice in most countries in which coronary heart disease is common. For more than two decades public health education has been under way together with such statutory measures as health warnings on cigarette packets and advertisements; in many countries at least part of the downward trend in coronary mortality rates is probably attributable to such measures [10]. There are two complementary approaches to the delivery of this package of preventive measures [11]. One is population based and aims, by improving health-related behaviour in the population at large, to decrease the level and prevalence of risk factors in the community. Thus the goal is to shift the distribution of serum cholesterol, blood pressure, and body weight in the direction of lower risk, and to decrease the prevalence of cigarette smoking. The fundamental importance of this strategy is that it is directed against the underlying societal causes of coronary heart disease.

The second approach is individual based, and in practice chiefly patient based. It comprises the identification, by systematic testing, of persons with high levels of risk for whom individually supervised management is necessary, and the provision of such care, with follow-up, by the doctor and/or health care team. This 'high-risk strategy' recognises that the measures comprising the public-health approach may be inadequate to reduce risk substantially in such persons; supervised care, on the other hand, with follow-up to evaluate the response, is likely to provide a greater beneficial change in risk-factor levels.

In the target group of the high-risk strategy, genetic factors often play a major role in determining risk, eg leading to hypertension, hyperlipidaemia, or obesity. One recently identified example is familial hyperlipidaemia associated with hypertension [12]. Among the hyperlipidaemic segment of the population of Western countries some persons have well defined, usually pronounced, lipid disorders caused by single mutant genes which may not be clinically distinguishable from common hypercholesterolaemia [13]; more result from the interactions between polygenic predisposition and environmental factors such as diet. As an example of the latter, apo E, a protein component of several plasma lipoproteins, is inherited in three forms. Persons with the E4 isoform have higher mean

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serum cholesterol levels than those bearing the E2 isoform [14]. The former absorb dietary cholesterol more efficiently and show larger changes in serum cholesterol in response to changes in diet [15]. It is well recognised that individuals vary widely in responsiveness to diet [16]; response is consistent on repeated testing [17] and is analogous to that seen in laboratory animals. One consequence is that some individuals, for genetic reasons, are likely to respond less well than others to dietary measures intended to reduce serum cholesterol levels [18]. Similarly, individuals differ in their blood pressure regulation in response to dietary sodium, probably also on a familial basis [19]; this too may prove to be clinically relevant.

The high-risk strategy has been codified in recent recommendations designed to assist general practitioners and other non-specialised physicians in managing patients with high levels of risk factors. The recommendations have focused on the management of hyperlipidaemia, because the expert panels responsible perceived a particular need for educating doctors in this area. Now that this deficiency is being made good, the next set of recommendations should include more guidance on the control of cigarette smoking and obesity, and on non-pharmacological and drug treatment of hypertension. The most efficient ways both of detecting and treating high risk are multifactorial: the importance of one factor depends critically on its context. At present, medical practice tends to be largely unifactorial.

Whose responsibility?

Both the population strategy and the high-risk strategy place considerable responsibility on the individual to learn, accept, and act upon the necessary preventive measures. This is self-evident in the former approach; but in the latter, too, the patient must complement the role of the medical team. The high-risk strategy does not in any way allow the individual to abdicate responsibility for his or her own health.

Interplay between the high-risk and population approaches

The population and high-risk strategies ultimately share the same preventive objectives and deliver many of the same measures; but they depend on different though overlapping areas of expertise, the latter clinical, the former educational, epidemiological, and political. Hence those practising these skills have sometimes perceived the two approaches as competing options. This perception is false; they are in many ways synergistic and complementary.

By shifting the distributions of blood pressure and serum cholesterol in the population downward, the population approach has a potentially large effect in decreasing the number of persons who require individual clinical care [20]; thus reducing the mean by one-third of a standard deviation will, for a normally distributed variable, lead to a 50% fall in the number of people with values above the top decile point. The cost and clinical workload of the high-risk approach will then decrease in proportion to the success of population measures. It is clear that application of the two approaches must be co-ordinated.

The high-risk strategy is predicated on the need for supervised management of individuals at high risk; for such persons population measures are inadequate but still valuable. A man with familial hypercholesterolaemia requires medical care but also benefits from the wider availability of suitable food, anti-smoking education, and exercise facilities. In the patient-oriented setting of the high-risk approach all these elements are concentrated in a particularly effective manner.

The interaction between the two strategies is especially important for the many people whose risk of coronary heart disease is moderately above the average. For them the high-risk approach offers risk-factor testing in a clinical setting and indicates to them their overall risk-factor status and hence both the need and motivation to comply with guidance on diet, smoking, and exercise. The patient's motivation then comes from knowledge of his or her own risk status based on direct measurement of weight, blood pressure, and serum cholesterol, enhanced by the doctor patient relationship, the individualised counselling, and the follow-up measurements [21]. For this section of the population, the high-risk approach serves a general educational role: diffusion of information and awareness enhances the population approach. This is well understood in Finland where the systematic use of cholesterol testing is regarded as a component of the population strategy [22].

