

Prevention of Cardiovascular Disease

Guidelines for assessment
and management of
cardiovascular risk



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Abbreviations and acronyms used in this document

ACE	angiotensin-converting enzyme
ALERT	Assessment of Lescol in Renal Transplantation
ALLHAT	Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ARB	angiotensin receptor blocker
ARIC	Atherosclerosis Risk in Communities
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
BMI	body mass index
CARDS	Collaborative Atorvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events [Study]
CCB	calcium-channel blocker
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
DALY	disability-adjusted life year
DASH	Dietary Approaches to Stop Hypertension
DCCT	Diabetes Control and Complications Trial
ECG	electrocardiogram
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes [Study]
GDG	Guideline Development Group
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
HDL-C	high-density lipoprotein cholesterol
HOT	Hypertension Optimal Treatment [Trial]
HPS	Heart Protection Study
HRT	hormone replacement therapy
ISH	International Society for Hypertension
LDL	low-density lipoprotein
LLT	Lipid Lowering Trial
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
QALY	quality-adjusted life year
RCT	randomized controlled trial
RR	relative risk
SCORE	Systematic Coronary Risk Evaluation
SIGN	Scottish Intercollegiate Guidelines Network
TC	total cholesterol
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organization
WOSCOPS	West of Scotland Coronary Prevention Study

Executive summary

Cardiovascular disease is a major cause of disability and premature death throughout the world, and contributes substantially to the escalating costs of health care. The underlying pathology is atherosclerosis, which develops over many years and is usually advanced by the time symptoms occur, generally in middle age. Acute coronary and cerebrovascular events frequently occur suddenly, and are often fatal before medical care can be given. Modification of risk factors has been shown to reduce mortality and morbidity in people with diagnosed or undiagnosed cardiovascular disease.

This publication provides guidance on reducing disability and premature deaths from coronary heart disease, cerebrovascular disease and peripheral vascular disease in people at high risk, who have not yet experienced a cardiovascular event. People with established cardiovascular disease are at very high risk of recurrent events and are not the subject of these guidelines. They have been addressed in previous WHO guidelines.^a

Several forms of therapy can prevent coronary, cerebral and peripheral vascular events. Decisions about whether to initiate specific preventive action, and with what degree of intensity, should be guided by estimation of the risk of any such vascular event. The risk prediction charts that accompany these guidelines^b allow treatment to be targeted according to simple predictions of absolute cardiovascular risk.

Recommendations are made for management of major cardiovascular risk factors through changes in lifestyle and prophylactic drug therapies. The guidelines provide a framework for the development of national guidance on prevention of cardiovascular disease that takes into account the particular political, economic, social and medical circumstances.

^a World Health Organization. *Prevention of recurrent heart attacks and strokes in low and middle income populations. Evidence-based recommendations for policy makers and health professionals*. Geneva, 2003 (<http://www.who.int/bookorders>).

^b Risk prediction charts for each WHO subregion (and country) are available with the pocket version of these guidelines.

Introduction

Background, scope and purpose of the guidelines

Of an estimated 58 million deaths globally from all causes in 2005, cardiovascular disease (CVD) accounted for 30%. This proportion is equal to that due to infectious diseases, nutritional deficiencies, and maternal and perinatal conditions combined (1). It is important to recognize that a substantial proportion of these deaths (46%) were of people under 70 years of age, in the more productive period of life; in addition, 79% of the disease burden attributed to cardiovascular disease is in this age group (2).

Between 2006 and 2015, deaths due to noncommunicable diseases (half of which will be due to cardiovascular disease) are expected to increase by 17%, while deaths from infectious diseases, nutritional deficiencies, and maternal and perinatal conditions combined are projected to decline by 3% (1). Almost half the disease burden in low- and middle-income countries is already due to noncommunicable diseases (3).

A significant proportion of this morbidity and mortality could be prevented through population-based strategies, and by making cost-effective interventions accessible and affordable, both for people with established disease and for those at high risk of developing disease (3–5).

To address the rising burden of noncommunicable diseases, in May 2000 the 53rd World Health Assembly adopted the WHO Global Strategy for the Prevention and Control of Noncommunicable Diseases (6). In doing so, it placed noncommunicable diseases on the global public health agenda. Since then, WHO has strengthened its efforts to promote population-wide primary prevention of noncommunicable diseases, through the Framework Convention on Tobacco Control (7) and the Global Strategy for Diet, Physical Activity and Health (8). These activities target common risk factors that are shared by CVD, cancer, diabetes and chronic respiratory disease, and their implementation is critical if the growing burden of noncommunicable diseases is to be controlled. These measures should make it easier for healthy people to remain healthy, and for those with established CVD or at high cardiovascular risk to change their behaviour. However, population-wide public health approaches alone will not have an immediate tangible impact on cardiovascular morbidity and mortality, and will have only a modest absolute impact on the disease burden (3, 4). By themselves they cannot help the millions of individuals at high risk of developing CVD (Table 1) or with an established CVD. A combination of population-wide strategies and strategies targeted at high risk individuals is needed to reduce the cardiovascular disease burden. The extent to which one strategy should be emphasized over the other depends on achievable effectiveness, as well as cost-effectiveness and availability of resources (1–4).

Although CVD already places a significant economic burden on low- and middle-income countries (9), the resources available for its management in these countries are limited because of competing health priorities. It is, nevertheless, essential to recognize that the transition to lower levels of infectious diseases and higher levels of noncommunicable diseases is already under way; failure to act now will result in large increases in avoidable CVD, placing serious pressures on the national economies (10–12). In this context, it is imperative to target the limited resources on those who are most likely to benefit. Thus, as envisioned in the Global Strategy for the Prevention

TABLE 1

Effect of three preventive strategies on deaths from coronary heart disease over 10 years in Canadians aged 20–74 years*

Strategy	No. (%) of population treated	% of treated population by 10-year risk of death (% of risk group treated)				No of deaths avoided ^a	
		<0.1%	0.1–0.99%	1–10%	>10%	Over 10 years	Per 100 000 population
Population health (Rose)	12 300 000 (100)	55.1 (100.0)	20.2 (100.0)	20.4 (100.0)	4.4 (100.0)	5 160	42
High baseline risk	1 590 000 (12.9)	0.1 (0.0)	2.2 (1.4)	64.0 (40.6)	33.8 (100.0)	35 800	290
Single risk factor	1 370 000 (11.1)	4.0 (0.8)	27.4 (15.1)	54.0 (29.5)	14.7 (37.5)	15 500	125

^a Assuming 100% community effectiveness for the single risk factor and high baseline risk strategies, and a 2% total cholesterol reduction for the Rose strategy.

* Source: ref. 4.

and Control of Noncommunicable Diseases (6), one of the major tasks for WHO and its Member States is to scale up cost-effective, integrated approaches for prevention of CVD.

This document provides guidance to policy-makers and health care workers on how to target individuals at high risk of developing CVD, at all levels of the health system and in different resource settings, using evidence-based and cost-effective preventive approaches. The objective is to reduce the incidence of heart attacks, strokes, and renal failure associated with hypertension and diabetes, as well as the need for amputation of limbs because of ischaemia, by reducing the cardiovascular risk. The focus is prevention of disability and early deaths and improvement of quality of life. This document should be considered as a framework, which can be adapted to suit different political, economic, social, cultural and medical circumstances.

Interpretation and implications of recommendations (13, 14)

The recommendations included here provide guidance on appropriate care. As far as possible, these are based on clear evidence that allows a robust understanding of the benefits, tolerability, harms and costs of alternative patterns of care. They are also feasible in different health care settings.

Recommendations can be defined as being strong when it is certain that their application will do more good than harm or that the net benefits are worth the costs. In this guide, such recommendations include the word “recommend” or “should”. Strong recommendations apply to most patients in most circumstances, and can be adopted as policy in most situations.

Recommendations can be defined as weak when it is uncertain that their application will do more good than harm or that the net benefits are worth the costs. In this guide, such recommendations include the words “suggest” or “should probably”. In applying weak recommendations, clinicians need to take into account each individual patient’s circumstances, preferences and values. Policy-making related to weak recommendations requires substantial debate and the involvement of a range of stakeholders.

Development of the guidelines

This guide was developed on the basis of the total risk approach to prevention of cardiovascular disease, elaborated in the World Health Report 2002 (2). Development of the risk prediction charts started in 2003, followed by preparations for the development of this guide in 2004, using an evidence-based methodology.

Published data related to primary prevention of cardiovascular disease were collated from existing guidelines, and by searching the Cochrane Library, Embase Medline, the trials register of the International Society for Hypertension (ISH), and the British Medical Journal clinical effectiveness reviews. Recent papers known to members of the Guideline Development Group (GDG) (see Annex 6), but not yet in a database or registry, were also included.

All references directly related to key issues dealt with in the guide were further evaluated for quality, using a Scottish Intercollegiate Guideline Network (SIGN) methodology checklist (13). Evidence-based reviews were prepared, based on data from good quality publications, and circulated to the GDG for input. They were further discussed at a consultation of the GDG in November 2005, with particular focus on the strength and applicability of the evidence to low-resource settings. Tables were compiled, summarizing the available scientific evidence to address key issues related to primary prevention. Evidence was graded and recommendations developed. SIGN and GRADE (Grades of Recommendation, Assessment, Development and Evaluation) systems were used to rate the evidence and grade the recommendations (13, 14).

A draft guide, prepared by the writing committee (see Annex 6), was circulated to the GDG for feedback. A revised draft was then sent for peer review (see Annex 7 for a list of reviewers). The present version of the guide reflects input from peer reviewers.

PART *1*

The total risk approach
to prevention of
cardiovascular disease

Rationale for targeting high-risk groups

The debilitating and often fatal complications of cardiovascular disease (CVD) are usually seen in middle-aged or elderly men and women. However, atherosclerosis – the main pathological process leading to coronary artery disease, cerebral artery disease and peripheral artery disease – begins early in life and progresses gradually through adolescence and early adulthood (15–17). It is usually asymptomatic for a long period.

The rate of progression of atherosclerosis is influenced by cardiovascular risk factors: tobacco use, an unhealthy diet and physical inactivity (which together result in obesity), elevated blood pressure (hypertension), abnormal blood lipids (dyslipidaemia) and elevated blood glucose (diabetes). Continuing exposure to these risk factors leads to further progression of atherosclerosis, resulting in unstable atherosclerotic plaques, narrowing of blood vessels and obstruction of blood flow to vital organs, such as the heart and the brain. The clinical manifestations of these diseases include angina, myocardial infarction, transient cerebral ischaemic attacks and strokes. Given this continuum of risk exposure and disease, the division of prevention of cardiovascular disease into primary, secondary and tertiary prevention is arbitrary, but may be useful for development of services by different parts of the health care system. The concept of a specific threshold for hypertension and hyperlipidaemia is also based on an arbitrary dichotomy.

The document provides evidence-based recommendations on how to assess and manage individuals with asymptomatic atherosclerosis, on the basis of their estimated total, or absolute, CVD risk. Total CVD risk is defined as the probability of an individual's experiencing a CVD event (e.g. myocardial infarction or stroke) over a given period of time, for example 10 years.

Total CVD risk depends on the individual's particular risk factor profile, sex and age; it will be higher for older men with several risk factors than for younger women with few risk factors. The total risk of developing cardiovascular disease is determined by the combined effect of cardiovascular risk factors, which commonly coexist and act multiplicatively. An individual with several mildly raised risk factors may be at a higher total risk of CVD than someone with just one elevated risk factor.

Timely and sustained lifestyle interventions and, when needed, drug treatment will reduce the risk of CVD events, such as heart attacks and strokes, in people with a high total risk of CVD, and hence will reduce premature morbidity, mortality and disability. Many people are unaware of their risk status; opportunistic and other forms of screening by health care providers are therefore a potentially useful means of detecting risk factors, such as raised blood pressure, abnormal blood lipids and blood glucose (18).

The predicted risk of an individual can be a useful guide for making clinical decisions on the intensity of preventive interventions: when dietary advice should be strict and specific, when suggestions for physical activity should be intensified and individualized, and when and which drugs should be prescribed to control risk factors. Such a risk stratification approach is particularly suitable to settings with limited resources, where saving the greatest number of lives at lowest cost becomes imperative (19).

In patients with a systolic blood pressure above 150 mmHg, or a diastolic pressure above 90 mmHg, or a blood cholesterol level over 5.0 mmol/l, drug treatment reduces the relative risk of cardiovascular events by between one-quarter and one-third (20–27). If blood pressure was

reduced by 10–15 mmHg (systolic) and 5–8 mmHg (diastolic) and blood cholesterol by about 20% through combined treatment with antihypertensives and statins, then cardiovascular disease morbidity and mortality would be reduced by up to 50% (28). People at very high CVD risk would benefit more, in terms of number of events avoided, because the relative risk reduction would be applied to a higher baseline risk (29). Therefore, targeting patients with a high risk is the first priority in a risk stratification approach.

As the cost of medicines is a significant component of total preventive health care costs, it is particularly important to base drug treatment decisions on an individual's risk level, and not on arbitrary criteria, such as ability to pay, or on blanket preventive strategies. In addition, guidelines based on total risk of CVD, which use risk scoring methods, have been shown to be both less expensive and more effective than guidelines based on single risk factor levels (30). Thus the use of guidelines based on risk stratification might be expected to free up resources for other competing priorities, especially in developing countries.

It should be noted that patients who already have symptoms of atherosclerosis, such as angina or intermittent claudication, or who have had a myocardial infarction, transient ischaemic attack, or stroke are at very high risk of coronary, cerebral and peripheral vascular events and death. These people are the top priority in clinical practice for prevention efforts. Risk stratification charts are unnecessary to arrive at treatment decisions for these categories of patients. They require both lifestyle and pharmacological interventions to help them to quit using tobacco, eat a healthy diet, increase physical activity, and manage their weight, blood pressure, blood lipids and blood glucose, as elaborated in other WHO guidelines and documents (5, 18).

The vast majority of the evidence on the benefits and potential harm of interventions to reduce CVD risk comes from high-income countries. The limited observational epidemiological data from low- and middle-income countries, recently extended by the Interheart case-control study (31), support the view that cardiovascular risk factors are equally predictive of CVD events in a wide range of low-, middle- and high-income countries. Thus, it seems reasonable to assume that the evidence related to lowering risk factors is also applicable to people in different settings.

Complementary strategies for prevention and control of cardiovascular disease

In all populations it is essential that the high-risk approach elaborated in this document is complemented by population-wide public health strategies (Figure 1) (11). Although cardiovascular events are less likely to occur in people with low levels of risk, no level of risk can be considered “safe” (32). Without population-wide public health prevention efforts, CVD events will continue to occur in people with low and moderate levels of risk, who are the majority in any population. Furthermore, public health approaches can effectively slow down the development of atherosclerosis (and also reduce the incidence of some cancers and chronic respiratory diseases) in young people, thereby reducing the likelihood of future epidemics of CVD, such as were seen in 1960–1990 in most high-income countries. Population-wide strategies will also support lifestyle modification in those at high risk. The extent to which one strategy is emphasized over the other depends on achievable effectiveness, cost-effectiveness and resource considerations.

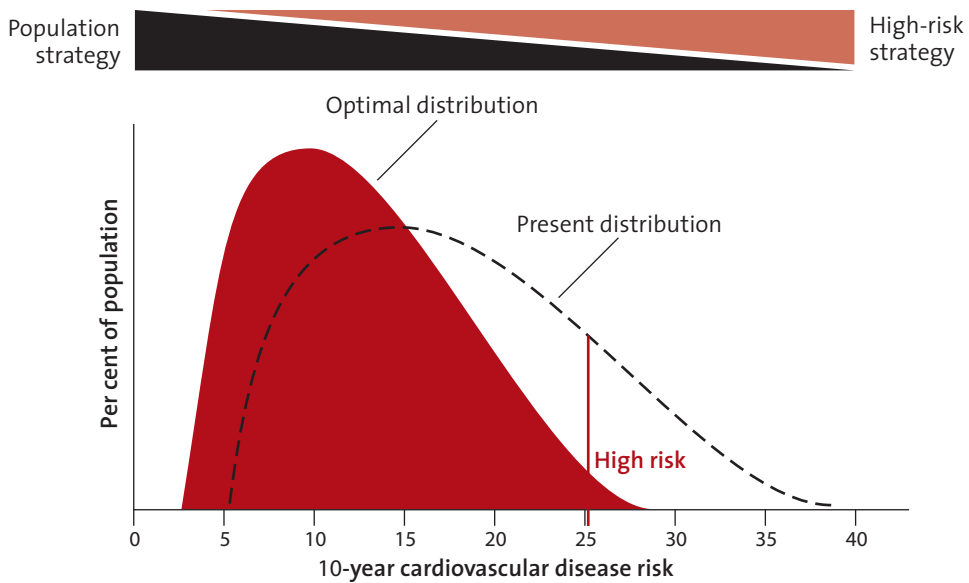


FIGURE 1

A combination of population-wide and high-risk strategies are required to reduce the cardiovascular disease risk distribution of the population (to shift the cardiovascular risk distribution to the left)
 source: ref. 11

Threshold for interventions

The appropriate threshold of an individual's total risk at which intensive lifestyle interventions and drug treatment are initiated depends on the availability of resources and the impact of specific interventions. The cost-effectiveness of pharmacological treatment for high blood pressure and blood cholesterol depends on the total cardiovascular risk of the individual before treatment (29–33); long-term drug treatment is justified only in high-risk individuals. If resources allow, the target population can be expanded to include those with moderate levels of risk; however, lowering the threshold for treatment will increase not only the benefits but also the costs and potential harm. People with low levels of risk will benefit from population-based public health strategies and, if resources allow, professional assistance to make behavioural changes.

Ministries of health have the difficult task of setting a risk threshold for treatment that balances the health care resources in the public sector, the wishes of clinicians, and the expectations of the public. For example, in England, a 30% risk of developing coronary heart disease over a 10-year period was defined as “high risk” by the National Service Framework for coronary heart disease (34). This threshold would apply to about 3% of men in the population aged between 45 and 75 years. When the cardiovascular risk threshold was lowered to 20% (equivalent to a coronary heart disease risk of 15%), a further 16% of men were considered “high risk” and therefore eligible for drug treatments.

Ministries of health or health insurance organizations may wish to set the cut-off points to match resources, as shown below for illustrative purposes.

10-year total CVD risk thresholds for intensive intervention:

high-resource setting: 20%

medium-resource setting: 30%

low-resource setting: 40%

As the threshold for intervention is lowered, the number of individuals eligible to benefit increases, but so do the costs and the number of adverse events caused by drug treatments. In a state-funded health system, the government and its health advisers are often faced with making decisions about the threshold at which drug and other interventions are affordable. In many health care systems, such decisions must be made by individual patients and their medical practitioners, on the basis of a careful appraisal of the potential benefits, hazards and costs involved.

Adoption of a high (40%) threshold for 10-year CVD risk in a population might seem economical; however, this would deny most of the population the opportunity to prevent or at least delay a first cardiovascular event. Countries that use a risk stratification approach have tended to reduce the threshold of risk used to determine treatment decisions as the costs of drugs, particularly statins, have fallen and as adequate coverage of the population at the higher risk level has been achieved. In low-income countries, lowering the threshold below 40% may not be feasible because of resource limitations. Nevertheless, use of risk stratification approaches will ensure that treatment decisions are transparent and logical, rather than determined by arbitrary factors or promotional activity of pharmaceutical companies.

Table 2 shows the percentage of the population, by age and sex, with a ten-year total CVD risk of 30% or more in each of the 14 WHO subregions. The countries included in each subregion are listed in Annex 1 (2). For data on all risk categories, see Annex 2.

Risk prediction charts: Strengths and limitations

Use of risk prediction charts to estimate total cardiovascular risk is a major advance on the older practice of identifying and treating individual risk factors, such as raised blood pressure (hypertension) and raised blood cholesterol (hypercholesterolemia). Since there is a continuous relationship between these risk factors and cardiovascular risk the concept of hypertension and hyperlipidemia introduces an arbitrary dichotomy.

