Action limits for serum total cholesterol

A statement for the medical profession by an *ad hoc* committee of the Heart Foundation of Southern Africa


Summary

Hypercholesterolaemia is common in many segments of the South African population, both by virtue of high mean population serum total cholesterol (TC) values and of a high prevalence of familial hypercholesterolaemia (FH). Age-specific action limits for TC are proposed in order to remove the variation in ‘normal values’ used by different laboratories. The action limits are derived from epidemiological studies rather than purely statistical norms. They are used to designate individuals as falling into high, moderate and ideal TC ranges. The high-risk action limit has also proved to be useful for screening for FH. After an initial screening TC estimation, the further management of a patient will depend on the TC risk category and the presence or absence of other risk factors. Risk factors such as hypertension, a smoking habit, a low high-density lipoprotein cholesterol value, diabetes, evidence of existing coronary heart disease (CHD) or a family history of premature CHD multiply the risk conferred by elevated TC, and change the moderate-risk status of an individual with moderately elevated TC to a high-risk status. Intensity of investigation, treatment and follow-up depend on the overall risk status of an individual patient. Drug therapy is reserved for high-risk patients who have not responded to a reasonable trial of non-drug measures. Other reversible risk factors are treated in their own right.

The guidelines embodied in this report are intended to facilitate and justify the clinical approach to individual patients with hypercholesterolaemia. They do not replace the need for a population strategy to reduce risk factors in the general population. The number of patients requiring individual management will decrease to the extent that the population strategy succeeds.

Background

This statement is based on the deliberations of the ‘Consensus Conference on Hypercholesterolaemia and Coronary Heart Disease in South Africa’, held by the Heart Foundation of Southern Africa at Kirstenbosch, Cape Town, on 18 - 19 May 1987. The conference, attended by 48 scientific participants and 18 observers, was chaired by Professor W. Gevers (University of Cape Town) and moderated by Professor H. Blackburn (University of Minnesota). The epidemiological, clinical, experimental and pathophysiological data linking serum total cholesterol (TC) values and other lipids and lipoproteins with coronary heart disease (CHD) were reviewed, TC values in South African populations were reported and the identification of TC values which require action to be taken were considered. The larger question as to what should be done about hypercholesterolaemia in South Africa was also addressed. An *ad hoc* committee was appointed to draw up specific guidelines for TC action limits and the management of hypercholesterolaemia, making use of data and viewpoints generated at the conference.

Rationale

The committee resolved that TC action limits should be based on epidemiological considerations rather than the purely statistical approach often used to define the reference (normal) range of a biological variable. The statistical method expresses normality by arbitrarily choosing some measure of the distribution of values around the mean of a ‘healthy’ population. Conventionally, values falling beyond ±2 standard deviations from the mean or, alternatively, below the 5th or above the 95th percentile, are regarded as ‘abnormal’. This approach is inappropriate to use for TC, not only because TC values vary enormously from population to population, but because the value of TC which confers a higher-than-optimal (basal) risk may start well below the upper limit of the statistical normal range, especially in a population with high TC values and a high incidence of CHD. All westernised South African populations fall into this category.

The epidemiological method, on the other hand, attempts to define optimal values of TC associated with good health. To do this it takes into account two kinds of evidence: TC values in populations with a low CHD incidence, and TC values in the lowest risk segment of high-CHD populations. Usually the latter is taken to be the lowest quintile or the lowest two...
The association between CHD risk and TC value has been most convincingly demonstrated in the Multiple Risk Factor Intervention Trial (MRFIT) cohort of 361 662 men aged 35 - 57 years, followed up for 6 years. The relationship of baseline TC value with subsequent CHD mortality was curvilinear, the slope being shallow over the first two quintiles and progressively steeper thereafter. The ceiling of the lowest quintile of TC corresponded to 4.7 mmol/l and that of the second quintile to 5.2 mmol/l. If a baseline risk ratio of 1 is assigned to 5.2 mmol/l, then a TC value of 6.5 mmol/l would have double baseline risk, and at 7.7 mmol/l it would double again. The MRFIT observations extend and refine the similar TC-CHD relationship observed in other prospective studies.

Almost all the prospective CHD studies have been performed in middle-aged (typically 40 - 59-year-old male) populations. Because of the strong relationship of TC with age, action limits derived from a middle-aged population may not be appropriate for younger individuals. For example, a TC value of 5.2 mmol/l would fall on the 20th percentile for a 45-year-old white South African man and confer borderline risk, while the same value would represent the 90th percentile in a 17-year-old and would carry with it a very high eventual risk, since the percentile position of TC in a given individual remains fairly constant with age. Such a value may even be an expression of familial hypercholesterolaemia (FH). Age-specific action limits can be derived by extrapolating the percentile value of TC conferring risk in the middle-aged down to younger age groups. Such age-specific action limits, apart from being appropriate for all ages, have a particular advantage for South Africa in that they improve the accuracy of screening for FH since TC values in FH heterozygotes appear to vary with age in the same way as in the general population (H. C. Seftel - unpublished observation). Age-specific action limits make intuitive sense, since a given value of TC carries less relative risk for an older than a younger patient, and most medical practitioners would prefer not to subject an older patient to vigorous drug therapy (with concomitant side-effects more likely in the elderly) when the potential benefit to the individual is less clear.