In an audit of persons referred to the St Thomas's Hospital lipid clinic with cholesterol levels in the range 5.2–6.5 mmol/l, and followed up, on average, on 1.4 further occasions in one year, diet counselling achieved target cholesterol levels in all (B. Lewis, unpublished data). This attests the effectiveness of counselling in a clinical setting. Similarly, even a single counselling session on cigarette smoking may be effective in which the doctor provides an explanation together with a firm injunction to stop smoking [23].

The concern is sometimes expressed that the costs of the high-risk approach will erode spending on the population strategy, or vice versa. We do not share this view. The two strategies largely make use of different resources (on the one hand clinical, and on the other educational, commercial, and political). These resources are not generally transferable and hence not in direct competition. The two strategies are mutually supportive, each enhancing the other's effectiveness; and each, by stimulating public concern and understanding, creates pressure for greater overall commitment to health promotion. Spending on care for persons at high risk is clinically and ethically necessary. Provided that inappropriate use of drugs is avoided,

the main extra cost is in staff time and training to provide personal health advice. For the population approach, few or no direct costs are involved in its main components (eg food labelling, marketing of preferred food products, restraint of tobacco promotion, changes in government and EEC policies on agriculture and food pricing). Others are anyway accepted as desirable, on general social and health grounds (eg improvements in childhood nutrition and access to exercise facilities).

The costing of a comprehensive health strategy has been studied in some detail [24]. Whatever the estimates, the need to treat patients with major risk factors is dictated by Hippocratic considerations, not by cost-effectiveness. Nevertheless, recent estimates suggest that the cost per year of quality-adjusted life saved by the treatment of hyperlipidaemia is in the same range as that of accepted procedures such as mammography and cervical cytology, and is less than that of relevant therapeutic measures such as coronary bypass grafting [25].

In some countries coronary heart disease is strikingly uncommon, attesting the role of environment, notably diet, in its aetiology. The wide difference in mean serum cholesterol between black and white South Africans is almost completely reversed by exchanging their diets [26]. It is possible that sufficiently extensive changes in a population's diet would reduce coronary mortality to low levels. The limits to this approach are set by powerful cultural determinants of dietary, smoking, and exercise habits; and within every population the existence of genetic and partly genetic sources of high risk (severe hypertension, some hyperlipidaemias, diabetes mellitus) would still require supervised medical care.

Drug therapy in the high-risk strategy

The primacy of dietary management of hyperlipidaemia cannot be overemphasised. An adequate trial of diet involves retesting and reinforcement over a period of 6–12 months [21], unresponsive patients being referred to a trained dietitian and/or lipid specialist. In experimental conditions a lipid-lowering diet exerts its complete effect in about three weeks, but the time course of the behavioural change needed for lifelong diet therapy is far longer.

Currently many hypertensives and diabetics, and most hyperlipidaemic individuals, remain undiagnosed and untreated; effective case-finding will inevitably increase the prescription of drugs for those patients who prove resistant to simpler management. Nevertheless, the high-risk strategy is not co-extensive with drug therapy. On the contrary, the main therapeutic instrument of the doctor practising this preventive strategy is the informed, response-monitored institution of healthier living habits. The doctor is using knowledge of the patient's risk-factor levels to prescribe, in the individual mode, recommendations similar to those of the population strategy. The recommendations are, in this case, tailored to the patient's needs, and are re-emphasised as indicated by observing the response at follow-up. The recommendations, moreover, are multifactorial: in managing moderate hypertension or hypercholesterolaemia, cessation of smoking is just as necessary as therapy directed to the specific risk factor.

Who, then, requires drug therapy for controlling cardiovascular risk factors? The present management of hypertension is largely pharmacological. In the case of mild-to-moderate hypertension this emphasis may shift in the light of evidence that substantial blood-pressure reduction is attainable in some patients by weight reduction and restricting sodium and alcohol intake; such measures have substantial drug-sparing effects. Dietary management may be improved by better understanding of apparently heritable sub-sets of hypertensives with differing responses to sodium intake [19].