The total risk approach acknowledges that many cardiovascular risk factors tend to appear in clusters; combining risk factors to predict total cardiovascular risk is consequently a logical approach to deciding who should receive treatment. Many techniques for assessing the cardiovascular risk status of individual patients have been described (35–40). Most of these techniques use risk prediction equations derived from various sources, most commonly the Framingham Heart Study (35, 41–46). The risk charts and tables produced use different age categories, duration of risk assessment and risk factor profiles. The current New Zealand (43) and Joint British Societies charts (40, 41) are similar in concept. The former assess the five-year risk for all cardiovascular disease in eight discrete categories, while the latter assess the ten-year risk of CVD in three age categories. Risk scores have different accuracy in different populations, tending to overpredict in low-risk populations and underpredict in high-risk populations. Risk scores using the Framingham equations have been widely tested in North American and European populations of European origin (38, 45–47), and validated

TABLE 2

The percentage of the population, by age and sex, with a ten-year CVD risk of 30% or more, 14 WHO subregions

WHO SUBREGION	MEN Age group (years)				WOMEN Age group (years)			
	<50	50–59	60–69	70+	<50	50–59	60–69	70+
African Region: D	0.32%	1.98%	11.15%	13.30%	0.04%	1.10%	8.78%	24.45%
African Region: E	1.26%	1.87%	4.05%	3.84%	0.37%	1.34%	2.43%	3.93%
Region of the Americas: A	0.85%	8.40%	31.77%	54.23%	0.24%	3.13%	14.38%	31.59%
Region of the Americas: B	0.43%	5.42%	19.24%	23.25%	0.31%	4.23%	12.95%	25.28%
Region of the Americas: D	0.08%	2.25%	5.62%	12.36%	0.28%	1.62%	4.36%	18.65%
Eastern Mediterranean Region: B	0.13%	4.53%	25.32%	36.64%	0.09%	5.98%	24.08%	49.01%
Eastern Mediterranean Region: D	0.19%	4.65%	18.73%	38.46%	0.16%	2.60%	15.49%	39.91%
European Region: A	0.15%	2.77%	16.13%	37.83%	0.05%	0.32%	2.79%	20.69%
European Region: B	0.88%	8.94%	28.12%	41.93%	0.46%	1.92%	10.79%	22.77%
European Region: C	1.31%	13.70%	40.29%	58.69%	0.50%	3.16%	22.48%	51.89%
South-East Asia Region: B	0.37%	4.13%	10.23%	13.54%	0.22%	2.02%	9.32%	13.29%
South-East Asia Region: D	0.47%	5.12%	22.23%	31.39%	0.22%	3.31%	19.23%	29.75%
Western Pacific Region: A	0.35%	2.63%	12.32%	26.41%	0.05%	0.61%	2.20%	8.92%
Western Pacific Region: B	0.16%	3.78%	15.06%	21.63%	0.10%	1.99%	6.74%	15.28%

in a Chinese population (48), but not in other populations. The European Guidelines on CVD prevention use a new model for total risk estimation based on the SCORE (Systematic Coronary Risk Evaluation) system (37). The risk charts based on the SCORE study are derived from a large dataset of prospective European studies (37). The risk estimation is based on sex, age, smoking, systolic blood pressure, and either total cholesterol (TC) or the ratio of total cholesterol to high-density lipoprotein cholesterol (HDL-C). SCORE predicts only the likelihood of fatal CVD events, unlike the risk scores based on the Framingham equations. The threshold for high risk is defined as a risk of death of 5% or greater, instead of the composite fatal and non-fatal coronary endpoint of 20%.

The evidence that underpins the use of risk factor scoring and management comes from a range of sources. There is now increasing evidence that cardiovascular risk factors are associated with clinical

events in a similar way in a wide range of countries (31). There is also strong epidemiological evidence that combining risk factors into scores is capable of predicting an individual's total cardiovascular risk with reasonable accuracy. Finally, there is strong evidence from clinical trials that reducing the levels of risk factors has beneficial effects. Risk factor scoring and management have now been widely taken up in cardiovascular prevention guidelines in most high-income countries (36, 41, 43, 44).

The risk factors included in current scoring systems are drawn from those used in the original Framingham score. There is currently debate about the inclusion of newer risk factors, such as C-reactive protein, fibrinogen, and waist–hip ratio (49). It is possible that, as more epidemiological data become available for low- and middle-income countries, a new generation of risk scoring systems may emerge that have greater predictive accuracy.

Older age and male sex are powerful determinants of risk; consequently, it has been argued that the use of the risk stratification approach will favour treatment of elderly people and men, at the expense of younger people with several risk factors and women. For example, a non-smoking 40-year-old man with a systolic blood pressure of 150 mmHg and a TC/HDL-C ratio of 6 has a 15% risk of a cardiovascular event over the next 10 years; this would classify him as low risk. A 65-year-old man with the same systolic blood pressure and TC/HDL-C ratio has a 10-year CVD risk of over 30%, classifying him as high risk and eligible for drug treatment. If benefit is measured in terms of potential years of life gained, rather than simply CVD events avoided, a case can be made for starting drug treatments among younger people. However, while younger people gain more life years if they have a non-fatal event, older people are a lot more likely to die from an event. When discounting is taken into consideration, the quality adjusted life years gained by preventing events in young people are very similar to those gained in old people (Table 3) (50).

Concern about the metabolic syndrome, characterized by central obesity, elevated blood pressure, dyslipidaemia, and insulin resistance (51, 52), has raised the question of whether identifying people with this syndrome should be a priority. While there are different definitions of the syndrome, proposed by WHO and other organizations (53–58), people with this combination of risk factors are at increased risk of developing coronary heart disease, stroke, and diabetes (59, 60), and have a worse

TABLE 3

Effect of discounting and 30-day case-fatality on life years lost after a cardiovascular disease event in men*

Age (years)	Average life expectancy (years)	Average life expectancy discounted at 3% per year (years)	30-day case fatality after a major CVD event ^a (%)	Average discounted life-years lost after a CVD event, attributable to 30-day case fatality (years)
80	6 · 8	6 · 2	60	3 · 7
70	12 · 2	10 · 3	50	5 · 2
60	19 · 2	14 · 8	40	5 · 9
50	27 · 6	18 · 9	30	5 · 7
40	36 · 8	22 · 4	25	5 · 6

^a Coronary heart disease case-fatality used as a proxy for cardiovascular disease case-fatality (note that the model does not account for morbidity after a cardiovascular disease event).

* Source: ref. 50.

prognosis after myocardial infarction (61, 62). There is, as yet, insufficient evidence to justify using metabolic syndrome as an additional risk prediction tool (63, 64). However, the proposed WHO risk prediction charts should be used for people with the syndrome, to predict their total cardiovascular risk and implement appropriate management. It has been argued recently that the CVD risk associated with the metabolic syndrome is nothing more than the sum of the risks of its individual components. Furthermore, in constructing the metabolic syndrome, risk factors that have a graded relation to CVD are reduced into two very broad categories using arbitrary cut-off points; thus, much information related to the risk prediction is lost. People with metabolic syndrome would, in any case, benefit from weight reduction, higher levels of activity (65–71), lowering of blood pressure, avoidance of drugs that tend to cause hyperglycaemia (72–75), lowering of cholesterol with a statin (76–80), and reduction of hyperglycaemia with metformin. There is insufficient evidence from randomized trials to support more specific management of dyslipidaemias (81).

In summary, the great strength of the risk scoring approach is that it provides a rational means of making decisions about intervening in a targeted way, thereby making best use of resources available to reduce cardiovascular risk. Alternative approaches focused on single risk factors, or concepts such as pre-hypertension or pre-diabetes, have been popular in the past, often because they represented the interests of specific groups in the medical profession and professional societies. Such an approach, however, leads to a very large segment of the population being labelled as high risk, most of them incorrectly. If health care resources were allocated to such false-positive individuals, a large number of truly high-risk individuals would remain without medical attention. Risk scoring moves the focus of treatment from the management of individual risk factors to the best means of reducing an individual's overall risk of disease. It enables the intensity of interventions to be matched to the degree of total risk (Figure 2).

Further research is required to validate existing subregional risk prediction charts for individual populations at national and local levels, and to confirm that the use of risk stratification methods in low- and middle-income countries results in benefits for both patients and the health care system.

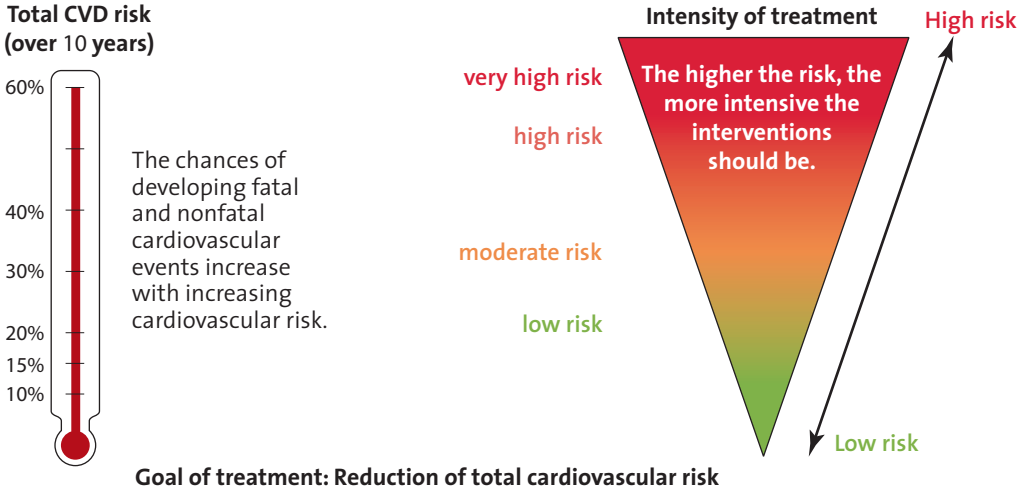


FIGURE 2
Intensity of interventions should be proportional to the total cardiovascular risk

The WHO/ISH cardiovascular risk prediction charts

Examples of WHO/ISH cardiovascular risk prediction charts, are shown in Annexes 3 and 4. Annex 1 provides specific information on the countries in each WHO subregion. Risk prediction charts for each WHO subregion (and country) are available with the pocket version of these guidelines (<http://www.who.int/bookorders>).

These charts are intended to allow the introduction of the total risk stratification approach for management of cardiovascular disease, particularly where cohort data and resources are not readily available for development of population-specific charts. The charts have been generated from the best available data, using a modelling approach (Annex 5), with age, sex, smoking, blood pressure, blood cholesterol, and presence of diabetes as clinical entry points for overall management of cardiovascular risk.

Some studies have suggested that diabetic patients have a high cardiovascular risk, similar to that of patients with established cardiovascular disease, and so do not need to be risk-assessed. However, some people with diabetes, particularly younger patients and those who are newly diagnosed, have low or moderate total CVD risk. In addition, in people with diabetes, there is no gender difference in the risk of coronary heart disease and stroke (82). Therefore, separate charts have been developed for assessment of cardiovascular risk in patients with type 2 diabetes.

In many low-resource settings, there are no facilities for cholesterol assay, although it is often feasible to check urine sugar as a surrogate measure for diabetes. Annex 4 therefore contains risk prediction charts that do not use cholesterol, but only age, sex, smoking, systolic blood pressure, and presence or absence of diabetes to predict cardiovascular risk.

Obesity, abdominal obesity (high waist–hip ratio), physical inactivity, low socioeconomic position, and a family history of premature cardiovascular disease (cardiovascular disease in a first-degree relative before the age of 55 years for men and 65 years for women) can all modify cardiovascular risk. These risk factors are not included in the charts, which may therefore underestimate actual risk in people with these characteristics. The risk charts also do not include other risk factors, such as low HDL-C, elevated triglycerides, left ventricular hypertrophy, raised serum creatinine, albuminuria, C-reactive protein, hyperuricaemia and fibrinogen. While including these risk factors in risk stratification would improve risk prediction in most populations, the increased gain would not usually be large, and does not warrant waiting to develop and validate further risk stratification tools. Nevertheless, these (and other) risk factors may be important for risk prediction, and some of them may be causal factors that should be managed. Clinicians should, as in any situation, use their clinical acumen to examine the individual's lifestyle, preferences and expectations, and use this information to tailor a management programme.

The risk prediction charts and the accompanying recommendations can be used by health care professionals to match the intensity of risk factor management with the likelihood of cardiovascular disease events. The charts can also be used to explain to patients the likely impact of interventions on their individual risk of developing cardiovascular disease. This approach may motivate patients to change their behaviour. The use of charts will help health care professionals to focus their limited time on those who stand to benefit the most.

It should be noted that the risk predictions are based on epidemiological data from groups of people, rather than on clinical practice. This means that the measures of blood pressure and blood

cholesterol may have been assessed only once rather than repeatedly, as is normal in clinical practice. However, these objections do not detract from their potential to bring much-needed coherence to the clinical dilemmas of how to apply evidence from randomized trials in clinical practice, and of who to treat with a growing range of highly effective but costly interventions.

Clinical assessment of cardiovascular risk

Clinical assessment should be conducted with four aims:

- to search for all cardiovascular risk factors and clinical conditions that may influence prognosis and treatment;
- to determine the presence of target organ damage (heart, kidneys and retina);
- to identify those at high risk and in need of urgent intervention;
- to identify those who need special investigations or referral (e.g. those with secondary hypertension (see Table 4)).

TABLE 4

Causes, clinical features and laboratory tests for diagnosis of secondary hypertension

Causes	Clinical features and Investigations
Renal parenchymal hypertension	<ul style="list-style-type: none"> ◆ family history of renal disease (polycystic kidney), ◆ past history of renal disease, urinary tract infection, haematuria, analgesic abuse ◆ enlarged kidneys on physical examination ◆ abnormalities in urine analysis – protein, erythrocytes, leucocytes and casts ◆ raised serum creatinine
Renovascular hypertension	<ul style="list-style-type: none"> ◆ abdominal bruit ◆ abnormal renal function tests ◆ narrowing of renal arteries in renal arteriography
Phaeochromocytoma	<ul style="list-style-type: none"> ◆ episodic headache, sweating, anxiety, palpitations ◆ neurofibromatosis ◆ raised catecholamines, metanephrines in 24-hour urine samples
Primary aldosteronism	<ul style="list-style-type: none"> ◆ muscle weakness and tetany ◆ hypokalaemia ◆ decreased plasma renin activity and/or elevated plasma aldosterone level
Cushing syndrome	<ul style="list-style-type: none"> ◆ truncal obesity, rounded face, buffalo hump, thin skin, abdominal striae, etc. ◆ raised 24-hour urinary cortisol excretion
Coarctation of the aorta	<ul style="list-style-type: none"> ◆ precordial or chest murmurs ◆ diminished and delayed femoral pulse ◆ reduced femoral blood pressure ◆ notching of ribs on chest X ray ◆ coarctation detected in arteriography

Clinical history

A comprehensive clinical history (83) should include:

- current symptoms of coronary heart disease, heart failure, cerebrovascular disease, peripheral vascular disease, diabetes, and renal disease;
- information on the use of drugs known to raise blood pressure (oral contraceptives, nonsteroidal anti-inflammatory drugs, liquorice, cocaine, amphetamine, erythropoietin, cyclosporins and steroids);
- the family history of high blood pressure, diabetes, dyslipidaemia, coronary heart disease, stroke and renal disease;
- the personal history of coronary heart disease, heart failure, cerebrovascular disease, peripheral vascular disease, diabetes, gout, bronchospasm, sexual dysfunction, and renal disease;
- symptoms suggestive of secondary hypertension, i.e. hypertension caused by an underlying condition (Table 4);
- information on behaviour, including tobacco use, physical activity and dietary intake of fat, salt and alcohol;
- personal, psychosocial, occupational and environmental factors that could influence the course and outcome of long-term care.

Physical examination

A full physical examination is essential, and should include careful measurement of blood pressure, as described below. Other important elements of the physical examination include:

- measurement of height and weight, and calculation of body mass index (BMI) (weight in kilograms divided by the square of height in meters); measurement of waist and hip circumference for calculation of waist–hip ratio;
- examination of the cardiovascular system, particularly for heart size, evidence of heart failure, evidence of disease in the carotid, renal and peripheral arteries, and physical signs suggestive of coarctation of the aorta, particularly in young people with hypertension;
- examination for features of secondary hypertension (phaeochromocytoma, Cushing syndrome, etc.) (Table 4);
- examination of the lungs for congestion ;
- examination of the abdomen for bruits, enlarged kidneys and other masses;
- examination of the optic fundi and of the central and peripheral nervous system for evidence of cerebrovascular disease and complications of diabetes.

Measuring blood pressure

Health care professionals need to be adequately trained to measure blood pressure. In addition, blood pressure measuring devices need to be validated, maintained and regularly calibrated to ensure that they are accurate (84). Where possible, blood pressure should be measured when the

patient is relaxed and seated with the arm outstretched and supported. Two readings should be taken; if the average is 140/90 mmHg or more, an additional reading should be taken at the end of the consultation for confirmation.

Blood pressure should be measured in both arms initially, and the arm with the higher reading used for future measurements. If the difference between the two arms is more than 20 mmHg for systolic pressure or 10 mmHg for diastolic pressure, the patient should be referred to the next level of care for examination for vascular stenosis. Patients with accelerated (malignant) hypertension (blood pressure \geq 180/110 mmHg with papilloedema or retinal haemorrhages) or suspected secondary hypertension should be referred to the next level immediately.

When can treatment decisions be made without the use of risk prediction charts? (40, 41, 43)

Some individuals are at very high cardiovascular risk because they have already experienced a cardiovascular event, or have very high levels of individual risk factors. Risk stratification is not necessary for making treatment decisions for these individuals as they belong to the high risk category; all of them need intensive lifestyle interventions and appropriate drug therapy (5). Risk prediction charts may tend to underestimate cardiovascular risk in such individuals, who include the following:

- patients with established angina pectoris, coronary heart disease, myocardial infarction, transient ischaemic attacks, stroke, or peripheral vascular disease, or who have had coronary revascularization or carotid endarterectomy;
- those with left ventricular hypertrophy (shown on electrocardiograph) or hypertensive retinopathy (grade III or IV);
- individuals without established CVD who have a total cholesterol \geq 8 mmol/l (320 mg/dl) or low-density lipoprotein (LDL) cholesterol \geq 6 mmol/l (240 mg/dl) or TC/HDL-C ratio $>$ 8;
- individuals without established CVD who have persistent raised blood pressure ($>$ 160–170/100–105 mmHg) (38–41, 43, 83);
- patients with type 1 or 2 diabetes, with overt nephropathy or other significant renal disease;
- patients with known renal failure or renal impairment.

Applying the WHO/ISH risk prediction charts

Individual risk charts are specific to the respective WHO subregion (Annex 1). Each chart has been calculated from the mean of risk factors and the average ten-year event rates from countries of the specific subregion. The charts provide only approximate estimates of CVD risk in people who do not have symptoms of coronary heart disease (CHD), stroke or other atherosclerotic disease. Importantly, these estimates represent the average for the subregion and do not capture the variation in CVD risk within each subregion or country. They are useful as tools to help identify those at high total cardiovascular risk, and to motivate patients, particularly to change behaviour and, when appropriate, to take antihypertensive and lipid-lowering drugs and aspirin.

In settings where facilities for measuring cholesterol are not available, risk prediction charts that do not include cholesterol can be used (see Annex 4).

An individual's risk of experiencing a cardiovascular event in the next 10 years is estimated as follows:

- Select the appropriate chart (see Annex 3), depending on whether the person has diabetes or not. (A person who has diabetes is defined as someone taking insulin or oral hypoglycaemic drugs, or with a fasting plasma glucose concentration above 7.0 mmol/l (126 mg/dl) or a postprandial (approximately 2 hours after a main meal) plasma glucose concentration above 11.0 mmol/l (200 mg/l) on two separate occasions).
- Select the appropriate element of the chart, corresponding to the person's sex, age (if age is 50–59 select 50, 60–69 select 60 etc) and whether he or she is a smoker. (All current smokers and those who quit smoking less than 1 year before the assessment are considered smokers for assessing cardiovascular risk.)
- Find the cell in the chart element that corresponds to the individual's systolic blood pressure and serum cholesterol. (Systolic blood pressure, taken as the mean of two readings on each of two occasions, is sufficient for assessing risk but not for establishing a pretreatment baseline. The mean of two non-fasting measurements of serum cholesterol by dry chemistry, or one non-fasting laboratory measurement, is sufficient for assessing risk.)
- The colour of the cell indicates the risk category (see key in Annexes 3 and 4).

CVD risk may be higher than indicated in the chart in people who are already on antihypertensive therapy, in women who have undergone premature menopause, in people approaching the next age category, and in individuals with any of the following:

- obesity (including central obesity);
- a sedentary lifestyle;
- a family history of premature CHD or stroke in a first degree relative (male < 55 years, female < 65 years);
- a raised triglyceride level (> 2.0 mmol/l or 180 mg/dl);
- a low HDL cholesterol level (< 1 mmol/l or 40mg/dl in males, < 1.3 mmol/l or 50 mg/dl in females);
- raised levels of C-reactive protein, fibrinogen, homocysteine, apolipoprotein B or Lp(a), or fasting glycaemia, or impaired glucose tolerance;
- microalbuminuria (increases the 5-year risk of diabetics by about 5%) (38, 83, 85);
- those who are not yet diabetic, but have impaired fasting glycemia or impaired glucose tolerance;
- a raised pulse rate.

