

Diagnosis, Management and Prevention of the Common Dyslipidaemias in South Africa-Clinical Guideline 2000

South African Medical Association and LASSA working group

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1 Summary

- The optimum management of dyslipidaemia requires a comprehensive, diagnostic work-up (Figure1). This, minimally, includes the:
 - characterisation of any hyperlipidaemic disorder present (Table 1).
 - identification of additional risk factors so as to assess overall (global) risk of future coronary heart disease (CHD). The global risk is best assessed by a calculation (Table 3) combining the risk factors in the individual. In severe monogenic dyslipidaemias and in patients with confirmed pre-existing CHD the risk is usually high; in most such cases the use of lipid-modifying drugs (LMDs) is indicated.
 - assessment of psychosocial, economic and educational factors relevant to management.
- Prevention and cost-effective management of even moderately dyslipidaemic patients requires appropriate modification of life-style: avoidance of tobacco smoking, participation in regular exercise and a health-promoting diet. Depending on individual circumstance, vigorous, personalised intervention and expert assistance from dietitians, biokineticists and other healthcare personnel may determine success.
- The correct choice of patient for drug treatment is a key therapeutic decision and is best done after full lifestyle modification. Recent evidence confirms that appropriately prescribed LMD therapy, can lower morbidity and mortality from CHD as well as all-cause mortality. Patients with the following features are candidates for LMD therapy:
 - have clinical CHD and a low density lipoprotein cholesterol (LDLC) level > 3.0 mmol/L despite optimum non-pharmacologic intervention, or
 - suffer from familial hypercholesterolaemia (FH) or equivalent severe, monogenic disorder, or
 - have a 10 year risk of an acute clinical coronary event of >20% – or > 30% risk if extrapolated to the age of 60 years – due to the presence of the hyperlipidaemia alone or in combination with contributory risk factors.
- The ideal target LDLC concentration is < or = 3 mmol/L but a reduction of at least 45% should be regarded as a minimum target in severe cases who do not reach this goal.
- Successful therapy requires on-going attention to compliance, therapeutic response and side-effects, and may necessitate adjustment or reinforcement. Concurrent or contributory conditions, such as smoking, hypertension and diabetes mellitus, must also be treated along with the clinically manifest CHD. Severely hyperlipidaemic, complicated or unresponsive high risk cases should be referred to an appropriate specialist or Lipid Clinic.
- Prevention of CHD in the community should be encouraged through public and professional education, the provision of community facilities for exercise and recreation and legislation directed at reducing the use of tobacco products and ensuring the appropriate labeling of food products.

Table 1: Classification of dyslipidaemia and its common causes

	Desirable lipid profile ¹	Hypercholesterolaemia		Mixed hyperlipidaemia	Hypertriglyceridaemia	
		Moderate	Severe		Moderate	Severe
TG	< or = 1.5	< 1.5	< 1.5	1.5 - 5.0	5 - 15	> 15
TC	< or = 5.0	5 - 7.5	> 7.5	> 5.0	< 5 - increased	> 5.0
LDLC	< or = 3.0	3.0 - 5.0	> 5.0	Variable	Variable	Variable
HDLC	> or = 1.2	Variable	Variable	Low	Low	Low
	Primary causes (2)	<ul style="list-style-type: none"> ● Atherogenic Lipoprotein Phenotype (3) ● Polygenic dyslipidaemia 	<ul style="list-style-type: none"> ● Familial hypercholesterolaemia (FH) ● Familial combined hyperlipidaemia (FCH) 	<ul style="list-style-type: none"> ● Atherogenic lipoprotein phenotype (ALP)(3) ● FCH ● Type III hyperlipidaemia 	<ul style="list-style-type: none"> ● Familial hypertriglyceridaemia ● FCH 	<ul style="list-style-type: none"> ● Type I hyperlipidaemia (3)

Secondary causes (2)	<ul style="list-style-type: none"> ● Hypothyroidism ● Nephrotic syndrome ● Pregnancy ● Obstructive jaundice 	<ul style="list-style-type: none"> ● Hypothyroidism ● Diabetes Mellitus ● Alcohol abuse 	<ul style="list-style-type: none"> ● Diabetes mellitus ● Alcohol abuse ● Retinoic acid derivatives ● Oestrogen treatment ● Pregnancy ● Cushing syndrome
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1. Concentrations are expressed in mmol/l.

2. In this context the definition of 'primary' includes those dyslipidaemias due to a major, identifiable single-gene mutation and those disorders in which genetic factors are important in causation. In the latter category secondary and lifestyle mechanisms are also significant. 'Secondary' dyslipidaemias include those in which an identifiable non-lipid disorder is mainly responsible for the abnormal plasma lipid profile.

3. The atherogenic lipoprotein phenotype (ALP): elevated TG and low HDLC levels in the presence of normal or slightly raised LDLC concentrations. The TC/HDLC ratio is >5. Other abnormalities include an increased number and abnormally small and dense LDL, but these need not be measured in clinical practice. Type III hyperlipidaemia may also be known as dysbetalipoproteinaemia and type I hyperlipidaemia is familial chylomicronaemia or lipoprotein lipase deficiency.

2 Abbreviations:

ALP atherogenic lipoprotein phenotype
AMI acute myocardial infarction
BAS bile acid sequestrants
BMI body mass index
BP blood pressure
CABG coronary artery bypass graft
CHD coronary heart disease
CQC Centre for Quality Care of the SA Medical Association
DM diabetes mellitus
EDTA ethylenediaminetetraacetic acid
FCH familial combined hyperlipidaemia
FDB familial defective binding apolipoprotein B
FH familial hypercholesterolaemia
HDLC high density lipoprotein cholesterol
LASSA Lipid & Atherosclerosis Society of Southern Africa
LDL low density lipoprotein
LDLC low density lipoprotein cholesterol
LMD(s) lipid-modifying drug(s)
MI myocardial infarction
SAMA South African Medical Association
SEMDSA Society for Endocrinology, Metabolism & Diabetes of Southern Africa
TC total cholesterol
TG total triglycerides
VLDL very low density lipoprotein

3 Introduction:

Dyslipidaemia is defined as a clinically significant alteration in the circulating lipids and lipoproteins predisposing to CHD and related disorders. In practice the most important and common is hypercholesterolaemia. The term hyperlipidaemia emphasises the importance of excess lipid in generating the adverse consequences of the common lipid (lipoprotein) disorders. The chief exception is a low HDLC concentration which is independently atherogenic whereas a high HDLC level (> 1.5 mmol/L) is generally protective.

