

## Coronary Heart Disease: Reducing The Risk A Worldwide View

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Worldwide, cardiovascular diseases are now the most common cause of death and a substantial source of chronic disability and health costs. In the light of new data from clinical trials and a fuller understanding of risk factors, the International Task Force for the Prevention of Coronary Heart Disease, in cooperation with the International Atherosclerosis Society, prepared a revised and comprehensive statement regarding the scientific basis of the primary and secondary prevention of cardiovascular disease. The following is a short account of the clinical implications of this statement. It is best read in conjunction with the full document, which can be found at <http://www.chd-taskforce.com>

### Assessing the Global Risk of Cardiovascular Disease

Assessing a patient's overall or global risk of cardiovascular disease is the first step in preventive care, for it enables the physician to identify and provide the appropriate level of treatment for risk factors. Much can be learned from measuring even a few risk factors. The fuller the knowledge of the patient's risk status, the sounder the treatment decisions. Initial costs may be offset by long-term rational treatment. The goals of treatment and, hence, the extent of dietary change and the need for (and choice and dosage of) drug treatment all depend on global risk assessment. Two methods for determining global risk follow.

#### Method I

Note and tabulate the following risk factors, including those laboratory investigations that are available.

#### *Age, Sex, and Menopausal Status*

Risk increases progressively with adult age, and coronary heart disease (CHD) is most common after the age of 60 years. In premenopausal women, CHD is rare (except in those who use oral contraceptives and smoke). After menopause,

risk increases steeply, approaching that of men after the age of 70 years.

#### *History of Cardiovascular Disease*

The risk of further CHD events or stroke is much higher in persons with a history of myocardial infarction, angina, stroke, or intermittent claudication and in those who have ischemic changes on resting or exercise ECG than in persons without such findings. Any of these features confers grade III status (high risk; Table 1) and warrants vigorous reduction of all risk factors.

#### *Positive Family History of CHD, Stroke, or Peripheral Vascular Disease*

Note any reliable cardiovascular family history, and grade its severity on the basis of the following.

- How early in life relatives were affected (discount events presenting after the age of 60 years)
- The closeness of the relationships (eg, CHD in a sibling or parent confers greater risk than CHD in an uncle)
- What proportion of adult relatives were affected

#### *Smoking*

Note the duration and amount of current and former use of cigarettes and other tobacco products; these are potent but potentially reversible causes of CHD.

#### *Psychosocial Risk Factors*

There is increasing evidence that stress, lack of social support, depression, and low socioeconomic status are associated with an increased risk of CHD. Although specific treatment for these factors is often difficult, assessing them is still an important part of the work-up. The psychosocial profile of the patient also has a large influence on the patient's ability to comply with measures such as lifestyle modifications designed to reduce risk.

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(*Circulation*. 1999;100:1930-1938.)

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*Circulation* is available at <http://www.circulationaha.org>

TABLE 1. Clinical Risk Assessment

Grade I*	Grade II†	Grade III‡
Presence of 1 risk factor of moderate degree in a middle-aged man, eg, plasma cholesterol 200–250 mg/dL (5.2–6.5 mmol/L), BP 170/100, or smokes 10 cigarettes per day	Presence of 1 risk factor of severe degree in a middle-aged man, eg, smokes 20 cigarettes per day, plasma cholesterol >250 mg/dL (>6.5 mmol/L), diabetes, or family history in a close relative  <b>OR</b> Presence of 2 risk factors of moderate degree in a middle aged man, eg, plasma cholesterol 200–250 mg/dL (5.2–6.5 mmol/L) and HDL cholesterol <35 mg/dL (<0.9 mmol/L) or obesity	History of myocardial infarction, angina, stroke, or peripheral vascular disease, ECG evidence of CHD, or evidence of coronary or carotid plaques  <b>OR</b> Presence of 2 risk factors of severe degree, eg, plasma cholesterol >250 mg/dL (>6.5 mmol/L) and smokes 20 cigarettes a day, diabetes, or severe family history  <b>OR</b> Presence of 3 risk factors of moderate degree  <b>OR</b> Familial hypercholesterolemia or remnant hyperlipidemia

BP indicates blood pressure.

\*≈3 CHD events per 1000 per year in middle-aged men; 3<sup>rd</sup> quintile of PROCAM algorithm.

†≈7 CHD events per 1000 per year in middle-aged men; 4<sup>th</sup> quintile of PROCAM algorithm.

‡≈23 CHD events per 1000 per year in middle-aged men; 5<sup>th</sup> quintile of PROCAM algorithm.

In PROCAM (1978–1996), more than 30 000 individuals at work in Germany were assessed for >30 anthropometric and laboratory parameters. Based on PROCAM, a formula for calculating CHD risk in middle-aged men was derived that takes into account age, systolic blood pressure, LDL cholesterol, HDL cholesterol, triglyceride, smoking behavior, presence of diabetes mellitus, positive family history of myocardial infarction, and presence of angina pectoris. It is available as an interactive program at <http://www.chd-taskforce.com>.