Other risk factors not included in these risk prediction charts such as socioeconomic deprivation and ethnicity should also be taken into account in addressing and managing a person's overall CVD risk.

Goals of applying the prevention recommendations

The purpose of applying the recommendations elaborated in these guidelines is to motivate and assist high-risk individuals to lower their cardiovascular risk by:

- quitting tobacco use, or reducing the amount smoked, or not starting the habit;
- making healthy food choices;
- being physically active;
- reducing body mass index (to less than 25 kg/m²) and waist–hip ratio (to less than 0.8 in women and 0.9 in men (these figures may be different for different ethnic groups));
- lowering blood pressure (to less than 140/90 mmHg);
- lowering blood cholesterol (to less than 5 mmol/l or 190 mg/dl);
- lowering LDL-cholesterol (to less than 3.0 mmol/l or 115 mg/dl);
- controlling glycaemia, especially in those with impaired fasting glycaemia and impaired glucose tolerance or diabetes;
- taking aspirin (75 mg daily), once blood pressure has been controlled.

The above goals represent the minimum that should be achieved. They are given for broad guidance in managing cardiovascular risk. In some subgroups of high-risk people, particularly those with established cardiovascular disease or diabetes, a case can be made for lower targets for blood pressure (< 130/80 mmHg), total cholesterol and LDL-cholesterol, which may require more intensive treatment. Similarly, in very high-risk patients, a total cholesterol of less than 4.0 mmol/l (152 mg/dl) and LDL-cholesterol of less than 2.0 mmol/l (77 mg/dl), or a reduction of 25% in total cholesterol and 30% in LDL-cholesterol, whichever achieves the lower absolute level, may be desirable goals.

PART 2

**Recommendations
for prevention of
cardiovascular disease**

Levels of evidence and grades of recommendations

Recommendations for prevention of cardiovascular disease, according to individual total risk, are given in Table 6. The strength of the various recommendations, and the level of evidence supporting them, are indicated as follows (13) in Table 5.

TABLE 5

Levels of evidence

	Clinical trial data	Behavioural risk factor data
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias	Systematic reviews of high-quality case-control or cohort studies with a very low risk of confounding, bias or chance, and a high probability that the relationship is causal
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias	Well conducted case-control and cohort studies with a very low risk of confounding, bias or chance, and a high probability that the relationship is causal
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias	Case-control and cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2++	High quality systematic reviews of case-control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal	
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal	
3	Non-analytical studies e.g. case reports, case series	
4	Expert opinion	

Grades of recommendations

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A *There is robust evidence to recommend a pattern of care.*

At least one meta-analysis, systematic review of RCTs or RCT rated as **1++** and directly applicable to the target population; or a body of evidence, consisting principally of studies rated as **1+**, that is directly applicable to the target population, and demonstrating overall consistency of results.

B *There is evidence to recommend a pattern of care.*

A body of evidence, including studies rated as **2++**, is directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as **1++** or **1+**.

C *On balance of evidence, a pattern of care is recommended with caution.*

A body of evidence, including studies rated as **2+**, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as **2++**.

D *Evidence is inadequate, and a pattern of care is recommended by consensus.*

Evidence is of level **3** or **4**; or extrapolated evidence from studies rated as **2+**.

- ✓ Recommended best practice based on the clinical experience of the guideline development group

Recommendations

TABLE 6

Prevention of cardiovascular disease according to individual total risk^a

10-year risk of cardiovascular event >30%	10-year risk of cardiovascular event 20–30%	10-year risk of cardiovascular event 10–20%	10-year risk of cardiovascular event <10%
Individuals in this category are at very high risk of fatal or nonfatal vascular events. Monitor risk profile every 3–6 months	Individuals in this category are at high risk of fatal or nonfatal vascular events. Monitor risk profile every 3–6 months	Individuals in this category are at moderate risk of fatal or nonfatal vascular events. Monitor risk profile every 6–12 months	Individuals in this category are at low risk. Low risk does not mean “no” risk. Conservative management focusing on lifestyle interventions is suggested ^b .
When resources are limited, individual counselling and provision of care may have to be prioritized according to cardiovascular risk.			
SMOKING CESSATION			
All nonsmokers should be encouraged not to start smoking. All smokers should be strongly encouraged to quit smoking by a health professional and supported in their efforts to do so. (1++, A) It is suggested that those who use other forms of tobacco be advised to stop. (2+, C)			
Nicotine replacement therapy and/or nortriptyline or amfebutamone (bupropion) should be given to motivated smokers who fail to quit with counselling. (1++, B)	Nicotine replacement therapy and/or nortriptyline or amfebutamone (bupropion) should be given to motivated smokers who fail to quit with counselling. (1++, B)		

continued ...

^a Excluding people with established coronary artery disease, cerebrovascular disease and peripheral vascular disease.

^b Policy measures that create conducive environments for quitting tobacco, engaging in physical activity and consuming healthy diets are necessary to promote behavioural change. They will benefit the whole population. For individuals in low risk categories, they can have a health impact at lower cost, compared to individual counselling and therapeutic approaches.

10-year risk of cardiovascular event >30%	10-year risk of cardiovascular event 20–30%	10-year risk of cardiovascular event 10–20%	10-year risk of cardiovascular event <10%
DIETARY CHANGES			
<p>All individuals should be strongly encouraged to reduce total fat and saturated fat intake (1+, A). Total fat intake should be reduced to about 30% of calories, saturated fat intake should be limited to less than 10% of calories and trans-fatty acids eliminated. Most dietary fat should be polyunsaturated (up to 10% of calories) or monounsaturated (10–15% of calories). (1+, A)</p> <p>All individuals should be strongly encouraged to reduce daily salt intake by at least one-third and, if possible, to <5 g or 90 mmol per day. (1+, A)</p> <p>All individuals should be encouraged to eat, at least 400 g a day, of a range fruits and vegetables, as well as whole grains and pulses. (2+, A)</p>			
PHYSICAL ACTIVITY			
<p>All individuals should be strongly encouraged to take at least 30 minutes of moderate physical activity (e.g. brisk walking) a day, through leisure time, daily tasks and work-related physical activity. (1+, A)</p>			
WEIGHT CONTROL			
<p>All individuals who are overweight or obese should be encouraged to lose weight through a combination of a reduced-energy diet (dietary advice) and increased physical activity. (1+, A)</p>			
ALCOHOL INTAKE			
<p>Individuals who take more than 3 units of alcohol^c per day should be advised to reduce alcohol consumption. (2++, B)</p>			

continued ...

^c One unit (drink) = half pint of beer/lager (5% alcohol), 100 ml of wine (10% alcohol), spirits 25 ml (40% alcohol)

10-year risk of cardiovascular event >30%	10-year risk of cardiovascular event 20–30%	10-year risk of cardiovascular event 10–20%	10-year risk of cardiovascular event <10%
ANTIHYPERTENSIVE DRUGS ✓			
All individuals with blood pressure at or above 160/100 mm Hg, or lesser degree of raised blood pressure with target organ damage should have drug treatment and specific lifestyle advice to lower their blood pressure and risk of cardiovascular disease (2++ , B).			
<p>Individuals with persistent blood pressure $\geq 130/80$ mmHg should be given one of the following drugs to reduce blood pressure and risk of cardiovascular disease: thiazide-like diuretic, ACE inhibitor, calcium-channel blocker, beta-blocker.^d</p> <p>A low-dose thiazide-like diuretic, ACE inhibitor, or calcium-channel blocker is recommended as first-line therapy. (1++, A).</p>	<p>Individuals with persistent blood pressure $\geq 140/90$ mmHg^e who are unable to lower blood pressure through life style strategies with professional assistance within 4–6 months, should be considered for one of the following drugs to reduce blood pressure and risk of cardiovascular disease: thiazide-like diuretic, ACE inhibitor, calcium-channel blocker, beta-blocker.^d</p> <p>A low-dose thiazide-like diuretic, ACE inhibitor, or calcium-channel blocker is recommended as first-line therapy. (1++, A)</p>	<p>Individuals with persistent blood pressure $\geq 140/90$ mmHg,^e should continue life style strategies to lower blood pressure and have their blood pressure and total cardiovascular risk reassessed annually depending on clinical circumstances and resource availability.</p>	<p>Individuals with persistent blood pressure $\geq 140/90$ mmHg,^e should continue life style strategies to lower blood pressure and have their blood pressure and total cardiovascular risk reassessed every two to five years depending on clinical circumstances and resource availability.</p>

continued ...

^d Evidence from two recent meta-analyses indicates that beta-blockers are inferior to calcium-channel blockers and ACE inhibitors in reducing the frequency of hard endpoints. In addition, beta-blockers are less well tolerated than diuretics (see Part III, section 4). Most of this evidence comes from trials where atenolol was the beta-blocker used.

^e Reducing blood pressure by 10–15/5–8 mmHg with drug treatment reduces combined CVD mortality and morbidity by about one-third, whatever the pretreatment absolute risk. However, applying this recommendation will lead to a large proportion of the adult population receiving antihypertensive drugs. Even in some high-resource settings, current practice is to recommend drugs for this group only if the blood pressure is at or above 160/100 mmHg.

10-year risk of cardiovascular event >30%	10-year risk of cardiovascular event 20–30%	10-year risk of cardiovascular event 10–20%	10-year risk of cardiovascular event <10%
LIPID-LOWERING DRUGS (STATINS) ✓			
All individuals with total cholesterol at or above 8 mmol/l (320 mg/dl), should be advised to follow a lipid-lowering diet and given a statin to lower the risk of cardiovascular disease (2++, B) .			
Individuals in this risk category should be advised to follow a lipid-lowering diet and given a statin. (1++, A) Serum cholesterol should be reduced to less than 5.0 mmol/l (LDL-cholesterol to below 3.0 mmol/l), or by 25% (30% for LDL cholesterol) which ever is greater. ^f	Adults over the age of 40 years with persistently high serum cholesterol (>5.0 mmol/l), and or LDL-cholesterol >3.0 mmol/l, despite a lipid-lowering diet, should be given a statin. (1+, A)	Should be advised to follow a lipid lowering diet ^g	
HYPOGLYCEMIC DRUGS ✓			
Individuals with persistent fasting blood glucose >6 mmol/l despite diet control should be given metformin. (1+, A)			Recommendations as for moderate risk, as resources permit.

continued ...

^f Reducing cholesterol level by 20% (approximately 1 mmol/l) with statin treatment would be expected to yield a coronary heart disease mortality benefit of 30%, whatever the pretreatment absolute risk. However, applying this to the general population may not be cost effective. It will lead to a large proportion of the adult population receiving statins. Even in some high-resource settings, current practice is to recommend drugs for this group only if serum cholesterol is above 8mmol/l (320 mg/dl).

^g There are no clinical trials that have evaluated the absolute and relative benefits of cholesterol lowering to different cholesterol targets in relation to clinical events.

10-year risk of cardiovascular event >30%	10-year risk of cardiovascular event 20–30%	10-year risk of cardiovascular event 10–20%	10-year risk of cardiovascular event <10%
ANTIPLATELET DRUGS ✓			
Individuals in this risk category should be given low-dose aspirin. (1++, A)	For individuals in this risk category cardiovascular risk, the balance of benefits and harms from aspirin treatment is not clear. ^h Aspirin should probably not be given to individuals in this risk category. (1++, A)	For individuals in this risk category, the benefits of aspirin treatment are balanced by the harm caused. Aspirin should not be given to. (1++, A)	For individuals in this risk category, the harm caused by aspirin treatment outweighs the benefits. Aspirin should not be given to individuals in this low risk category. (1++, A)
DRUGS THAT ARE NOT RECOMMENDED			
Hormone replacement, vitamin B, C, E and folic acid supplements, are not recommended for reduction of cardiovascular risk.			

^h Consider aspirin in areas where coronary heart disease rates exceed stroke rates.

- ✓ Best Practice point: Unless there are compelling indications to use a specific drug, the least expensive preparation of the above classes of drugs should be used. Good quality generic preparations of medicines listed in WHO essential medicines list are recommended.

PART 3

**Basis of
recommendations
(the best available
evidence)**

1. Modification of behaviour

There is little controversy over the benefits to cardiovascular health of not smoking, eating a well balanced diet, maintaining mental well-being, taking regular exercise and keeping active, as demonstrated in large cohort studies. These health behaviours also play an etiological role in other noncommunicable diseases, such as cancer, respiratory disease, diabetes, osteoporosis and liver disease (86), which makes interventions to promote them potentially very cost-effective. However, there is considerable uncertainty about the best ways of helping people at high CVD risk to modify their behaviour.

Reducing cigarette smoking, body weight, blood pressure, blood cholesterol, and blood glucose all have a beneficial impact on major biological cardiovascular risk factors (83–88). Behaviours such as stopping smoking, taking regular physical activity and eating a healthy diet promote health and have no known harmful effects. They also improve the sense of well-being and are usually less expensive to the health care system than drug treatments, which may also have adverse effects. Further, while effects of drug therapy cease within a short period of discontinuation of treatment the impact of life style modification if it is maintained are longer standing.

A variety of lifestyle modifications have been shown, in clinical trials, to lower blood pressure (89, 90). These include weight loss in the overweight (91, 92), physical activity (93, 94), moderation of alcohol intake (95), increased fresh fruit and vegetables and reduced saturated fat in the diet (96), reduction of dietary sodium intake (96–98), and increased potassium intake (99). It is important to recognize, however, that most of the trials of lifestyle modification have been of short duration and have tested intensive interventions, which are unlikely to be feasible in routine primary care in many countries. Still, the evidence supports the notion that it is possible to modify health behaviours and reduce blood pressure. More encouragingly, randomized trials, involving a programme of weight reduction, dietary manipulation and physical activity, reduced the incidence of type 2 diabetes among people at high risk of developing it (100–102). Also, trials of reduction of saturated fat and its partial replacement by unsaturated fats have improved dyslipidaemia and lowered risk of cardiovascular events (103–105). Disappointingly, several large randomized trials of multiple risk factor interventions, using individual counselling and education, found no reduction in cardiovascular morbidity or mortality (106). These interventions, however, did bring about modest changes in risk factor profiles. In a meta-analysis of 18 trials, 10 of which reported clinical data, net changes were seen in systolic blood pressure (–3.9 mmHg; 95% CI –4.2 to –3.6 mmHg), diastolic blood pressure (–2.9 mmHg; 95% CI –3.1 to –2.7 mmHg), smoking prevalence (–4.2%; 95% CI –4.8 to –3.6%), and blood cholesterol (–0.08 mmol/l; 95% CI –0.1 to –0.06 mmol/l). It was, however, not possible to determine whether these changes were the result of concurrent drug treatments or regression to the mean. If real, these reductions are important, since even small reductions in major risk factors have been associated with a reduced risk of cardiovascular diseases in long-term, large-scale population studies (107).

Observational studies have found that other behavioural modifications, in particular cessation of smoking, are associated with a reduction in cardiovascular disease mortality (108–112). In men in the United Kingdom, a healthy lifestyle and increased physical activity have been shown to reduce the chances of developing cardiovascular disease (113).

While interventions targeted at individuals could be expected to bring about behavioural changes if they are implemented in a supportive environment, evidence for this view is not strong (106–114).

In a very large community intervention trial for smoking cessation, in which a wide range of community and individual interventions were used jointly, no specific effect of the programme could be detected (115). However, fiscal interventions and legislation on smoking in public places are capable of bringing about widespread and useful reductions in smoking prevalence. Since there is limited evidence on the effects of public health policy in tandem with individual interventions, it is recommended that population-wide strategies should be implemented to improve public health and create environments conducive to behaviour change in those at high CVD risk. Appropriate policies might address: agricultural subsidies for fruits and vegetables; food pricing and availability; labelling of food; public transport; pedestrian- and cyclist-friendly road planning; school health education; and tobacco control measures, including prohibition of advertising and price control. The overall objective should be to make it easy for the population to make healthy choices related to diet, physical activity and avoidance of tobacco.

1.1 Tobacco

Issues

- Does quitting use of tobacco products reduce cardiovascular risk?
- How can smokers be helped to stop smoking?

Evidence

There is a large body of evidence from prospective cohort studies regarding the beneficial effect of smoking cessation on coronary heart disease mortality (116). However, the magnitude of the effect and the time required to achieve beneficial results are unclear. Some studies suggest that, about 10 years after stopping smoking, coronary heart disease mortality risk is reduced to that of people who have never smoked (109, 110, 117, 118). Other reports suggest that a much longer time is required (119). It has also been shown that cigarette smokers who change to a pipe or cigar (119), and those who continue to smoke but reduce the number of cigarettes, have a greater mortality risk than those who quit smoking (112). A 50-year follow-up of British doctors demonstrated that, among ex-smokers, the age of quitting has a major impact on survival prospects; those who quit between 35 and 44 years of age had the same survival rates as those who had never smoked (120). The benefits of giving up other forms of tobacco use are not clearly established (121–124). General recommendations are therefore based on the evidence for cigarette smoking. Recent evidence from the Interheart study (31) has highlighted the adverse effects of use of any tobacco product and, importantly, the harm caused by even very low consumption (1–5 cigarettes a day).

The benefits of stopping smoking are evident; however, the most effective strategy to encourage smoking cessation is not clearly established. All patients should be asked about their tobacco use and, where relevant, given advice and counselling on quitting, as well as reinforcement at follow-up. There is evidence that advice and counselling on smoking cessation, delivered by health professionals (such as physicians, nurses, psychologists, and health counsellors) are beneficial and effective (125–130). Several systematic reviews have shown that one-time advice from physicians during routine consultation results in 2% of smokers quitting for at least one year (127, 131).

Similarly, nicotine replacement therapy (132, 133) can increase the rate of smoking cessation. Nicotine may be administered as a nasal spray, skin patch or gum; no particular route of administration seems to be superior to others.

Antidepressant drugs, particularly amfebutamone (bupropion), increase rates of smoking cessation at 12 months (134). In combination with the use of nicotine patches, amfebutamone may be more effective than nicotine patches alone, though not necessarily more effective than amfebutamone alone (135, 136). Nortriptyline has also been shown to improve abstinence rates at 12 months compared with a placebo. Both agents have appreciable discontinuation rates because of side-effects (135–137).

Data from observational studies suggest that passive cigarette smoking produces a small increase in cardiovascular risk (138–140). Whether reducing exposure to passive cigarette smoke reduces cardiovascular risk has not been directly established.

The interventions described above targeted at individuals may be less effective if they are implemented in populations exposed to widespread tobacco advertising, sponsorship of sporting activities by the tobacco industry, low-cost tobacco products, and inadequate government tobacco control policies. There is evidence that tobacco consumption decreases markedly as the price of tobacco products increases. Bans on advertising of tobacco products in public places and on sales of tobacco to young people are essential components of any primary prevention programme addressing noncommunicable diseases (140).

1.2 Diet

Issue

Are there specific dietary changes that can reduce cardiovascular risk?

1.2.1 Effect on cardiovascular risk of saturated fat, unsaturated fat, trans-fatty acids and cholesterol in the diet

The relationship between dietary fat and coronary heart disease has been extensively investigated. Saturated fats as a whole have been shown to raise LDL-cholesterol levels (104, 141–145). However, individual fatty acids within the group have different effects, with myristic and palmitic acids having the greatest effect on LDL-cholesterol (146). Saturated fatty acids are not all equally hypercholesterolaemic. The cholesterol-raising properties of saturated fats are attributed to lauric acid (12:0), myristic acid (14:0), and palmitic acid (16:0). Stearic acid (18:0) and saturated fatty acids with fewer than 12 carbon atoms are thought not to raise serum cholesterol concentrations (146, 147). The effects of different saturated fatty acids on the distribution of cholesterol over the various lipoproteins are not well known.

When substituted for saturated fatty acids in metabolic studies, n-6 polyunsaturated fatty acids (which are abundant in soybean and sunflower oil) and monounsaturated fatty acids (which are abundant in olive oil) lower total cholesterol, LDL cholesterol and triglyceride concentrations (145, 148). More research is needed to determine the appropriate mixture of unsaturated fatty acids that will produce maximum effect on CVD risk.

