# South African dyslipidaemia guideline consensus statement: 2018 update

## A joint statement from the South African Heart Association (SA Heart) and the Lipid and Atherosclerosis Society of Southern Africa (LASSA)

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South Africa (SA) is home to a heterogeneous population with a wide range of cardiovascular risk factors. Cholesterol reduction in combination with aggressive management of modifiable risk factors, including nutrition, physical activity, blood pressure and smoking, can help to reduce and prevent morbidity and mortality in individuals who are at increased risk of cardiovascular events. This updated consensus guide to management of dyslipidaemia in SA is based on the updated European Society of Cardiology and European Atherosclerosis Society dyslipidaemia guidelines published in 2016. For individuals who are not considered to be at high or very high cardiovascular risk, the decision whether to treat and which interventional strategy to use is based on a cardiovascular risk score calculated using total cholesterol, high-density lipoprotein cholesterol (HDL-C), gender, age and smoking status. The cardiovascular risk score refers to the 10-year risk of any cardiovascular event and includes 4 categories of risk (low, moderate, high and very high). People with established cardiovascular disease, diabetes mellitus, chronic kidney disease and genetic or severe dyslipidaemias are considered to already be at high or very high risk and do not require risk scoring. Therapeutic lifestyle change is the mainstay of management for all patients. The need for and intensity of drug therapy is determined according to baseline low-density lipoprotein (LDL-C) levels and the target LDL-C concentration appropriate to the individual. LDL-C treatment targets are based on pre-treatment risk and are as follows: <3 mmol/L in low- and moderate risk cases; <2.5 mmol/L and a reduction of at least 50% if the baseline concentration is 2.5 - 5.2 mmol/L in high-risk cases; and <1.8 mmol/L and a reduction of at least 50% if the baseline concentration is 1.8 - 3.5 mmol/L in very high-risk cases. A statin is usually recommended first-line; the specific agent is based on the required degree of cholesterol reduction, comorbidities and co-prescribed medication.
Special attention should be paid to children with a family history of genetic or severe dyslipidaemia, who should be screened for dyslipidaemia from 8 years of age. In SA, HIV infection is not considered to be a significant cardiovascular risk factor and treatment recommendations for HIV-positive individuals are the same as for the general population, with careful choice of pharmacotherapy to avoid potential adverse drug-drug interactions. The benefit of statins in individuals older than 70 years is uncertain and clinical judgement should be used to guide treatment decisions and to avoid side-effects and overmedication in this group.

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## 1. Introduction

In 2003, the South African Heart Association (SA Heart) and the Lipid and Atherosclerosis Society of Southern Africa (LASSA) officially adopted the European Guidelines for the Prevention of Cardiovascular Disease[1] to replace the South African Lipid Guidelines published in 2000.[2] Based on the 2011 publication of the European Society of Cardiology (ESC)/European Society of Atherosclerosis (EAS) Guideline for the Management of Dyslipidaemias,[3] a comprehensive South African Dyslipidaemia Guideline Consensus Statement was published in 2012.[4] When the European document was revised in 2016,[5] it was necessary to update the South African Guideline Consensus Statement to ensure that it is based on the most recent

and best available data. Additionally, it is necessary to place the latest international guidelines in a context that is relevant to South Africans and to make the main recommendations of the guideline available in a succinct and accessible format.

All ESC guidelines are developed using a rigorous, standardised and transparent process. This process involves selection of a task force that includes members from multiple relevant societies, careful review and grading of evidence, consensus achievement and external peer review. All guidelines are reviewed annually by the task force chairman and a selected expert group who decide whether there is sufficient new evidence that would influence the recommendations made. All guidelines are formally revised at least once every 5 years. Further details on the ESC guideline development process can be found at https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines.

The 2018 South African update aims to ensure and promote current best management of dyslipidaemia in South Africa (SA). We strongly recommend that these guidelines be adopted by all South African healthcare professionals and healthcare funders in both the private and public sectors. The South African Guideline Consensus Statement is adopted from the ESC guidelines and will be updated in concert with their guideline updates. Because the guidelines on which this consensus statement is based were subjected to a rigorous process of external peer review this statement has not been submitted for further external peer review. Readers that are interested in the full ESC guidelines and the stringent review process followed, should refer to the full text of the ESC guidelines that reviews the evidence base for each recommendation in detail and grades the strength of each recommendation.[6] As our aim was to keep this statement short and accessible, in contrast to the 78 pages of the full guideline, we have not included all the information in the consensus statement.

