Prevention of cardiovascular disease and the future of cardiovascular disease epidemiology

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Background Coronary heart disease is preventable. The improved interpretation of risk factors, in vivo non-invasive measuring of arteries, brain and heart, and proven efficacy of both non-pharmacological and pharmaceutical therapies provides the model for both cardiovascular prevention programmes and new epidemiological studies.

Methods Risk factors can be subdivided into those related to the development of atherosclerosis with relatively long incubation periods, and risk factors that moderate the changes in atherosclerotic plaque, thrombosis and fibrinolysis, i.e. those with short incubation periods, or proximate risk factors.

Results The level of ApoB containing lipoproteins, low density lipoprotein (LDL) and very low density lipoprotein (VLDL) are the primary determinants of atherosclerosis. Using non-invasive methods of measuring atherosclerosis, we can evaluate the efficacy of intervention to both prevent the development of atherosclerosis and the progression of disease. The importance of proximate risk factors, especially inflammatory markers, is less estimated than long incubation period factors. It is possible that a combination of measures of subclinical atherosclerosis and proximate risk factors may provide the best estimate of the risk of clinical disease, especially among higher risk older individuals.

Conclusions The measurement of subclinical disease and new proximate risk factors (i.e. inflammation, fibrinolysis) may be useful for comparing reported differences in rates of clinical disease among populations and monitoring the emerging epidemic of cardiovascular disease in countries that currently have low death rates due to cardiovascular disease.

Keywords Coronary heart disease, lipids, subclinical disease, inflammation, thrombosis

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The approach to prevention of cardiovascular disease (CVD) is rapidly changing because of new and better methods of risk prediction, efficacious therapies such as lipid-lowering drugs, anti-hypertensive therapy, development of new technology to measure subclinical CVD and methods of measuring host susceptibility, i.e. genetics. Risk prediction has improved because major advances in molecular biology and biochemistry make it possible to evaluate not only total cholesterol levels, but also lipoproteins, apoproteins, enzymes related to the metabolism of the lipoproteins and their specific receptors. These new techniques are now being applied in both longitudinal studies of CVD and in clinical trials.

Recent clinical trials of lipid-lowering drugs, both in primary and secondary prevention of CVD, have clearly shown efficacy in reducing low density lipoprotein cholesterol (LDLc) levels and have resulted in substantial declines in coronary heart disease (CHD), stroke and total mortality. The introduction of the statin drugs has had a major impact on CVD prevention. These drugs appear to be very safe and efficacious. The critical question now is at what level of LDLc and risk of CHD should an individual be treated with drug therapy to lower their LDLc? The widespread use of lipid-lowering drug therapies in preventive medicine has been limited primarily by the cost of drugs and concern about their long-term adverse effects.

The new technologies for measuring subclinical atherosclerosis have provided the first approaches for epidemiologists to study the determinants of atherosclerosis in vivo, the progression of disease and the relationship of subclinical atherosclerosis to risk of clinical CVD. These new measures of atherosclerosis include ultrasound measurement of carotid intimal-media wall thickness, ankle-brachial blood pressure, echocardiography and MRI of the heart, electron-beam computed tomography (EBCT) and spiral CT to measure the extent of coronary atherosclerosis, measures of vascular stiffness, compliance and pulse characteristics and endothelial
function.\textsuperscript{4,11} The extent of subclinical measures such as carotid intimal wall thickness, decreased ankle-brachial blood pressure, and the increased amounts of arterial coronary calcium are clearly powerful predictors of the risks of clinical CVD.\textsuperscript{12-16} These new measures of subclinical disease can be used to evaluate the relationships between specific risk factors and measures of atherosclerosis in vivo,\textsuperscript{17} particularly important in younger individuals where long-term follow-ups to clinical outcomes would be difficult. It is now possible to compare the extent of atherosclerosis within and across populations in relation to both genetic and lifestyle factors. We can determine variables that relate to the progression of atherosclerosis and identify higher-risk individuals based on the extent of subclinical disease. Measures of subclinical disease have been especially valuable in the study of older individuals.\textsuperscript{4} The epidemiological studies have further substantiated the powerful role of traditional cardiovascular risk factors, especially levels of LDLc, cigarette smoking, elevated blood pressure, waist circumference, diabetes, triglyceride levels, and low high density lipoprotein cholesterol (HDLc) levels, on the extent of subclinical disease in both younger and older individuals.\textsuperscript{17} More recently, studies have also utilized these non-invasive methods to evaluate short-term effects of pharmacological and non-pharmacological interventions such as the effects of lipid lowering and anti-hypertensive drug therapy on carotid intimal-media wall thickness.\textsuperscript{7,11}