Dyslipidaemia is common in Westernised, industrialised communities (1-3). In South Africa, CHD is most prevalent in the Indian and white groups, with a somewhat lower incidence in the coloured community (4). CHD in the black population is still relatively uncommon but risk-factors for the possible emergence of future CHD are already apparent including hypertension, diabetes, hyperlipidaemia, obesity and tobacco smoking (5). While the bulk of CHD occurs in persons without major gene defects of lipid metabolism, some genetic disorders such as FH, powerfully predispose to CHD and should be considered in all severe hyperlipidaemias. FH and other severe genetic defects have been well described in many South Africans communities, including blacks.

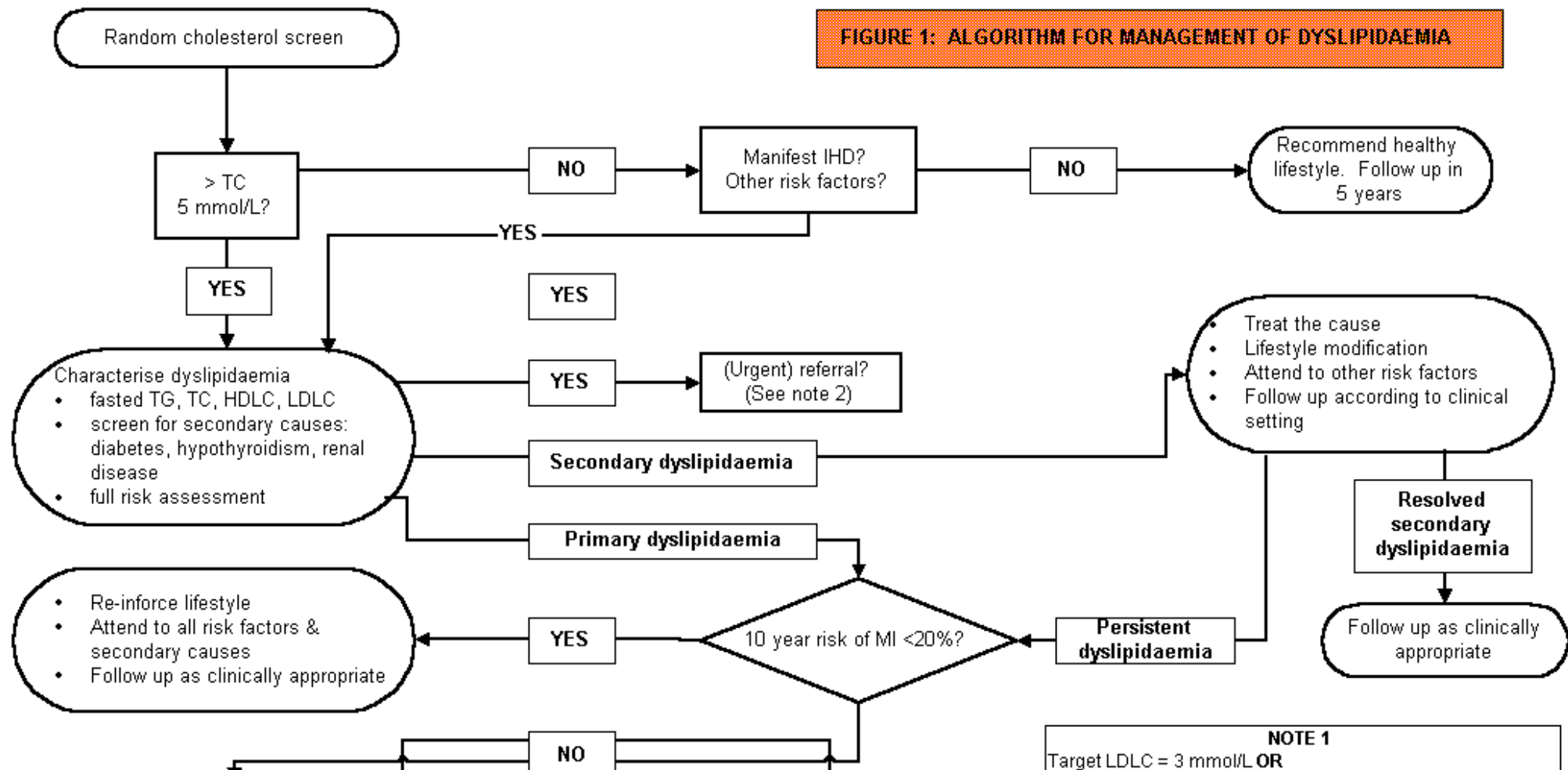
The chief objective of this guideline is to assist health care providers in the effective diagnosis and management of the more common dyslipidaemias. It reflects advances in the diagnostic approach and drug therapy of dyslipidaemias since the previous guidelines published in 1986 (6). A holistic approach to cardiovascular risk factors and prevention of CHD is adopted which goes beyond cholesterol reduction, though this remains an important, quantifiable component of therapy. There is evidence that hyperlipidaemia is both inappropriately and undertreated in