## Examination

### Weight and Height

Derive the body mass index (BMI) by nomogram or calculation (BMI=weight in kg/height in m<sup>2</sup>). Overweight is defined as a BMI>25 and obesity as a BMI>30. Excess adipose tissue in the truncal region is an important cardiovascular disease risk factor, and it adversely affects blood pressure, cholesterol (total, HDL, and LDL), and triglyceride levels and glucose tolerance. Truncal obesity can be assessed and treatment can be monitored by estimating the weight/hip ratio (circumference of waist at umbilicus/circumference of hips at widest part; it is normally <1.0 in men and <0.85 in women) or by measuring girth horizontally at the level of the umbilicus (normally <94 cm in men and <80 cm in women).

Truncal obesity syndrome is often accompanied by some or all of the following features: high plasma triglycerides, low HDL cholesterol, type 2 diabetes, hypertension, and an increased risk of CHD. A key mechanism is insulin resistance. Reducing overweight is often highly effective against all features of the syndrome.

### Blood Pressure

Blood pressure is continuously related to the risks of stroke and CHD over a wide range, although a systolic pressure of ≥160 mm Hg and/or a diastolic pressure ≥90 mm Hg is used to define hypertension. Isolated systolic hypertension (>160 mm Hg) is an important risk factor in the elderly. Blood pressure is best measured with the subject seated, after he or she has rested for 5 minutes.

### Cardiovascular Examination

The cardiovascular examination may reveal a carotid bruit or a missing peripheral pulse, denoting existing atherosclerotic disease and conferring grade III risk.

## Investigations

### Plasma Lipids and Lipoproteins

The preferred investigation for plasma lipids and lipoproteins is one that measures total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol after a 14-hour fast (water permitted). If the full profile is unavailable, plasma cholesterol alone is useful in defining risk and diagnosing some major familial hyperlipidemias.

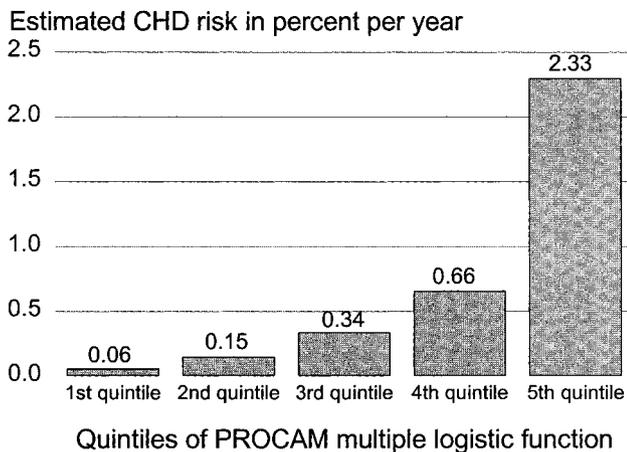
Lipid levels are continuously related to risk. Take particular note of an LDL cholesterol level >135 mg/dL (>3.5 mmol/L), a HDL cholesterol level <35 mg/dL (<0.9 mmol/L), and a triglyceride level of 150 to 400 mg/dL (1.7 to 4.5 mmol/L). Lipids can be assessed in a blood sample taken within 24 hours of the onset of myocardial infarction; thereafter, LDL cholesterol levels often fall and only return to their previous level after ≈3 months. Lipid measurements can also be reduced for 3 months after a severe illness and for 2 weeks after a minor illness. Levels of lipoprotein(s) exceeding 30 mg/dL confer increased risk.

### Blood Glucose

Type 1 and type 2 diabetes confer a markedly increased risk of CHD; even impaired glucose tolerance is often accompanied by lipid risk factors and elevated blood pressure.

Diabetes should be suspected in persons with diabetic symptoms and random plasma glucose levels >200 mg/dL (>11.1 mmol/L). Diabetes is now defined as a plasma glucose level >126 mg/dL (>7 mmol/L) after fasting for 8 hours and/or a plasma glucose level >200 mg/dL (>11.1 mmol/L) at 2 hours during an oral glucose tolerance test using 75 g glucose.

Other CHD risk factors that are now measured in many laboratories include fibrinogen and homocysteine.



Estimated risk of a coronary event among men aged 40 to 65 years in the Münster Heart Study, expressed as quintiles of the PROCAM multiple logistic function. Reproduced with permission from *Nutr Metab Cardiovasc Dis.* 1998;8:205–271 (also available at <http://www.chd-taskforce.com>).

On the basis of the presence, number, and severity of some or all of these 11 groups of risk factors, increased risk is assigned to 1 of 3 grades: I, II, or III, as seen in Table 1. Appropriate treatment decisions are based on this grading.

In asymptomatic patients at increased risk, the precision of risk assessment may be enhanced by imaging methods. Noninvasively, quantitative carotid Doppler ultrasound can be used. Increased intermedial thickness is predictive of a 2-fold increase in CHD risk, and detection of carotid plaques indicates a 4-fold increase.

## Method II

### Quantitative Risk Assessment

On the basis of 9 risk factors, data from the Prospective Cardiovascular Münster (PROCAM) Study are used to provide a quantitative estimate of risk (Figure) using an algorithm that is currently applicable to men aged 40 to 65 years (Appendix 1). This is available as an interactive program on the Task Force website (<http://www.chd-taskforce.com>).