Host susceptibility, i.e. genetic factors, in part, determines both the levels of risk factors (phenotype), and the relationship of risk factors to atherosclerosis and to clinical disease. In the past, most genetic studies primarily focused on family history as a predictor of the risk of CVD. A critical question was whether family history was an independent risk factor for CHD. Early genetic metabolic studies focused primarily on major single-gene disorders such as familial hypercholesterolaemia. The so-called genetic ‘revolutions’ has changed the concept of host susceptibility. It is likely that many genes will be identified that modify the levels of specific risk factors. Most of these newly identified genetic polymorphisms will likely have a relatively small effect on any risk factor level, but in combination with lifestyle or environmental factors will be of considerable importance in determining levels of risk factors, phenotypes and the risk of CVD. Of specific interest for prevention in the future will be the study of gene-lifestyle and gene-drug interactions, i.e. pharmacogenetics. Individuals will vary in their response to various dietary or lifestyle factors, i.e. the amount of saturated fat or cholesterol in the diet and levels of LDLc, as well as in their response to specific drug therapy, such as anti-hypertensive drugs, and in the reduction in blood pressure levels and risk of disease. It is extremely unlikely, however, that we will ever reach the point that genetic analysis will divide the population into those who are likely to develop a heart attack over their lifetime, irrespective of lifestyle exposures, and those who are ‘immune’.\textsuperscript{18}

Development of atherosclerosis

The prevalence of atherosclerosis is very high in most ‘industrialized populations’.\textsuperscript{19,20} Post-mortem pathology studies and, more recently, in vivo studies using EBCT have clearly documented the very high prevalence of atherosclerosis with increasing age, especially in populations that consume relatively high amounts of saturated fat and cholesterol. The critical step from subclinical atherosclerosis to clinical events, i.e. myocardial infarction or sudden CHD death, is likely determined in part by the characteristics of coronary plaque morphology, such as rupture, haemorrhage, erosion of the plaques, and by secondary thrombosis.\textsuperscript{5,18} There are three hypotheses related to the development of atherosclerosis.\textsuperscript{21} First, the response to injury hypothesis, originally developed by Russell Ross, proposed that injury to the endothelium and smooth muscles was the initiating event and downplayed, to some degree, the importance of lipoproteins. These injuries included infectious agents, toxic chemicals and hypertension. The oxidative hypothesis proposed that oxidative modification of LDLc and secondary inflammation is the critical step in the development of atherosclerosis. The response to retention hypothesis proposed that ApoB-containing lipoproteins, LDL and VLDL (very low density lipoprotein), are primary determinants of atherosclerosis. Four key factors are responsible for the development of atherosclerosis: the plasma concentration of the atherogenic lipoproteins, the difference between the arterial wall influx and efflux of the atherogenic lipoproteins, modification of the lipoproteins within the arterial wall and the inflammatory response to modified LDL. The last hypothesis includes major components of the first two and is probably the most supported at the present time. The only variables that can be relatively easily measured in epidemiological studies are the levels of LDLc, VLDLc, ApoB, LDL particle size, genetic characteristics such as ApoE polymorphisms and, to a limited degree, oxidized LDL and other lipoproteins such as HDLc and VLDLc, size distributions, and apolipoproteins. Elevated ApoB lipoproteins are required for the development of atherosclerosis irrespective of the presence or absence of other risk factors.\textsuperscript{21,22} The hypothesis is also consistent with the linear relationship between blood cholesterol levels and risk of CHD, as was noted in the Multiple Risk Factor Intervention Trial screenees.\textsuperscript{23} and the linear association between the average blood cholesterol level and the extent of coronary atherosclerosis found in pathology studies.\textsuperscript{24}

The recent report from the Pathobiology Determinants of Atherosclerosis in Youth (PDAY) studies showed that at an average age of 34, 20% of men and 8% of women who had died primarily from traumatic causes had >40% stenosis of their left anterior descending coronary artery at the post-mortem examination.\textsuperscript{19,20} The risk of stenosis was directly related to levels of non-HDLc, i.e. ApoB-containing lipoproteins. The hypothesis also suggests that other factors may determine the extent of atherosclerosis at any ApoB lipoprotein level. In post-mortem examination, the average levels of LDLc and atherosclerosis are strongly and positively correlated. At any level of LDLc, however, there is substantial variation in the extent of coronary atherosclerosis. Part of this variation is likely due to the metabolism within the arterial wall, genetic susceptibility, the secondary inflammatory response, and growth factors which may be determined, in part, by other risk factors such as blood pressure levels or cigarette smoking.\textsuperscript{24}