Based on these considerations, the committee agreed that South African TC action limits should be age-specific. This approach is in line with that taken by the 1984 National Institutes of Health (NIH) Consensus Development Conference and the American Heart Association. The committee was not persuaded by these considerations since the populations which do not show a relationship between TC and age may have a marginal nutritional status. Also, they are vastly different from Western populations in many other respects which may impinge upon CHD risk. The feasibility of a westernised population changing its lifestyle sufficiently to duplicate this TC pattern is questionable. Intermediate populations, such as urbanised blacks and Japanese, do not have a high risk of CHD even though they already show some increase of TC with age. One cut-point for all adults does not address the issue of appropriate cut-points for children and young adults, and is not very useful for the diagnosis of genetic hyperlipoproteinaemias. This is particularly relevant to South Africa, where between 1 in 50 and 1 and 100 of Afrikaners have heterozygous FH.

The committee focussed on TC since it is a useful and relatively inexpensive screening measure, and most of the available epidemiological data pertain to TC. However, it is recognised that determination of low-density lipoprotein cholesterol (LDLC) may improve CHD prediction. It may be appropriate to determine LDLC, particularly in individuals who are classified as high risk on TC or in whom lipoprotein phenotyping is indicated (particularly for the genetic hyperlipoproteinaemias). LDLC follows the same trend with age as TC, since it usually constitutes about two-thirds of the TC value. By analogy with the argument for age-specific TC cut-points, LDLC cut-points should similarly be age-specific.

High-density lipoprotein cholesterol (HDLC) is thought to have an independent and inverse influence on CHD risk. HDLC values do not change markedly with age, and therefore a single cut-point for HDLC is reasonable. The independent risk factor status of triglycerides (Tgs) is less certain, although it does seem that elevated plasma concentrations of Tgs are associated with increased risk in certain individuals (especially in the presence of low HDLC values). Because of the uncertainty surrounding the clinical significance of an isolated mild-to-moderate increase in Tg values and their marked biological variability, the committee does not recommend age-specific cut-points for Tgs and does not regard their inclusion in initial screening as essential. It is, however, useful to measure Tgs in obese, gouty or diabetic patients, in those with a history or a family history of ischaemic heart disease, in those with substantial alcohol consumption, and especially in those with lipaemic plasma. Elevated Tg values often respond to vigorous non-pharmacological measures and influence the choice of lipid-lowering medication. In addition, knowledge of the Tg concentration is required for the calculation of LDLC values and for lipoprotein phenotyping, where these are indicated.

It is further recognised that the presence of additional risk factors such as a low HDLC concentration, hypertension, smoking, diabetes, a family history of premature CHD or evidence of CHD in the patient considerably amplifies the risk attached to an elevated TC value. A TC value indicating moderate risk in the absence of any other risk factors may denote high risk in the presence of one or more additional risk factors. Additionally, risk factors tend to cluster in individuals. For these reasons, a TC measurement should always be accompanied by screening for other risk factors, particularly if the TC value is found to be elevated. It is especially important not to overlook the effects of multiple marginal abnormalities which may profoundly influence risk. The interaction of risk factors is more than simply additive. For example, a 45-year-old man with a TC value of 6.5 mmol/l may be regarded as being at moderate risk, with a 3.6% probability of developing CHD over the next 6 years, but in a smoker with a low HDLC concentrations of 0.9 mmol/l and a systolic blood pressure of 150 mmHg the risk rises to 28% (Fig. 1). This is considerably higher than the 6.4% risk attached to a TC value of 8.1 mmol/l with no other risk factors.

For any given value of TC, the absolute risk for men is much greater than for women, particularly before the menopause. This is mainly related to the higher HDLC found in women. To obtain comparable absolute risk estimates, it would therefore be necessary to adjust risk estimates for HDLC values. Owing to a lack of standardisation of HDLC measurements, this is not practicable at present. In any event, the relative risk attached to TC values within sexes is not affected by the male-female HDLC differences, and the age-specific TC action limits can therefore be applied to both sexes.

Recommendations

**Total cholesterol**

**Reference population**

Having elected to use age-specific action limits for TC values, it was necessary to select a reference population on
The choice of action limits must of necessity involve some arbitrary decisions and value judgements. Factors to be considered include the risk of developing CHD at a given value of TC; the importance the medical profession and the patient attaches to a particular risk; the potential for reversal of risk; how many individuals fall within a given risk category; the prevalence of additional risk factors; and the data available on the distribution of TC values in the population and in individuals with specific genetic or acquired disorders.