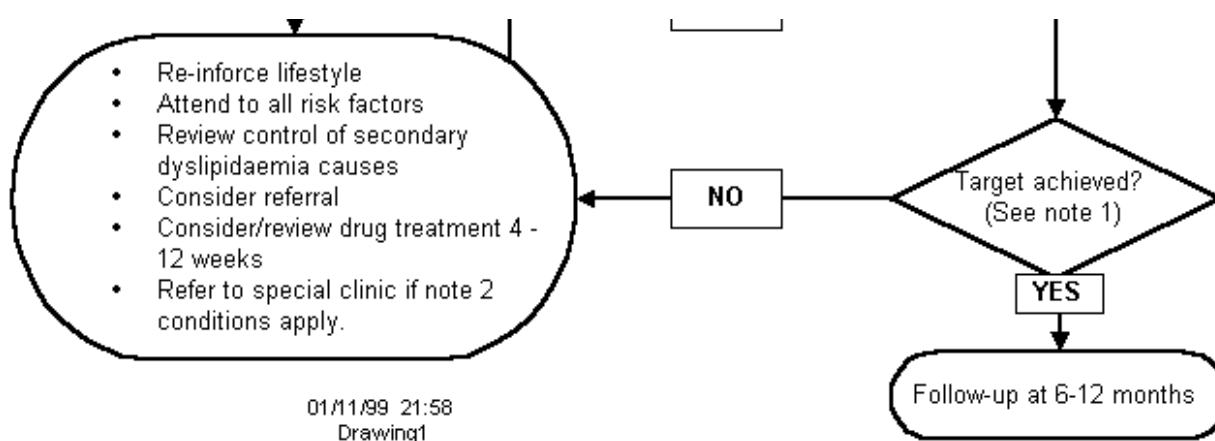
4 Approach to diagnosis:

The most common and clinically significant lipid abnormality is hypercholesterolaemia. Total plasma cholesterol concentration is minimally affected by recent food intake. Thus, in the absence of clinical risk factors or evidence of pre-existing CHD or atherosclerotic vascular disease elsewhere, determination of non-fasting cholesterol level will suffice to detect most clinically significant hyperlipidaemias in new patients. Screening for hypercholesterolaemia should be undertaken in any person considered to be at risk for CHD, and probably at least once in the life of each adult. A full serum or plasma lipoprotein profile should be done for the following indications: hypercholesterolaemia of > 5 mmol/L on screening, patients with existing clinical CHD and in the presence of physical signs of a lipid disorder. It is useful to view the plasma cholesterol concentration in three broad categories of risk (Table 2).

An approach to diagnosis and treatment is outlined in Figure 1, which emphasises the need to interpret cholesterol values in the context of other relevant clinical and laboratory data. A systematic assessment of overall risk in persons who have no clinical evidence of CHD is outlined in Table 3. This assessment should be performed on all patients under consideration for LMD. Some of the key decisions required of the practitioner are whether:

- drug treatment is indicated on the basis of global risk and which of the available LMDs would be most appropriate.
- the patient has a monogenic hyperlipidaemia, notably FH, which requires family investigation and genetic counseling in addition to vigorous, individualised management. Identification of FH is important as such patients are at high risk of CHD (> 60% of males present with overt CHD at <50 years of age) and require genetic counseling about the possibility of producing homozygous FH offspring. Referral is advised for initial family investigation and implementation of management.
- The hyperlipidaemia is secondary to current medication, or an underlying clinical disorder or physiological state requiring specific management (Table 1).
- The severity or complexity of the hyperlipidaemia is such as to require referral to an appropriate specialist.
- Additional risk factors are present which require targeted management on their own account: smoking, unhealthy diet, obesity, hypertension, and diabetes mellitus.





reduction of at least 45% if the primary target cannot be achieved in severe hypercholesterolaemia. Hypertriglyceridaemia or low HDLC may also require attention (see guideline text)

NOTE 2: EARLY/URGENT REFERRAL
Consider early referral if one or more of the following present:

- xanthomata before adulthood,
- lipaemic plasma especially if associated with abdominal pain
- CHD occurs before the age of 40 years.

Table 2: Broad Categories of CHD risk according to cholesterol concentration

CATEGORY DESCRIPTION

1: Cholesterol level < 5.0 mmol/L

- In an otherwise healthy individual the level of cholesterol value is considered to contribute insignificant risk.
- Other than general advice concerning a health-promoting life-style such patients do not require further specific diagnostic investigation or individualised attention, but follow-up in 5 years is recommended.
- If overt CHD or obvious additional risk factors are present, further evaluation is required.

2: Cholesterol level 5.0 - 7.5 mmol/L

- This range carries an elevated and increasing risk for which, in the absence of additional risk factors, generally introduction of LMD therapy is NOT merited.
- More vigorous non-pharmacologic intervention and more frequent follow-up is warranted, as is careful clinical and laboratory assessment for additional risk factors and for the possible cause of the hyperlipidaemia.
- A significant proportion of patients in this category have additional risk factors which elevate the overall likelihood of future CHD sufficiently to merit the use of appropriate LMDs - the high risk group.
- A smaller number will have an underlying clinical disorder predisposing toward hyperlipidaemia, the so-called "secondary hyperlipidaemias" (Table 1). Treatment of the underlying illness may mitigate the severity of the lipid abnormality.

3: Cholesterol level > 7.5 mmol/L

- Above this level the use of drug therapy should be considered in all patients in whom life-style modification does not achieve the desired lipid profile (Table 1).
- A variable proportion of patients will have conditions listed below all of which further increase the need for effective management:
 - FH or
 - overt CHD or
 - other additional clinical risk factors.
- As for category 2 some patients will be hyperlipidaemic secondary to an independent underlying clinical disorder. A full lipoprotein profile and general diagnostic work-up is required

Table 3: Calculation of absolute risk of MI over 10 years in individuals without ischaemic heart disease by combining several conventional risk factors
Adapted from Kannel and Wilson, (8)

To derive the absolute risk as percentage of subjects who will develop MI over 10 years, add the points for each risk category. For men consult section A and for women, section B. For the BP score, use the highest score of either diastolic or systolic pressure. The risk associated with the total points is derived from section C for men and for women. The average population risk from which the data were derived is given in section D over various age intervals. The following risk factors are not included: obesity, family history, definite diagnosis of FH (to be considered in cases where cholesterol concentration is >7.5 mmol/L), sedentary lifestyle. These factors add to risk and should be borne in mind when assessing global risk.