Prevention of cardiovascular disease

Stamler recently reported that, in three relatively young cohorts, primarily 18–39 years of age, followed for up to 22 years, there
was a linear relationship between serum cholesterol levels and deaths from CHD. In one of the cohorts (Multiple Risk Factor Intervention Trial, MRFIT, screenees) the rate of CHD death was only 2.3 per 1000 persons/year for men with cholesterol <160 mg% as compared to 27.3, over a 10-fold difference, for men with cholesterol >280 mg% at baseline. Unfortunately, <10% of the men had serum cholesterol levels <160 mg%. Further evaluation of the MRFIT screenees by Stamler et al. demonstrated that it was possible to identify men at very low risk of CHD based on a low serum cholesterol level, non-cigarette smoking and systolic blood pressure <120 mmHg. Unfortunately, there are very few men in this very low risk stratum, at least in the US. A recent report from the Nurses Health Study in the US has also shown that it is possible to identify women at very low risk of disease even without including biochemical measurements. Thus, a ‘healthy’ diet, non-cigarette smoking, higher levels of physical activity, moderate alcohol, and not being overweight and obese was associated with a very low risk of CHD. Unfortunately, only 3% of the nurses were in this low risk category. These studies from both the Nurses’ and MRFIT as well as others strongly suggest that CHD is preventable but that, at least in the US, very few individuals have adopted lifestyles that are associated with low risk of CHD. The majority of individuals in most countries that have high rates of CHD are not in this low risk category and, therefore, require some type of preventative approach to reduce their risk of CHD.

The efficacy of reducing LDLc and hence the risk of heart disease has now been established by the results of statin trials. Previous dietary trials, such as the Oslo Trial, demonstrated similar benefits of dietary intervention. These drug trials, in both primary and secondary prevention settings, have demonstrated about a 25% reduction of the risk of heart attack associated with probably a 30–40% reduction in LDLc levels. The efficacy of therapy has now been demonstrated even in relatively low risk populations with an average LDL level of 150 mg%: not much higher than that of the US population overall—142 mg%. Approximately one-third of the US adult population might be candidates for lipid-lowering therapies and a similar high percentage in other countries. The cost of widespread use of lipid-lowering therapies and potential long-term adverse effects have raised concerns in the US and other countries about such widespread use, especially as a replacement for more aggressive, non-pharmacological dietary interventions.

Risk prediction equations have been developed from Framingham and other studies and have been used to estimate the long-term risk of coronary artery disease (CAD) based on a combination of risk factors, age and sex. Several committees in the US and Europe are attempting to determine what level of risk, i.e. 15, 20 or 30% over 10 years, might be considered high risk in primary prevention and therefore provide candidates for specific drug therapy. Most now agree that individuals who have already had a heart attack are candidates for lipid-lowering therapy to reduce their LDLc levels below 100 mg%. A basic problem with the high risk approach, i.e. 20 or 30% risk, is that the majority of heart attacks occur among individuals who are not in this high risk category, i.e. >20% risk over 10 years, except for older individuals. In the MRFIT screenees, age 35–39 followed over 16 years, 56% of the heart attacks occurred among men with baseline serum cholesterol levels between 160–239 mg% and only 14% among those with cholesterol >280 mg%. Thus, focusing only on the high risk population for aggressive drug therapy will likely have only a small effect on reducing the population burden of clinical CHD. The current dietary approaches for reducing LDLc are not nearly as efficacious as drug therapy with statins. However, new evolving dietary approaches may provide a much more successful method of reducing LDLc or VLDL, ApoB and the subsequent risk of heart attack. Jenkins estimated that an increase in viscous fibres, soy proteins, and plant sterols as well as a decrease in saturated fat and cholesterol and a modest, 10-pound, weight loss would result in a reduction in LDLc of about 35%, similar to that obtained from lipid-lowering statin therapy. It is uncertain, however, whether the current small reductions in many dietary trials of LDLc, perhaps only 5–10%, will have any appreciable effect on the individual risk of heart attack. The potential benefits of other nutrients in the prevention of CAD are currently being evaluated in clinical, epidemiological and animal experimental studies. There is considerable interest in the potential value of antioxidant nutrients such as vitamin E, flavinoids, omega-3 fatty acids, folic acids and soy proteins.