The committee agreed that action limits indicating high and moderate risks be specified, since the vigour with which management is pursued, and the potential benefit of treatment, are strongly influenced by the value of TC.

**High-risk action limit.** Approximately half of the excess (i.e. above basal) CHD deaths attributable to TC in American and British populations occur in individuals who fall into the upper 20% (i.e. above the 80th percentile) of the TC distribution. These individuals are at high relative risk compared with those in the lowest 20% (below the 20th percentile) of the TC distribution. For instance, at age 45 - 49 years the risk may be four times higher in the uppermost quintile than in the lowest quintile. A similar gradient of relative risk for prevalent CHD across the quintiles of TC distribution pertains in the CORIS population (J. E. Rossouw — unpublished observations). The 80th CORIS percentile has also been found to be a sensitive (although not specific) discriminator of FH in South African whites, with virtually all cases falling above this level (H. C. Seftel — unpublished observations; K. Steyn — unpublished observations).

On the basis of these considerations, the committee decided that the 80th CORIS percentile would be a suitable action limit for the identification of individuals at high risk of CHD and of FH. Such individuals need vigorous management including, in all likelihood, drug therapy. The benefits of therapy are likely to be highest in these patients. The 80th percentile of TC in a 45-year-old is 7.1 mmol/l (275 mg/dl). This value approximates the 95th percentile of the MRFIT study.

It should be noted that the 80th percentile of the MRFIT study (6.3 mmol/l or 244 mg/dl) corresponds to the CORIS 50th percentile. Thus, if the American 80th percentile were to be used to identify South African high-risk patients, half the westernised population would have to be considered for possible drug therapy. Since this would place an intolerable burden on the health services, the use of a local 80th percentile to identify those subjects at the highest risk relative to the population is preferred.

**Moderate-risk action limit.** The committee accepted a TC action limit of 5.2 mmol/l (200 mg/dl) for the designation of moderate risk in middle-aged adults. It appears that the CHD risk starts rising appreciably once this TC value is exceeded. This moderate-risk action limit is derived from the MRFIT data and from low-CHD populations, and is in typical of a high-risk westernised population, and are higher than current North American levels.

A smoothed graph of selected TC percentiles versus age was constructed (Fig. 2). For the sake of simplicity, age-specific male and female values were combined. The basic CORIS data were expanded by including data on 1 - 4-year-olds from the CORIS study area (P. L. Jooste — unpublished observations), and data on 11-year-old urban and rural whites obtained from a random representative sample from the western Cape (L. J. Rossouw — unpublished observations). All the cholesterol estimations from the western Cape on which the action limits are based were performed by the same laboratory (National Research Institute for Nutritional Diseases of the South African Medical Research Council). Where age gaps in the data exist (mainly for 5 - 10-year-olds), the shape of the graph has been checked against results from North American studies.

![Fig. 1. Probability of a 45-year-old man developing CHD over 6 years at various levels of TC and certain other risk factors. Note the semilogarithmic scale. Calculated from multiple logistic functions in the Framingham Study.](image)

![Fig. 2. Graph of age-specific action limits for TC, derived from the CORIS 20th and 80th percentiles for both sexes combined.](image)
line with recommendations at present being made by European and American groups. However, the committee does not accept that a single cut-point should be applied to all ages, and in this respect it diverges from some of the above groups. The TC value of 5.2 mmol/l corresponds with the 20th percentile of the CORIS distribution (and to the 40th percentile of the MRFIT distribution). Extension of the 20th percentile line across the age groups provides the age-specific action limits for moderate risk. In a high-CVD population, the 60% of individuals falling between the 20th and 80th TC percentiles provide approximately half of the excess CVD events attributable to TC. These individuals do not normally require vigorous therapy for TC (unless additional risk factors are present) and can be managed by means of essentially the same healthy lifestyle and dietary advice applicable to the entire population. Generally, they will not require intensive investigation and drug therapy, thereby lessening the potential burden on the health care system.

The population distribution of TC values can be expected to shift to the left to the extent that the population health education programme succeeds. With this shift of mean population TC values, the proportion falling above the action limits for moderate and high risk respectively will decrease. The number of patients needing specific management of hypercholesterolaemia will thereby also decrease in time.

The graph of the 20th and 80th percentile of TC values by age (Fig. 2) has been used to divide the population cholesterol distribution into a 'desirable' category below the 20th percentile, a 'moderate-risk' category between the 20th and 80th percentile, and a 'high-risk' category above the 80th percentile. If a baseline risk of 1.0 is ascribed to the 20th percentile, individuals in the desirable range will have a risk of approximately 0.7, those in the moderate risk range about 2.0 and those in the high risk range 4.0 or greater. These risk ratios were derived from MRFIT data and assume that the relative risk of a particular value of TC is similar in North American and South African populations. It is intended that the risk zones of the graph be used to make decisions regarding a stepped-care approach to management of hypercholesterolaemia, taking due cognisance of the presence of other risk factors (see 'Use of action limits for TC' below and Table I).