SECTION A: MEN									
Age	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74
Points	-1	0	1	2	3	4	5	6	7
TC	< 4.1		4.2-5.2		5.3-6.2		6.3-7.2		> 7.2
Points	-3		0		1		2		3
HDLC	< 0.91		0.91-1.16		1.17-1.29		1.3-1.55		> 1.55
Points	2		1		0		0		-2
BP	< 120/<80		120-129/80-84		130-139/85-89		140-159/90-99		> 160/>100
Points	0		0		1		2		3
Other	Non-smoker			Smoker		Not diabetic		Diabetic	
Points	0			2		0		2	

SECTION B: WOMEN									
Age	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74
Points	-9	-4	0	3	6	7	8	8	8
TC	< 4.1		4.2-5.2		5.3-6.2		6.3-7.2		> 7.2
Points	-2		0		1		1		3
HDLC	< 0.91		0.91-1.16		1.17-1.29		1.3-1.55		> 1.55
Points	5		1		1		0		-3
BP	< 120/<80		120-129/80-84		130-139/85-89		140-159/90-99		> 160/>100
Points	-3		0		0		2		3
Other	Non-smoker			Smoker		Not diabetic		Diabetic	
Points	0			2		0		4	

SECTION C: RISK (% of cohort defined by the score who will have MI in 10 years)																				
Points	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Men %			2	3	3	4	5	7	8	10	13	16	20	25	31	37	45	>53		
Women %	1	2	2	2	3	3	4	4	5	6	7	8	10	11	13	15	18	20	24	27

SECTION D.: RISK FOR POPULATION (% who have MI in 10 years)									
Age	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74
Men %	3	5	7	11	14	16	21	25	30
Women %	< 1	< 1	2	5	8	12	12	13	14

Note 1: % = risk per 100 individuals with a specified point score of developing AMI within 10 years. The score is gender dependent: a score of 7 for men and 13 for women both have a 13% risk. To extrapolate the risk to age 60 years in a younger person, simply add the difference in age points to the total score. E.g., women of 30-34 years have -9 age points whereas women of age 60-64 have +8 age-related points. The difference, 17 points, should be added to a 30-34 year-old female, patient's score when calculating her risk at age 60 years.

4.1 Risk factors for CHD

These are clinical or biochemical markers of increased risk for CHD. Many risk factors represent about a 2 to 3 fold increase in risk while major risk factors (established CHD, major genetic defect) have worse risk implications. The most important risk factors in common clinical practice are used in the risk calculation in Table 3. Some risk factors are modifiable while others are not modifiable. A combination of risk factors may enhance risk many fold.

Table 4: Categories of risk factors

Risk factor group	Risk factors
Biological	Risk increases with age and is highest in males and post-menopausal women
Clinical	<ul style="list-style-type: none"> ● Clinically manifest CHD or atherosclerotic vascular disease such as classical and other forms of angina pectoris, previous coronary artery surgery, MI or peripheral and carotid vascular disease. ● A family history of the above has to be assessed individually to determine its impact on the patient. ● Diabetes mellitus imparts a high risk of CHD in both sexes, especially in women. ● Hypertension increases with degree of BP elevations. ● Obesity also increases risk, notably truncal obesity. ● Cigarette smoking. Stopping smoking leads to a rapid decline in risk.
Behavioural	<ul style="list-style-type: none"> ● Atherogenic diet ● Lack of physical exercise
Genetic or familial	FH and other major gene defects are readily linked to a high familial risk, whereas in other families the cause of the increased incidence of CHD is not readily ascertainable. In some cases of familial predisposition to atherosclerosis, certain laboratory findings may be the relevant risk factor. <ul style="list-style-type: none"> ● hyperglycaemia (DM)
Biochemical	<ul style="list-style-type: none"> ● low HDL cholesterol ● high plasma concentrations of lipoprotein (a) ● hyperfibrinogenaemia, and other emerging risk factors (e.g. hyperhomocysteinaemia) may also contribute to the risk of CHD but the latter is seldom part of risk assessment in primary care.

4.2 Classification of dyslipidaemia (Table 1)

Although it is not a pre-requisite to management to make an accurate aetiological or phenotypic diagnosis, greater diagnostic precision does improve ability to determine risk, to tailor treatment including drugs, and to counsel the family. The lipoprotein phenotype is most conveniently classified in terms of hypercholesterolaemia, hypertriglyceridaemia or as a mixed picture in which cholesterol and triglyceride levels are more-or-less equally elevated. In addition, the ALP is a clinically significant dyslipidaemia in which triglyceride, cholesterol and HDL are all variably abnormal. Pure hypertriglyceridaemia is the least atherogenic, but not totally innocuous form of the different profiles, but severe hypertriglyceridaemia can result in acute pancreatitis and other clinically adverse outcomes. Causally, dyslipidaemia is defined as either primary or secondary, though in many disorders the aetiology is significantly mixed; an important consideration in treatment KH feels this is not clear enough. What does it mean?.

4.2.1 Primary dyslipidaemias

These were defined in Table 1. In the more common, clinically important monogenic disorders the inheritance is autosomal dominant. In FH and similar dyslipidaemias one may expect half the children in an affected family to present with hyperlipidaemia. In the rarer autosomal recessive disorders, such as familial lipoprotein lipase defect, only 25% of the children are generally affected and both parents carry the abnormal gene. Evidence for a familial cause is not always easy to elicit in this group. In those families in which the genetic basis may be multiple or in which lifestyle and secondary contributions to pathogenesis are significant – the so-called mixed or polygenic category – the family history does not manifest a Mendelian pattern, but is important in assessing the total risk in the affected patient. Some important examples of primary dyslipidaemias should be borne in mind in management.