Trans-fatty acids come from both animal and vegetable sources and are produced by partial hydrogenation of unsaturated oils. Dietary intake of trans-fatty acids increases LDL-cholesterol and, at high intakes, lowers HDL cholesterol (143–145, 149–151). Metabolic and epidemiological studies have indicated that trans-fatty acids increase the risk of coronary heart disease (145, 152, 153).

A high intake of fat (more than one-third of total calories) generally increases intake of saturated fat and is associated with consumption of excess calories and weight gain. A low intake of fats and oils (less than one-fifth of total calories) increases the risk of inadequate intakes of vitamin E and essential fatty acids, and may contribute to unfavourable changes in HDL-cholesterol and triglycerides (154). It has also been demonstrated that replacing saturated and trans-unsaturated fats with monounsaturated and polyunsaturated fats is more effective in preventing coronary heart disease events than reducing overall fat intake (145, 153, 155). Current guidelines recommend a diet that provides less than 30% of calories from dietary fat, less than 10% of calories from saturated fats, up to 10% from polyunsaturated fats, and about 15% from monounsaturated fats (86, 88, 148).

Metabolic studies have shown that dietary cholesterol is a determinant of serum cholesterol concentration (156–158). Reducing dietary cholesterol by 100 mg a day appears to reduce serum cholesterol by about 1% (147). However, there is marked individual variation in the way serum cholesterol responds to dietary cholesterol (159); dietary cholesterol seems to have a relatively small effect on serum lipids, compared with dietary saturated and trans-fatty acids (88, 104, 158). Studies have demonstrated that, in controlled conditions, it is possible to modify behaviour, but in daily life the required intensity of supervision may not be practicable.

The effects of advice about reducing or modifying dietary fat intake on total and cardiovascular mortality and cardiovascular morbidity in real-life settings were assessed in a systematic review of 27 studies, comprising 30 902 person-years of observation (160). The interventions included both direct provision of food and, in most trials, dietary advice to reduce intake of total fat or saturated fat or dietary cholesterol, or to shift from saturated to unsaturated fat. The pooled results indicate that reducing or modifying dietary fat reduces the incidence of combined cardiovascular events by 16% (rate ratio 0.84; 95% CI 0.72 to 0.99) and cardiovascular mortality by 9% (rate ratio 0.91; 95% CI 0.77 to 1.07). No effect was seen on total mortality. The reduction in cardiovascular mortality and morbidity was more pronounced in trials lasting at least 2 years. The protective effect of polyunsaturated fats is similar in high- and low-risk groups for both sources (seafood and plants), and in women and men (104, 155, 161, 162).

1.2.2 Omega-3 fatty acids, fish and cardiovascular risk

The main dietary sources of omega-3 fatty acids are fish and fish oils (which contain eicosapentaenoic acid and docosahexaenoic acid), and certain nut and plant oils, such as canola, soybean, flaxseed and walnut (which contain alpha-linoleic acid). Epidemiological studies and clinical trials suggest that people at risk of coronary heart disease benefit from consuming omega-3 fatty acids (104, 161, 163, 164). The proposed mechanisms for a cardioprotective role include altered lipid profile, reduced thrombotic tendency, and antihypertensive, anti-inflammatory and antiarrhythmic effects (165–168).

A systematic review showed a significant benefit of fish-based dietary supplemental omega-3 fatty acids on cardiovascular morbidity and mortality in patients with coronary heart disease (169, 170). Cohort studies analysing omega-3 fatty acid intake and risk of cardiovascular diseases have shown inconsistent findings, however, and a recent large trial of omega-3 fatty acids did not find any benefits (171). In an attempt to clarify their role, an updated meta-analysis has also been conducted (170, 172). Using data from 48 randomized controlled trials and 41 cohort analyses, an assessment was made of whether dietary or supplemental omega-3 fatty acids altered total mortality, cardiovascular events or cancers. Pooled trial results did not show a reduction in the total mortality risk or the risk of combined cardiovascular events in those taking additional omega-3 fats.

Although there is no evidence that people should be advised to stop taking rich sources of omega-3 fats, further high quality studies are required to confirm suggestions of a protective effect of omega-3 fats on cardiovascular health.

1.2.3 Effects of dietary sodium on blood pressure

Issue

Is dietary salt associated with high blood pressure?

Population studies have demonstrated that high salt intake is associated with an increased risk of high blood pressure (173). Several observational studies have linked baseline sodium intake, estimated from either 24-hour urinary sodium excretion or dietary intake, to morbidity and mortality. In a Finnish study, the hazard ratios for coronary heart disease, cardiovascular disease, and all-cause mortality, associated with a 100 mmol increase in 24-h urinary sodium excretion in men and women, were estimated as 1.51 (95% CI 1.14 to 2.00), 1.45 ((95% CI 1.14 to 1.84), and 1.26 (95% CI 1.06 to 1.50), respectively (174). A prospective study in a Japanese cohort also showed that high dietary salt intake increased the risk of death from stroke (175). A study in hypertensive patients reported an inverse relation between sodium intake and cardiovascular outcomes (176) and suggested a J-curve relationship. This discordant finding has been attributed to methodological limitations and further study is needed.

The efficacy of reduced sodium intake in lowering blood pressure is well established (176, 177). An average reduction of 77 mmol/day in dietary intake of sodium has been shown to reduce systolic blood pressure by 1.9 mmHg (95% CI, 1.2 to 2.6 mmHg) and diastolic blood pressure by 1.1 mmHg (95% CI, 0.6 to 1.6 mmHg) (175). Phase 2 of the Trials of Hypertension Prevention Studies has also documented that a reduced sodium intake can prevent hypertension (178).

In a meta-analysis of dietary interventions to alter salt intake, which included 17 randomized controlled trials in people with high blood pressure and 11 in people with normal blood pressure, a reduction of 100 mmol (6 g) per day in salt intake was associated with a fall in blood pressure of 7.11 mmHg (systolic) and 3.88 mmHg (diastolic) ($P < 0.001$ for both) in those with hypertension, and 3.57 mmHg (systolic) and 1.66 mmHg (diastolic) in those with normal blood pressure ($P < 0.001$ and $P < 0.05$, respectively) (179). This information strongly supports other evidence that a modest, long-term reduction in population salt intake would immediately reduce stroke deaths by about 14% and coronary deaths by about 9% in people with hypertension, and by approximately 6% and 4% in those with normal blood pressure. This review has been produced and updated as a Cochrane systematic review (180). The authors concluded that, in trials of four or more weeks duration, a reduction in salt intake had a significant and, from a population viewpoint, important effect on blood pressure in individuals with normal or high blood pressure. In individuals with elevated blood pressure, the median reduction in 24-h urinary sodium excretion was 78 mmol (equivalent to 4.6 g of salt), the mean reduction in systolic blood pressure was 4.97 mmHg (95%CI 4.18 to 5.76 mmHg), and the mean reduction in diastolic blood pressure was 2.74 mmHg (95% CI 2.26 to 3.22 mmHg). In individuals with normal blood pressure, the median reduction in 24-h urinary sodium excretion was 74 mmol (4.4 g of salt), the mean reduction in systolic blood pressure was 2.03 mmHg (95% CI 1.50 to 2.56 mmHg), and the mean reduction in diastolic blood pressure was 0.99 mmHg (95% CI 0.57 to 1.40 mmHg). This demonstrates a correlation between the magnitude of salt reduction and the magnitude of blood pressure reduction.

Within the daily intake range of 3 to 12 g, the lower the salt intake achieved, the lower the blood pressure.

These findings may, however, exaggerate the reductions achievable in routine clinical practice. While people may find it possible to reduce their dietary sodium intake through individual effort in the short term, a more plausible estimate of effect is obtained when long-term trials are assessed. Hooper et al. (181) performed a meta-analysis of all unconfounded randomized trials in healthy adults aimed at reducing sodium intake over at least 6 months. Three trials in normotensive people ($n = 2326$), five trials in people with untreated hypertension ($n = 387$), and three trials in people being treated for hypertension ($n = 801$) were included, with follow-up of between six months and seven years. The large, high-quality (and therefore most informative) studies used intensive behavioural interventions. Deaths and cardiovascular events were inconsistently defined and reported. There were 17 deaths, equally distributed between intervention and control groups. Systolic and diastolic blood pressures were reduced by 1.1 mmHg (95% CI 0.4 to 1.8 mmHg) and 0.6 mmHg (95% CI 0.3 to 1.5 mmHg), respectively, at 13–60 months; 24-hour urinary sodium excretion was reduced by 35.5 mmol (95% CI 23.9 to 47.2 mmol). Degree of reduction in sodium intake and change in blood pressure were not related.

It is clear that intensive interventions, in particular the Dietary Approaches to Stop Hypertension (DASH) (182), are capable of reducing salt intake and lowering blood pressure. Such interventions, however, would not be easy to implement in primary care on a wide-scale long-term basis, because most salt is already in food as purchased. Reducing sodium intake may allow people taking antihypertensive drugs to stop their medication, while maintaining good blood pressure control (183). Further work is required to develop more effective methods of changing dietary behaviour to reduce sodium intake in primary care settings and in population prevention programmes. Alternative public health approaches, such as reducing salt in processed foods and bread, and labelling of processed food, are likely to be more effective and need to be taken up by the food industry on a wide scale.

On the basis of the above, current recommendations on salt intake (< 5 g (90 mmol) per day) are appropriate (86, 183).

1.2.4 Increasing the intake of fruits and vegetables

Issue

Does increased fruit and vegetables consumption reduce the risk of cardiovascular disease?

Fruits and vegetables may promote cardiovascular health through a variety of micronutrients, antioxidants, phytochemicals, flavonoids, fibre and potassium. The evidence on the role of the individual constituents is so far inconclusive.

Ness & Powles (184) reviewed ecological, case-control and cohort studies examining the association of dietary fruits and vegetables with cardiovascular disease. No attempt was made to arrive at a summary measure of the association, because of the differences in study type, quality and exposure measures used. For coronary heart disease, nine of ten ecological studies, two of three case-control studies and six of sixteen cohort studies found a significant protective association with consumption of fruits and vegetables or surrogate nutrients. For stroke, three of the five ecological studies and six of eight cohort studies found a significant protective association. For

circulatory disease, one of two cohort studies reported a significant positive association. Overall, the results support a protective effect of fruits and vegetables on stroke and coronary heart disease (185, 186).

Joshiyura et al. (185) evaluated the association between consumption of fruits and vegetables and risk of coronary heart disease in the Nurses' Health Study and the Health Professionals' Follow-Up Study. In these two studies, 84 251 women aged 34–59 years were followed for 14 years, and 42 148 men aged 40–75 years were followed for 8 years. All were free of diagnosed cardiovascular disease, cancer, and diabetes at the start. After adjustment for standard cardiovascular risk factors, people with fruit and vegetable intake in the highest quintile had a relative risk for coronary heart disease of 0.80 (95% CI 0.69 to 0.93) compared with those with intake in the lowest quintile. Each increase of one serving per day in intake of fruits or vegetables was associated with a 4% lower risk of coronary heart disease (relative risk 0.96; 95% CI 0.94 to 0.99; $P = 0.01$, test for trend).

The relationships between intake of whole grains, refined grains, and fruit and vegetables, and total mortality risk and incidence of coronary artery disease and ischaemic stroke, were also evaluated in the Atherosclerosis Risk in Communities (ARIC) cohort ($n = 15\,792$) (187). Over an 11-year follow-up period, whole-grain intake was inversely associated with total mortality and incidence of coronary artery disease. The relative risks of death for people with fruit and vegetable intake in quintiles 2–5 were 1.08 (95% CI 0.88 to 1.33), 0.94 (95% CI 0.75 to 1.17), 0.87 (95% CI 0.68 to 1.10), and 0.78 (95% CI 0.61 to 1.01), respectively (P for trend = 0.02). An inverse association between fruit and vegetable intake and coronary artery disease was observed among African Americans but not among Whites (P for interaction = 0.01). The risk of ischaemic stroke was not significantly related to consumption of whole grains, refined grains, or fruit and vegetables.

In a prospective cohort study of 40 349 Japanese men and women followed up for 18 years (188), daily consumption of green and yellow vegetables and fruits was associated with a lower risk of stroke, intracerebral haemorrhage, and cerebral infarction mortality in both men and women. A recent meta-analysis of 10 prospective cohort studies (189) has also shown that the consumption of fibre from cereals and fruits is inversely associated with risk of coronary heart disease.

On the basis of the available evidence, a daily intake of at least 400 g of fruit and vegetables is recommended (86).

1.2.5 Summary

Dietary intakes of fat, cholesterol, fruits and vegetables, fish and sodium are linked to cardiovascular risk. There is a considerable body of evidence regarding the nutritional background of atherosclerosis in general and CHD in particular. However, much of this evidence is from observational studies, in which control for potential confounding factors, in particular socioeconomic position, is often inadequate. The inferences that can be made from these studies are necessarily guarded.

A cardioprotective diet should consist of a variety of foods, and should aim to achieve four major goals: a healthy overall diet, a healthy body weight, a desirable lipid profile, and a desirable blood pressure. There is strong observational evidence that reducing intakes of total fat (to less than 30% of calories), saturated fat (to less than 10% of calories), and salt (to less than 5 g or 90 mmol per day), and increasing fruits and vegetables (to 400–500 g daily) are likely to be beneficial. Applying these principles to develop diets that match individual preferences and local customs, and demonstrating their effectiveness in reducing cardiovascular risk, are important priorities for research.

A recent review assessed the effectiveness of dietary advice in reducing cardiovascular risk in healthy adults (190). Advice was focused largely on decreasing intake of salt and fat and increasing intake of fruits, vegetables and fibre. Interventions included one-to-one advice, group sessions and written materials, and ranged in intensity from a single contact to multiple contacts over several years. Of the 23 trials reviewed, nine enrolled participants on the basis of screening for cardiovascular disease risk factors. The majority of studies involved interventions in health care settings; other settings included workplaces, community centres and homes. Results showed modest improvements in reported dietary intake (lower salt and fat, higher fruit, vegetables and fibre) and cardiovascular risk factors (blood pressure, total cholesterol, and LDL-cholesterol). Greater effectiveness was observed among individuals told they were at greater risk of heart disease, and in interventions with greater intensity and duration. The authors estimated that the summary effects of the dietary interventions reviewed could reduce incidence of coronary heart disease by 12% and of stroke by 11%. This estimate is based on the assumption that dietary changes are sustained, and that the relative risk reductions attributable to changes in cholesterol and diastolic blood pressure can be combined additively.

1.3 Physical activity

Issue

Does regular physical activity reduce cardiovascular risk?

Evidence

It has been estimated that inadequate physical activity is responsible for about one-third of deaths due to coronary heart disease and type 2 diabetes (191). There is evidence from observational studies that leisure-time physical activity is associated with reduced cardiovascular risk and cardiovascular mortality in both men and women (192–194) and in middle-aged and older individuals (195, 196).

Several meta-analyses have examined the association between physical activity and cardiovascular disease (197–202). Berlin & Colditz (200) found a summary relative risk of death from coronary heart disease of 1.9 (95% CI 1.6 to 2.2) for people with sedentary occupations compared with those with active occupations. A meta-analysis of studies in women showed that physical activity was associated with a reduced risk of overall cardiovascular disease, coronary heart disease and stroke, in a dose–response fashion (197).

Physical activity improves endothelial function, which enhances vasodilatation and vasomotor function in the blood vessels (199). In addition, physical activity contributes to weight loss, glycaemic control (203, 204), improved blood pressure (205), lipid profile (206–208) and insulin sensitivity (209). The possible beneficial effects of physical activity on cardiovascular risk may be mediated, at least in part, through these effects on intermediate risk factors. Physical inactivity and low physical fitness are independent predictors of mortality in people with type 2 diabetes (210).

Overall, the evidence points to the benefit of continued regular moderate physical activity, which does not need to be strenuous or prolonged, and can include daily leisure activities, such as walking or gardening (197). Taking up regular light or moderate physical activity in middle or older age significantly reduces CVD and all-cause mortality, and improves the quality of life (85, 86, 196–198, 211, 212).

In summary, a sedentary lifestyle is associated with increased risk of cardiovascular disease. Moreover, physical activity is associated with reduced risk of coronary heart disease and CVD mortality, in both men and women, and in middle-aged and older individuals. Studies indicate a dose–response relationship between overall physical activity and cardiovascular disease, which is linear at least up to a certain level of activity. A similar relationship has also been seen with stroke.

Two reviews support the effectiveness of interventions to promote physical activity in the health care setting. The first, a review of seventeen randomized controlled trials (RCTs) promoting physical activity in adults, found that professional advice and guidance with continued support had a moderate effect on self-reported physical activity and cardiorespiratory fitness, but not on achieving a predetermined level of physical activity (213). Specific interventions included individual and group counselling, self-directed or prescribed physical activity, supervised and unsupervised physical activity, home- or facility-based physical activity, face-to-face and telephone support, written materials, and self-monitoring. Interventions were conducted by one or several practitioners, including physicians, nurses, health educators and exercise leaders. Of the seventeen trials reviewed, eight took place in the primary health care setting. The second review considered only studies in the primary health care setting, and found that brief interventions to promote physical activity produced moderate short-term improvements in self-reported physical activity levels (214). In 12 of 15 RCTs and quasiexperimental studies, the intervention was delivered during a routine primary health care visit, and walking was the activity most commonly recommended. No clear relationship was found between the person doing the intervention (e.g. physician, nurse, health educator, public health student) and effectiveness, or between the length of the initial intervention and effectiveness. In both reviews, it was noted that the length of follow-up of the studies (typically 1 year or less) was insufficient to draw conclusions about long-term effectiveness or whether outcomes would be maintained. Trials using more objective indicators of activity patterns and changes in cardiovascular risk factors would be helpful in determining how primary care teams can intervene most effectively.

1.4 Body weight

Issue

Does losing weight reduce the cardiovascular risk for those who are overweight or obese?

Evidence

Obesity is a growing health problem in both developed and developing countries (2). Prospective epidemiological studies have shown a relationship between overweight or obesity and cardiovascular morbidity, CVD mortality and total mortality (215–221). Obesity is strongly related to major cardiovascular risk factors, such as raised blood pressure, glucose intolerance, type 2 diabetes, and dyslipidaemia (215, 218, 220, 222).

Meta-analyses of RCTs have shown that a weight-reducing diet, combined with exercise, produces significant weight loss, reduces total cholesterol and LDL-cholesterol, increases HDL-cholesterol, and improves control of blood pressure and diabetes (223, 224).

Weight loss programmes using dietary, physical activity, or behavioural interventions have been shown to produce significant reductions in weight among people with pre-diabetes, and a significant decrease in diabetes incidence (225). A meta-analysis of randomized controlled trials (226)

found that a net weight reduction of 5.1 kg (95% CI 4.25 to 6.03 kg), resulting from restricted energy intake, increased physical activity or both, reduced systolic blood pressure by 4.44 mmHg (95% CI 2.95 to 5.93 mmHg) and diastolic blood pressure by 3.57 mmHg (95% CI 2.25 to 4.88 mmHg). The long-term benefit of weight reduction on blood pressure control has been confirmed in several studies, including Phase II of the Trials of Hypertension Prevention Collaborative Research Group (227, 228). Prospective studies are needed to determine the impact of weight reduction in the long term on cardiovascular morbidity and mortality trends.

In a review of data from 24 prospective observational studies, Blair & Brodney (229) found that regular physical activity attenuated many of the health risks associated with overweight and obesity. Physically active obese individuals have lower morbidity and mortality than individuals of normal weight who are sedentary; physical inactivity and low cardiorespiratory fitness are as important as overweight and obesity as predictors of mortality.

Evidence from a substantial number of RCTs supports a combined approach of a low-calorie diet, physical activity, and behavioural therapy as the most successful strategy for sustained weight loss (230, 231). A limited number of RCTs have shown that non-physician health professionals, such as nurses, nutritionists and psychologists, can play an important role in an individual's weight loss and management plan. The results of non-randomized trials and observational studies indicate that interventions involving a greater frequency of contacts between patient and provider, and those provided over the long term, lead to more successful and sustained weight loss (226).

A review of the effectiveness of weight-loss diets in adults with raised blood pressure (systolic blood pressure \geq 140 mmHg or diastolic blood pressure \geq 90 mmHg) found modest weight losses, of 3–9% of body weight (227). The diets were associated with modest decreases in systolic and diastolic blood pressure of about 3 mmHg, and may lead to reduced dosage requirements for patients taking blood-pressure-lowering medications. Of the 18 RCTs reviewed, all but one took place in an ambulatory care setting, and most included only obese patients (obesity defined either as a body weight of 10% or more above the ideal weight or as BMI $>$ 25 kg/m²). In most trials, the provider/instructor was a dietician; however, the nature and duration of interventions varied significantly, with intervention periods ranging from 2 weeks to 3 years. In the two trials that reported post-intervention follow-up, it was found that participants tended to regain some, though not all, of the weight lost.