From the graph, a tabulation of action limits by year of age has been derived (available on request), which can be utilised by pathologists who wish to report TC results in the form of a computer print-out.

### Low-density lipoprotein cholesterol

The Committee considered that in most circumstances nonfasting TC estimations are adequate for screening and monitoring purposes. However, with TC values falling into the high-risk category it becomes desirable to ascertain the lipoprotein profile on a fasting blood sample. This is also desirable in subjects in the moderate-risk category who have additional risk factors.

In particular, a lipoprotein profile (lipogram) allows for the calculation of LDLc according to the following formula: LDLc = TC - (HDL + Trig/5), all lipid values being expressed in mmol/l. Since LDLc is the most important lipid determinant of coronary artery disease (CAD) risk, it is rational to have this information available for patients at substantially increased risk owing to raised TC values, before embarking upon more vigorous therapy (e.g. step 2 diet or drugs). Occasionally it will be found that the LDLc value falls clearly into the normal range while HDLc values are high and account for the raised TC values. Such subjects are not at increased risk of CAD attributable to TC values and should be managed as if their TC values fell into the desirable range. The majority of patients with high TC values will have clearly elevated LDLc values. It is the committee's decision not to provide detailed age-specific action limits for LDLc, partly because of difficulty in the accurate determination of LDLc values owing to current uncertainties in Tg and HDLc assays, and partly because of the absence of published age-specific South African population LDLc values. As a guide, however, the values in Table II should be useful. The levels approximate the 50th and 95th percentile values of the Lipid Research Clinics (LRC) Program Prevalence Study. These percentiles were selected because the corresponding TC percentile values agree with the TC action limits proposed by the committee.

### Table I. Management decisions based on initial TC values

<table>
<thead>
<tr>
<th>TC category</th>
<th>Investigations</th>
<th>Treatment steps</th>
<th>Minimum goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desirable TC every 5 yrs</td>
<td>Healthy lifestyle</td>
<td>Maintain desirable TC</td>
<td></td>
</tr>
<tr>
<td>Moderate risk TC annually</td>
<td>Healthy lifestyle</td>
<td>Reduce towards desirable TC</td>
<td></td>
</tr>
<tr>
<td>Moderate risk Lipogram TC every 3 mo.</td>
<td>Healthy lifestyle</td>
<td>Step 1 diet Desired TC</td>
<td></td>
</tr>
<tr>
<td>plus additional risk Exclude 2 hyperlipidaemias</td>
<td>Healthy lifestyle</td>
<td>Step 2 diet Drugs</td>
<td></td>
</tr>
<tr>
<td>High risk Lipogram TC every 6 mo.</td>
<td>Healthy lifestyle</td>
<td>Moderate TC</td>
<td></td>
</tr>
<tr>
<td>factors</td>
<td>Healthy lifestyle</td>
<td>Step 1 diet Drugs</td>
<td></td>
</tr>
</tbody>
</table>

* Those steps are additive. A healthy lifestyle and a step 1 diet precede a step 2 diet, which in turn precedes drug therapy.

### Table II. Guide to LDLc action limits (mmol/l)

<table>
<thead>
<tr>
<th>Young adult (&lt; 30 yrs)</th>
<th>Moderate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.80 - 4.15</td>
<td>&gt; 4.15</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Middle-aged and older adults (&gt; 30 yrs)</th>
<th>Moderate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.40 - 5.20</td>
<td>&gt; 5.20</td>
<td></td>
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</table>

### High-density lipoprotein cholesterol

In prospective epidemiological studies within populations, relatively small differences in HDLc values influence CHD risk markedly and independently of other risk factors. It would thus be desirable to adjust the risk for HDLc level. In the Framingham study a HDLc value of 1.2 mmol/l in men and 1.4 mmol/l in women denote average levels of risk. Unfortunately, lack of a standard method can lead to widely divergent HDLc values being reported by different laboratories, even on the same sample. In the interim, and until standardisation is achieved, the committee recommends that a conservative HDLc value of 1.0 mmol/l be used to define an action limit below which risk increases. This value is close to the 0.9 mmol/l (35 mg/dl) recommended by the European Atherosclerosis Society and the NIH National Cholesterol...
Education Program Adult Treatment Panel. HDLc values greater than 1.7 mmol/l in men or 2.2 mmol/l in women are generally associated with a particularly favourable prognosis.

Triglycerides
The committee accepted the European Atherosclerosis Society recommendation that a Tg value above 2.3 mmol/l (200 mg/dl) be regarded as abnormal. This corresponds with approximately the 80th percentile for South African whites (Vermaak et al. — in preparation). More severe hypertriglyceridaemic syndromes are defined by values exceeding 5.6 mmol/l (500 mg/dl), while values above 11 mmol/l (1.000 mg/dl) carry a risk of pancreatitis and must be vigorously treated.