Among metabolic indications for drug therapy are non-insulin-dependent diabetes and hypercholesterolaemia that have proved resistant to an adequate trial of diet. Some genetic hyperlipidaemias are characteristically resistant to diet therapy, notably familial hypercholesterolaemia which in most communities affects about two persons per thousand, ie some 120,000 people in the UK. Remnant hyperlipidaemia (type III in the Fredrickson classification) is somewhat less common. It is more responsive to diet but the majority of patients require additional drug treatment to achieve proper control. Both these disorders are frequently associated with coronary atherosclerosis (the latter also with peripheral atherosclerosis), often presenting early in adult life [27]. A study of 692 patients with heterozygous familial hypercholesterolaemia has predicated that angiographically demonstrable coronary narrowing is present at an average age of 17 years in men and 25 years in women [28]. Severe familial hypertriglyceridaemia, a relatively rare disorder, usually requires medication to avert recurrent pancreatitis. Familial combined hyperlipidaemia, a common group of disorders strongly associated with coronary heart disease [29], leads to comparatively mild elevation of serum lipids and is often controllable by diet; some patients require drug therapy. In a subset of such patients, lipid abnormalities and hypertension coincide on a strongly familial basis [12]. A further dominantly transmitted form of hypercholesterolaemia results from a single amino-acid substitution in apo B [13]; it varies in severity and can resemble familial hypercholesterolaemia but may require different therapy.

Common hypercholesterolaemia is the term used to describe the condition of most persons with elevated cholesterol levels who do not have the features of the genetic diseases mentioned. The great majority respond adequately to a determined and prolonged trial of dietary control including weight control if necessary. Drug therapy is considered in non-responders

who are judged to be at substantial risk of coronary heart disease; this is a small minority but, as the disorder is so prevalent, this indication is not a rare one.

Therapeutic audit on 148 referrals to the St Thomas's Hospital lipid clinic (B. Lewis, unpublished) showed that drug therapy was needed in 8% of those referred with cholesterol levels in the range 6.5–8 mmol/l, and in 45% of those with initial levels >8 mmol/l in order to achieve or approach target levels [21]. In this study the period of observation was one year or longer, and since this clinic was a tertiary referral centre there was a probable bias towards seeing patients with resistant hyperlipidaemia; for example, a positive diagnosis of familial hypercholesterolaemia was made in one-half of the group with levels >8 mmol/l, and all such patients required medication.

There is no greater need for good clinical judgment than in striking the correct balance between profligacy and austerity in the use of drugs to decrease risk factors for coronary heart disease. For example, recommendations codifying the indications for lipid-lowering drugs greatly assist therapeutic decision-making, but judgment is essential to their proper use. In the UK, and probably in most countries, the great majority of patients with familial hypercholesterolaemia are unrecognised and untreated. The age-specific risks of myocardial infarction and sudden cardiac death are about 20 times greater in affected men than in age-matched controls [27].

Table 1. Determinants of risk of coronary heart disease

Information mandatory to risk assessment and appropriate management of corrective risk factors	
History	Personal history of coronary heart disease
	Personal history of diabetes mellitus
	Family history of cardiovascular disease
	Cigarette smoking
Examination	Overweight
	Elevated blood pressure
	Corneal arcus xanthelasmas appearing before age 50; xanthomas
Laboratory	Elevated serum cholesterol
Information of value but has cost implications and should be obtained in patients shown to be at high risk	
	Elevated serum triglyceride
	Low HDL cholesterol
	(At research level, elevated fibrinogen and Lp(a) levels)

Detection of risk factors

Risk detection is only of value if it is linked with proper facilities for management. This will involve additional training of practice nurses, eg by practice facilitators [30], and an increased number of referral centres. Hence risk detection and risk management must be instituted in parallel as a comprehensive programme.

The greatest benefit will result from a multifactorial approach to risk reduction; this will be more effective in the community than selective attention to individuals with high values of single-risk factors, though such individuals will continue to be underdiagnosed and undertreated unless the programme encompasses their needs.

Several determinants (Table 1) contribute to the estimation of an individual's excess risk of coronary heart disease. Simple schemes have been developed to interpret these data. In one such scheme the presence of any two risk determinants (male sex being counted as one) is an indication for more vigorous care and for setting more stringent targets for lipid reduction; in another, any one risk factor present in marked degree (examples are heavy smoking, pronounced family history of premature coronary disease, and prolonged diabetes) has the same connotation as two co-existing risk factors [21]. The latter scheme has the virtue of recognising the graded nature of many risk factors.

Such schemes are simple to use but fail to take into account that the interaction between risk factors is multiplicative rather than additive; nor do they allow, even semiquantitatively, for the graded nature of many risk determinants. To assist clinical decisions on the need for lipid-lowering or antihypertensive medication, there is scope for the development of easily used but more accurate measures of risk. As an example, a nomogram or simple calculator incorporating the non-linear interaction between risk factors and allowing for the grading of continuously variable risk determinants has been prepared (H. D. Turnstall-Pedoe, personal communication). Among the latter, for instance, cigarette use could be graded as nil, 1–20 per day or 20+ per day; HDL cholesterol (now taken into account only when it is <0.9 mmol/l) would be more informative if the ranges <0.8, 0.9–1.3, and over 1.3 mmol/l were considered.

Which risk factors to measure?