1.5 Alcohol

Issue

Does alcohol consumption reduce cardiovascular risk?

Evidence

Many studies have shown a U- or J-shaped association between mortality and alcohol consumption, in which people who drink light or moderate amounts have a lower death rate than non-drinkers, while those who drink large amounts have a higher death rate (232–240). People who drink heavily have a high mortality from all causes and cardiovascular disease, including sudden death and haemorrhagic stroke. In addition, they may suffer from psychological, social and other medical problems related to high alcohol consumption (237–240).

A meta-analysis of 28 cohort studies of alcohol consumption and CHD showed that risk decreased as consumption increased from 0 to 20 g/day (RR = 0.80, 95% CI 0.78 to 0.83); there was evidence of a protective effect of alcohol up to 72 g/day (RR = 0.96, 95% CI 0.92 to 1.00), and increased risk at consumptions above 89 g/day (RR = 1.05, 95% CI 1.00 to 1.11). Smaller protective associations and more harmful effects were found in women, in men living in countries outside the Mediterranean area, and in studies where fatal events were used as the outcome (238). The amount of alcohol associated with the lowest mortality rates was between 10 and 30 g (1–3 units) per day for men and half these quantities for women (1 unit is equivalent to 150 ml of wine, 250 ml of beer or 30–50 ml of spirits) (239). Various mechanisms have been proposed for the protective effect of modest alcohol consumption, including the demonstrated beneficial effects of alcohol on lipid profile, particularly an increase in HDL-cholesterol level, thrombolytic profile, and platelet aggregation (237, 240–242).

The benefits of alcohol in light to moderate drinkers may be overestimated in meta-analyses of observational studies, as a result of confounding and reverse causality. The meta-analysis was dominated by a few very large studies, which did not carefully assess the reasons for not drinking, and did not measure multiple potential confounders. It is primarily the non-drinking group that causes the U-shaped relationship, and this may contain both life-long abstainers and people who stopped drinking because of ill-health; this could result in a spurious association suggesting that there is a safe level of alcohol intake. A recent meta-analysis of 54 published studies concluded that lack of precision in the classification of abstainers may invalidate the results of studies showing the benefits of moderate drinking (243). If the authors' claim is correct, it implies that there is no level of alcohol consumption that is beneficial with respect to coronary heart disease; rather, risk increases with increasing consumption in a linear fashion. Interestingly, the beneficial effect of hormone replacement therapy (HRT) on HDL-cholesterol convinced many that cohort studies showing a protective effect of HRT on coronary heart disease risk were valid. However, subsequent randomized controlled trials have found either no benefit or a harmful association; the earlier results are likely to be due to uncontrolled confounding. It is possible that the protective association between light-to-moderate alcohol consumption and coronary heart disease is also an artefact caused by confounding. Light-to-moderate drinkers may be “light-to-moderate” in other behaviours, such as tobacco use which could be responsible for their lower risk of CHD (244).

It is also important to note that alcohol consumption is associated with a wide range of medical and social problems, including road traffic injuries. Some individuals are also at risk of progression to problem drinking. Other risks associated with moderate drinking include fetal alcohol syndrome, haemorrhagic stroke, large bowel cancer, and female breast cancer (237, 245). Consequently, from both the public health and clinical viewpoints, there is no merit in promoting alcohol consumption as a preventive strategy.

2. Psychosocial factors

Issue

Are there specific psychosocial interventions that can reduce cardiovascular risk?

Evidence

Observational studies have indicated that some psychosocial factors, such as depression and anxiety, lack of social support, social isolation, and stressful conditions at work, independently

influence the occurrence of major risk factors and the course of coronary heart disease, even after adjusting for confounding factors (246–248). Other psychosocial factors, such as hostility and type A behaviour patterns, and anxiety or panic disorders, show an inconsistent association (249, 250).

Rugulies (246), in a meta-analysis of studies of depression as a predictor for coronary heart disease, reported an overall relative risk for the development of coronary heart disease in depressed subjects of 1.64 (95% CI 1.29 to 2.08, $P < 0.001$). Other studies have also found a strong association between depression and CHD (250–252). Depression was shown to be a predictor for risk of myocardial infarction in the Interheart case–control study (odds ratio 1.55, 95% CI 1.42 to 1.69). This finding was consistent across regions, in different ethnic groups, and in men and women (247).

In the MRFIT cohort study (248) greater depressive symptoms were associated with increased mortality after 18 years of follow-up. Significantly higher risks of all-cause mortality (HR 1.15; 95% CI 1.03 to 1.28; $P < 0.01$), CVD mortality (HR 1.21; 95% CI 1.03 to 1.41; $P < 0.05$), and stroke mortality (HR 2.03; 95% CI 1.20 to 3.44; $P < 0.01$) were found in the quintile with the highest level of depressive symptoms compared with those in the lowest quintile.

More recent trials have cast doubt on the causal nature of the association between depression and CHD. In a large randomized trial of psychological intervention after myocardial infarction, no impact on recurrence or mortality was found (253). Another large trial that provided social support and treatment for depression also found no impact (254). Depression has a negative impact on quality of life (255, 256), and antidepressant therapy has been shown to significantly improve quality of life and functioning in patients with recurrent depression who are hospitalized with acute coronary syndromes (257, 258).

Kivimäki et al. (255), in a 25.6-year prospective cohort study in Finland, found that metal industry employees with high job strain (a combination of high demands at work and low job control) had a cardiovascular mortality risk 2.2 times that of their colleagues with low job strain (95% CI 1.2 to 4.2). This association between stressful conditions at work and CHD is supported by other studies (250, 257).

There is also some evidence that social isolation and lack of quality social support are independent risk factors for CHD onset and prognosis: the risks are increased 2–3-fold and 3–5-fold, respectively, in both men and women (259). The association has been demonstrated in subjects in different countries, and in various age groups (250, 259–262). While these findings provide some support for a causal interpretation of the associations, it is quite possible that they represent confounding or a form of reporting bias, as illustrated in a large Scottish cohort (263).

Well planned trials of interventions to reduce work stress and social isolation are required to elucidate whether there is a true cause–effect relationship and, more importantly, whether intervention reduces cardiovascular risk. In the meantime, physicians and health care providers should consider the whole patient. Early detection, treatment and referral of patients with depression and other emotional and behavioural problems are, in any case, important for reducing suffering and improving the quality of life, independent of any effect on cardiovascular disease. Mobilizing social support to avoid or solve social and work concerns is also a legitimate response to a patient's difficulties (258).

3. Multiple risk factor interventions

Issue

Are multiple risk factor interventions effective in reducing cardiovascular risk?

Evidence

A Cochrane systematic review has evaluated the effectiveness of multiple risk factor interventions for the primary prevention of cardiovascular disease in adults from general populations, occupational groups and high-risk groups (106). Eighteen randomized controlled trials involving counselling and/or health education, with or without pharmacological treatment, which aimed to affect more than one cardiovascular risk factor (smoking, diet, physical activity, blood pressure and blood cholesterol) were included. Overall, modest reductions in smoking prevalence, systolic blood pressure, diastolic blood pressure, and blood cholesterol were observed. The studies with the highest baseline levels of smoking prevalence, diastolic blood pressure or cholesterol levels demonstrated greater intervention-related reductions in these risk factors. The pooled effects of the ten trials with clinical event endpoints showed no significant effect on total or cardiovascular disease mortality; this is consistent with the extent of changes in risk factors. However, trials that focused on participants with elevated blood pressure, and those that used drug treatment, demonstrated significant reductions in coronary heart disease mortality and total mortality. Interventions using personal or family counselling and education, with or without drug treatment, were more effective in modifying risk factors and reducing mortality in people at high risk because of raised blood pressure. These results argue in favour of multiple risk factor interventions for prevention of cardiovascular disease in multifactorial high-risk groups. For the general low-risk population, policy measures that create a conducive environment which facilitates behavioural change may have a greater impact at lower cost than individual counselling and therapeutic approaches.

4. Blood pressure lowering

Issue

Does lowering blood pressure reduce cardiovascular risk?

Evidence

Raised blood pressure is estimated to cause about 7 million premature deaths throughout the world, and 4.5% of the disease burden (64 million disability-adjusted life years (DALYs)) (1–3). It is a major risk factor for cerebrovascular disease, coronary heart disease, and cardiac and renal failure. Treating raised blood pressure has been associated with a 35–40% reduction in the risk of stroke and at least a 16% reduction in the risk of myocardial infarction (264). Raised blood pressure often coexists with other cardiovascular risk factors, such as tobacco use, overweight or obesity, dyslipidaemia and dysglycaemia, which increase the cardiovascular risk attributable to any level of blood pressure. Worldwide, these coexisting risk factors are often inadequately addressed in patients with raised blood pressure, with the result that, even if their blood pressure is lowered, these people still have high cardiovascular morbidity and mortality rates (265–267).

Almost all clinical trials have confirmed the benefits of antihypertensive treatment at blood pressure levels of 160 mmHg (systolic) and 100 mmHg (diastolic) and above, regardless of the pres-

ence of other cardiovascular risk factors (264, 268). Observational data support lowering of these systolic and diastolic thresholds (269, 270).

Several trials in patients at high cardiovascular risk (271–273) have confirmed these observational data, showing reductions in cardiovascular morbidity and mortality in people whose blood pressure is reduced to levels significantly below 160 mmHg systolic and 90 mmHg diastolic. These trials support the view that, in patients at high cardiovascular risk, with blood pressures in the range 140–160 mmHg (systolic) and 90–100 mmHg (diastolic), lowering blood pressure reduces the number of cardiovascular events. These trial results suggest that treatment for such high-risk patients should begin at the lower blood pressure thresholds.

Although women are at lower total risk of cardiovascular disease for a given level of blood pressure, and randomized controlled trials generally include a greater proportion of men than women, the treatment thresholds for systolic and diastolic pressure should be the same in men and women (274).

Total risk of cardiovascular disease for any given level of blood pressure rises with age. However, evidence from RCTs is currently limited and inconclusive about the benefits of treating those over 80 years of age. For now, the treatment threshold should be unaffected by age, at least up to 80 years. Thereafter, decisions should be made on an individual basis; in any case, therapy should not be withdrawn from patients over 80 years of age (275, 276).

Targets for blood pressure

In low- and medium-risk patients with elevated blood pressure, the Hypertension Optimal Treatment (HOT) trial found maximal cardiovascular benefit when blood pressure was reduced to 139/83 mmHg (277). Clinic and population-based survey data continue to suggest that the lower the blood pressure achieved, the lower the rate of cardiovascular events (278–280). In people over 55 years of age, the systolic blood pressure is more important (281), so the primary goal of therapy is to lower systolic blood pressure to 140 mmHg or less. There is no apparent reason to modify this target for women or older patients.

Several trials (277, 282–285) have shown that, in patients with diabetes, reduction of diastolic blood pressure to about 80 mmHg and of systolic blood pressure to about 130 mmHg is accompanied by a further reduction in cardiovascular events or diabetes-related microvascular complications, in comparison with patients with less stringent blood pressure control (277, 284, 285). In patients with high or very high cardiovascular risk, including diabetes or established vascular or renal disease, therefore, blood pressure should be reduced to 130/80 mmHg or less.

Choice of initial drug therapy

Many randomized controlled trials have been conducted since 1967 to compare the effects of diuretics, beta-blockers, and calcium-channel blockers (CCBs) with placebo in hypertensive patients (264, 286, 287). These trials have demonstrated reductions in both cardiovascular mortality and morbidity with all three drug classes.

Meta-analyses of data from RCTs comparing angiotensin-converting enzyme (ACE) inhibitors, CCBs, diuretics and beta-blockers have been published (268, 287). For the endpoint of total cardiovascular mortality, these meta-analyses showed no strong evidence of differences between drug classes. However, the available data do not exclude small to modest differences between

different classes of drugs in relation to specific fatal or non-fatal outcomes. For instance, ACE inhibitors were associated with a lower incidence of coronary heart disease than CCBs, whereas CCBs were associated with a lower incidence of stroke than diuretics, with or without beta-blockers (268). Data are also emerging on an increased incidence of diabetes in patients treated with thiazides or beta-blockers compared with other classes of antihypertensive drugs, which may influence the choice of first-line drug therapy (288–292).

The ALLHAT trial (288) compared the effects of a calcium-channel blocker or an angiotensin-converting enzyme inhibitor and a diuretic on the incidence of coronary heart disease and other cardiovascular disease events. A total of 33 357 participants aged 55 years or older with raised blood pressure and at least one other CHD risk factor were randomly assigned to receive chlorthalidone (12.5–25 mg/day), amlodipine (2.5–10 mg/day), or lisinopril (10–40 mg/day), and followed up for an average of 4.9 years. The rates of primary outcomes – death from CHD and non-fatal myocardial infarction – were not different between treatment groups. Likewise, all-cause mortality was not different in the three groups. At the beginning of the study, there was a fourth group treated with an alpha-blocker; this treatment was stopped prematurely because of an increased risk of combined cardiovascular disease, to which heart failure was a major contributor. Some differences were seen in protection against various secondary endpoints; in particular a higher risk of stroke was associated with the ACE inhibitor in Afro-American subjects, and a higher risk of heart failure was found with both the ACE inhibitor and the CCB.

The Second Australian National Blood Pressure Study (ANBP2) (289) also compared a diuretic (hydrochlorothiazide) and an ACE inhibitor (enalapril), but in older people with elevated blood pressure who had had few previous cardiovascular events. The risk of the primary outcome of all cardiovascular events or death from any cause was 11% lower in the ACE inhibitor group than the diuretic group, and the benefit was seen only in the men.

In the LIFE trial (75), among patients with left ventricular hypertrophy, as seen on ECG, therapy based on an angiotensin receptor blocker (ARB) was more protective against a composite cardiovascular endpoint than therapy based on a beta-blocker, despite very similar reductions in blood pressure. The benefits were largely attributable to protection against stroke, and were particularly striking in the diabetic group (290).

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (291), patients at moderate risk were randomly assigned to receive either amlodipine and perindopril or atenolol and bendroflumethiazide. Fewer individuals on the amlodipine-based regimen had a primary endpoint (non-fatal myocardial infarction or fatal CHD), but the difference between the groups was not significant. The incidence of diabetes was also lower in the group on the amlodipine-based regimen. However, this difference could be largely explained by the difference in systolic blood pressure in the two groups (292).

The efficacy of beta-blockers has been investigated in several studies (293–296). One such study included clinical trials in which a beta-blocker was used as the first-line antihypertensive drug in at least half of all patients in one treatment group, with outcome data for cardiovascular morbidity and mortality, and all-cause mortality. This analysis found no difference in all-cause mortality or myocardial infarction, but the risk of stroke was lower with other antihypertensive drug regimens. However, when beta-blockers were compared with placebo or no treatment, they were found to significantly reduce the risk of stroke. Beta-blockers are as efficacious as other classes of anti-

hypertensive drugs in reducing all-cause mortality and myocardial infarction, but appear to be less effective in reducing the risk of stroke (293). Another meta-analysis (295) investigated the efficacy of beta-blockers in different age groups. The efficacy was found to be similar to that of other antihypertensive agents in younger patients, but lower in older patients, with the excess risk being particularly marked for stroke. A recent Cochrane review assessed the effect of beta-blockers on mortality and morbidity endpoints, compared with placebo or no therapy for hypertension (296). Results showed a relatively weak effect of beta-blockers in reducing stroke and no effect on coronary heart disease. A trend towards worse outcomes with beta-blockers in comparison with thiazide diuretics, CCBs and ACE inhibitors was reported. Most of the trials included used atenolol as the beta-blocker.

In choosing an antihypertensive drug therapy, there are a number of specific compelling indications (Table 7). In the absence of any compelling indication, and of major adverse effects (Table 8), currently available evidence from comparative trials of efficacy and cardiovascular outcomes supports the use of any one of the following classes of drugs as initial therapy: ACE inhibitor, calcium-channel blocker, or low-dose diuretic. Beta-blockers should be considered for first-line antihypertensive therapy only if there is a compelling indication (294–296) (Table 7).

For the majority of patients in resource-constrained settings, if there is no compelling indication for another class of drug, a low dose of a thiazide-like diuretic should be considered as the first choice of therapy, on the basis of comparative trial data, availability and cost-effectiveness (286) (Table 7).

As previously noted, for many patients, blood pressure should be reduced to lower levels than previously recommended, and more than one drug will often be required (75, 271, 272, 277, 284). It is important to increase gradually the dose of each drug to achieve optimum effect before adding another drug. Adherence to treatment is important to achieve the optimal reduction in blood pressure, and may be facilitated by a once-a-day dosage. If a second antihypertensive drug is added, it should be from a different drug class.

In addition to the compelling indications listed in Table 7, other factors may favour the choice of certain drugs. Thus, when used as monotherapy, a diuretic or CCB may lower blood pressure more in Black people than an ACE inhibitor or a beta-blocker. Response to beta-blockers and ACE inhibitors is poor in Black people, unless they are combined with a thiazide diuretic (297, 298). An alpha-blocker will relieve symptoms of prostatism (299). Central alpha-agonists, such as clonidine, or peripheral adrenergic blockers may be used as inexpensive therapies, despite the absence of outcome data.

In certain conditions, specific drugs are contraindicated or should be used with caution (Table 7). A few of the contraindications, such as use of ACE inhibitors and ARBs in pregnancy, are absolute; most, however, are related to the fact that certain drugs could aggravate various conditions. While certain drugs may be more likely to induce side-effects in particular patients, they may still be used if they are strongly indicated and if the patients are carefully monitored. For example, ACE inhibitors or ARBs may be beneficial in chronic renal failure (300) and renovascular hypertension (301), but should be used only under close supervision and with specialist advice. Beta-blockers, such as carvedilol and metoprolol, are increasingly used to treat stable heart failure. However, they may worsen heart failure and should not be given to individuals with decompensated heart failure (302).

TABLE 7

Compelling indications, contraindications, and cautions for specific antihypertensive drugs

Class of drug	Compelling indications		Compelling contraindications	Cautions
	Condition	Reference and grade of recommendation		
ACE inhibitors ^{a,b}	Type 1 diabetic nephropathy	Lewis et al. (303) 1++ , A	Pregnancy Bilateral renal artery stenosis Hyperkalaemia	
	Non-diabetic nephropathy	Jafar et al. (304) 1++ , A		
	Left ventricular dysfunction	SOLVD investigators (305) Flather et al. (306) 1++ , A		
ARBs ^b	Type 2 diabetic nephropathy	Parving et al. (283) Brenner et al. (282) Lewis et al. (307) 1+ , A	Pregnancy Bilateral renal artery stenosis Hyperkalaemia	
	Left ventricular hypertrophy	Pitt et al. (308) Dahlof et al. (309) Lindholm et al. (290) 1+ , A		
	Heart failure in ACE-inhibitor intolerance	Granger et al. (310) 1+ , A		
CCBs (dihydropyridine)	Elderly with isolated systolic hypertension	Staessen et al. (311) 1+ , A	Congestive heart failure	Following myocardial infarction (short-acting CCBs)
	Black patients	Cushman et al. (297) 1+ , A		
Diuretics	Elderly with isolated systolic hypertension	SHEP (312) 1+ , A	Gout	
	Black patients	Radevski et al. (298) 1+ , A		
Beta-blockers	Following myocardial infarction	Teo et al. (313) 1++ , A Freemantle et al. (314) Yusuf et al. (315)	High-degree heart block, Severe bradycardia (< 50/min) Obstructive airways disease Raynaud	Heart failure Peripheral vascular disease, Diabetes (except with CHD)
Alpha-blockers	Benign prostatic hypertrophy	Oesterling (299)	Urinary incontinence	Congestive heart failure
Central alpha-agonist	Pregnancy (methyldopa)			Withdrawal syndrome (clonidine) Hepatotoxicity (methyldopa)
Peripheral alpha-agonist	When other medicines are ineffective or not available or affordable	Lindholm et al. (316)		Depression Active peptic ulcer

^a Type 2 diabetic nephropathy is possible indication for ACE inhibitors.

^b Chronic renal disease and proteinuric renal disease are possible indications for ACE inhibitors and ARBs; however, they should be used with caution, under close supervision and with specialist advice.