The continued lower CHD incidence and mortality rates in parts of southern Europe do not appear to be explained by the differences in the amount of saturated fat and cholesterol and total fat in the diet. However, it is important to note that any data regarding incidence and mortality in older age groups born prior to World War II may reflect prior lifestyles and a specific cohort effect. Changes in lifestyles, especially diet, may be less apparent in older age groups than younger age groups and similarly, the dietary changes may have less of an effect in individuals with extensive atherosclerosis. Steinberg suggested that antioxidants, such as vitamin E, may have their primary effect early in the progression of atherosclerosis or in the prevention of atherosclerosis and have less of an effect in individuals who already have extensive atherosclerosis. We have previously reported that the CHD mortality rates for ages 35–44 are still relatively low in southern Europe, especially France, Italy, and Spain, but are now also low in former high rate cardiovascular countries such as in Finland.

If the reported large differences in incidence and mortality due to CHD among countries persists, even in the younger post-World War II birth cohorts, then it would be very important to determine whether such differences are consistent with the extent of atherosclerosis measured in vivo by such techniques as EBCT. There are several possible options. For example, the extent of atherosclerosis, especially in these post-World War II birth cohorts, may be substantially lower in southern European countries than in other parts of Europe in spite of the apparent increases in risk factor levels and higher consumption of saturated fat and cholesterol following World War II. On the other hand, the extent of atherosclerosis across these populations may be similar and the differences in morbidity and mortality, i.e. incidence, may be related to endothelial function, inflammation, or thrombosis. Other risk factors than diet and lipoprotein B levels may determine clinical disease.

One of the most interesting observations has come from the Leon Diet Heart Study, a secondary prevention diet trial that has shown that increases in alpha-linolenic acid, as well as
decreases in dietary cholesterol and saturated fat, but little change in blood cholesterol levels, were associated with a substantial reduction in the risk of recurrent coronary events.\textsuperscript{37}

We have recently evaluated changes in CHD mortality and CVD mortality over time among young men in Japan, age 35–44.\textsuperscript{38} There has been a substantial change in risk factors in post-World War II birth cohorts in Japan including an increase in total fat and saturated fat in the diet, increases in LDLc, a substantial increase in cigarette smoking, and a decrease in blood pressure levels. The levels of LDLc and blood pressure are very similar now to US men in the age range 35–44 years and smoking rates are much higher in men. In spite of these substantial changes in risk factors, there appears to be only a small increase in CHD mortality, even after a careful evaluation of the quality of the information on the death certificates. On the other hand, there has been a substantial increase in CHD mortality in younger men in Korea. The potential protective effects in Japanese lifestyles may include higher intakes of soy proteins, fish and omega-3 fatty acids and high alcohol intake and the continued relatively low prevalence of obesity. Further studies evaluating the development and progression of atherosclerosis in these young cohorts in relation to specific lifestyles and risk factors will provide important information about potential beneficial lifestyles and dietary factors that can then be applied to other populations. The addition of the study of atherosclerosis to traditional, clinical studies of risk factors of heart attacks may provide important and interesting new information to explain the marked geographical variations across populations, especially in post-World War II birth cohorts.\textsuperscript{39}

The lower risk of CHD, as noted, in southern Europe has also been attributed to higher alcohol intake, especially in countries such as France, Northern Italy and Spain. The increased alcohol intake is clearly associated with higher levels of HDLc in these populations and may also have some effect on clotting and thrombosis. Studies in the US have clearly documented that moderate alcohol intake is associated with reduced risk of CHD in both men and women. Although higher levels of HDLc are associated with lower risks of heart attack in most populations, evidence that raising the level of HDLc will reduce the risk of heart attack is limited. Several trials have used fibrate drugs for raising HDLc to reduce the risk of CAD. The results have not been consistent with the VA HIT trial demonstrating a substantial reduction in CHD and the Bezofibrate Intervention (BIP) trial showing no effect.\textsuperscript{40,41} Part of the differences in the results of the trials appear to be related to the levels of LDLc, prevalence of diabetes and elevated blood triglycerides.