Our recommendations are accepted to be best-practice care and are based on the current available evidence. In their purest form, guidelines do not consider the cost of therapeutic decisions. However, one cannot be blind to the financial implications in the SA context. The effectiveness of lipid-lowering therapy is well established, but the raw cost of the drugs can vary according to individual, institutional, provider and governmental factors. It is not possible for this writing committee to take all these factors into account when compiling this consensus statement. It is therefore up to each participant in the healthcare system to decide what is 'affordable' or not. Taking the latter into account will enable a rational decision as to the cost effectiveness of therapy (i.e. in the high- and very high-risk secondary prevention patient as opposed to the lower-risk primary prevention scenario). However, at all times a decision with regard to cost should not detract from the ultimate goal of reducing the actual burden of cardiovascular disease.

The INTERHEART study conducted in 52 countries throughout Africa, Asia, Australia, Europe, the Middle East, and North and South America showed that more premature acute myocardial infarctions occur in sub-Saharan Africa than anywhere else.[7,8] This statistic underscores a lack of prevention, early detection and effective management of cardiovascular (CV) risk factors in the countries of this region in general.[7] In particular, South Africans are at high risk of cardiovascular disease (CVD), having among the highest prevalences of obesity, undiagnosed diabetes mellitus, smoking and high cholesterol in Africa.[9,10] In some communities, type 2 diabetes is remarkably common. Age-standardised prevalences are estimated at 13% in Asian Indians, 11% in coloured (mixed ancestry) communities (26% in the Western Cape), and up to 8% among urban black South Africans.[11] Familial hypercholesterolaemia (FH), characterised by markedly elevated low-density lipoprotein cholesterol (LDL-C) and premature CVD is an inherited autosomal dominant disorder that is more than 3 times more common among certain South African populations than in other global populations.[12,13]

The SA population is multi-ethnic, with considerable sociodemographic and economic diversity and a large range of cultures and lifestyles at different stages of epidemiological transition. This heterogeneity is reflected also in levels of CVD risk, which vary considerably depending on race group, socioeconomic status and education level. For example, among black South Africans, CVD risk increases with years of formal education and income level, whereas an opposite trend is evident among the coloured population and those of European descent.[7] Although the mortality rates attributable to CVD have traditionally been lower among black South Africans than in the other racial groups, the prevalence of CVD and the incidence of premature death is increasing among both rural and urban communities and across the socioeconomic spectrum in this population. Factors that account for this include demographic change predominantly driven by an increase in older people who are at greatest risk of developing chronic diseases, increasing urbanisation and adoption of an unhealthy lifestyle, and inequalities in access to healthcare.[7,10,14,15]

Consequently, the timely institution of lifestyle modification, early diagnosis and effective management of CVD risk factors are essential to prevent the impending epidemic of CVD in SA.[10]

Dyslipidaemia is an important target for intervention in all population groups. Data collected up until 2000 indicated that 28% of black South Africans and >80% of white, coloured and Indian adults >30 years of age have serum total cholesterol (TC) levels ≥5 mmol/L. Although there was marked variation between population groups, it was estimated that more than half of all ischaemic heart disease (IHD) and more than one-quarter of all ischaemic strokes were associated with high serum cholesterol levels.[16]

## 2. Screening

In the absence of risk factors for CVD, all individuals should be screened, preferably with a full lipogram or at least TC or LDL-C, from the age of 40 years. However, earlier screening during infancy, before puberty or at around 20 years is indicated for certain individuals, depending on genetics, family history and other cardiac risk factors (Table 1).

Screening for FH is recommended for all potentially affected relatives of patients with severe dyslipidaemia, and testing should be extended, in turn, to relatives of each one of those in whom FH is diagnosed (cascade screening).[17] Screening should start before puberty (around 8 years) in children of affected families. Initial screening is based on clinical evaluation and LDL-C sampling. Genetic screening for specific mutations in FH-associated genes is available at some private laboratories and university research clinics, and may be useful in certain families. However, a negative genetic test does not exclude FH.