- In FH the genetic abnormality is in the LDL receptor, resulting in high plasma LDL concentration. In South Africa it is especially prevalent in Afrikaners (about 1%) as well as other groups including Asians, Jews and Lebanese. It is also known in the coloured and black population. Familial defective binding (FDB) apolipoprotein B100 in which the apoprotein of LDL does not bind the LDL receptor, has similar but possibly less severe clinical and biochemical manifestations. Both FH and FDB generally have severe hypercholesterolaemia and tendon xanthomata, best palpated at the Achilles tendon and extensor tendons on the dorsum of the hand. Typically the family history is of premature ischaemic heart disease, generally affecting one of the parental lineages, mostly in men aged <55 years. In adults the plasma cholesterol is usually >7.5 mmol/L (LDL >5) and often > 9 mmol/L before dietary modification.
- Familial combined hyperlipidaemia (FCH) may cause an autosomal dominant inheritance of hypercholesterolaemia but often presents later in life and may manifest in affected family members with a variable dyslipoproteinaemic profile, ranging from pure hypercholesterolaemia through a mixed picture to predominant hypertriglyceridaemia. It does not lead to tendon xanthomata and the gene defect or defects are not known. The dyslipidaemia may present with the atherogenic lipoprotein phenotype. Familial hypertriglyceridaemia and type III hyperlipidaemia have variable patterns of inheritance, often presenting only in adulthood. In this group of disorders, secondary and lifestyle factors are significant, notably, obesity and DM, excessive alcohol intake, drugs such as steroids and even secondary diseases such as hypothyroidism.

4.2.2 Secondary dyslipidaemias

The genetic constitution of the person is normal or contains only minor gene defects but the environment or underlying incidental disease brings out the dyslipidaemia.

- Diet: An unhealthy diet (high saturated fat, high cholesterol, low fibre and high energy intakes) can directly or indirectly bring about a moderate dyslipidaemia, often contributing to the primary disorders mentioned above.

- Diseases that cause hypercholesterolaemia include: hypothyroidism, nephrotic syndrome, obstructive jaundice . Diseases that predispose to hypertriglyceridaemia include: truncal obesity, diabetes mellitus, Cushing's syndrome.
- Pregnancy causes a rise in plasma cholesterol concentration and may also induce severe hypertriglyceridaemia in susceptible women.
- Drugs that influence the lipid profile in deleterious ways included: steroids, some betablockers, diuretics at high doses, retinoic acid derivatives and protease inhibitors used in HIV infection.

5 Laboratory procedures:

The determination of the lipoprotein profile is an essential component of the diagnostic process for patients in cholesterol categories 2 and 3, and for the patient with a cholesterol <5.0 mmol/L but established CHD.

A specimen for a lipoprotein profile requires a 12 hours overnight fast (water is permitted) in adults and older children. Blood should be taken between 08:00 and 10:00. The patient should be sitting and it is important to avoid undue venostasis. Blood should be collected into tubes without anticoagulant and allowed to clot (serum), or into tubes containing heparin or EDTA (plasma) and mixed carefully by inversion. If EDTA is used, the tubes should be filled to the top to avoid dilution errors. Plasma or serum should ideally be separated from the cells within 2 hours of sampling but definitely within 6 hours. The separated plasma/serum can be stored at 4°C for four days; otherwise freeze at below -20°C if possible.

Care should be taken to avoid preanalytical errors (recent or current illness, non-fasting state, delayed processing). Normal biological variation of between 5-10% for TC, LDLC, HDLC and apolipoprotein B and 25% for triglycerides must also be considered in assessing results. Bearing this in mind, the clinician should base decisions to initiate treatment with LMDs, where possible, on at least 2 separate results obtained 1 week or more apart, using a single laboratory to minimise variability. If there is a discrepancy > 10% between these two, a third sample is advisable. The acute phase response seen with severe illnesses sets in within a day and results in a lower cholesterol measurement for at least 6 weeks. This is particularly important in the diagnosis of dyslipidaemia after myocardial infarction. Severe hypertriglyceridaemia may also be underestimated and renders cholesterol estimations less accurate too. Note that laboratory investigations for exclusion of secondary dyslipidaemia should include thyroid, renal and liver function tests as well as a random or fasting glucose, serum albumin and protein electrophoresis, and a urinary screen for protein, glucose and bilirubin and urobilinogen.

6 Management of hyperlipidaemia

The two key elements in the management of hyperlipidaemia are:

- Lifestyle modification, which is desirable in virtually all patients, and,
- The use of appropriate LMDs in those patients at high risk.

6.1 Lifestyle modification

The main targets of lifestyle or behavioural modification are: cessation of tobacco use, a healthy diet, regular aerobic exercise, and, where indicated, loss of weight. The principles of a prudent diet and exercise are outlined below. The enthusiastic endorsement of desirable lifestyle changes by the practitioner is most important. The initiation and maintenance of the appropriate changes may be promoted by the use of qualified dietitians and by referring the patient to an exercise group or gymnasium with some expertise in preventative cardiology. The use of support groups can assist patients attempting to stop smoking or curtail alcohol intake.

6.1.1 Cessation of tobacco use

This is the single most important therapeutic action in patients with hyperlipidaemia and may require considerable motivation and reinforcement; consider support groups with relevant expertise in selected cases. Risk falls rapidly with cessation.

6.1.2 Prudent diet

The main elements of a prudent or anticoronary diet are a reduction of saturated fat, cholesterol and energy intake relative to the typical Westernised intake. This may be achieved by substitution of low fat or zero-fat dairy products for full cream varieties, by the use of plant oils and soft margarine in place of butter, coconut oil and palm oil, by avoiding pastries and by grilling or steaming food rather than frying it. It is important to reduce or minimise the intake of fatty meats including, especially, sausages and other processed meats (salami, polony, pies). Poultry (without skin), small cuts of lean beef and fish can replace meat dishes with a high fat content. Reduce egg yolk intake to 1 or 3 times per week or less, depending on the fat content of the rest of the diet. Increased fruit, vegetables and fibre are important components of a healthy diet. In addition to lowering total fat intake, reduce alcohol if clinically indicated and in hypertriglyceridaemic states and also simple carbohydrates - in sugar, sweetened soft drinks, white bread and rolls - especially where weight loss is required. Ideal weight may be defined by a BMI < 25 kg/m² in the general population. A body mass index can be calculated as mass/height² where mass is described in kg and height in m. A figure around 23 kg/m² is desirable for patients with DM or hypertriglyceridaemic, low HDLC profiles.