The role of oxidation of LDLc and antioxidants is also a research topic of great interest. Results, to date, are not consistent with benefits from antioxidant therapy. There are continued attempts to identify new and novel risk factors for atherosclerosis. Some of them may help to explain the geographical variation in CHD incidence and mortality that are unaccounted for by traditional cardiovascular risk factors.\textsuperscript{42–45}

Inflammation, thrombosis and fibrinolysis
Pathology studies have demonstrated inflammation within plaques, such as infiltration of macrophages and T-cells. Elevated levels of inflammatory markers such as C-reactive protein, IL\textsubscript{6}, TNF\textsubscript{α}, higher white blood cell counts, and sedimentation rate have all been associated with increased risk of initial heart attack and recurrent heart attack.\textsuperscript{46–49}

Higher levels of fibrinogen have been associated with an increased risk of heart attack. Whether the measure of fibrinogen is a marker of inflammation or of an increased risk of thrombosis is not certain. The association of specific measures of clotting or thrombosis, platelet function and fibrinolysis and risk of CAD have been less consistent. However, studies have clearly shown relationships between higher levels of PAI-1 and TPA antigen levels and risk of CAD as well as between measures of fibrinolysis, D-dimer and risk of CAD. Recent emphasis has focused on markers of soluble adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) as well as e-selectin and p-selectin. These have also been shown to be related to the risk of CHD in some, but not all, studies. Therapies focused on the prevention of thrombosis, such as aspirin and low-dose warfarin, have also demonstrated benefit in reducing the risks of CHD.

The potential effects of inflammation, thrombosis, and fibrinolysis on the risk of CAD occur primarily in the context of significant atherosclerosis. Most individuals who die from CHD have extensive coronary atherosclerosis. Whether these measures provide a marker for the identification of ‘vulnerable’ plaques likely to rupture and lead to thrombosis and a clinical event is a much debated and unresolved hypothesis. It is possible that the inflammatory markers are an indirect measure of the extent of atherosclerosis or the characteristics of the plaque but have little role in the pathogenesis of the clinical disease. On the other hand, it is also possible that these measures of inflammation play a key role in the progression from atherosclerosis to clinical disease.\textsuperscript{18}

Future epidemiological studies that can combine measures of subclinical atherosclerosis, perhaps using MRI or other techniques to characterize the atherosclerotic plaque along with measures of thrombosis, fibrinolysis and inflammation may identify specific lifestyle factors, such as nutrients, physical activity, etc., that may modify these proximate risk factors for heart attack.

Implications for the future
Prevention of the initial development of atherosclerosis and progression over time with age must be the number one goal of any cardiovascular disease prevention programme. Populations with a low prevalence of atherosclerosis do not have endemic clinical CHD.

In many countries the prevalence of atherosclerosis, especially in older ages, is so high that individualized preventive efforts require substantial resources. The level of LDLc is the primary determinant of the extent of atherosclerosis. The amount of saturated fat and cholesterol in the diet remain the primary factors determining the population levels of LDLc. The development and progression of atherosclerosis is not a function of ageing, but primarily determined by the distribution of cardiovascular risk factors related to specific lifestyles. Thus, prevention is possible by modification of specific lifestyles.

The primary prevention of atherosclerosis must begin early in life and focus on factors that will lower the LDLc, probably below 100 mg%, and possibly also VLDL (ApoB) lipoproteins. A
second major goal must be the prevention of the rise in LDLc with increasing age. The effects of other dietary modifications, such as specific polyunsaturated fatty acids, viscous fibre, and plant sterols in modifying both the LDLc level and perhaps atherosclerosis need further evaluations.50,51

It is very important to monitor trends in LDLc levels and other risk factors among populations that continue to have low incidence of CHD and likely a low prevalence of atherosclerosis. It is probable that in these populations, as the LDLc begins to rise above 100–130 mg%, there will be an increase in atherosclerosis and over time development of CHD.52 The long incubation period from the time of the development of atherosclerosis to the onset of clinical heart disease may delude investigators into thinking that the rising LDLc level is not associated with any increase in CHD in the population. This is most likely a mistake and in future years these populations will have epidemic CHD. Thus the monitoring of these populations in transition should include measures of LDLc as well as other cardiovascular risk factors, especially in younger age groups to look at specific cohort effects and secondarily, the monitoring of the extent of atherosclerosis using new, non-invasive measures in defined population samples. Only later, and perhaps too late, in terms of development of cardiovascular disease will incidence and mortality rates increase.