TABLE 8Major adverse effects of antihypertensive medicines^a

Class of drug	Major adverse effects
ACE inhibitors	dry cough, renal dysfunction in patients with impaired renal function
ARBs	increase in hepatic enzyme levels
CCBs (dihydropyridines)	headache, palpitation, rash, gravitational oedema
Diuretics (thiazide-like)	dry mouth, thirst, muscle cramps, impotence, hyperglycaemia, hypercholesterolaemia, abnormality in electrolytes (hypokalaemia, hypomagnesaemia, hypercalcaemia, hyponatraemia), pancreatitis
Beta-blockers	high-degree atrioventricular block, bradycardia, heart failure, Raynaud phenomenon, impotence, fatigue, sleep disturbance including nightmares, depression, alteration of lipid profiles
Alpha-blockers	orthostatic hypotension, syncope, dizziness, headache, drowsiness
Central alpha-agonist	orthostatic hypotension, bradycardia, drowsiness, dry mouth, galactorrhoea, sexual dysfunction
Peripheral alpha-agonist (reserpine)	depression, sedation, nasal stuffiness

^a Source: ref. 317.

5. Lipid lowering

Issue

Does treatment with statins reduce cardiovascular risk?

Evidence

Many studies have shown that the benefits of cholesterol-lowering therapy depend on the initial level of cardiovascular risk: the higher the total risk, the greater the benefit. This is because the relative reductions in risk as a consequence of lipid lowering are approximately the same at different levels of cardiovascular risk.

The effectiveness of statins in patients with established atherosclerotic disease (principally coronary artery disease) is well established. Primary prevention trials, on the other hand, are more limited; however, the benefits seen in these trials, as demonstrated by meta-analyses, are consistent with the overall results for all statin trials.

Benefits

The benefits of statins for primary prevention have been examined in several RCTs and subsequent meta-analyses.

In the West of Scotland Coronary Prevention Study (WOSCOPS) (318), 6595 men aged 45–64 years, with no history of myocardial infarction and plasma total cholesterol concentrations

of 6.5–8.0 mmol/l (250–310 mg/dl) at initial screening, were randomly allocated to receive pravastatin (40 mg daily) or placebo, and followed up for an average of 4.9 years. Those in the treatment group had 31% fewer primary cardiovascular events than those given placebo ($P < 0.001$). There were also significant reductions in non-fatal myocardial infarction and death from all cardiovascular causes.

In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (319), lovastatin, together with modifications of diet and lifestyle, reduced the risk of a first major acute coronary event by 37% ($P < 0.001$) over 5.2 years, compared with placebo, in individuals with average TC and LDL-cholesterol levels, below-average HDL-cholesterol levels, and no overt cardiovascular disease. In addition, the risks of myocardial infarction, unstable angina, coronary events, and cardiovascular events, and the need for coronary revascularization procedures, were significantly reduced in the treatment group.

In the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – Lipid Lowering Trial component (ALLHAT–LLT), more than 10 000 patients aged over 55 years with hypertension and one other risk factor were randomly assigned to either pravastatin, 20–40 mg/day, or usual care (320). This was a mixed primary and secondary prevention trial, with 14% of patients having had prior coronary disease and 35% being diabetic. Compared with placebo, pravastatin produced only a modest reduction of lipids: total cholesterol was reduced by 10% and LDL-cholesterol by 17%. Pravastatin given in addition to antihypertensive drug therapy did not significantly reduce all-cause mortality or CHD deaths in comparison with usual care, over a mean follow-up period of 4.8 years. The failure to show a reduction in coronary heart disease events was attributed to this increased use of statins and other hypolipidaemic therapy in the patients given “usual care”. At 6 years of follow-up, 26.1% of the “usual care” patients were taking statins and 2.4% were taking other hypolipidaemic drugs. On the other hand, after 6 years, 16.2% of the pravastatin group were not taking any lipid-lowering therapy. Thus, the difference in cholesterol levels in the two groups of patients was not as large as expected.

In the Heart Protection Study (321), a wide range of high-risk individuals aged 40–80 years ($n = 20\,536$) were randomly allocated to receive 40 mg of simvastatin daily or a placebo. Simvastatin reduced the rates of myocardial infarction, stroke and revascularization by about one-quarter. The proportional reduction in the event rate was similar and significant in each subcategory, including individuals without diagnosed coronary heart disease who had cerebrovascular disease or peripheral arterial disease or diabetes, and even those who presented with an LDL-cholesterol level below 3.0 mmol/l (116 mg/dl) or total cholesterol below 5.0 mmol/l (193 mg/dl). The benefits of simvastatin were additional to those of other treatments, such as aspirin, beta-blockers, ACE inhibitors and other antihypertensive therapy. The size of the 5-year benefit depended on the individuals' overall risk of major vascular events rather than on their blood lipid concentrations. About one-third of the participants in this study were free of coronary heart disease. In this group, statin therapy reduced major vascular events by 22% compared with placebo ($P = 0.0006$) in the patient subpopulation with LDL-cholesterol levels below 2.6 mmol/l (100 mg/dl) at baseline.

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (322), statins reduced the risk of non-fatal MI and fatal coronary heart disease by 36% compared with placebo ($P = 0.0005$), in patients with hypertension and at least three other cardiovascular risk factors, but no history of coronary heart disease and average or mildly elevated TC levels.

The Collaborative Atorvastatin Diabetes Study (CARDS) (323) examined the effectiveness of atorvastatin, 10 mg daily, for primary prevention of major cardiovascular events in 2838 patients aged 40–75 years with type 2 diabetes and an LDL-cholesterol concentration of 4.1 mmol/l (160 mg/dl) or lower. All patients had at least one of the following: retinopathy, albuminuria, current smoking, or hypertension. Acute coronary heart disease events were reduced by 36% (95% CI 9% to 55%), coronary revascularizations by 31% (95% CI 16% to 59%), and stroke by 48% (95% CI 11% to 69%). Atorvastatin reduced the death rate by 27% (95% CI 1% to 48%, $P = 0.059$).

The Assessment of Lescol in Renal Transplantation (ALERT) study investigated the effects of statin therapy on cardiac and renal endpoints in patients who had had a kidney transplant (324). Patients ($n = 2102$) were randomly assigned to receive fluvastatin or placebo, and followed up for 5.1 years. Although cardiac deaths and non-fatal MI were reduced, rates of coronary intervention procedures and mortality were not reduced.

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial randomly assigned 5804 patients aged 70–82 years to receive either pravastatin, 40 mg/day, or placebo (325). This was a mixed primary and secondary prevention study, designed to test the benefits of statin treatment in the elderly. Participants either had existing vascular disease (coronary, cerebral or peripheral) or were at risk of such disease (because of smoking, hypertension or diabetes). The primary endpoint was a composite of coronary death, non-fatal myocardial infarction, and fatal and non-fatal stroke. After an average follow-up of 3.2 years, the treatment group had a significantly lower rate of primary endpoints (RR 0.85; 95%CI 0.74 to 0.97, $P = 0.014$). The reduction was related to a lower risk of coronary death and non-fatal myocardial infarction (RR 0.81; 95%CI 0.69 to 0.94; $P = 0.006$); there was no significant change in incidence of stroke.

Pignone et al. (326) conducted a meta-analysis of randomized trials of at least one year's duration that examined drug treatment in patients with no known coronary heart disease, cerebrovascular disease, or peripheral vascular disease, and that measured clinical endpoints, including all-cause mortality, coronary heart disease mortality, and non-fatal myocardial infarctions. Four studies met these criteria: the Lipid Research Clinic Primary Prevention Trial, the Helsinki Heart Study, the West of Scotland Coronary Prevention Study, and the Air Force/Texas Coronary Prevention Study (318, 319, 327, 328). Lipid-lowering drug treatment reduced the odds of a coronary heart disease event by 30% (summary odds ratio 0.70; 95% CI 0.62 to 0.79). The effect on all-cause mortality over five years was not significant. When the analysis was limited to trials that used statins a slightly stronger effect on all outcomes was found, but there was still no significant reduction in all-cause mortality (although none of these studies was individually powered for this endpoint).

Another review of lipid-lowering treatment with statins found that coronary heart disease events and all-cause mortality were reduced in primary prevention populations (329). This review, unlike the meta-analysis mentioned above (326), did not include the large Air Force/Texas trial, which was conducted later. It included the Kuopio atherosclerosis prevention study, a trial in which about 10% of subjects had a history of myocardial infarction (330), and which was not included in the more recent meta-analysis.

Vreecer et al. (331) conducted a meta-analysis to estimate the relative risk reduction for clinical outcomes (coronary events, strokes, and cardiovascular, non-cardiovascular and all-cause mortality) associated with statin therapy in primary and secondary prevention. Data from 15 trials with 63 410 participants and a mean duration of treatment of 3.6 years were included in the

analysis. Statin therapy was associated with a 22% reduction in total cholesterol, a 29% reduction in LDL-cholesterol, a 12% reduction in triglycerides, and a 6% increase in HDL-cholesterol. Overall, statin treatment reduced the relative risk of coronary events, cardiovascular disease mortality, non-fatal strokes and all-cause mortality. The authors concluded that, while secondary prevention with statins considerably improved cardiovascular morbidity and mortality outcomes, primary prevention with statins provides absolute benefits, which are related to the individuals' absolute risk and the absolute reduction in LDL-cholesterol achieved.

The lack of effect on all-cause mortality seen in some of these studies may be attributable to the statistical power of the studies, the absolute risk of the patients, the reduction in LDL-cholesterol achieved, and the relatively short follow-up periods in the trials (5–7 years), which may not allow sufficient time for differences to emerge in relatively low-risk patients.

The results of the Cholesterol Treatment Trialists Collaboration (332), based on 90 056 patients in 14 randomized trials, showed that statin therapy can reduce the 5-year incidence of coronary events, coronary revascularization, and stroke by about one-fifth for each mmol-per-litre reduction in LDL-cholesterol. All-cause mortality fell by 12% for each mmol-per-litre reduction in LDL-cholesterol, reflecting a 19% reduction in coronary mortality and non-significant reductions in non-coronary vascular mortality and non-vascular mortality. There was a 23% reduction in myocardial infarction and coronary death, a 24% reduction in the need for coronary revascularization, and a 17% reduction in fatal and non-fatal strokes, giving a 21% reduction overall in major cardiovascular events. The absolute benefit of therapy depended mainly on the individual's absolute risk of such events and the absolute reduction in LDL-cholesterol achieved.

The effect of statins on LDL-cholesterol, ischaemic heart disease and stroke have been quantified in a meta-analysis, which comprised: (1) 164 short-term randomized placebo-controlled trials of six statins and LDL-cholesterol reduction; (2) 58 randomized trials of cholesterol lowering by any means and ischaemic heart disease events; and (3) the stroke component of the same 58 trials plus nine cohort studies of stroke (333). Participants in most trials were healthy with above-average lipid levels. In some trials, participants had high blood pressure, diabetes or ischaemic heart disease. The results of these studies showed that simvastatin, 40 mg/day, lovastatin, 40 mg/day, and atorvastatin, 10 mg/day, lowered LDL-cholesterol by about 37%, irrespective of pre-treatment concentration. Statins reduced ischaemic heart disease events at age 60 by an estimated 61% in the long term; there was little reduction in the first year but a 51% reduction by the third year. They also reduced the overall risk of stroke by 17%, preventing thromboembolic stroke but not haemorrhagic stroke. Any possible excess of haemorrhagic stroke was greatly outweighed by the protective effect against ischaemic heart disease events and thromboembolic stroke.

Costa et al. (334) conducted a systematic review and meta-analysis to evaluate the clinical benefits of lipid-lowering drug treatment for primary and secondary prevention in patients with and without diabetes. Twelve randomized placebo-controlled double-blind trials, with a follow-up of at least 3 years, were included. The analysis confirmed that patients, whether diabetic or not, benefit from lipid-lowering in accordance with their absolute cardiovascular risk.

The evidence for efficacy of other lipid-lowering agents in primary prevention is weak. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (335) assessed the effect of fenofibrate on cardiovascular disease events in patients with type 2 diabetes. This was a mixed primary and secondary prevention study, which randomly assigned 2131 patients with previ-

ous cardiovascular disease and 7664 without to receive either fenofibrate or a placebo. At 5 years follow-up, fenofibrate did not significantly reduce the risk of coronary events.

A meta-analysis of different lipid-lowering strategies, involving over 275 000 patients, demonstrated that only the statins (RR 0.87, 95% CI 0.81 to 0.94) and n-3 fatty acids (RR 0.77, 95% CI 0.63 to 0.94) reduced total mortality (336). Cardiovascular mortality was reduced with statins (RR 0.78, 95% CI 0.72 to 0.84), resins (RR 0.70, 95% CI 0.5 to 0.99) and n-3 fatty acids (RR 0.68, 95% CI 0.52 to 0.9). While statins and resins had a significant lipid-lowering effect, n-3 fatty acids did not significantly affect cholesterol levels. In 17 fibrate trials, non-cardiovascular mortality was higher in the treated group than in controls (RR 1.13, 95% CI 1.01 to 1.27)

The above trials primarily enrolled middle-aged men of European descent; however, the Cholesterol Treatment Trialists Collaboration found a similar proportionate reduction in risk in women, and there is no age at which the benefits have not been shown. Older people, who are at higher absolute risk of CVD, have relative reductions in risk similar to those in younger people. Although there is little reason to believe that the effects would be different in non-Europeans with similar baseline risks of cardiovascular disease and similar lipid profiles, research is needed to examine the effects of lipid-lowering treatment in other racial groups. The overall conclusion is that the absolute benefits of statin therapy are related to individual total CVD risk and the reduction in LDL-cholesterol achieved.

Risks

There is no evidence from the large studies that cholesterol-lowering therapy increases the risk of death from other causes (333, 337, 338). Meta-analysis of data from statin trials has not shown an excess of adverse symptoms, including muscle pain and various gastrointestinal symptoms, in the treated group. The absolute risks of rhabdomyolysis and liver failure from hepatitis were low. Rhabdomyolysis (indicated by serum creatine kinase ≥ 10 times the upper limit of normal) was reported in 55 treated patients (0.17%) and 43 placebo patients (0.13%). The incidence of rhabdomyolysis is estimated to be about one per million person-years of use. There were no cases of liver failure in the trials. Hepatitis (indicated by alanine aminotransferase ≥ 3 times the upper limit of normal) was reported in 449 treated patients (1.3%) and 383 placebo patients (1.1%). From 1987 to 2000, the Food and Drug Administration in the USA recorded 30 cases of liver failure attributable to statins – about one per million person-years of use (339, 340).

Data from randomized trials of cholesterol reduction and disease events have not provided evidence that a low serum cholesterol concentration increases mortality from any cause, other than possibly haemorrhagic stroke. Too few haemorrhagic strokes were observed in the randomized trials to resolve the uncertainty related to this condition. Further, the risk of haemorrhagic stroke affected only people with a very low cholesterol concentration and, even in this group, the risk was outweighed by the benefits from the reduced risk of coronary heart disease.

In some trials, the possibility of an excess risk of cancer has been raised. In the Cholesterol Treatment Trialists Collaboration meta-analysis, there was no evidence of an effect on cancer deaths. There was also no evidence of an increased risk of developing cancer (RR 1.00; 95% CI 0.95 to 1.06; $P = 0.9$), no evidence of an excess incidence of cancers with increasing duration of

treatment, and no excess of any particular site-specific cancer (303). However, in the PROSPER study, new cancer diagnoses were more frequent in the pravastatin-treated patients (RR 1.25; 95% CI 1.05 to 1.51; $P = 0.02$), apparently supporting earlier concern about the potential carcinogenic dangers of statin therapy (325). In the Heart Protection Study (HPS) (341), 28% of the study population (5806 patients) were over 70 years of age. The reduction in major vascular events was as marked in these elderly patients as in those aged under 65 years. However, there was an apparent excess of non-melanoma skin cancer in the simvastatin-treated group, compared with the placebo group (2.4% vs. 2.0%, $P = 0.06$). In the Scandinavian Simvastatin Survival Study (342), 21 patients in the statin group developed non-melanoma skin cancer, compared with seven in the placebo group. In the Cholesterol and Recurrent Events (CARE) study (343), which involved pravastatin, the occurrence of 12 cases of breast cancer in the statin-treated group, compared with one case in the placebo group, was attributed to chance. Overall, there is no statistically significant evidence that statin therapy increases the incidence of cancer.

No therapy is completely free from adverse effects. Treatment of those most at risk will bring the most benefit; treatment of patients not at high risk of cardiovascular disease may expose them to adverse effects without much benefit. As the side-effects of liver and muscle damage are dose-dependent (340), the high-dose statin regimens evaluated in some of the trials (344) will have a worse side-effects profile when applied to patients treated in everyday clinical practice.

Other lipid lowering drugs

Fibrates are primarily used for lowering triglycerides and raising low HDL levels. They also have a LDL cholesterol lowering effect. Results of one primary prevention and two secondary prevention fibrate trials (345–347) support the view that triglyceride reduction and HDL-C elevation offer cardiovascular benefit which, at least in part is independent of LDL cholesterol reduction.

Nicotonic acid is an effective HDL raising agent. A meta-analysis of 53 trials using fibrates and 30 trials using niacin showed that each drug significantly lowered total cholesterol, LDL-C and triglycerides and raised HDL-C (348). Fibrates reduced the risk of major coronary events by 25% and niacin by 27% (349).

Monitoring of treatment

Some guidelines recommend that treatment should aim to reduce total and LDL-cholesterol levels below particular targets, e.g. total cholesterol to less than 5 mmol/l (190 mg/dl) or LDL-cholesterol to less than 3 mmol/l (115 mg/dl) (350). However, recent studies have not found a cholesterol level below which there is no benefit, suggesting that taking a trial-validated dose of a statin is more important than aiming for a particular target cholesterol level (321). Thus, continued monitoring of blood lipids may not be necessary in settings with limited resources.

Primary prevention trials (320, 322, 323) have demonstrated that patients at highest total risk of cardiovascular events obtain the greatest benefit from statin therapy. Treatment should therefore be targeted at the group with highest total risk, rather than simply those with highest lipid levels. The relative importance of resource considerations and patient preference will increase as the total CVD risk decreases.

6. Cost-effectiveness, feasibility and resource implications of antihypertensive and statin therapy

The cost-effectiveness of a treatment is determined by the relationship between the benefits obtained and the expenditure. The prevalence of a condition and the total cost of treating it in a specific setting, on the other hand, determine affordability. Because resources are limited, even a cost-effective treatment may not be affordable. The two main determinants of cost-effectiveness are the cost of drug therapy and the initial cardiovascular risk of the patient.

In the case of antihypertensive treatment, the major classes of antihypertensive drugs are largely equivalent in terms of efficacy. However, diuretics and beta-blockers, singly or in combination, are associated with an increased incidence of diabetes; thus, in populations with an increasing burden of diabetes, other classes of antihypertensive therapies may be preferable. In most parts of the world, a diuretic is the cheapest option and is, therefore, generally most cost-effective. However, for certain compelling indications, other classes will provide additional benefits; even if they are more expensive, they may be more cost-effective.

There is no evidence to support claims of superior performance of any particular drug within each of the major drug classes. Therefore, the least expensive will be the most cost-effective. In patients with very high CVD risk, who obtain great benefits from treatment with multiple drugs, even expensive drugs can be cost-effective. Conversely, the treatment of patients with very low CVD risk may be cost-effective only if inexpensive antihypertensive drugs are used (316). As populations age, increasing numbers of elderly people are being diagnosed as hypertensive and requiring treatment. For this group, diuretic-based therapy is the most cost-effective; therapy that includes either atenolol or low-dose reserpine has been shown to be a relatively inexpensive approach to prevention of cardiovascular events in older adults with isolated systolic hypertension (351).

In the case of lipid lowering drugs, overall, primary prevention trials have provided evidence that lipid-lowering with a statin is justifiable on risk–benefit grounds, and is cost-effective in subjects who have a high risk of developing cardiovascular disease ($\geq 20\%$ over 10 years, equivalent to a CHD risk of $\geq 15\%$ over the same period (352). Treatment policy will need to specify the total CVD risk to be targeted, taking into consideration how many people will need to be treated to prevent one CVD event, the proportion of the population requiring treatment, the cost-effectiveness of treatment, and the total cost. In addition, the extra workload and financial resources needed to implement primary prevention strategies will need to be assessed, keeping in mind that managing patients with established cardiovascular disease should remain the first priority for a CVD programme.