Individuals identified with the FH genotype and/or phenotype who have very raised LDL-C (>10 mmol/L) or who do not respond adequately to treatment with a potent statin (atorvastatin or rosuvastatin) plus ezetimibe should be referred for specialist evaluation where possible.

## 3. Laboratory investigations of dyslipidaemia

### 3.1 Initial consultation: Screening and assessment of CV risk using Framingham tables

Estimating CV risk with the Framingham tables is used to guide clinical decisions for primary prevention only and patients who have

**Table 1. Recommended ages to start screening for dyslipidaemia**

| From age 8 years | From age 20 years | From age 40 years |
|---|---|---|
| 1. Family history of severe dyslipidaemia<br>2. Relative of subject with FH (if both parents have FH, testing should be undertaken within the first 6 months of life to identify infants with homozygous FH) | Presence of CV risk factors:<br>1. Hypertension and/or on antihypertensive medication<br>2. Smoking: any smoking<br>3. Family history of premature CVD in first degree relative (male ≤55 years of age; female ≤65 years of age)<br>4. BMI ≥30 kg/m$^2$ or waist circumference >94 cm (men), >80 cm (women)<br>5. Autoimmune chronic inflammatory disease, e.g. rheumatoid arthritis, systemic lupus erythematosus, psoriasis<br>6. CKD | All other individuals (asymptomatic adults without evidence of CVD, diabetes, CKD or FH) |

FH = familial hypercholesterolaemia; CV = cardiovascular; CVD = cardiovascular disease; CKD = chronic kidney disease; BMI = body mass index.

already presented with features of atherosclerosis and cardiovascular events are not scored. In addition to TC and high-density lipoprotein cholesterol (HDL-C), the Framingham Score requires the patient's age, blood pressure (BP) (on or off antihypertensive therapy) and smoking status.

Although a finger-prick test of TC is the least expensive and easiest measurement of blood cholesterol, if it is elevated (>5 mmol/L) then, in order to use the Framingham tables (Appendix 1), a full lipogram is required.

## 3.2 Timing of testing at diagnosis

A full lipogram (TC, HDL-C, LDL-C and triglycerides (TG)) is recommended for initial diagnosis of dyslipidaemia. Although it was previously recommended that blood samples for lipid estimation be drawn in the fasting state, recent evidence indicates that fasting and non-fasting blood samples yield similar results for TC, LDL-C and HDL-C and are comparable for estimation of CV risk.[18,19] To improve patient compliance and encourage measurement of plasma lipids at the clinic visit, non-fasting samples may be used for screening, diagnosis and monitoring of treatment effect. Blood samples reported as 'lipaemic' by the laboratory indicate elevated TG, which requires further investigation or referral as necessary. TG levels are affected following a meal and, providing metabolism of TG-rich proteins is normal, TGs may vary by ~0.3 mmol/L depending on the interval between the last meal and when the blood sample is taken. Therefore, a TG level that should be flagged as abnormally raised is ≥2 mmol/L in a non-fasting sample and ≥1.7 mmol/L in a fasting sample. A TG level >5 mmol/L in a non-fasting sample requires a confirmatory fasting sample.

## 3.3 Follow-up consultation: Assessing treatment goals and monitoring effectiveness of therapy

After initiating therapeutic lifestyle change (TLC) alone, follow-up testing of plasma lipids should be performed 6-monthly. After initiating pharmacotherapy, changing the dose or changing medication for dyslipidaemia, testing should be repeated at 8 (±4) weeks. Thereafter, once the patient is at goal, testing should be repeated 6-monthly.

### 3.3.1 Low-density lipoprotein cholesterol (LDL-C)

Although TC and HDL-C are required to initially score individuals for primary prevention, once the score has been completed, the pretreatment LDL-C level is used to assign the correct statin dose to achieve the LDL-C goal as described in Table 4.

LDL-C may be measured directly or calculated from the Friedewald equation (provided the TGs do not exceed 4.5 mmol/L):

[LDL-C] = [TC] - [HDL-C] – [TG/2.2] (all units in mmol/L).

### 3.3.2 Full lipogram

In patients with pure hypercholesterolaemia, LDL-C alone is adequate for follow-up, but a full lipogram is recommended where increased LDL-C is not the only abnormality in the lipid profile.