Standardisation
The use of a single set of action limits for lipids and lipoproteins will eliminate one important source of variation between laboratories. As indicated by Vermaak et al. (in preparation), the action limits or reference (normal) ranges used by South African laboratories vary by 50% for TC and Tg, and by 217% for HDLc. The establishment of universally applicable and recognised action limits will eliminate a source of current confusion and facilitate implementation of an effective strategy to combat hyperlipidaemia in the population.

Implementation of the TC action limits
Screening
The action limits for TC are primarily intended as an aid to the initial identification of individuals who, because they have TC values placing them at increased risk of CHD, need further investigation or treatment of hypercholesterolaemia. The graph of TC action limits should also aid the monitoring or response to treatment.

Who should be screened? Mass population screening programmes are not feasible in South Africa because of the cost involved and the immediate burden it would place on medical services. About 20% of the white, Asian and urban coloured populations have TC values which put them at high risk, and up to another 60% have levels which put them at moderate risk. These numbers will be progressively reduced as greater health awareness shifts the TC distribution to the left. Selective screening involving individuals who are likely to have elevated TC values or are at increased risk owing to the presence of additional risk factors is justified and probably feasible. This strategy would require a programme to inform and alert the public regarding criteria for selective screening.

Case-finding
Case-finding by the inclusion of a TC measurement in the conventional health assessment is perhaps the most feasible way of, in time, identifying a large proportion of hypercholesterolaemic individuals. First visits, executive health checks, insurance examinations, employment medical examinations and army induction all offer such opportunities. Ideally, a TC estimation should be done in all patients before the age of 50 years, (iv) diabetes mellitus, (v) hypertension; (vii) smoking habits; (viii) severe obesity; and (ix) gout.

Selective screening also requires the co-operation of fully informed and positively orientated primary care physicians and other clinical services. Since a large proportion of the population will qualify on one or more of the above criteria, the potential patient load presenting for screening is still very large.

Use of action limits for TC
The management of the patient after screening non-fasting TC measurement depends on the TC value, on whether the elevated TC value is primary or secondary, and on the presence of other risk factors. The TC measurement should therefore form part of a full clinical evaluation (Table III).

Primary (inherited) hypercholesterolaemia may be due to a major abnormality of a single gene (e.g. a defective LDL-receptor gene in FH) or may be polygenic in origin. Patients with single-gene disorders often have a family history of premature CHD or of hyperlipidaemia, and may have stigmata such as cutaneous or tendon xanthomas, xanthelasma or arcus cornea. In the polygenic disorders many genes interact with the environment (particularly with diet) to produce hypercholesterolaemia. Polymorphic disorders are the most common cause of hypercholesterolaemia. Environmental factors also affect the clinical expression of single-gene disorders.

Secondary hypercholesterolaemias are less common, but it is important to recognise the underlying disease since its treatment
The TC risk to be repeated except as part of evidence as value. If clinical suspicion of secondary hyperlipidaemia exists, and in all high risk adherence to the step I diet and the response to therapy need.

The recommendations regarding the management of the hypercholesterolaemia included in this report are intended as general presenting mean relative risk of CHD by value of TC. Owing to individual case. The graph (Fig. 2) is simply a guide representing the risk potential of a particular value of TC and therefore influence treatment decisions. While obesity and physical inactivity are not regarded as primary risk factors by many, they contribute to acknowledged risk factors such as hyperlipidaemia. low HDLC levels, glucose intolerance and hypertension. These risk factors should be vigorously treated in their own right. Hypertension can often be ameliorated by non-drug measures such as weight reduction, salt restriction, abstinence from alcohol and stress management, and these actions should always precede or accompany drug therapy. If medications are indicated in the more severe cases, those drugs which do not aggravate hyperlipidaemia are to be preferred. Low-dose diuretics (equivalent to 12.5 - 25 mg hydrochlorothiazide), \( \beta \)-blockers (and also alcohol) elevated Tgs. Beta-blockers, a-methyldopa, rauwolfia alkaloids, pindolol (among the \( \beta \)-blockers), vasodilators, calcium channel blockers and angiotensin-converting enzyme inhibitors can be considered.

<table>
<thead>
<tr>
<th>TABLE III. CLINICAL EVALUATION OF THE PATIENT WITH ELEVATED TC VALUES</th>
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<tbody>
<tr>
<td><strong>History</strong></td>
</tr>
<tr>
<td>Alcohol, drugs, smoking habit</td>
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<tr>
<td>Family history of premature CHD</td>
</tr>
<tr>
<td><strong>Examination</strong></td>
</tr>
<tr>
<td>Stigmata of hyperlipidaemia</td>
</tr>
<tr>
<td>Blood pressure</td>
</tr>
<tr>
<td>Peripheral pulses</td>
</tr>
<tr>
<td>Clinical evidence of hypothyroidism, liver disease, renal disease</td>
</tr>
<tr>
<td>Side-room</td>
</tr>
<tr>
<td>Urine protein</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
</tr>
<tr>
<td>Fasting blood glucose*</td>
</tr>
<tr>
<td>Liver function tests, renal function tests*</td>
</tr>
<tr>
<td>Thyroid function tests*</td>
</tr>
</tbody>
</table>

* In patients who are being considered for a step 2 diet or for drug therapy.
* If clinical suspicion of secondary hyperlipidaemia exists, and in all high risk patients.