### Primary and Secondary Prevention

Evidence of a myocardial infarction, stroke, or other atherosclerotic disease confers a high risk of further cardiovascular events and has a risk level of grade III. Patients in this category require vigorous intervention against risk factors, and clear evidence exists showing the benefits of such intervention. Reducing risk in such patients is termed secondary prevention, whereas risk reduction in persons without such evidence is termed primary prevention. Evidence of CHD is a special case within the high-risk group (ie, among persons with grade III risk). Primary prevention in persons with grade III risk requires equally vigorous intervention against risk factors, and equally cogent evidence exists showing its benefits. Because 30% of patients with a first manifestation of CHD (such as myocardial infarction) survive for <3 months and because such first events may lead to prolonged or permanent disability, the potential benefits of primary prevention exceed those of secondary prevention.

## Management of CHD Risk Factors

### Smoking

Simple counseling is the first approach in the management of smoking cessation, and it is often effective. Ask how concerned the smoker is with his or her habit and how much he or she wants to stop. Reinforce the patient's desire (verbally and by providing written materials) to stop smoking by spelling out the following benefits of smoking cessation.

- How rapidly her or his well being will improve after quitting (eg, food tastes better, effort tolerance improves, and morning cough subsides)
- The risks of continuing to smoke, including the high risk of CHD (including sudden death, stroke, and peripheral vascular disease), the several smoking-related cancers, and disabling chronic lung disease
- The progressive decline of the above risks in ex-smokers
- The financial savings

Clearly and firmly counsel the patient to stop smoking with a positive, encouraging, and sympathetic attitude. Second or further attempts are often more successful than the first. Try to help arrange for support by others (eg, the patient's spouse). Help the smoker identify trigger factors for smoking (eg, drinking alcohol or coffee, using the telephone, or driving a car); awareness of the trigger lessens its impact. If possible, the trigger should be avoided.

If the attempt to stop smoking fails, the next attempt may be more successful if preceded by a period of "minimum smoking:" when subjects feel the urge to smoke, they ask themselves whether they really need to do so at that moment. Often, they realize that smoking can be postponed. Another approach for the unsuccessful quitter is referral to a smoking cessation class run by a skilled counselor or psychologist.

Nicotine dependence can be dealt with by coupling the above approach with nicotine replacement in patients without CHD. Use nicotine skin patches or nasal spray and progressively decrease the dosage.

### Treating Overweight and Obesity

The physician's attitude is important when treating patients with weight problems. Encouragement, patience, and enthusiasm are needed. Encourage the patient to combine an exercise program (see below) with changes in diet. Emphasize that some elements of lifestyle change will need to be life-long, and spell out the benefits of weight reduction. The immediate and expected future benefits of weight reduction include the following:

Immediate:

Improved ability to exercise

Improved:

appearance and self-esteem

Expected:

Longer life span

Lower LDL cholesterol and triglyceride levels and higher HDL cholesterol levels

Lower blood pressure

Lesser risk of diabetes, certain cancers, accidents, and chronic lung disease.

TABLE 2. Choice of Foods in the Cholesterol-Lowering Diet

	Recommended Foods	Foods for Use in Moderation	Foods to Be Avoided
Cereals	Whole-grain bread; whole-grain breakfast cereals with emphasis on low-sugar, low-salt brands; porridge; muesli; pasta; rice; crispbread (crackers); matzo		Croissant; brioche
Dairy products	Skim milk; very low-fat cheeses, (eg, cottage cheese, fat-free fromage frais, or quark); low-fat yogurt; egg whites and egg substitutes	Low-fat milk; fat-reduced and lower fat cheeses (eg, brie, camembert, edam, gouda, feta, ricotta); low-fat yogurt; 2 whole eggs per week	Whole milk; condensed milk and cream-imitation milk; full-fat cheeses; full-fat yogurt
Soups	Consommés; vegetable soups		Thickened or cream soups
Fish	All white and oily fish (grilled, poached, smoked); avoid skin (eg, on sardines or whitebait)	Fish fried in suitable oils	Roe; fish fried in unknown or unsuitable oils or fats
Shellfish	Oysters; scallops	Mussels; lobster; scampi	Prawns; shrimp; calamari
Meat	Turkey, chicken, veal, game, rabbit, spring lamb (remove skin from poultry)	Very lean beef, ham, bacon, or pork; veal, chicken, turkey sausage; liver up to twice a month	Duck; goose; all visibly fatty meats; usual sausages; salamis; meat pies; pâtés; poultry skin
Fats		Monounsaturated oils, (eg, olive oil, canola [rapeseed] oil); polyunsaturated oils, (eg, sunflower, corn, walnut, safflower); soft (unhydrogenated) margarines rich in monounsaturated or polyunsaturated oils; low-fat spreads	Butter; suet; lard; dripping; palm oil; hard margarines; hydrogenated fats
Fruit and vegetables	All fresh and frozen vegetables, emphasis on legumes: beans, dried beans, lentils, chick peas, sweet corn; boiled or jacket (baked) potatoes; all fresh, canned, or frozen fruit (unsweetened)	Roasted or chipped (French fries) potatoes cooked in permitted oils	Roasted or chipped (French fries) potatoes; vegetables or rice fried in unknown or unsuitable oils or fats; potato crisps (chips); salted, canned vegetables
Desserts	Sorbet; jellies; puddings based on skim milk; fruit salad; meringue		Ice cream, puddings, dumplings; sauces based on cream or butter
Baked foods		Pastry and biscuits (cookies) prepared with unsaturated margarine or oils	Commercially produced pastry and biscuits (cookies), pies, snacks, and puddings
Confectionery		Marzipan; Halva Turkish delight; nougat; boiled sweets (hard candy)	Chocolate; toffees; fudge; coconut bars; butterscotch
Nuts	Walnuts; almonds; hazelnuts; chestnuts; peanuts	Brazils; pistachios	Cashews, coconut, salted nuts
Beverages	Tea; filtered or instant coffee*; water, calorie-free soft drinks	Alcohol; low-fat chocolate drinks	Chocolate drinks; Irish coffee; full-fat malted drinks; boiled "Turkish" coffee*
Dressings, flavoring	Pepper; mustard; herbs; spices	Low-fat salad dressings	Added salt; salad dressings; salad cream (ie, Miracle Whip); mayonnaise