### 3.3.3 Total cholesterol as a surrogate for LDL-C

In patients where LDL-C has been used to initiate and monitor treatment, once the relationship between on-treatment TC and LDL-C is known, monitoring TC only is an alternative if LDL-C measurements are not readily available. However, it must be borne in mind that measuring TC alone is not optimal and it is preferable to measure LDL-C. Nevertheless, finger-prick testing of TC may be used as an alternative for monitoring treatment efficacy if there are cost constraints or if there is difficulty in obtaining either direct or indirect LDL-C values.

- When TC = 4.5 mmol/L, the approximate value of LDL-C = 2.5 mmol/L.
- When TC = 4.0 mmol/L, the approximate value of LDL-C = 1.8 mmol/L.

If an LDL-C measurement is unavailable and TC values remain uncontrolled, the patient should be referred to a higher level of care.

## 3.4 Point-of-care finger-prick testing

Various point-of-care (POC) testing devices are available that can measure a variety of lipid parameters, ranging from TC alone to a full lipogram. Where finger-prick testing is performed, the facility should ensure that adequate quality controls are in place, that the test strips and devices are stored under appropriate conditions of temperature, humidity and light, and that precautions are taken to perform the test properly, with an adequate blood sample volume and without contamination.[20] The finger should not be squeezed or 'milked', as this will give inaccurate results.

It must be borne in mind that machines that are not approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMA) may not be accurate and may under-read. Therefore, it is recommended that only suitably approved devices are used and that POC devices at each centre be calibrated regularly according to the manufacturer's instructions.

POC finger-prick testing is appropriate for population screening. However, POC testing is not appropriate to commit a patient to a lifetime of therapy, nor is it adequate to diagnose dyslipidaemias in high-risk individuals or those with a family history of FH. These patients require formal assessment. Similarly, where a screening finger-prick TC measurement is high (>5 mmol/L), patients should be referred back to their doctor for a full laboratory-performed lipogram and formal cardiovascular risk assessment. Because underestimation of LDL-C and inappropriately low results are a concern, TC <3.0 mmol/L on a finger-prick test should be confirmed with a laboratory result. Finger-prick testing that measures TC alone will not detect raised triglycerides.

## 4. Diagnosis of familial hypercholesterolaemia

There are a number of different approaches to the diagnosis of FH, including the Dutch Lipid Clinic criteria and the Simon Broome criteria, among others.[21] The Simon Broome diagnostic criteria are easier to use (Table 2).

## 5. Secondary causes of dyslipidaemia

Dyslipidaemia may occur in response to another condition or medication (Table 3) and suspicion of secondary dyslipidaemia should prompt appropriate investigations and treatment. Importantly, hypothyroidism, which is easily missed, should be considered before committing a patient to a lifetime of therapy for dyslipidaemia, and measurement of thyroid stimulating hormone (TSH) is recommended where appropriate. Diabetes can cause severe hypertriglyceridaemia if there is an otherwise mild genetic variant in triglyceride metabolism.

## 6. Cardiovascular risk scoring

### 6.1 Very high risk and high risk individuals do not need to be scored

Individuals who are considered to be at very high risk or high risk of cardiovascular events are listed in Table 5. Patients in this group do not require Framingham cardiovascular risk scoring, because the algorithm will underestimate the risk in these settings.

#### 6.1.1 Other individuals at high risk and very high risk

Individuals who are regarded at high or very high risk according to their score on the Framingham 10-year risk tables are

- score >15% but <30% (high risk)
- score >30% (very high risk)

### 6.2 How to use the Framingham Risk Charts

Management decisions for patients who do not fall into the very high- or high risk categories based on clinical evaluation are guided by risk scoring algorithms. The European guidelines use the Systematic Coronary Risk Estimation (SCORE) system to estimate CV risk. Because this scoring system is based on a fatal CV risk endpoint in a European population, it may not accurately reflect coronary risk in South Africa. While it is recognised that it would be impossible to accurately estimate risk in all SA subpopulations with a single data set, the Framingham risk tables, which provide an estimate of the 10-year risk of total CVD (fatal and non-fatal coronary events, cerebrovascular and peripheral arterial disease, and heart failure) have been validated in white and black populations in the USA and are applicable to other culturally diverse populations.[24,25] Consequently, this approach is considered to be more appropriate for the multi-ethnic SA society. Nevertheless, it should be borne in mind that these