If the goal of risk assessment is to identify reversible risk factors for which supervised management is likely to be beneficial, such risk factors should be directly and systematically measured in the adult population of countries in which the incidence of coronary heart disease is high (subject to the proviso, stated earlier, that facilities for screening and management must develop in parallel). In the case of lipid-mediated risk, selective cholesterol testing has been considered as a means of cost containment. Prioritisation based on age and sex can be very cost-effective [31]. However, other criteria

for selection are necessarily wide and the scope for further economy may be modest.

Priorities in the assessment and management of risk

From the Whitehall Study (unpublished results) it has been calculated that 59% of men aged 40–64 would qualify for testing on the basis of a personal or family history of coronary heart disease, or a personal history of diabetes, or cigarette smoking, or obesity (body mass index >30), or systolic blood pressure >160 mm Hg. On the other hand, 88% of men and 81% of women aged 25–59 would be selected [32] on the basis of one or more of personal or family history of coronary heart disease, cigarette smoking, blood pressure >140/90, body mass index >25, presence of xanthoma, xanthelasma, or arcus. Thus high sensitivity is possible only at the price of low selectivity, if risk factors are treated as dichotomous variables.

In practices which systematically record non-lipid risk factors, such information could be entered into a continuous-risk score in order to select patients in greatest need of lipid measurements. The initial cut-off level could then be set to yield the number of persons appropriate to resources. The level would then be reduced so that additional categories, including age and sex groups, are included. Though short-term cost-effectiveness in prevention may be greatest in middle age, primary prevention should start as early in life as possible.

In practices in which such risk-factor data are not readily available, an alternative basis is needed for allocating priority for entry into a programme of risk-factor testing (including non-lipid risk factors and cholesterol) and management. Priority may then be based on information already available to the practitioner (age, sex, receiving treatment for hypertension or diabetes), plus a simple self-completion questionnaire; the patient records family and personal cardiovascular history and smoking habits and indicates whether he or she wishes to enter the programme. The doctor can then rapidly assess priority, and appointments will be offered at a rate suited to the capacity of the practice and the local laboratory.

To detect and treat persons at high risk due to major genetic hyperlipidaemias, early diagnosis is vital, hence early comprehensive testing is called for. For the community, the cost is high because the prevalence and yield are relatively low. To reach at least a proportion of such persons early, a high priority (overriding age) must be afforded to all who have a family history of early coronary heart disease, as well as to the small number of people with a family history of known hyperlipidaemia.

Relative and absolute risks of elevated serum cholesterol

The relative risk associated with a given elevation of serum cholesterol level is the ratio of the coronary event rate in people with elevated levels to the rate in people with lower levels. In a recent report on men screened for entry into the Multiple Risk Factor Intervention Trial (MRFIT) and then followed for six years [33], the relative risk of cholesterol elevation was estimated in a large number of men. When men with cholesterol levels in the top fifth of the distribution were compared with those in the lowest fifth, the relative risk was about the same regardless of the presence or absence of smoking and/or raised blood pressure.

But strategies designed to reduce the number of cardiac events occurring in the population in a given time must take into account that these events are determined by the relative risk conferred by one or more risk factors, by the distributions of such risk factors, and by the frequency with which multiple risk factors coincide in the same person. In the MRFIT study the excess number of cardiac events associated with being in the top fifth of the cholesterol distribution, compared with being in the lowest fifth, was about 25% greater when associated with smoking and raised blood pressure than when these two factors were absent. There are two practical implications. First, the presence of multiple factors identifies a priority need for preventive action; but second, even an isolated factor carries an increased risk and hence a degree of need. This is particularly true of severe hypercholesterolaemia.

Priorities in the assessment and management of risk

Simple methods for the bedside evaluation of risk do serve a necessary practical role. In order to confine the work load and annual cost of risk-factor detection and management within acceptable limits, entry of the adult population into such a programme is likely to be spread over several years; a duration of five years has often been suggested but the period is likely to vary considerably. In the private sector of health care such testing is already well advanced.

It follows that an equitable system of priorities is called for in order to target risk-factor detection and management promptly to those in greatest need; for persons at lower risk, testing can reasonably be deferred. According to this view it is the timing rather than the availability of testing that should be selective. While any or all of the findings listed in Table 1 could be used to rank people according to need, simplicity is a necessary feature of any scheme of priorities; it should be workable by relatively untrained members of the practice team in a primary health care setting.

If such a system of priorities is adopted, it will be seen that the concept of universal risk-factor testing, including serum cholesterol measurement, is not greatly different from the view that only those with non-lipid risk factors require cholesterol measurement. In practice, the two approaches are likely to be closely similar at first. The difference will emerge later when those at highest priority are already receiving

care. In the comprehensive approach, individuals without overt risk indicators will then be entered, while the selective approach would leave this minority untested for hyperlipidaemia.

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