If there is a poor response to these measures or in more severe cases of hypercholesterolaemia, it is advisable to make use of a dietitian who may aim for a more restrictive, but still palatable diet along the following lines:

- Cholesterol: < 200 mg daily
- Total fat: 20-30% of total energy intake
- Fatty acids: Saturated and trans-fatty acids 7-10% of total energy intake with monounsaturated fats 15-20% of total energy intake
- Polyunsaturates in plants and fish should constitute the remainder
- Fibre 30 g daily
- In severe hypertriglyceridaemia the daily fat intake should be <30 g for an adult.

DIETARY RECOMMENDATIONS (9)

More detailed dietary recommendations are to be found in the next article. These recommendations are a summary of: The Adsa (1999) Dietary Management of People with Dyslipidaemia. For further information contact ADSA: P O Box 1310, Cramerview, 2060.

6.1.3 Regular aerobic exercise

The minimum effective target is 30 minutes of brisk walking, 3 times weekly. This can be further enhanced by simple measures such as using stairs rather than lifts, walking rather than driving to local shops and venues, gardening and housework. A preferable minimum target would be 4 hours of moderate exercise per week spread over 5-6 sessions. A planned exercise programme should be appropriate to age (gender) and clinical status - a cardiology opinion should be obtained where clinical CHD is present or suspected. The exercise should elevate heart rate to about 75% of age-related maximum heart rate (220 beats/minute minus age in years). Introduce variety and support (clubs, groups, gyms) to promote long-term compliance. In addition to aerobic exercise, resistive training is appropriate for both sexes and enhances weight loss, bone density and muscle strength thus reducing postural and other musculoskeletal problems. The practitioner should emphasise the importance of regular exercise to general, as well as cardiovascular, health and should monitor compliance and progress.

6.2 Medication

The introduction of LMDs should be approached with care considering the:

- expense,
- possibility of side-effects
- necessity for lifetime compliance.

Nevertheless, evidence from large-scale, prospective, double-blind, randomised clinical trials clearly indicates a reduction of total and cardiovascular morbidity and mortality for both pravastatin (Prava®) and simvastatin (Zocor®) (10-12). Similar trials have demonstrated a reduction in cardiovascular mortality, but not total mortality, using gemfibrozil (Lopid®) (13) and cholestyramine (Questran®) (14). Less rigorous additional studies (15, 16) provide evidence to suggest that other statins and fibrates on the market may have similar beneficial clinical outcomes.

The use of medication must balance cost against clinical efficacy and risk of CHD. No general consensus has been reached on the use of a universal threshold, but the recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention are proposed: namely, that the introduction of LMDs should mainly be confined to patients with a ten year risk of an overt CHD event of $\geq 20\%$, projected to the age of 60 years (17). A more conservative approach would use a threshold of $>30\%$ at age 60 years. Clinical judgement should be exercised, but all commentators agree that patients with FH or a related monogenic dyslipidaemia or the presence of established CHD, especially a previous AMI, should be candidates for LMDs - unless LDL cholesterol is drastically lowered by non-pharmacologic means alone to ≤ 3.0 mmol/L, in the case of established CHD cases. Use Table 2 to calculate the risk of MI based on defined risk factors, bearing in mind the risk factors not included in the table in borderline cases. Careful consideration should be given in this setting to correcting modifiable risk factors and the healthcare context in which the patient is being managed.

In most circumstances, LMDs should not be introduced without a prior trial of vigorous lifestyle modification; more rarely it may be appropriate to initiate drug therapy concurrently with non-pharmacologic management in severely hyperlipidaemic subjects or those at high risk due to the presence of overt CHD. Titrate the drug dose so that the minimal amount may be used to achieve the desirable profile of Table 1. The central aim is to reduce LDLC to ≤ 3 mmol/L. There is considerable variation in the average responses to drugs as given in Table 5. Only the LDLC responses are given in detail while a general range of response is given for TG and HDLC. In general, the lipoprotein response will be complete by 4 weeks. Given below is a brief summary of the drugs that are available on the South African market. For more detailed information about the drugs larger texts or package inserts should be consulted.

The response to medication varies from individual to individual. The Table has rounded off responses and is a guide to the average that can be expected in the majority of patients. An anticoronary diet, weight loss and exercise can significantly enhance the effects of LMDs. Statins were compared directly in one study (18) while fibrate comparisons were pooled for miscellaneous common dyslipidaemic patterns (19). Fibrates should be used in lower doses if there is impairment of renal function. Responses to older drugs are summarised (20) while information was incomplete for acipimox (21).

6.2.1 Statins (Table 5)

The statins, or HMG CoA reductase inhibitors, are the drugs of first choice in patients with pure hypercholesterolaemia and in those with mixed hyperlipidaemia in whom cholesterol elevation is prominent. In addition to reducing cholesterol and LDLC levels by increasing the number of hepatic LDL receptors, they variably elevate HDLC and lower triglyceride concentrations. Statins may also reduce coronary atherosclerosis by effects other than lipoprotein modulation (22). Maximal cardiovascular benefit has been demonstrated with LDLC lowering as little as 24% in primary prevention (23) and it appears that there is little gain from their use below LDLC concentrations of about 3 mmol/L in secondary prevention except for CABG (24). Nevertheless, additional evidence suggests that the degree of cholesterol lowering does influence the angiographic change and clinical outcome (25)

Statins vary in potency, as defined by the capacity to lower plasma cholesterol level per unit mass of drug (Table 5). The statins have a non-linear dose-response curve so that most of the benefit occurs at the lower dose range, with diminishing returns as the maximal dose is approached. With the exception of atorvastatin, the statins are better taken at night when most of the de novo synthesis of cholesterol occurs. Side effects are generally mild. Attention should be paid to transaminase levels, to creatine kinase and to symptoms of muscle pain and stiffness. Rhabdomyolysis is a rare complication, but may be facilitated by the concurrent administration of fibrates, immunosuppressive drugs and erythromycin. In many cases this is due to interactions of the other drugs with the catabolism of some of the statins by cytochrome P450. Occasionally patients complain of gastro-intestinal intolerance, headache and other vague symptoms which may be ameliorated by the use of a different statin. Insomnia may remit if the drug is taken in the morning.