**Table 2. Simon Broome criteria for diagnosis of familial hypercholesterolemia (FH)[21-23]**

| | |
|---|---|
| Definite FH | 1. Severely elevated cholesterol* *and* tendinous xanthomata in the patient or a first-degree relative.<br>2. DNA-based evidence of mutation in the LDLR, APOB or PCSK9 gene. |
| Probable FH | 1. Severely elevated cholesterol* *and* family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative;<br>OR<br>2. Severely elevated cholesterol* *and* family history of raised total cholesterol concentration >7.5 mmol/L in a first or second-degree relative. |

LDLR = low-density lipoprotein receptor; APOB = apolipoprotein B; PCSK9 = proprotein convertase subtilisin/kexin type 9.
*Adult: TC>7.5 mmol/L or LDL-C >4.9 mmol/L; Child (<16 years): TC >6.7 mmol/L or LDL-C >4.0 mmol/L

**Table 3. Common secondary causes of dyslipidaemia**

| Raised LDL-C | Mixed dyslipidaemia | Raised TG |
|---|---|---|
| • Diabetes mellitus<br>• Hypothyroidism<br>• Liver disease (biliary obstruction)<br>• Renal disease, e.g. nephrotic syndrome<br>• Pregnancy<br>• Medications:<br>  • Diuretics<br>  • Glucocorticoids<br>  • Cyclosporin<br>  • Antiretroviral agents | • Weight gain and obesity<br>• Diabetes mellitus<br>• Medications:<br>  • Retinoids<br>  • Beta-blockers<br>  • Oestrogens<br>  • Glucocorticoids<br>  • IV lipid emulsion<br>  • Protease inhibitors | • Diabetes mellitus<br>• Weight gain and obesity<br>• Pregnancy<br>• Chronic renal disease<br>• Alcohol excess<br>• Medications:<br>  • Retinoids<br>  • Beta-blockers<br>  • Oestrogens<br>  • Glucocorticoids<br>  • IV lipid emulsion<br>  • Protease inhibitors |

LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; IV = intravenous.

risk tables may under- or overestimate the risk in SA black, coloured and Indian patients. The Framingham CVD risk tables for men and women and an algorithm for management and cholesterol goals have been incorporated into these recommendations (Appendix 1).

Various downloadable mobile device applications ('apps') for risk scoring are available and clinicians are encouraged to make use of these to facilitate management decisions at point of care or at the bedside. An app that is appropriate to this guideline is available via the App store under 'SADyslipidaemia'. Other helpful app-based scoring systems are listed in Appendix 2.

## 7. Goals of therapy

Although TC and HDL-C are used to estimate CV risk, LDL-C is the target of therapy. Target LDL-C values for patients at different levels of Framingham CV risk are listed in Table 4. For those at low or moderate risk, target LDL-C is <3 mmol/L. The target for individuals at high or very high risk is dependent on the baseline LDL-C level.

For those at high risk, the target LDL-C is <2.5 mmol/L and if baseline LDL-C is between 2.5 and 5.2 mmol/L then at least a 50% reduction in LDL-C must also be achieved. For those at very high risk, the target LDL-C is <1.8 mmol/L and if the baseline LDL-C is between 1.8 and 3.5 mmol/L, then at least, a 50% reduction in LDL-C must also be achieved.

Notwithstanding these recommendations, clinical studies indicate that there is no apparent LDL-C threshold below which CV benefit does not continue to accrue or which may be detrimental to health. Consequently, particularly for patients at high risk of CV events, the primary goal should be to achieve the largest LDL-C reduction possible.[26-29]

At their maximum doses, different lipid-lowering therapies do differ in their capacity to reduce LDL-C, but CV benefit is dependent on the *extent* to which LDL-C is lowered and not on the *type* of therapy used.[30]

Meta-analyses of statin trials have shown that every 1 mmol/L reduction in LDL-C is associated with a:[31]

- 10% reduction in all-cause mortality
- 20% reduction in deaths due to CHD
- 24% reduction in major coronary events
- 15% reduction in stroke.