\*Coffee grounds contain a substance that may increase blood cholesterol; hence, filtered or instant coffee is preferable in patients with hyperlipidemia. Reproduced with permission for *Nutr Metab Cardiovasc Dis*. 1998;8:205–271 (also available at <http://www.chd-taskforce.com>).

The reducing diet consists of a maintained or increased intake of low energy-density foods (which help control appetite), such as green vegetables, salad vegetables, and clear soups and a decreased intake of high energy-density and nonsatiating foods, including alcohol, all fats and oils, and sugar-containing foods. An example of such a diet is given in Appendix 2 and Table 2.

### Physical Exercise

A suitable exercise program is recommended for all sedentary persons; a clear and detailed prescription is needed for effectiveness, safety, and personal enjoyment.

Examples of suitable aerobic activities include walking (an excellent exercise), jogging, cycling, and calisthenics, such as aerobic classes and rowing; individual preference is important for long-term compliance. Before more strenuous exercise, a warm-up period of 5 minutes of stretching and other gentle activity is advised, as is a final cool-down period of progressively decreasing vigor.

Exercise dosage is determined by its duration, intensity, and frequency. For persons who have been sedentary in recent months, those with known cardiovascular disease or with grade III risk, and those aged >40 years, initial training should be gentle (eg, 10 minutes of walking daily). As fitness and tolerance increase, the dose increases in

**TABLE 3. Target Pulse Rate During Aerobic Exercise for Persons not at High Cardiovascular Risk\***

Age Range, y	Maximum Rate for Age	60% of Maximum Rate, bpm	75% of Maximum Rate, bpm
21–30	190	115	145
31–40	188	110	140
41–50	175	105	130
51–60	170	100	125
61–70	160	95	115

\*Rates listed are inappropriate for patients taking  $\beta$ -blockers and other cardioactive drugs.

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weekly increments, initially by extending the duration. Later, intensity can be increased if suitable, eg, by brisk walking or by alternating walking and jogging or gentle swimming. Young persons and fit middle-aged subjects may ultimately undertake 20 to 30 minutes of aerobic activity 4 to 5 times weekly.

Exercise intensity can be judged subjectively; persons should aim for a comfortable intensity, sufficient to extend themselves slightly. Mild shortness of breath during exercise should abate within 4 minutes or less of resting. The subject should be told to stop and to report to a physician if recovery time is prolonged or if chest pain, syncope, or persistent cough occur. Another way to judge intensity requires monitoring pulse rate during exercise; target pulse rates are shown in Table 3. A training effect is obtained at rates of 60% of the maximum rate for age, and this is the initial target rate. With increasing fitness, in persons at low cardiovascular risk, the target may be increased gradually to 75% of maximum, for example, by increasing the speed of walking.

Exercise should be supervised, at least initially, and ECG monitoring should be performed in patients at higher risk; this includes those with overt cardiovascular disease, such as angina or silent ischemia, and especially those with high-grade ventricular arrhythmias, low ejection fractions, hypotension on exercise, and inappropriate exercise-induced tachycardia. The type and amount of exercise must also take into account respiratory or musculoskeletal disease and peripheral vascular disease.

### Treatment of Hyperlipidemia

Clinical trial evidence justifies placing a strong emphasis on plasma lipid-lowering as part of primary and secondary prevention. Accompanying risk factors are treated at the same time. Past concerns about the safety of lowering plasma cholesterol are no longer tenable. The intensity of lipid-lowering treatment is determined by the patient's global risk and by his or her responsiveness to treatment.

The value of conservative treatment, ie, diet (including the extremely important element of reduction of overweight) and exercise, cannot be too strongly emphasized; under controlled conditions, diet even without weight reduction can lower plasma cholesterol by 10% to 25%. Hence, efforts should be made to maximize skills in dietary counseling. The patient

**TABLE 4. Suggested Target Levels for LDL Cholesterol Lowering\***

Global Risk†	Reduce LDL Cholesterol to:	
	mg/dL	mmol/L
Grade I (somewhat increased risk)	<160	<4.1
Grade II (moderately increased risk)	<135	<3.5
Grade III (high risk, including secondary prevention)	<100	<2.6

\*Until further information becomes available, a suggested target for triglyceride lowering is 150 mg/dL (1.7 mmol/L).

†See Table 1.