In populations in which the level of LDLc is already elevated, i.e. above 100–130 mg% or total cholesterol is over 200, atherosclerosis is prevalent. A multifaceted approach is necessary. First, the public health approach should lower the population LDLc level. Second, other lifestyle risk factors may enhance the progression of atherosclerosis and the risk of clinical disease.53-55

Weight gain during young adult life is an important determinant in the rise in LDLc. The prevention of increases in weight, which is primarily due to a more calorically dense diet, as well as decreased physical activity, is an important determinant of the evolution of early atherosclerosis and elevated LDLc levels.56 However, not all populations with a high prevalence of obesity, necessarily have high LDLc levels or increased prevalence of atherosclerosis. The composition of the diet also plays a critical role.57

A major challenge for epidemiological and prevention research is to document that non-pharmacological interventions, i.e. diet modification, can successfully reduce the LDLc in ways that will prevent the progression of atherosclerosis. At the present time we have no good evidence in recent studies in primary prevention that non-pharmacological therapies will reduce or delay the progression of atherosclerosis among individuals with moderately elevated LDLc, i.e. in the range 130–160 mg%, etc.

The availability of non-invasive methods of measuring atherosclerosis provides an interesting opportunity to test alternative dietary and drug therapies in relation to the progression of atherosclerosis. This will be particularly important in evaluating not only the traditional methods of reducing LDLc, i.e. saturated fat, cholesterol, but also the effects of different polyunsaturated fats, antioxidants in the diet, fibre and possibly the effects of weight loss, as well as the effects of dietary interventions on other risk factors, i.e. lowering blood pressure through reduction of total fat, increase in fruit and vegetables, low salt diet, weight reduction, etc.57

In the older age group, 65+, we have a unique problem. Life expectancy has increased for these older individuals, and active life expectancy, i.e. functional status, can now be as much as over 20 years for women and perhaps 15 or so years for men. The prevalence of atherosclerosis is very high, and as noted, traditional measures such as lipoprotein levels do not predict the extent of atherosclerosis very well. There are three possible choices to deal with therapies in these older ages: (1) to presume that practically every relatively healthy person over 65 has significant atherosclerosis and would benefit from lipid-lowering therapy and other pharmacological therapies, i.e. to provide pharmacological therapy universally except where there is major disability or contraindications to such therapy; (2) to use non-invasive methods of measuring atherosclerosis, i.e. coronary calcium, carotid, ankle/brachial blood pressure, major ECG abnormalities, MRI of brain, to stratify older individuals with regard to the extent of atherosclerosis and risk of disease and then provide therapy for those with moderate to high levels of subclinical atherosclerosis; and (3) to treat very few of the elderly and limit treatment to those older individuals who also have diabetes, hypertension, and/or cigarette smokers and/or moderate symptomatology associated with early coronary heart disease. However, this approach will result in a substantial number of older individuals being treated with lipid-lowering drugs since about 20% of the population of older individuals will be diabetic and probably 60% or so have systolic hypertension.53,58

Recently lipid-lowering therapy has been shown to also reduce the risk of ischaemic stroke. The incidence of stroke, especially among women, is practically the same as that of myocardial infarction in the older age groups, and disability from stroke especially the development of post-stroke dementia can be even more devastating than that from coronary heart disease among older individuals. Thus, the decision to treat with lipid-lowering drugs in older individuals should include not only the risk of myocardial infarction, but also the risk of stroke.

The maintenance of plaque stability and the prevention of thrombosis can also have an immediate and important role in delaying the onset of heart attack and stroke. The identification of the proximate risk factors and interventions are less well established than that regarding lipid-lowering therapy, anti-hypertensive therapy, etc.59,60

Clinical trials which specifically focus on modifying inflammatory markers are probably the only way to provide definitive information on whether these markers have a role in a specific causal pathway to risk of disease, or whether they are just measures of inflammation in the plaque and the burden of atherosclerosis, i.e. are expensive sedimentation measurements.

National programmes to reduce incidence and mortality due to CHD and stroke should be a major component of all public health programmes. The objective evaluation of such programmes in terms of reduction in incidence and mortality will require innovative epidemiological approaches to surveillance and measures of both clinical events and subclinical atherosclerosis.
KEY MESSAGES

- Coronary heart disease is preventable.
- The knowledge of key risk factors, measurement of atherosclerosis and efficacy of both pharmacological and nonpharmacological therapies provide a strategy to substantially reduce cardiovascular morbidity and mortality.
- Proximate risk factors such as inflammatory markers and measures of thrombosis may enhance prediction of risk of disease.

References