This relative effect of lipid-lowering therapy is similar in all patient subgroups (with or without vascular disease, male and female, high and low CV risk) and becomes significant after 1 year, increasing progressively thereafter.[26,27,31-34] The number needed to treat (NNT) to prevent adverse CV events is lowest in patients with the highest risk at baseline.

There are no target values for HDL-C or TG. However, HDL-C >1.0 mmol/L in men and >1.2 in women, and TG <1.7 mmol/L indicate lower risk. Higher TG levels should prompt investigation for other risk factors.

**Table 4. Low-density lipoprotein (LDL-C) treatment targets**

| Total Framingham CVD risk (%) | ESC/EAS risk classification | ESC/EAS LDL-C target |
|---|---|---|
| <3 | Low risk | <3.0 mmol/L |
| 3 - 15 | Moderate risk | <3.0 mmol/L |
| 15 - 30 | High risk | <2.5 mmol/L<br>**and** a reduction of at least 50% if the baseline* is between 2.5 and 5.2 mmol/L. |
| >30 | Very high risk | <1.8 mmol/L<br>**and** a reduction of at least 50% if the baseline* is between 1.8 and 3.5 mmol/L. |

CVD = cardiovascular disease; ESC =European Society of Cardiology; EAS European Atherosclerosis Society (EAS).
*Baseline LDL-C refers to the level in a subject who is not taking any lipid-lowering therapy.

**Table 5. Subjects considered to be at very high or high risk of CV events who DO NOT require Framingham risk scoring**

**Very high risk**

- Established atherosclerotic disease,* i.e.
  - Coronary artery disease
  - Cerebrovascular disease
  - Peripheral arterial disease
- Type 2 diabetes plus one or more other risk factors (smoking, hypertension, dyslipidaemia) or age >40 years
- Type 1 diabetes with micro-albuminuria or proteinuria
- Genetic dyslipidaemia, e.g. FH, dysbetalipoproteinaemia, individuals with TC >7.5 mmol/L and/or LDL-C >5 mmol/L
- Severe CKD (GFR <30 mL/min/1.73 $m^2$)
- Asymptomatic individuals with arterial plaque demonstrated on imaging modalities

**High risk**

- Markedly elevated BP (systolic BP ≥180 mmHg and/or diastolic BP ≥110 mmHg)
- Uncomplicated type 1 diabetes and type 2 diabetes aged <40 years without other risk factors
- Chronic kidney disease (GFR 30 - 59 mL/min/1.73 $m^2$)

CV = cardiovascular; FH = familial hypercholesterolaemia, TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; CKD = chronic kidney disease; GFR = glomerular filtration rate; BP = blood pressure.
*Documented cardiovascular disease on imaging is what has been shown to be strongly predisposed to clinical events, such as plaque on coronary angiography or carotid ultrasound.[5]

**Table 6. Recommended intervention strategies as a function of Framingham total CVD risk score and LDL-C levels[5]***

| Total CVD risk score† | LDL-C levels (mmol/L) | | | |
|---|---|---|---|---|
| | <1.8 | 1.8 - <2.5 | 2.5 - 4.9 | >4.9 |
| <3%<br>Low risk | No lipid intervention | No lipid intervention | Lifestyle intervention | Lifestyle intervention, consider drug if uncontrolled |
| 3 - 15%<br>Moderate risk | Lifestyle intervention | Lifestyle intervention | Lifestyle intervention, consider drug if uncontrolled | Lifestyle intervention, consider drug if uncontrolled |
| 15 - 30%<br>High risk | Lifestyle intervention, consider drug‡ | Lifestyle intervention, consider drug‡ | Lifestyle intervention and immediate drug intervention | Lifestyle intervention and immediate drug intervention |
| >30%<br>Very high risk | Lifestyle intervention, consider drug‡ | Lifestyle intervention and immediate drug intervention | Lifestyle intervention and immediate drug intervention | Lifestyle intervention and immediate drug intervention |

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.
*Adapted from Catapano *et al.* (Table 5).
†Based on the Framingham CVD risk tables (Appendix 1).
‡In patients with myocardial infarction, statin therapy should be considered regardless of LDL-C levels.

## 8. Management of dyslipidaemia

Because the total cardiovascular risk in an individual is the product of a number of risk factors, the treatment of dyslipidaemia must always be seen within the broader framework of CVD prevention. Table 6 sets out the recommended appropriate intervention strategies according to the percentage risk calculated from the Framingham risk score and LDL-C values.