CHD = coronary heart disease; MI = myocardial infarction; PVD = peripheral vascular disease.

will be important in the management of the hypercholesterolaemia. Obesity, diabetes, alcoholism, liver disease, renal disease and hypothyroidism must be looked for. Certain drugs, e.g. steroids, retinoids and diuretics elevate TC values, and others, e.g. \( \beta \)-blockers (and also alcohol) elevated Tgs. Beta-blockers also lower HDLC.

The presence of CHD, stroke or peripheral vascular disease, a family history of premature CHD, hypertension, smoking, diabetes and a low HDLC are all risk factors which aggravate the risk potential of a particular value of TC and therefore influence treatment decisions. While obesity and physical inactivity are not regarded as primary risk factors by many, they contribute to acknowledged risk factors such as hyperlipidaemia. low HDLC levels, glucose intolerance and hypertension. These risk factors should be vigorously treated in their own right. Hypertension can often be ameliorated by non-drug measures such as weight reduction, salt restriction, abstinence from alcohol and stress management, and these actions should always precede or accompany drug therapy. If medications are indicated in the more severe cases, those drugs which do not aggravate hyperlipidaemia are to be preferred. Low-dose diuretics (equivalent to 12.5 - 25 mg hydrochlorothiazide), \( \alpha \)-methyldopa, rauwolfia alkaloids, pindolol (among the \( \beta \)-blockers), vasodilators, calcium channel blockers and angiotensin-converting enzyme inhibitors can be considered.

The recommendations regarding the management of hypercholesterolaemia included in this report are intended as general guidelines only, and do not replace clinical judgement in the individual case. The graph (Fig. 2) is simply a guide representing mean relative risk of CHD by value of TC. Owing to individual and laboratory variations in TC estimations, and to individual factors influencing the impact of a given value of TC, it would be inappropriate to be overly dogmatic in assigning a patient to a risk category by virtue of a TC value which is marginally above or below an action limit. Certainly, intensive dietary (step 2) or drug therapy should not be started before the TC (and LDLc) status of an individual has been confirmed by repeat measurement and other factors which may influence therapy have been considered.

The management follows a stepwise approach, determined by the initial TC value. Investigations become progressively more extensive, and treatment more intensive, as the TC risk category changes from 'desirable' to 'high' (Table II). The investigation and treatment modalities of a lower-risk category are incorporated into those of the next higher category. So, for example, a trial of step 1 diet usually precedes a step 2 diet, and drug therapy is always preceded, and supported by, a step 2 diet. All patients receive advice concerning a healthy lifestyle, and for patients in the ideal TC category this will generally suffice. Patients with TC values in the moderate-risk category need more specific (step 1) dietary advice. Patients in this category who have additional risk factors, and patients who have TC values in the high-risk category, usually require a more stringent (step 2) diet, and frequently drug therapy as well.

**Desirable category**

When the TC value is in the desirable category the investigation does not generally need to be repeated except as part of the 5-yearly health examination. Other reversible risk factors, if present, should be treated, and the patient advised on a healthy lifestyle (Table I). Participation in regular moderate exercise, adequate rest and relaxation and balanced and moderate eating habits, combined with avoidance of cigarette smoking and excessive use of alcohol, are all components of a healthy lifestyle and should be recommended to every patient.

**Moderate-risk category**

A TC value falling in this category conveys a risk of CHD (and of overall mortality) approximately twice higher than baseline risk. If further risk factors are also present, the high-risk category is entered.

**In the absence of other known risk factors**, the patient should be advised on a healthy lifestyle (as above), but in addition the principle of a lipid-lowering diet should be carefully explained, preferably with the aid of a take-home pamphlet. The step 1 diet recommended for all moderate-risk patients involves reduction of the obvious sources of saturated fat and cholesterol (fatty red meat, full-cream dairy products, eggs and many convenience foods) in the diet, so as to reduce total fat intake to less than 30% of energy intake, saturated fat to less than 10%, and cholesterol intake to less than 300 mg/d. Total energy intake should be restricted in obese patients. A high-fibre intake is also recommended, together with a low-salt intake. The patient should be re-examined annually, the examination including a TC estimation. In the majority of cases falling into the moderate-risk category the TC value can be lowered towards the desirable range by means of dietary and other lifestyle measures. If, however, on repeat assessment the TC value remains significantly elevated, a fasting lipogram should be performed and, depending on the value of TC, vigorous therapy should be considered (see below).