Adapted from *Nutr Metab Cardiovasc Dis*. 1998;8:205–271 (also available at <http://www.chd-taskforce.com>).

should know that current dietary guidelines fully maintain the pleasures of eating and are similar to the habitual diets of countries in which mortality from CHD and many cancers is far lower than in Western countries.

Lipid-lowering drugs should be introduced only after a careful trial of conservative management, if indicated by the grade of risk, and always used together with ongoing dietary measures.

### Target Levels for Lipid Lowering

Table 4 shows suggested goals for lipid-lowering based on the grade of global risk. Pending the results of further trials to determine optimal goals, Table 4 is consistent with epidemiological studies and with meta-analyses of trials. Treatment is best monitored by LDL cholesterol levels.

History and physical examination may reveal the features of major familial hyperlipidemias. Most are uncommon, but they require detection because they may confer a particularly high risk of CHD or pancreatitis. These disorders are tabulated in Appendix 3.

A determined effort should be made to reduce or correct even minor degrees of overweight using the means described in the section on weight reduction together with those in the section on exercise. These measures have a strong favorable effect on most common plasma lipid disorders.

Causes of secondary hyperlipidemia should be treated or removed, if possible. Among these causes are medications, including corticosteroids, anabolic steroids, thiazides, and retinoids; diabetes mellitus; hypothyroidism; alcohol abuse; chronic renal failure; nephrotic syndrome; and bulimia and anorexia nervosa.

### Lipid-Lowering Diet

A lipid-lowering diet is shown in Appendix 2; it is designed for persons whose habitual diet is Western and requires adaptation. In the lipid-lowering diet, fat provides up to 30% of food energy; saturated plus hydrogenated fat contributes no more than 7% to 10% of energy intake, monounsaturated fat 10% to 15%, and polyunsaturated fat up to 7% to 8%. The diet has a high content of complex carbohydrates, and it provides at least 25 g of fiber per day, with an emphasis on soluble fiber. It contains less than 300 mg of cholesterol per day. This is achieved with a generous intake of whole-grain cereal foods, fruit and vegetables, fat-free and low-fat dairy

products, fish, low-fat poultry, moderate amounts of low-fat meats and of eggs, and unsaturated vegetable oils as the main source of fats. Preferred cooking methods include grilling, steaming, boiling, microwave cooking, and barbecue cooking.

Some patients whose response to this diet is incomplete will achieve satisfactory control when a diet is given that provides 25% to 27% of energy from fat (6% to 8% of which is from saturated fat) and 200 to 250 mg of cholesterol per day.

For patients with hypertriglyceridemia, the standard lipid-lowering diet is prescribed, with particular emphasis on controlling overweight and specific advice on moderating or avoiding alcohol consumption and increasing the intake of oily fish. Patients with severe hypertriglyceridemia caused by excess chylomicron particles need a minimal intake of long-chain fatty acids but can substitute medium-chain triglycerides.

### **Lipid-Lowering Drugs**

In patients at grade I risk, conservative treatment is usually effective in achieving target lipid levels. In those at grade III risk, a short (eg, 2 month) trial of diet is warranted, during which at least 2 sets of lipid measurements should be made and averaged; if target values are not attained, a drug should be introduced, with ongoing attention to diet. In those at grade II risk, an extended trial of conservative treatment is required, with repeated counseling, for a period of at least 6 months. Whenever possible, the use and choice of drug should be based on clinical trial data. A discussion of commonly used lipid-lowering drugs follows.

*Hepatic hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors* offer a major advance in CHD prevention. They effectively lower LDL cholesterol, and they have a moderate effect in lowering triglycerides, which may be more marked with some newer statins. HMG CoA reductase inhibitors are now the drugs of first choice for familial hypercholesterolemia, and they can be of value in combined (mixed) hyperlipidemia. Treatment commences at a minimum dosage, with dose titration at 6- to 8-week intervals. Lipid levels and alanine transaminase (ALT) levels should be monitored. Severe hypercholesterolemia may require combination treatment with a resin. Most statins are not licensed for use in children, and they are not given to women of child-bearing age unless effective contraception is assured. Headache, constipation, flatulence, and dyspepsia are recognized side effects. Liver function can be impaired, and statins are contraindicated in the presence of active liver disease or elevated ALT levels. Myopathy and potentially fatal rhabdomyolysis are rare side effects, the risk of which is increased by drug interactions with erythromycin, fibrates, azole antifungals, cyclosporin, tacrolimus, nicotinic acid, and some calcium-channel blockers.

*Resins (bile acid sequestrants)* are effective cholesterol-lowering drugs. Being nonabsorbable, they are largely free from systemic side effects. They are presented as a powder and taken in water or fruit juice with meals. Patient acceptance is sometimes imperfect. Side effects include constipation, dyspepsia, abdominal pain, and malabsorption of folic

acid and several concomitantly administered drugs. In a larger dose, resins can increase triglyceride levels.

*Fibric acid derivatives* are effective triglyceride-lowering drugs; they increase HDL cholesterol substantially and (particularly the more recent members of the class) also lower plasma cholesterol. Abnormal liver function is a contraindication. Side effects include dyspepsia, rashes, abnormal liver function and (rarely) hepatitis (ALT should be monitored), gallstones, impotence, myopathy and rhabdomyolysis, and sensitivity to warfarin. Great caution is needed in using fibrates together with statins.