6.2.2 Fibrates (Table 5)

Fibrates primarily lower triglyceride levels, and elevate HDLC concentrations. Total and LDLC values are generally reduced to a lesser extent and paradoxical increases in LDLC may occur in some hypertriglyceridaemic patients. Fibrates are chiefly indicated in predominantly hypertriglyceridaemic subjects with low HDLC levels. Many are obese with an atherogenic lipoprotein phenotype and possibly frank diabetes mellitus. Combining a fibrate with a low dose of a statin or BAS is often effective in normalizing all components of a mixed hyperlipidaemic phenotype. While cardiovascular mortality was reduced on clofibrate (Atromid-S®) (26), non-cardiovascular and total mortality were not reduced. It is thus not recommended for treating hypercholesterolaemia. Later, the Helsinki Heart Trial (13), using gemfibrozil in hyperlipidaemic subjects with clinical features of CHD, reduced cardiovascular deaths, especially in the

subgroup with an atherogenic lipoprotein phenotype (27). However, overall mortality was unaltered. Bezafibrate has achieved angiographic and clinical improvement in young hyperlipidaemic males with a prior acute myocardial infarction (16).

Side-effects include anorexia, alopecia, a reduced glomerular filtration rate, muscle pain and stiffness and increased transaminase levels. Creatinine and liver enzymes may be used to monitor potentially vulnerable or symptomatic patients. Substantially lower doses should be used in elderly patients or in patients with renal or hepatic disease. In general, loss of weight and vigorous non-pharmacologic intervention potentiates the action of fibrates, allowing the use of lower doses.

6.2.3 Bile Acid Sequestrants or Resins (Table 5)

These cannot be recommended as first line drugs, except in children with FH. They are useful as supplementary medication in combination with statins in severely hypercholesterolaemic patients, or, with fibrates in managing some mixed hyperlipidaemias. In the Lipid Research Clinics Primary Prevention Trial (14) on hyperlipidaemic males with overt CHD, cholestyramine was shown to reduce CHD end-points in a dose-dependent relationship.

The chief contra-indication is the high incidence of gastro-intestinal side-effects, notably gastric discomfort and bloating, constipation and nausea. Drugs of the BAS class should be thoroughly mixed with water, the total dose kept as low as possible and introduced slowly over a period of one to two weeks in a stepped fashion. Concomitant prescription of a bulk laxative and stool softener (e.g., psyllium) may ameliorate constipation. Since this class of medication interferes with the absorption of many other drugs, they should be administered some hours apart from other medication.

6.2.4 Nicotinic acid (Niacin) (Table 5)

Nicotinic acid has the advantage of being inexpensive and, when tolerated, is useful to reduce triglyceride levels and increase HDLC as well as lowering LDLC in larger doses. Unfortunately, usage is complicated by significant side-effects, including flushing and sensations of heat and cutaneous discomfort. Hyperuricaemia and gout, hyperglycaemia and diabetes, and hepatic and ophthalmic toxicity are described and may be more frequent with delayed-release preparations (18). A skilled and experienced practitioner may achieve considerable success if time is invested to give the patient a good understanding into the prescription. Flushing is reduced by taking a half or whole aspirin (dissolved in water) between half and one hour before the niacin is taken, this can later be reduced to half an aspirin per day in the morning. Niacin should always be taken with food. The dose should be gradually increased: 100 mg 3 or 4 times daily for a week, then 200 mg 3 or 4 times daily for a week, then further increases by 100 mg 3 or 4 times daily at weekly intervals. A good effect is seen on HDLC at about 1 g daily while LDLC will still improve at higher doses of up to about 3 g daily. If the regimen is interrupted, then the patient should build up the dose from the beginning again. Note that niacinamide or nicotinic acid amide is ineffective and also does not lead to flushing.

Acipimox is a drug derived from niacin with similar but weaker action and, unlike niacin, may be anti-diabetogenic.

6.2.5 Combination therapy

A patient whose lipoprotein concentrations are not controlled by dietary modification and compliance to a drug, should be evaluated at a referral clinic (Table 5). This table will be updated as necessary on the SAMA Centre for Quality Care Internet site: www.samedical.org/cqc

Occasionally severe hypercholesterolaemia may require combinations of a statin and a BAS or a statin together with niacin for better control. Severe hypertriglyceridaemia persisting after maximal dietary fat reduction and control of secondary causes may require the combination of a fibrate with niacin or a statin, but such patients should generally be referred to a Lipid Clinic. In severe mixed hyperlipidaemias a fibrate and a statin may also be combined with good effect.

6.3 Referral of patients

Table 6 lists the lipid clinics at referral hospitals that can provide expertise in lipid disorders in South Africa. This table will be updated as necessary on the SAMA Centre for Quality Care Internet site: www.samedical.org/cqc

Urgent referral is required if the plasma triglyceride concentration is >15 mmol/L while persistence of hypertriglyceridaemia of >5 mmol/L after all other measures have been attempted also merits referral.

Persistent hypercholesterolaemia of >7.5 mmol/L should also be referred, as should any patient with a TC >15 mmol/L. With the exception of xanthelasma, the presence of a cutaneous or tendon xanthoma indicates a potentially serious metabolic disorder and merits referral, this is especially true to children.

Table 5: Dosages & average responses to lipid modifying drugs registered in South Africa, arranged according to classes

Group	Substance	Trade name	Dose range (per day)	LDLC (%)	TG (%)	HDLC (%)
Statin	Atorvastatin *	Lipitor	10-80 mg	-35 to -55	-5 to	+4
	Cerivastatin	Baycol	0.1-0.3 mg	-20 to -33	-25,	to +12
	Fluvastatin	Lescol	20-80 mg	-20 to -35		
	Pravastatin	Prava	10-40 mg	-20 to -30		
	Simvastatin *	Zocor	10-80 mg	-30 to -50		
					relating to baseline	
Resin	Cholestyramine	Questran	4-16 g	-15 to -25	+25 to 100	5
Niacin	Niacin/nicotinic acid		0.4-3 g	-15 to -25	-20 to -30	35
	Acipimox Olbetam		0.6 g		-10 to -15	

Fibrates	Bezafibrate	Bezalip	400 mg	-15	-30	Varies
	Fenofibrate	Lipsin	0.3-0.6 g	-20	-35	+5 to
	Gemfibrozil	Lopid	1.2 g	-12	-45	+30

* Note: Atorvastatin and simvastatin 80mg are not registered for general use in South Africa at this time.