**If other risk factors are present**, management needs to be more vigorous. The goal is to reduce the TC value into the desirable range and to control the additional risk factors. Adherence to the step 1 diet and the response to therapy should be assessed not later than at 3 months, at which time a fasting lipogram should be performed. The lipogram will allow a more accurate assessment of lipid risk status, as previously discussed. If a desirable TC value has been achieved, 6-monthly follow-up TC estimation will thereafter suffice. Non-achievement of the goal TC value will usually be owing to failure to comply with the diet. If compliance appears to be good, it may be necessary to implement a step 2 lipid-lowering diet (see below). The services of a dietician, where available, may be valuable. Drug therapy to lower the TC value may be indicated if it has not been adequately lowered after 6 months of appropriate therapy (see below). The TC value (or the lipogram, in mixed hyperlipidaemias) should be monitored every 3 months until goal values are achieved, after which 6-monthly estimations will suffice.
High-risk category

In this category the CHD risk conferred by the TC value is four or more times higher than baseline. This category will also contain a significant proportion, perhaps as high as 10%, of individuals with a single major gene defect resulting in familial hyperlipidaemia, as well as other patients with hyperlipidaemia secondary to some other disorder.

The patient with an initial TC value in the high-risk category should be recalled within 1 month for a fasting lipogram to make a definitive diagnosis. In a proportion of patients the TC value will have dropped into the moderate-risk category upon re-examination, or they will be found not to have high-risk LDLC values. If follows that their management is as for moderate-risk TC (see above).

However, if the lipogram confirms high-risk values of TC and LDLC, causes of secondary hypercholesterolaemia need to be excluded by the appropriate tests (Table III). If FH is suspected (e.g. in the presence of tendon xanthomas or a family history of premature CHD), the first-degree relatives need to be screened for hypercholesterolaemia.

Initial therapy of high-risk cases starts with a 3-month trial of a step 1 diet and other lifestyle measures, together with appropriate treatment of other risk factors.

However, the successful management of a confirmed high-risk patient usually requires more vigorous dietary restrictions (step 2 diet). The step 2 diet as initial therapy is justified in those with very high TC values at screening. This diet further restricts total fat to 25% of dietary energy, saturated fat to 7% and dietary cholesterol to less than 200 mg/d. Response should be assessed at 3 months, after which drug therapy should be instituted if the goal TC value is not achieved.

The minimum goal is to reduce the TC value into the moderate-risk range in patients without other risk factors, and into the desirable range in patients with other risk factors. Follow-up TC measurements (or lipograms) are performed every 3 months until the goal TC value is achieved, whereafter every 6 months will suffice.

In most cases the management of hyperlipidaemia does not require specialised skills. Far more important is knowledge of the basic principles of management as outlined in this report, together with a positive, encouraging and persistent approach to therapy. Refractory high-risk patients should be referred to a specialist physician or a lipid clinic. Certain other patients qualify for referral ab initio. These include: (i) all children with xanthomas of any description — these are almost always due to homozygous FH, type 1 hyperlipoproteinaemia (chylomicronaemia, Old age, unless extreme (above 75 years), is not a bar to the judicious use of lipid-lowering therapy, although the criteria for use must be more carefully assessed than in the younger adult.

Lipid-lowering drug therapy

With the relatively rare exceptions of patients with extremely high TC values, lipid-lowering medication should only be considered if vigorous and persistent (for at least 3 months) efforts at ameliorating the hyperlipidaemia by non-pharmacological means have failed to reduce the TC value to within the target range. This will be more common in the high-risk group. Occasionally, for clinical reasons, lipid-lowering drugs may not be prescribed even when target values have not been achieved on non-pharmacological treatment, e.g. if clinical or socio-economic factors make drug compliance impossible or risky. Old age, unless extreme (above 75 years), is not a bar to the judicious use of lipid-lowering therapy, although the criteria for use must be more carefully assessed than in the younger adult.

Some important principles must be borne in mind when prescribing lipid-lowering agents: (i) the response of individual patients to drugs varies — treatment should be individualised, with trials of different drugs and combinations until the optimum regimen is found; (ii) the full dose need not be prescribed initially and may not be necessary or appropriate in a significant proportion of patients; (iii) administration of lipid-lowering medication necessitates more frequent follow-up initially to monitor results and to detect side-effects; (iv) the use of combination drug therapy can be helpful owing to synergistic effects on lipid values and the possibility of avoiding side-effects by using lower doses; (v) it must be emphasised that non-pharmacological therapy is an essential adjunct to the use of lipid-lowering drugs; (vi) the choice of lipid-lowering drug depends on the nature of the lipid disorder and the likelihood of side-effects in a particular patient — considerable flexibility is possible in treating the hypercholesterolaemia syndromes; and (vii) secondary hyperlipidaemias require management of the underlying disorder as the first priority — lipid-lowering medication may be helpful, but the fibrates in particular must be used with extreme caution in the presence of renal or hepatic diseases.