Overall, the cost-effectiveness data suggest that it is appropriate to initiate statin therapy in people with an annual risk of CHD greater than 1.5% (approximately equivalent to a 10-year CHD risk of 15% and a 10-year CVD risk of 20%). The estimated cost per quality-adjusted life year (QALY) for statin therapy is lower at higher levels of risk and in younger age cohorts. Although people over the age of 75 years get less benefit from statin therapy, such therapy is cost-effective for people in all age groups with a 10-year cardiovascular risk of 20% or more (352, 353). The CVD risk threshold for treatment should be decided at national level, because whether a risk threshold is cost-effective will largely depend on the financial resources available; it will also be sensitive to the cost of statins, which differs from country to country.

There are currently no data to suggest the superiority of one statin over others in reducing cardiovascular events. Thus, if the decision is made to initiate statin therapy, the least expensive statin should usually be chosen.

7. Control of glycaemia

Issue

Does control of glycaemia reduce cardiovascular risk in patients with diabetes?

Evidence

Cardiovascular disease accounts for about 60% of all mortality in people with diabetes. The risk of cardiovascular events is 2–3 times higher in people with type 1 or type 2 diabetes (354, 355) and the risk is disproportionately higher in women (354, 356). Patients with diabetes also have a poorer prognosis after cardiovascular events compared with non-diabetics (357, 358).

Epidemiological evidence also suggests that the association between blood glucose and cardiovascular disease begins before diabetes manifests itself (357–361). In a meta-analysis of non-diabetic subjects, those with the highest blood glucose levels had a relative risk for cardiovascular disease events of 1.26 compared with those with the lowest blood glucose. This suggests that cardiovascular risk increases as glucose tolerance becomes impaired and then progresses to diabetes (362). Further, abnormal glucose regulation tends to occur together with other known cardiovascular risk factors, such as central obesity, elevated blood pressure, low HDL-cholesterol and high triglyceride level (363, 364).

The Diabetes Control and Complications Trial (DCCT) (365), which included 1441 young adults with type 1 diabetes, demonstrated that intensive treatment to ensure good glycaemic control substantially reduced the risks of cardiovascular events, neuropathy, nephropathy and retinopathy. However, the difference in the number of events in the two groups was not significant. Among the more than 1300 volunteers who continued to participate in the DCCT follow-up study, those who had received intensive treatment had 57% fewer serious cardiovascular events, such as heart attacks and strokes, than those given conventional treatment (366).

The United Kingdom Prospective Diabetes Study (UKPDS) found that glycaemic control in people with type 2 diabetes reduced the frequency of microvascular complications, such as blindness, amputation, and end-stage renal disease (367). Each 1% increase in HbA1c level was associated with a 14% increase in the incidence of fatal or nonfatal myocardial infarction (368). However, intensive treatment of patients with newly diagnosed type 2 diabetes, with sulfonylureas or insulin, resulted in a 16% reduction ($P = 0.052$) in the relative risk of myocardial infarction compared with patients treated conventionally (367). The UKPDS concluded that there is a direct relationship between level of glycaemia and the risk of complications of diabetes. There was no “threshold” of glycaemia at which there was a significant change in risk for any of the clinical outcomes examined. The rate of increase of microvascular disease with hyperglycaemia was greater than that of macrovascular disease. The UKPDS also showed that lowering the HbA1c level by an average of 0.9%, for a median follow-up period of 10 years after diagnosis of type 2 diabetes, was associated with a significant reduction in microvascular endpoints, retinopathy and nephropathy (367).

A later study suggested that stringent blood sugar control in people with type 2 diabetes, combined with targeted reductions in blood lipids and blood pressure, reduced macrovascular events in diabetic patients with microalbuminuria (369).

Metformin is safe and effective for treatment of type 2 diabetes, either as monotherapy or in combination with other drugs. The role of the newer insulin secretagogues, the thiazolidinediones, is still being evaluated in clinical trials. In most circumstances, metformin is the drug of choice for initial therapy of obese patients with type 2 diabetes and mild to moderate hyperglycaemia (370).

For each patient the risk of hypoglycaemia must be considered when determining the target HbA1c level, especially in people treated with insulin and those with type 1 diabetes. Health care practitioners should be aware that more intensive glycaemic control increases the risk of hypoglycaemia. Treatment guidelines often set therapeutic goals at the level of lowest risk. However, it is important to set targets appropriate to the individual and in consultation with him or her. It is also important to recognize that adherence to medicines is much lower in real-life settings than in clinical trials. The results of controlled trials are unlikely to be achieved in clinical practice unless specific measures are taken to improve compliance with treatment.

In summary, good glycaemic control should be a key goal of treatment of diabetes, to delay the onset and progression of microvascular and macrovascular disease. Treatment should aim to achieve:

- a fasting blood glucose level of 4–7 mmol/l (72–126 mg/dl);
- an HbA1c level of 6.5% or less.

The first approach to controlling glycaemia should be through diet alone; if this is not sufficient, oral medication should be given, followed by insulin if necessary. The decision on whether to give statins to people with diabetes needs to be made if their CVD risk is estimated to be 20% or more over 10 years (371).

8. Aspirin therapy

Issue

Does long-term treatment with aspirin reduce cardiovascular risk?

Evidence

Several RCTs (277, 372–377) and meta-analyses (377–379) have evaluated the role of aspirin in the primary prevention of cardiovascular disease. Overall, the results of the randomized trials indicated that, compared with placebo, aspirin was associated with a 32% reduction in myocardial infarction (RR 0.68; 95% CI 0.54 to 0.86; $P = 0.001$) and a non-significant increase in the risk of stroke. The numbers of women enrolled in most of these trials were too small to allow robust conclusions to be drawn about the role of aspirin in primary prevention for women. In the Women's Health study (376), women aged 45 years or older ($n = 39\,876$) were randomly assigned to receive low-dose aspirin therapy or placebo, and followed up for 10 years. Aspirin had no significant effect on the risk of myocardial infarction. However, there was a 17% lower risk of stroke in the

treated group (RR 0.83; 95% CI 0.69 to 0.99; $P = 0.04$). The reason for these different results in women may simply be that the study was seriously underpowered for some CVD outcomes, because of the lower total risk of CVD in women. Further investigation, however, is needed.

Risks

Aspirin roughly doubles the risk of gastrointestinal haemorrhage. A review of observational studies (380) suggested that the background risk of major gastrointestinal complications is about 1–2 per 1000 per year at age 60 years. The excess risks attributable to aspirin are therefore 1–2 per 1000 per year at age 60. Among unselected people under 60 years, therefore, the expected benefit in terms of myocardial infarction (2 per 1000 per year avoided) does not exceed the expected risk of a major gastrointestinal bleed. Further observational studies strongly suggested that the risk of bleeding associated with aspirin increases substantially in older people, rising to 7 per 1000 per year at age 80; the balance of benefit and risk, therefore, needs to be clearly defined before aspirin can be recommended for all elderly people.

Estimates of the rate of excess haemorrhagic stroke associated with the use of aspirin in three primary prevention trials were 0.20, 0.05, and 0.12 bleeding events per 1000 patients treated per year (372–374). In Hypertension Optimal Treatment (HOT) trial and Primary Prevention Project (PPP) (277, 375), approximately 0.03 and 0.12 bleeding events were caused per 1000 patients treated per year, respectively. The meta-analysis of these studies (378) also found that aspirin was associated with an increased risk of haemorrhagic stroke (summary odds ratio 1.4; 95% CI 0.9 to 2.0). Estimates of the beneficial and harmful effects of aspirin have been used to project the impact of aspirin on populations of patients at different levels of 5-year risk for CHD. In 1000 patients with a 5% (high) risk, aspirin would be expected to prevent 14 CHD events and cause 0–2 haemorrhagic strokes; in patients with a 3% (moderate) risk, aspirin would prevent 8 CHD events and cause 0–2 haemorrhagic strokes; and in patients with a 1% (low) risk, aspirin would prevent 3 CHD events and cause 0–2 haemorrhagic strokes (381). A similar analysis using the same primary prevention studies estimated comparable effects for haemorrhagic stroke, confirming that the absolute excess risk of haemorrhagic stroke attributable to aspirin is small (around 0.1 per 1000 per year) (382).

Balance of risks and benefits

When considering the use of aspirin, the benefits must be weighed against the possible risks associated with its use, particularly the risk of haemorrhagic stroke but also gastrointestinal bleeding. A meta-analysis by the Antiplatelet Trialists Collaboration demonstrated that, at low CVD risk, the benefits of aspirin are matched by the risks of major bleeding and haemorrhagic stroke, and therefore aspirin is not indicated (383). In people at high risk, the risk–benefit ratio of aspirin therapy is favourable in some European countries and North America, but may be less favourable in populations with a high incidence of gastrointestinal bleeding or haemorrhagic stroke and a low prevalence of coronary heart disease (382). In clinical practice, physicians should consider the individual's probable risk–benefit profile before using aspirin for primary prevention.

If there are no contraindications (allergy or history of gastrointestinal haemorrhage), low-dose aspirin (75 mg/day) is recommended for all patients at high risk of developing CVD ($\geq 20\%$ over 10 years), provided the blood pressure is controlled to $<150/90$ mmHg.

9. Fixed-dose combinations

As many high-risk patients would benefit from treatment with several drugs proven to reduce cardiovascular disease, the notion of a combination pill, using fixed-dose formulations of effective drugs, was originally proposed to overcome two problems: the difficulty of adherence to treatment involving multiple pills; and the inadequate dosages often prescribed in routine clinical practice (384). The idea was further developed in the context of finding effective preventive strategies for low- and middle-income countries (385), and gained widespread attention with Wald & Law's paper (386) describing a fixed-dose "polypill", which comprised a statin, three antihypertensive agents at half doses (a beta-blocker, a diuretic, and an ACE inhibitor), aspirin (75 mg), and folic acid (0.8 mg). The polypill was conceived as a means of mass treatment for everyone over 55 years of age, regardless of their risk factor profile or estimated total cardiovascular risk. The risk reduction was estimated to be 88% for coronary heart disease and 80% for stroke.

The rationale for the components in a combination pill require scrutiny. While the efficacy of aspirin in men is established, for example (387), the recently completed women's health study found no difference in all-cause mortality or fatal and non-fatal myocardial infarction between groups of women given 100 mg of aspirin every other day or placebo (388). In addition, although observational evidence favours a possible causal association between raised plasma homocysteine concentrations and cardiovascular disease (389), there is growing evidence from RCTs that the expected beneficial effects of folic acid may not be confirmed (390–392).

In reviewing the evidence supporting the use of combination therapy, a recent working group report commented that: (a) the estimates of effect may have been exaggerated; (b) adherence to treatment may be low in healthy populations; (c) new studies of efficacy, effectiveness and cost-effectiveness are needed; and (d) social and behavioural issues related to population coverage, adoption, and long-term maintenance need to be examined (393). In addition, the potentially damaging effect of a mass-medication approach on population-wide public health measures for tobacco control, healthy diets and physical activity need to be considered. Commentators are generally agreed on the need for further research on the combination pill, and for continued strong engagement with public health programmes for cardiovascular disease prevention (394, 395).

A pill containing amlodipine and atorvastatin (in a range of dose combinations) has been licensed by the Food and Drug Administration in the USA, and marketed at slightly less than the cost of the two drugs separately since 2003.

Marketing a polypill directly to individuals without testing, thus avoiding the costs of clinical consultation, risk factor measurement and scoring, and individualized prescription of treatments, sounds tempting, but runs the risk of overtreating people who are at low cardiovascular risk and undertreating people at substantial risk. Use of the polypill to treat people who have been classified according to their total cardiovascular risk does have attractions, as it would simplify selection of drugs and ensure predefined doses. Meta-analyses of RCTs have found limited evidence of advantages of single-pill treatments over use of multiple drugs (396–399); thus, use of a combination pill to treat people at moderate levels of total cardiovascular risk might have advantages, but further studies of adherence, side-effects and effectiveness are required. In summary, while a combination pill has some promise as a means of targeted treatment, it raises major challenges that would have to be addressed if it is to meet the claims made for it.

10. Hormone therapy

Issue

Does hormone replacement therapy reduce cardiovascular risk?

Evidence

On the basis of data from observational studies (400), hormone therapy has been used for prevention of cardiovascular disease, osteoporosis and dementia. This practice has been called into question following publication of the results of several randomized clinical trials, which showed no coronary protection, and the Women's Health Initiative (401), which indicated that long-term use of estrogen plus progestin was associated with increased risks of cancer and cardiovascular disease.

A Cochrane systematic review (402) of 15 randomized double-blind trials (involving 35 089 women aged 41 to 91 years) examined the effect of long-term hormone replacement therapy on mortality, heart disease, venous thromboembolism, stroke, transient ischaemic attacks, cancer, gallbladder disease, fractures and quality of life. All were placebo-controlled trials, in which perimenopausal or postmenopausal women were given estrogens, with or without progestogens, for at least one year.

The only statistically significant benefits of hormone therapy were decreased incidences of fractures and colon cancer with long-term use. In relatively healthy women, combined continuous hormone therapy significantly increased the risk of coronary events and venous thromboembolism (after one year's use), stroke (after 3 years), breast cancer (after 5 years) and gallbladder disease. Long-term estrogen-only hormone therapy also significantly increased the risk of stroke and gallbladder disease. In relatively healthy women over 65 years taking continuous combined hormone therapy, there was an increase in the incidence of dementia.

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Annex 1

WHO Member States by subregion, classified according to mortality stratum^a (based on World Health Report 2002)

Subregion	WHO Member States
African Region	
D	Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo
E	Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
Region of the Americas	
A	Canada, Cuba, United States of America
B	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela
D	Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru
Eastern Mediterranean Region	
B	Bahrain, Iran (Islamic Republic of), Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates
D	Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen
European Region	
A	Andorra, Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom
B	Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Serbia and Montenegro, Slovakia, Tajikistan, The Former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan
C	Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine

continued ...

^a *Mortality strata*: A: very low child mortality and very low adult mortality; B: low child mortality and low adult mortality; C: low child mortality and high adult mortality; D: high child mortality and high adult mortality; E: high child mortality and very high adult mortality.

Subregion	WHO Member States
South-East Asia Region	
B	Indonesia, Sri Lanka, Thailand
D	Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal
Western Pacific Region	
A	Australia, Brunei Darussalam, Japan, New Zealand, Singapore
B	Cambodia, China, Lao People's Democratic Republic, Malaysia, Mongolia, Philippines, Republic of Korea, Cook Islands, Fiji, Kiribati, Marshall Islands, Micronesia (Federated States of), Nauru, Niue, Palau, Papua New Guinea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam

Annex 2

Proportion of the population in each risk category, by WHO subregion^a

Distribution of the population, by age and sex, according to 10-year total CVD risk, in the 14 WHO subregions

MEN					WOMEN				
African Region: D									
Risk category	Age group (years)				Risk category	Age group (years)			
	<50	50–59	60–69	70+		<50	50–59	60–69	70+
<10%	96.29%	86.26%	64.34%	42.57%	<10%	98.06%	83.30%	63.72%	42.39%
10–19.9%	3.28%	7.53%	12.67%	29.35%	10–19.9%	1.57%	12.14%	6.63%	19.97%
20–29.9%	0.12%	4.23%	11.83%	14.78%	20–29.9%	0.33%	3.46%	20.87%	13.19%
30–39.9%	0.28%	1.45%	7.61%	8.96%	30–39.9%	0.01%	0.68%	5.94%	19.80%
≥40%	0.04%	0.53%	3.54%	4.34%	≥40%	0.03%	0.42%	2.84%	4.65%
African Region: E									
Risk category	Age group (years)				Risk category	Age group (years)			
	<50	50–59	60–69	70+		<50	50–59	60–69	70+
<10%	96.05%	86.43%	73.26%	57.98%	<10%	95.38%	83.33%	68.90%	56.83%
10–19.9%	1.24%	7.49%	15.53%	28.08%	10–19.9%	4.22%	11.93%	11.48%	18.42%
20–29.9%	1.45%	4.21%	7.18%	10.10%	20–29.9%	0.03%	3.39%	17.18%	20.83%
30–39.9%	0.75%	1.40%	2.77%	2.93%	30–39.9%	0.33%	0.98%	1.84%	2.31%
≥40%	0.51%	0.47%	1.28%	0.91%	≥40%	0.04%	0.36%	0.59%	1.62%
Region of the Americas: A									
Risk category	Age group (years)				Risk category	Age group (years)			
	<50	50–59	60–69	70+		<50	50–59	60–69	70+
<10%	96.00%	69.27%	19.27%	3.15%	<10%	98.18%	86.91%	50.09%	15.84%
10–19.9%	2.63%	17.18%	35.27%	18.76%	10–19.9%	1.18%	6.45%	27.03%	32.09%
20–29.9%	0.51%	5.14%	13.69%	23.86%	20–29.9%	0.40%	3.51%	8.50%	20.47%
30–39.9%	0.29%	2.95%	12.83%	20.31%	30–39.9%	0.05%	1.10%	5.69%	11.66%
≥40%	0.56%	5.45%	18.94%	33.92%	≥40%	0.19%	2.03%	8.69%	19.93%

^a For definition of subregions, see Annex 1.

MEN					WOMEN				
Region of the Americas: B									
Risk category	Age group (years)				Risk category	Age group (years)			
	<50	50–59	60–69	70+		<50	50–59	60–69	70+
<10%	97.08%	77.25%	39.76%	16.74%	<10%	97.51%	85.66%	59.37%	17.52%
10–19.9%	1.92%	12.82%	29.87%	37.97%	10–19.9%	1.75%	7.45%	20.29%	35.71%
20–29.9%	0.57%	4.51%	11.14%	22.04%	20–29.9%	0.43%	2.67%	7.39%	21.49%
30–39.9%	0.22%	2.15%	7.93%	9.32%	30–39.9%	0.11%	1.32%	6.01%	9.27%
≥40%	0.21%	3.27%	11.31%	13.93%	≥40%	0.20%	2.91%	6.94%	16.01%
Region of the Americas: D									
Risk category	Age group (years)				Risk category	Age group (years)			
	<50	50–59	60–69	70+		<50	50–59	60–69	70+
<10%	98.65%	89.86%	66.86%	35.78%	<10%	98.38%	90.09%	68.94%	36.96%
10–19.9%	1.13%	5.30%	21.35%	36.12%	10–19.9%	1.12%	3.79%	15.79%	32.83%
20–29.9%	0.14%	2.59%	6.17%	15.74%	20–29.9%	0.22%	4.50%	10.91%	11.56%
30–39.9%	0.01%	1.32%	3.39%	5.74%	30–39.9%	0.22%	0.93%	2.60%	12.87%
≥40%	0.07%	0.93%	2.23%	6.62%	≥40%	0.06%	0.69%	1.76%	5.78%
Eastern Mediterranean Region: B									
Risk category	Age group (years)				Risk category	Age group (years)			
	<50	50–59	60–69	70+		<50	50–59	60–69	70+
<10%	99.08%	83.91%	34.55%	8.60%	<10%	99.23%	81.68%	24.27%	2.81%
10–19.9%	0.72%	7.81%	28.47%	34.16%	10–19.9%	0.54%	9.22%	32.00%	29.45%
20–29.9%	0.07%	3.74%	11.67%	20.60%	20–29.9%	0.13%	3.11%	19.66%	28.73%
30–39.9%	0.10%	2.20%	9.14%	11.64%	30–39.9%	0.07%	3.13%	8.00%	14.84%
≥40%	0.03%	2.33%	16.18%	25.00%	≥40%	0.02%	2.85%	16.08%	24.17%
Eastern Mediterranean Region: D									
Risk category	Age group (years)				Risk category	Age group (years)			
	<50	50–59	60–69	70+		<50	50–59	60–69	70+
<10%	98.63%	82.09%	30.20%	5.44%	<10%	99.01%	84.43%	46.54%	14.49%
10–19.9%	0.89%	9.31%	35.33%	28.35%	10–19.9%	0.67%	9.18%	26.62%	34.28%
20–29.9%	0.29%	3.95%	15.73%	27.76%	20–29.9%	0.16%	3.79%	11.35%	19.32%
30–39.9%	0.07%	1.12%	4.82%	14.11%	30–39.9%	0.10%	1.28%	8.04%	12.99%
≥40%	0.12%	3.53%	13.91%	24.35%	≥40%	0.06%	1.32%	7.45%	18.92%