Table 6: Lipid clinics in South Africa

Place	Telephone	Address
Cape Town (Dr AD Marais)	(021) 404-2265	Lipid Clinic, Internal Medicine, UCT Medical School, Anzio Rd, Observatory 7925
Durban (Dr C Rajput)	(031) 403-3223 X 2271	Lipid Clinic, R K Khan Hospital, 336 Westcliff, Chatswood 4092
East London (Dr T Sole)	(043) 709-1111	Frere Hospital, East London 5201
Johannesburg (Dr FJ Raal)	(011) 488-3256	Lipid Clinic, Area 456, Johannesburg Hospital, 7 York Rd, Parktown, Johannesburg 2193
Pretoria (Prof HWJ Vermaak)	(012) 354-2354	Lipid Clinic, 1st Floor, Outpatients East, Pretoria Academic Hospital, Pretoria 0002
Port Elizabeth (Dr G White)	(041) 392-3333	Heart Clinic, Port Elizabeth Provincial Hospital, Port Elizabeth 6001
Tygerberg (Dr E Brice)	(021) 938-4000	Lipid Clinic, Cardiology Unit, Tygerberg Hospital, Tygerberg 7550

7 Conclusion:

Management of dyslipidaemia and patients at risk for cardiovascular disease requires a thorough clinical as well as risk assessment. Appropriately tailored lifestyle modification is indicated in all patients. LMDs should be used in high risk patients in whom adequate response is not achieved by diet and exercise alone. This is especially applicable to patients with overt CHD or FH in whom vigorous lowering of cholesterol is clinically mandatory. The central aim is to obtain an LDLC of #3 mmol/L or failing this in severe hypercholesterolaemia, a reduction in LDLC of at least 45%. The statins are the agents of choice for all hyperlipidaemic subjects except those with predominant hypertriglyceridaemia and low HDLC levels. For this group, one of the newer generation fibrates is indicated. BAS and nicotinic acid should be used mainly as supplementary drugs and require significant investment of time and skill in order to achieve good results without toxicity. Clinical judgement regarding the introduction of LMDs must be exercised in borderline cases and recourse to risk tables assists in making informed decisions.

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Annexure A: Dyslipidaemia Working Group:

Association of Dieticians of SA: E Wentzel
 Consumer/Patient representative: A Coetzee
 Department of Health: Pharmacy, Essential Drug List: L Coetzer
 Department of Health: Directorate Chronic Diseases, Disabilities and Geriatrics: Dr M Ahern
 Heart Foundation of South Africa: S Biesman-Simons
 International consultants: Prof G Thompson, Dr J Rossouw
 LASSA: Prof H Vermaak, Prof M Berger, Drs D Marais, C Rajput, F Maritz
 LASSA and SEMDSA: Dr FJ Raal, F.J. Maritz
 LASSA and Hypertension Society of Southern Africa: Dr K Steyn
 National Pathology Group: Dr C Pretorius
 Nutrition Society of South Africa: W Oosthuizen
 Pharmacy Association of South Africa: L Osman
 South African Medical Association: Dr EM Barker (Chairperson); Dr MN Chetty (General Practice Committee); V Pinkney-Atkinson (Centre for Quality Care)
 South African Academy of Family Practice: Dr B Vallabh
 South African Society of Cardiac Practitioners: Dr DP Naidoo
 Southern African Cardiac Society: Dr JJP Jacobs

Observer delegates

Bayer: Dr DF van Veenhuizen
 Bristol-Myers Squibb: D Webb, R Savy
 Hoechst Marion Roussel: G Allen
 MSD: Dr H McLoughlin, D Johnson, Dr B Cowper
 Novartis: Dr G Goolab, D Craythorne
 Parke-Davis: D Tucker
 PBM: Dr B Taylor
 Pfizer: Dr C Hopkinson

Annexure B: Methodology

In 1995 MSD approached the SAMA with a view to amending the existing outdated guideline. In 1996 SAMA and LASSA negotiated a joint venture in terms of which Professor M Berger was nominated to complete the draft guideline. A nationally representative dyslipidaemia consensus meeting was held on 11-12 August 1997 in Gauteng. Participants were invited as representatives of professional, government and consumer groups with an interest in the lipid field. Sponsorship in the form of unrestricted educational grants for the guideline development process were obtained from Bayer, Bristol-Myers Squibb, Hoechst Marion Roussel, MSD, Novartis, Parke-Davis, Pfizer. These grants were made in accordance with the SAMA code of sponsorship which precludes attempts by sponsors to unethically influence the content of the guideline. All money was paid directly to SAMA and all disbursements were made from that fund. LASSA reviewed the funding statements in 1999 and stated it was satisfied.

The draft dyslipidaemia clinical guideline and all references were circulated to participants before the national consensus meeting. All participants listed in Annexure A attended the meeting as delegates of a national group. The meeting was recorded and the tapes transcribed. SAMA selected a neutral chairperson to facilitate the meeting.

The main dyslipidaemia working group asked the Association for Dietetics of South Africa and other stakeholders to develop a clinical guideline relating to the dietary management of people with dyslipidaemia. This group met and produced the attached dietary management guideline and also parts of this document. Additional funding for this working group was obtained from Unifoods.

The endorsement draft document was revised and circulated to all participants and many other interested persons and groups. This draft was not acceptable to a significant number of participants and it was revised by the LASSA executive. These amendments were made available on the Centre for Quality Care Internet site (GOTOBUTTON BM_1_ www.samedical.org/cqc). The document as revised was endorsed by the SAMA Guideline Committee according to the set criteria. The endorsed guideline was published in the SA Medical Journal and is available in the compendium and on the Centre for Quality Care's Internet site <http://www.samedical.org/cqc>