*Nicotinic acid* in large doses lowers triglyceride and cholesterol levels and increases HDL cholesterol. Flushing, pruritus, and dyspepsia are common and tend to limit compliance; abnormal liver function may occur. A gradually increasing dose schedule is needed. Liver disease, gout, and diabetes are relative contraindications.

*Fish oil* in large doses effectively lowers triglyceride levels.

### **Management of Hypertension**

The prevalence of hypertension is about 20% in most countries, rising with age to about 50% by the age of 65 years. In the US in 1988, the proportion of hypertensives who were detected, treated, and achieved good control was 29%; similarly limited success has been observed in Europe.<sup>1</sup>

The usual goal of treatment is to achieve a systolic blood pressure <140 mm Hg and a diastolic blood pressure <90 mm Hg. Particular care is directed to patients at highest risk, including the elderly, those with target organ damage (heart, brain, kidneys, and retina), diabetics, hyperlipidemics, smokers, patients with left ventricular hypertrophy, and those with impaired renal function.

### **Nonpharmacological Treatment**

The following measures are appropriate in all hypertensives.

- Reduction of overweight; even a loss of 4 to 5 kg lowers blood pressure in many hypertensives
- Reduction of alcohol intake, if excessive (ie, >30 mL/d), lowers blood pressure in susceptible hypertensives
- Increase in aerobic physical activity
- Reduction of salt intake to 4 g (70 mmol) per day
- Increase intake of fruit and vegetables (which provides a substantial intake of potassium) and lower intake of fat and saturated fat; these items are of proven value in lowering blood pressure
- Deal with coexisting cardiovascular risk factors (eg, smoking and hyperlipidemia)

### **Drug Treatment**

Drug treatment commences with low doses followed by slow dose titration to achieve 24-hour control with once-daily medication at a minimum dosage. If systolic pressure >160 mm Hg and target organ damage are present, initiate drug treatment immediately; if diastolic pressure >90 mm Hg and target organ damage are present, start drug treatment within 1 to 2 weeks if a trial of nonpharmacological measures is not promptly effective. Conversely, if hypertension is mild

and no target organ damage exists, a trial of nonpharmacological management for up to 6 months is warranted. Available clinical trial data suggest that thiazides and  $\beta$ -blockers are the preferred initial drugs for uncomplicated hypertensives. Nonpharmacological measures are continued after the start of drug treatment.

### Initial Drugs

Low-dose thiazides or  $\beta$ -blockers should be the first drugs used for pharmacological management of hypertension, unless contraindicated. Angiotensin-converting enzyme (ACE) inhibitors should be prescribed for patients with CHD and reduced ejection fraction, those with decreased left ventricular function due to other causes, diabetics with microalbuminuria or frank proteinuria, and those with impaired renal function and heavy proteinuria. For hypertensives who have had an uncomplicated myocardial infarction, prescribe  $\beta$ -blockers without intrinsic sympathomimetic activity. For isolated systolic hypertension, prescribe a low dose of thiazide,  $\beta$ -blocker,  $\alpha$ -blocker, or long-acting calcium-channel blocker.

### Subsequent Management

If the blood pressure target is not achieved or if side effects occur, first try substituting a drug from another class. If unsuccessful, add a second drug from another class (eg, a diuretic), if not already used, and, if problems still persist, add a third drug from another class or consider referral to a specialist.

The following is a list of the most commonly used drugs.

- **Thiazides.** The use of thiazides is supported by controlled trial evidence. Low dosage (eg, hydrochlorothiazide 6.25 mg/d up to 12.5 mg/d) lessens the risk of metabolic side effects such as potassium depletion, hyperlipidemia, hyperuricemia, and worsening of glucose tolerance.
- **$\beta$ -blockers.** Use of  $\beta$ -blockers without intrinsic sympathomimetic activity is supported by clinical trial data. Side effects include severe asthma in predisposed patients, worsening of intermittent claudication, aching of the legs, cardiac failure, and an increased grade of heart block (possibly less frequent with cardioselective and vasodilator  $\beta$ -blockers).
- **ACE inhibitors.** The indications for the use of these drugs are listed above. Side effects include a cough. ACE inhibitors should be avoided in patients with bilateral renal artery stenosis (which should be suspected in patients with peripheral vascular disease or abdominal aortic aneurysm), because renal failure may be precipitated.
- **Calcium-channel blockers.** Long-acting formulations of these drugs should be chosen because short-acting ones have precipitated ischemic events. Evidence of reduced cardiovascular events was found in 1 trial using calcium-channel blockers for systolic hypertension in the elderly. These drugs do not have metabolic side effects, but other untoward effects include headache and dependent edema.
- **$\alpha$ -blockers.** These drugs are useful in older patients with systolic hypertension; they have a small favorable effect on plasma lipids and lipoproteins, do not worsen glucose tolerance, and lessen symptoms of benign prostatic hyper-

**TABLE 5. Suggested Target Lipid Levels in Diabetic Patients**

Treatment Goals	Macrovascular Disease	
	No Evidence of	Evidence of
LDL cholesterol, mg/dL (mmol/L)	<130 (<3.4)	<100 (<2.6)
Triglycerides, mg/dL (mmol/L)	<150 (<1.7)	<150 (<1.7)

Adapted from *Nutr Metab Cardiovasc Dis.* 1998;8:205–271 (also available at <http://www.chd-taskforce.com>).

trophy. They are generally well tolerated, but the first dose may lower blood pressure excessively.