Cholestyramine is still recommended by many authorities as the drug of first choice in hypercholesterolaemia despite its unpalatability and the fairly common gastrointestinal problems of nausea, indigestion, bloating and constipation reported. Compliance can generally be achieved by starting with low doses, e.g. half a scoop twice a day with meals, and then building up if necessary to a full dose of 2 – 3 scoops twice a day. The powder must be thoroughly mixed with water before ingestion and constipation can often be avoided by the use of dried fruit and wheat bran with the morning cereal. Occasionally a laxative used appropriately may enable the patient to continue with cholestyramine without problems. Antacids can ameliorate the dyspepsia, while metoclopramide can also counteract the gastro-intestinal side-effects.

Cholestyramine can interfere with the absorption of a number of drugs, and it is therefore safer for the patient to take any other drugs half an hour before the cholestyramine.

The concurrent administration of small amounts of fatsoluble vitamins as well as folic acid has been recommended as a useful precautionary measure in patients on long-term, full-dose cholestyramine treatment.

The fibrates are especially useful in the mixed hyperlipidaemias or in the pure hypertriglyceridaemias, but can also be effective in the patient with uncomplicated hypercholesterolaemia. At present clofibrate, fenofibrate and bezafibrate are available in South Africa, while gemfibrozil may be introduced soon. It would seem that the newer fibrates may have some therapeutic and safety advantages over the original clofibrate in hypercholesterolaemia. This class of medication lowers the glomerular filtration rate and is metabolised to a significant degree by the liver. Lower doses must therefore be used in patients with hepatic or renal dysfunction, and the package inserts should be consulted for this purpose. Other less common side-effects include impotence, alopecia, a myotonic-like syndrome and, rarely, gastro-intestinal symptoms and gallstones. Clinical and biochemical monitoring is therefore important in the early phases of fibrate administration and at regular (annual) intervals thereafter. These precautions should not preclude the use of an effective and generally safe class of medication.

Probucol is not commonly associated with side-effects, although diarrhoea, nausea, a skin rash and eosinophilia have been individually reported. HDLC values can fall significantly with probucol, and this may be especially marked when it is combined with a fibrate. The clinical significance of the reduction in HDLC values is still debatable, although there is evidence that probucol may prevent atherosclerosis in rabbits and cause regression of xanthomas in humans with hypercholesterolaemia despite the reduction in HDLC. Animal
studies have suggested that the anti-oxidant properties of probucol may prevent the development of atherosclerotic lesions independently of its cholesterol-lowering properties. Nevertheless, this medication should probably be reserved for patients with isolated hypercholesterolemia and is best confined to individuals with reasonably good basal HDLc values until more information is available on the significance of the HDLC reduction.

Nicotinic acid (2-6 g/d in divided doses) is effective in lowering both TC and TG values, but has unpleasant side-effects (flushing, heartburn, nausea, diarrhea). Blood glucose and liver functions need to be monitored in higher doses. Starting with a small dose taken with meals and taking half an aspirin with each dose may limit the flushing.

Drugs which inhibit cholesterol synthesis (hydroxymethyl CoA reductase inhibitors) show promise of being very effective in reducing LDLc, particularly in combination with cholestyramine. However, some questions about their long-term safety need to be resolved. They have not as yet been registered in South Africa, but trials are in progress.

When a combined combination therapy, cholestyramine and a fibrate or nicotinic acid should be considered for the mixed hyperlipidaemias as well as the pure hypercholesterolaemias. In the latter situation, both nicotinic acid and the fibrate may counteract the tendency of cholesterylamine to elevate TG values. Other combinations of the drugs may be used but do not share this effect. Although probucol and fibrates may be combined, a marked lowering of HDLC should be watched for. Probucol may to some extent counteract the constipation caused by cholestyramine.

Nicotinic acid, clofibrate and gemfibrozil have been shown to reduce CHD mortality in large-scale trials of high-risk patients. In the short term a concomitant reduction in total mortality has not been achieved but it has been observed after longer follow-up.

Conclusion

The evidence that lowering raised TC values in individuals and in populations will bring health benefits is now conclusive. Population values can be addressed by a continued health education campaign, focussing on dietary and other measures (physical activity, smoking prevention) which will lower CHD risk. However, the need for specific treatment of individuals at high risk requires them to be identified by TC measurement. Before those members of the public who may be at high risk can be encouraged to undergo TC screening, it is essential that the medical profession has a uniform approach to the measurement, interpretation and management of elevated TC values. It is hoped that the age-specific TC action-limit graph and guidelines encompassed in this statement will make a useful contribution to this process. It is intended that the graph and guidelines, together with a guide to dietary management, will be made available to all medical practitioners and clinics. The age-specific action limits will be made available to pathology laboratories, and it is hoped that a uniform reporting of TC values in terms of risk categories will result.

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