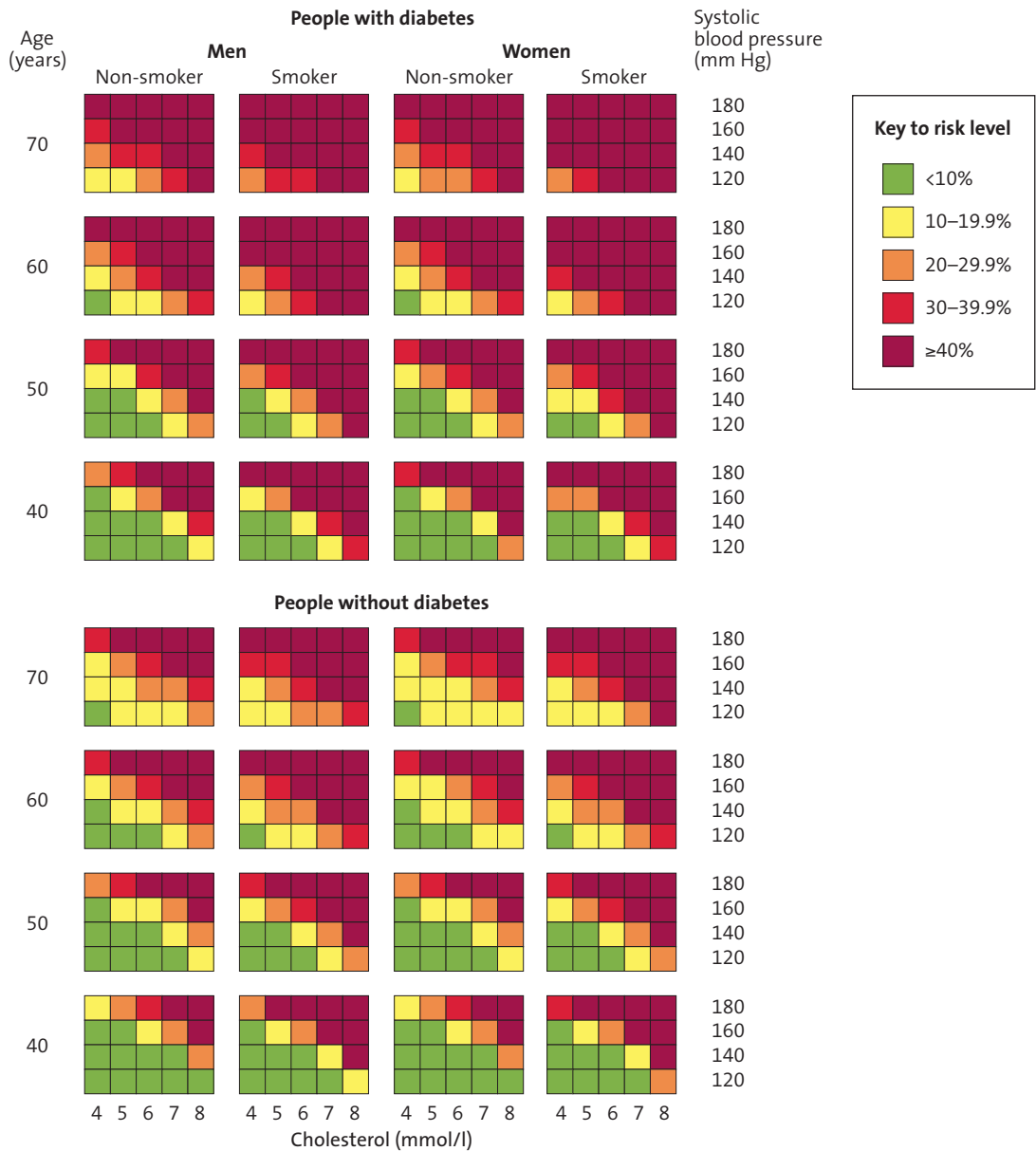
MEN					WOMEN				
European Region: A									
Risk category	Age group (years)				Risk category	Age group (years)			
	<50	50–59	60–69	70+		<50	50–59	60–69	70+
<10%	98.11%	82.59%	40.17%	8.54%	<10%	99.32%	94.50%	65.76%	22.27%
10–19.9%	1.63%	10.78%	30.40%	31.03%	10–19.9%	0.53%	3.54%	23.75%	34.31%
20–29.9%	0.10%	3.87%	13.29%	22.60%	20–29.9%	0.10%	1.64%	7.70%	22.73%
30–39.9%	0.00%	1.75%	6.88%	12.44%	30–39.9%	0.04%	0.29%	1.55%	8.77%
≥40%	0.15%	1.02%	9.25%	25.39%	≥40%	0.01%	0.03%	1.24%	11.92%
European Region: B									
Risk category	Age group (years)				Risk category	Age group (years)			
	<50	50–59	60–69	70+		<50	50–59	60–69	70+
<10%	95.99%	76.50%	35.12%	14.75%	<10%	97.44%	83.87%	53.78%	29.44%
10–19.9%	2.02%	7.84%	26.21%	29.32%	10–19.9%	1.49%	7.77%	14.83%	19.99%
20–29.9%	1.10%	6.72%	10.56%	14.01%	20–29.9%	0.61%	6.44%	20.61%	27.80%
30–39.9%	0.48%	4.81%	11.45%	19.84%	30–39.9%	0.22%	0.87%	5.25%	9.78%
≥40%	0.40%	4.13%	16.67%	22.09%	≥40%	0.24%	1.05%	5.54%	12.99%
European Region: C									
Risk category	Age group (years)				Risk category	Age group (years)			
	<50	50–59	60–69	70+		<50	50–59	60–69	70+
<10%	92.57%	69.69%	13.59%	4.30%	<10%	97.30%	79.51%	48.02%	16.78%
10–19.9%	5.06%	10.54%	28.02%	14.20%	10–19.9%	1.73%	11.68%	16.24%	24.24%
20–29.9%	1.05%	6.07%	18.10%	22.81%	20–29.9%	0.47%	5.66%	13.26%	7.10%
30–39.9%	0.01%	4.77%	8.39%	17.58%	30–39.9%	0.37%	2.72%	10.94%	25.75%
≥40%	1.30%	8.93%	31.90%	41.11%	≥40%	0.13%	0.44%	11.54%	26.14%
South-East Asia Region: B									
Risk category	Age group (years)				Risk category	Age group (years)			
	<50	50–59	60–69	70+		<50	50–59	60–69	70+
<10%	97.43%	85.78%	56.81%	32.84%	<10%	98.71%	89.35%	67.86%	41.82%
10–19.9%	1.54%	6.60%	22.50%	35.43%	10–19.9%	1.06%	6.52%	12.54%	29.34%
20–29.9%	0.65%	3.48%	10.47%	18.20%	20–29.9%	0.02%	2.11%	10.28%	15.55%
30–39.9%	0.17%	2.04%	4.68%	5.70%	30–39.9%	0.15%	1.35%	4.50%	8.98%
≥40%	0.20%	2.09%	5.55%	7.84%	≥40%	0.07%	0.67%	4.82%	4.31%

MEN					WOMEN				
South-East Asia Region: C									
Risk category	Age group (years)				Risk category	Age group (years)			
	<50	50–59	60–69	70+		<50	50–59	60–69	70+
<10%	97.99%	83.02%	35.97%	10.17%	<10%	98.39%	84.58%	29.80%	6.64%
10–19.9%	1.30%	7.45%	27.48%	44.02%	10–19.9%	0.65%	8.72%	38.52%	40.66%
20–29.9%	0.25%	4.41%	14.32%	14.42%	20–29.9%	0.74%	3.39%	12.45%	22.95%
30–39.9%	0.23%	2.13%	9.48%	15.00%	30–39.9%	0.09%	0.28%	6.97%	14.25%
≥40%	0.24%	2.99%	12.75%	16.39%	≥40%	0.13%	3.03%	12.26%	15.50%
Western Pacific Region: A									
Risk category	Age group (years)				Risk category	Age group (years)			
	<50	50–59	60–69	70+		<50	50–59	60–69	70+
<10%	97.86%	83.88%	48.59%	15.61%	<10%	99.10%	91.88%	73.60%	38.30%
10–19.9%	1.45%	7.22%	24.64%	36.44%	10–19.9%	0.64%	6.32%	20.06%	33.76%
20–29.9%	0.34%	6.27%	14.46%	21.54%	20–29.9%	0.21%	1.18%	4.14%	19.03%
30–39.9%	0.24%	1.61%	5.95%	9.92%	30–39.9%	0.03%	0.45%	1.53%	4.15%
≥40%	0.11%	1.02%	6.37%	16.49%	≥40%	0.02%	0.16%	0.67%	4.77%
Western Pacific Region: B									
Risk category	Age group (years)				Risk category	Age group (years)			
	<50	50–59	60–69	70+		<50	50–59	60–69	70+
<10%	98.92%	84.99%	49.54%	24.15%	<10%	99.16%	91.39%	72.72%	48.11%
10–19.9%	0.52%	8.72%	25.37%	39.98%	10–19.9%	0.58%	4.33%	7.54%	26.53%
20–29.9%	0.40%	2.51%	10.03%	14.25%	20–29.9%	0.16%	2.29%	13.00%	10.08%
30–39.9%	0.08%	1.25%	5.46%	9.20%	30–39.9%	0.08%	1.14%	3.65%	11.39%
≥40%	0.08%	2.53%	9.60%	12.43%	≥40%	0.02%	0.85%	3.09%	3.89%

Annex 3

Sample WHO/ISH risk prediction chart, for use where measurement of cholesterol level is possible

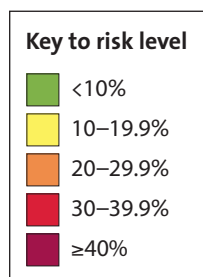
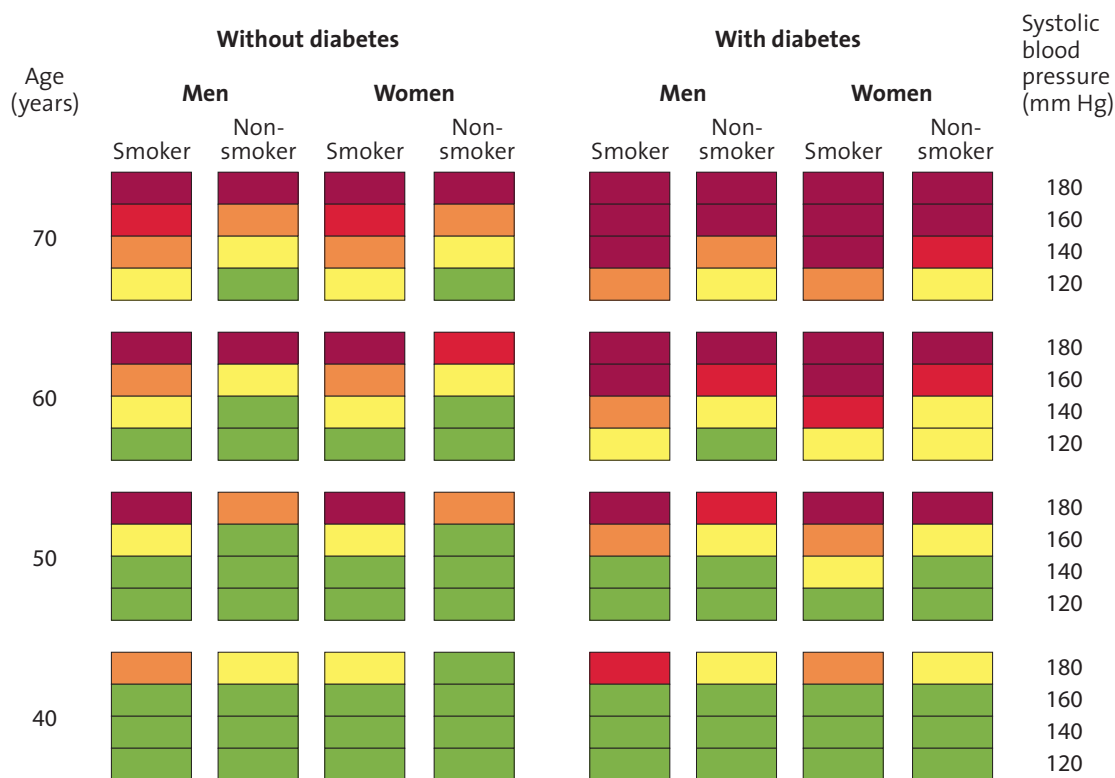
The chart below indicates total 10-year risk of a fatal or non-fatal cardiovascular event (myocardial infarction or stroke), according to age, sex, blood pressure, presence or absence of diabetes, smoking status, and cholesterol level, for the WHO Region of South-East Asia, subregion D.



Annex 4

Sample WHO/ISH risk prediction chart for use where measurement of cholesterol level is not possible

The chart below indicates total 10-year risk of a fatal or non-fatal cardiovascular event (myocardial infarction or stroke), according to age, sex, blood pressure, presence or absence of diabetes, and smoking status, for the WHO Eastern Mediterranean Region, subregion B.



Annex 5

Methods of development of WHO/ISH risk prediction charts

Several equations have been developed previously to predict individual absolute risk of a cardiovascular event over a specified time period.^{a,b} Most of these equations have been derived from Caucasian populations in developed countries and are not necessarily valid in other populations.

The Comparative Risk Assessment (CRA) Project,^c conducted by the World Health Organization and described in the *2002 World Health Report*,^d determined the burden of disease attributable to selected major risk factors, including high blood pressure, high blood cholesterol, high body mass index and smoking. This project involved the standardized collection and assessment of data on risk factor prevalence and relative risk by WHO epidemiological subregion. The WHO/ISH risk prediction charts (see Annexes 3 and 4) were based on these data.

A hypothetical cohort was created for each WHO subregion, consisting of 1 000 000 people for each age and sex group, using Stata Statistical Software release 7.0.^e The age groups used were 30–44, 45–59, 60–69, and 70–79 years. Individuals were assigned values for the following cardiovascular risk factors: systolic blood pressure, total blood cholesterol, and smoking status (as a yes/no variable), using the estimates of risk factor prevalence by WHO subregion from the CRA Project. The risk factor values were assigned using log–normal distributions of the reported mean and standard deviation for each risk factor. Correlations between risk factor distributions were based on information from the Asia-Pacific cohort.

Estimates of relative risk per unit increase in continuous risk factors, i.e. per mmHg for systolic blood pressure and per mmol/l for total cholesterol, as well as for the presence of smoking were determined from the CRA project (largely from prospective cohort studies^{c,f}). These relative risk estimates were applied to the hypothetical cohort to determine the relative risk of each individual in the cohort.

Absolute risk of a cardiovascular event was determined by scaling individual relative risk to population incidence rates of cardiovascular disease (ischaemic heart disease and stroke), estimated from the Global Burden of Disease Study.^g The probability of a cardiovascular event was extrapolated to a 10-year period. The mean absolute risk for various combinations of risk factor levels was then calculated and tabulated.

^a D'Agostino RB et al. Primary and subsequent coronary risk appraisal: new results from The Framingham Study. *Am Heart J.* 2000;139:272–281.

^b Conroy RM et al., SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J.* 2003;24(11):987–1003.

^c Ezzati M et al., Comparative Risk Assessment Collaborating Group. Estimates of global and regional potential health gains from reducing multiple major risk factors. *Lancet.* 2003;362(9380):271–280.

^d *The World Health Report 2002: reducing risks, promoting healthy life.* Geneva, World Health Organization, 2002.

^e StataCorp, College Station, Texas 77845.

^f Ezzati M, Lopez, A.D., Rodgers, A., Murray, C.J.L. *Comparative Quantification of Health Risks: Global and Regional Burden of Diseases Attributable to Selected Major Risk Factors.* World Health Organization: Geneva, 2004

^g Murray CJL, Lopez AD. *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020.* Cambridge, MA, Harvard University Press, 1996.

Annex 6

Guideline Development Committee*

Dr Habiba Ben Romdhane, Laboratoire de Recherche Epidémiologie et Prévention des Maladies Cardiovasculaires, Tunis, Tunisia

Dr Albertino Damasceno, Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique

Dr Shah Ebrahim, Department of Social Medicine, Canynge Hall, University of Bristol, Bristol, England (Chair and member of writing committee)

Dr Cristina Escobar, Ministry of Health, Santiago, Chile

Dr François Gueyffier, Centre d'Investigation Clinique, Lyon, France

Dr Rodney Jackson, Faculty of Medical and Health Sciences, Tamaki Campus, University of Auckland, Auckland, New Zealand

Dr Ulrich Keil, Institute of Epidemiology and Social Medicine. Univeristy of Münster, Münster, Germany

Dr Stephen Lim, University of Queensland, School of Population Health, Herston, Australia

Dr Lars H. Lindholm, Umea University Hospital, Umea, Sweden

Dr C. Snehalatha, Diabetes Research Centre, Chennai, India

Dr Jaako Tuomilehto, Diabetes and Genetic Epidemiology Unit, Helsinki, Finland

Dr David Wood, Imperial College, London, England (Co-Rapporteur and member of writing committee)

Dr Dong Zhao, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China

Observers

Dr James Wright, University of British Columbia, Vancouver, BC, Canada

Dr Eugene Zhelenyakov, St Petersburg, Russian Federation

WHO, Geneva, Switzerland

Dr Catherine Le Galès-Camus, Noncommunicable Diseases and Mental Health

Dr Robert Beaglehole, Department of Chronic Diseases and Health Promotion

Dr Shanthy Mendis, Cardiovascular Diseases (Co-Rapporteur and member of writing committee), Department of Chronic Diseases and Health Promotion

Mrs Mona Nassef, Cardiovascular Diseases, Department of Chronic Diseases and Health Promotion

Dr Porfirio Nordet, Cardiovascular Diseases, Department of Chronic Diseases and Health Promotion

* See http://www.who.int/cardiovascular_diseases for declaration of conflict of interests

Annex 7

Peer reviewers

Members of the WHO/International Society of Hypertension Committee

Dr Michael H Alderman, Albert Einstein College of Medicine, New York, USA

Dr Lawrie Beilin, University of Western Australia, Perth, Australia

Dr Robert Fagard, University of Leuven, Leuven, Belgium

Dr Terrence Forrester, University of the West Indies, Kingston, Jamaica

Dr Giuseppe Mancia, University of Milan-Bicocca, Milan, Italy

Dr Alberto Morganti, San Paolo Hospital, Milan, Italy

Dr Judith Whitworth, John Curtin School of Medical Research, Canberra, Australia

Other external experts

Dr Aloyzio Achutti, Porto Alegre, Brazil

Dr Antonio Bayés de Luna, Catalonia Institute of Cardiovascular Sciences, Barcelona, Spain

Dr Pascal Bovet, University Institute of Social and Preventive Medicine, Lausanne, Switzerland

Dr Flavio Burgarella, Cardiac Rehabilitation Centre, Bergamo, Italy

Dr John Chalmers, University of Sydney, New South Wales, Australia

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Dr Alfredo Dueñas, Cuban Institute of Cardiology, Havana, Cuba

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Dr Lisheng Liu, Fuwai Hospital, Beijing, China

Dr Mario Maranhao, Curitiba, Brazil

Dr Jean-Claude Mbanya, Faculty of Medicine, Yaoundé, Cameroon

Dr Churchill Onen, Gaborone Hospital, Gaborone, Botswana

Dr Philip Poole-Wilson, National Heart and Lung Institute, London, England

Dr Neil Poulter, Imperial College, London, England

Dr Pekka Puska, National Public Health Institute, Helsinki, Finland

Dr Yacoob Seedat, Nelson R Mandela School of Medicine, Durban, South Africa

Dr Cesari R Sirtori, University of Milan, Milan, Italy

Dr Krisela Steyn, Medical Research Council, Capetown, South Africa

Dr Suh Il, Department of Preventive Medicine, Seoul, Republic of Korea

Dr Diego Vanuzzo, Centre for Cardiovascular Diseases, Udine, Italy

Dr A Wielgosz, Ottawa Hospital, Ontario, Canada

Dr Alberto Zanchetti, Centre for Clinical Physiology and Hypertension, Milan, Italy

World Health Organization

Dr Alberto Barcelo, WHO Regional Office for the Americas, Washington, DC, USA

Dr Rufaro Chatora, WHO Regional Office for Africa, Brazzaville, Congo

Dr Jill Farrington, WHO Regional Office for Europe, Copenhagen, Denmark

Dr Antonio Filipe Jr, WHO Regional Office for Africa, Brazzaville, Congo

Dr Gauden Galea, WHO Regional Office for the Western Pacific, Manila, Philippines

Dr Alexandre Kalache, WHO Headquarters, Geneva, Switzerland

Dr Oussama Khatib, WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt

Dr Jerzey Leowski, WHO Regional Office for South-East Asia, New Delhi, India

Dr Aushra Shatchkute, WHO Regional Office for Europe, Copenhagen, Denmark

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