- **Angiotensin II receptor ( $AT_1$ ) antagonists.** These drugs were introduced recently. They do not have adverse metabolic effects, do not cause cough or angioedema, and are generally well tolerated. They can worsen renal function in patients with bilateral renal artery stenosis.

### Cardiovascular Risk Reduction in Diabetes

In a trial of patients with type 1 diabetes (ie, insulin-dependent diabetes), careful insulin therapy reduced microvascular complications, with a 60% (nonsignificant) reduction of macrovascular events. Although trial data in patients with type 2 diabetes are scanty, the consensus is that careful glycemic control is essential for minimizing diabetic complications (hemoglobin  $A_{1c}$  <7.0%). General recommendations are correcting overweight to improve control, particularly in type 2 diabetics; lowering blood pressure; and controlling lipid abnormalities (Table 5). Frequent aerobic exercise facilitates glycemic control and weight control, as does a diet similar to the lipid-lowering diet, but with no sugar other than that in fruit and saturated fat (<7%). Stopping smoking is mandatory.

Drug treatment may be commenced at the same time as the above measures in patients with severe metabolic abnormalities, CHD, or diabetic complications; in patients with mild diabetes, it may be deferred pending the outcome of a 2- to 4-month trial of diet and exercise. Drug options include insulin, metformin, sulfonylureas, acarbose, and the new thiazolidinediones.

Hypertriglyceridemia and low HDL cholesterol may be fully corrected by diabetic control and the measures listed above. However, lipid-lowering drugs should be considered if hyperlipidemia persists; the main options are a statin if LDL elevation predominates or a fibrate if triglycerides remain elevated (the risk of fibrate myopathy is increased in the presence of renal failure or diabetic nephropathy).

### Management of Thrombogenic Risk Factors

To manage thrombogenic risk factors, health-related behavior is important. Such behavior includes the following.

- Cessation of smoking
- Reduction of overweight
- Low intake of saturated fat
- Increased intake of polyunsaturated fatty acids from the omega-6 and omega-3 classes (from seed oils and oily fish)

Drug therapy can also be used. The 3 main drugs used and their doses are as follows. Acetylsalicylic acid (75 to 160 mg

per day), preferably enteric-coated, is often used; the risk of gastrointestinal bleeding is least with lower dosages. Ticlopidine (250 mg per day) is an alternative; it does carry a risk of neutropenia, so monitoring white cell count is important. Clopidogrel (75 mg per day) may be more effective than acetylsalicylic acid, and warfarin dosage should be adjusted to maintain an International Normalized Ratio (INR) in the range of 2.0 to 3.5.

### CHD Prevention in the Elderly

After the age of 60 years, risk factors such as plasma cholesterol, systolic blood pressure, smoking, and low HDL cholesterol confer an increased absolute risk of CHD to at least the same extent as in younger persons. Clinical trial data on risk factor reduction in older persons are few, but some evidence exists that cholesterol lowering by diet or by statin therapy lowers risk.

Risk factor reduction is appropriate in older persons in good general health who have reasonable life expectancy and the capacity to enjoy life. Diets must take eating difficulties, food preferences, and nutritional soundness into account. Drug interactions are of particular concern, and untoward effects can be sources of difficulty.

### CHD Prevention in Postmenopausal Women

Most CHD risk factors operate in both sexes. In women, plasma cholesterol, low HDL cholesterol, and blood pressure are related to risk; diabetes, triglyceride levels, and cigarette smoking confer greater risks than in men. Limited data from clinical trials in women suggest that cholesterol lowering lowers CHD incidence and promotes regression of coronary artery disease.

Estrogen replacement therapy lowers LDL cholesterol and increases HDL cholesterol, effects that are attenuated by those progestogens that have androgenic activity. Progestogens such as medroxyprogesterone have only small effects in reducing the favorable influence of estrogens. Many observational studies suggest that postmenopausal estrogen replacement may reduce CHD incidence,<sup>2</sup> but such data are inconclusive and controlled trial evidence is needed to clarify benefits and untoward effects.

### Appendix 1

The multiple logistic function from PROCAM has the form:

$$I = 1/[1 + \exp(-y)]$$

where  $y = -12.3199 + (\text{age in years} \times 0.1001) + (\text{systolic blood pressure in mm Hg} \times 0.0118) + (\text{LDL cholesterol in mg/dL} \times 0.0152) +$

$(\text{HDL cholesterol in mg/dL} \times -0.045) + (\log_e [\text{triglyceride level in mg/dL}] \times 0.3346) + (\text{smoking behavior [no=0, yes=1]} \times 0.9266) + (\text{diabetes mellitus [no=0, yes=1]} \times 0.4015) + (\text{positive family history of myocardial infarction [no=0, yes=1]} \times 0.4193) + (\text{angina pectoris [no=0, yes=1]} \times 1.319).$

This algorithm was derived from a population of white men aged 35 to 65 years and, therefore, its applicability to women, men outside this age range, and other ethnic groups has yet to be established. The output of the PROCAM algorithm is expressed as the risk of a coronary event (definite fatal myocardial infarction, definite nonfatal myocardial infarction, or sudden coronary death) in percentage over 8 years. In the German population of middle-aged men, the output of the algorithm may be divided into quintiles with the following cut-off points: first quintile,  $\leq 0.91\%$  in 8 years ( $\leq 0.11\%$  per annum); second quintile, 0.92% to 1.40% in 8 years (0.12% to 0.18% per annum); third quintile, 1.41% to 3.65% in 8 years (0.18% to 0.46% per annum); fourth quintile, 3.66% to 7.60% in 8 years (0.46% to 0.95% per annum); and fifth quintile,  $> 7.60\%$  in 8 years ( $> 0.95\%$  per annum).

## Appendix 2

### Recommended Foods

The following foods may be given as generous helpings in meals (preferably as a first course) or as snacks. Table 2 has a more complete list.

Low-calorie vegetables (fresh or frozen, not canned); use cooked, in salad, and as crudité. These include: artichokes, asparagus, cabbage, cauliflower, carrot, celery, chicory, cress, cucumber, eggplant, endive, French (green) beans, green pepper, leek, lettuce, marrow, mushroom, onion (boiled), pumpkin (boiled), radish, spinach, tomato, and turnip.

Soup: broth, consommé, and other clear soups.

Beverages: coffee or tea with skim milk, sugar-free soft drinks, and mineral water; use aspartame and saccharine as sweeteners.

### Foods Permitted in Controlled Quantities

The following foods are permitted in controlled quantities.

Fruit: 4 pieces per day.

Vegetables: 1 small boiled or baked potato.

Cereal foods: 5 U per day. 1 U = 1 thin slice of wholemeal bread cut from a large loaf, 1 cup of sugar-free breakfast cereal, 1/2-cup pasta, or 1/2-cup rice.

Fish, chicken, turkey, very lean meat: 120 to 180 g per day.

Dairy foods: 2 U per day. 1 U = 1 cup skim milk, 1/2-cup low-fat milk, 1 cup very-low-fat yogurt without added sugar, 30 g of skim milk-based cottage cheese, or 30 g of fat-free fromage frais; 2 eggs per week are allowed.

Legumes (pulses): 1/2-cup serving, 3 to 4 times per week. These include boiled lentils, mung beans, chick peas, butter beans, kidney beans, and pinto beans.

Oils and fats: 10 g (2 to 3 teaspoons) per day. These include olive oil, canola oil, corn oil, and sunflower oil, plus 10 g per day of very-low-fat (20%) margarine.

1 cup = 200 mL = 7 fluid ounces; 30 g = 1 ounce

### Appendix 3

#### Classification of the Primary Hyperlipidemias

Disorder	Lipid Abnormality*		Lipoprotein Class	Clinical Manifestations	Risk Conferred	Prevalence†
	Cholesterol	Triglyceride				
Common (polygenic) hypercholesterolemia	+		LDL		CHD	Depends on definition, but very common
Familial hypercholesterolemia	+++		LDL	Tendon xanthomas	CHD +++	1/500
Familial defective apoB	+++		LDL	Tendon xanthomas	CHD +++	1/1000
Familial combined hyperlipidemia	++	++	LDL and/or VLDL		CHD ++	≈1/100
Remnant hyperlipidemia	+++	+++	IDL (remnant particles)	Skin xanthomas (elbows, palms, hepatosplenomegaly)	CHD/PVD +++	≈1/1000
Familial hypertriglyceridemia	+	+++	VLDL (± chylomicrons)	Skin xanthomas (back, elbows, palms, hepatosplenomegaly, retinal lipemia)	Pancreatitis	≈1/1000
Chylomicronemia syndrome	+	+++	Chylomicrons	Skin xanthomas (back, elbows, palms, hepatosplenomegaly, retinal lipemia)	Pancreatitis	≈1/10 000
Low HDL syndromes			HDL	Depends on cause. Tangier disease, a rare familial form of HDL deficiency, is associated with enlarged, orange-colored tonsils, hepatosplenomegaly, neuropathy, and lymphadenopathy.	CHD risk may be ↑ in some forms of HDL deficiency.	Very rare in Caucasians; may be higher in other ethnic groups.
HDL hyperlipidemia	+		HDL	None	CHD risk may be low	Not uncommon in women but seen also in older men

CHD indicates coronary heart disease; HDL, high density lipoprotein; IDL, intermediate density lipoprotein; PVD, peripheral vascular disease; VLDL, very low density lipoprotein; +, slight to moderate increase; ++, moderate to marked increase; and +++, marked to extreme increase.

\*Depending on which lipoprotein class is present in excess, the primary hyperlipidemias may manifest as predominantly elevated levels of cholesterol or of triglyceride, or both lipids may be involved (see below).

Lipoprotein Class Affected	Manifests As
Hypercholesterolemia	LDL (occasionally HDL)
Hypertriglyceridemia	VLDL, uncommonly chylomicrons
Mixed (combined) hyperlipidemia	LDL + VLDL, uncommonly IDL

†The prevalence of genetic hyperlipidemias varies from population due to genetic drift, founder effects, and selection bias. The data shown in Appendix 2 apply to most Caucasian populations.

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