### 8.1 Lifestyle modification

It should be emphasised that the cornerstone of any programme to reduce cardiovascular risk is TLC. Specific lifestyle changes that have the most pronounced benefit on lipids are reduction of dietary trans and saturated fats, increase in dietary fibre, reduction of excessive body weight, reduced alcohol intake and increase in habitual physical activity.[5]

Nutrition may also need to be modified for people with unusual or specific disorders (e.g. hypertriglyceridaemia). Referral to a dietitian and fitness professional is encouraged. The lifestyle and dietary advice that is relevant to the South African population is listed in Appendix 3.

#### 8.1.1 Nutrition

Dietary patterns that are most strongly associated with proven reduction in long-term CV risk are the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diets.[35-43] They are characterised by increased consumption of vegetables, fruits and wholegrain products; frequent intake of legumes, nuts, fish, poultry and low-fat dairy products, and limited intake of red meat, sweets, added sugar and sugar-sweetened drinks. Dietary fat is predominantly provided by non-tropical vegetable oil rather than animal sources. Incorporating either of these eating patterns into a lifestyle is achievable and sustainable. The South African food-based dietary guidelines are in line with these recommendations.[44]

Other specific diets may be tailored to achieve weight loss (especially in the short-term) or to address particular health concerns, such as dyslipidaemia, celiac disease or diabetes. In short term studies (up to 2 years), weight loss was comparable regardless of the macronutrient composition of the diet (e.g., low-carbohydrate v. low-fat diet), and was not predicted by polymorphisms in genes associated with fat or carbohydrate metabolism (low-fat responsive and low-carbohydrate responsive genotypes), or insulin concentration following a glucose challenge.[45-48] In contrast, large, long-term (6 to >25 years) observational studies indicate that habitual adherence to a diet low in carbohydrate and high in animal-based sources of protein and fat is associated with increased all-cause mortality rates, including deaths from CVD and cancer.[49-54]

The overall nutritional content of the diet is important. Low-carbohydrate diets tend to be associated with a reduced intake of fibre (fruits and vegetables) and increased intake of protein from animal sources, cholesterol and saturated fat.[54] Conversely, in people following a low-saturated-fat diet, the health benefits may be offset by higher consumption of refined carbohydrates.[55] Any diet that concentrates on individual or limited food groups, or an imbalance of food groups, will not be sustainable and is likely to be nutritionally deficient.

Considering the multitude and diversity of dietary approaches recommended in the media, and the inconsistency of nutritional messages from one 'expert' to the next, it is no wonder that both consumers and health professionals are confused from time to time as to what foods are really healthy! Nevertheless, there is convincing evidence that the basic principles guiding dietary choices that are conducive to maintaining a healthy body weight and optimising cardiovascular and life-long health are relatively simple. A healthy diet is one of moderation that is nutrient dense, and which emphasises adequate intake of fruits, vegetables, whole grains, legumes and nuts, and limits consumption of refined grains, processed foods, added sugar and sodium, and saturated and trans fats. In order to be sustainable, a diet should be culturally acceptable and above all, enjoyable.[44,56-58]

Examples of foods that can improve overall lipoprotein profile or which should be consumed sparingly are listed in Appendix 4.

#### 8.1.2 Dietary fats

Fats is an all-encompassing term that includes cholesterol and TG, both consumed in food. Dietary TG may be in the form of a solid or a liquid (oil). Fats are important in that they confer texture and taste to food and promote satiety. However, preference should be given to consumption of polyunsaturated fats rather than saturated fats to improve the quality of fat in the diet.[59]

##### 8.1.2.1 Unsaturated fats

Unsaturated fats are classified as mono- or polyunsaturated. Dietary polyunsaturated fatty acids are key as they provide the two essential fatty acids that the human body cannot manufacture. These are derived mainly from plant and vegetable oils and are the omega-6 linoleic acid (from sunflower and soybean oils) and the omega-3 alpha-linolenic acid (from green leafy vegetables, canola oil and flaxseeds). Alpha-linolenic acid is also the precursor of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), but these two fatty acids are mainly provided by marine sources. Replacing saturated fat with polyunsaturated fatty acids (PUFAs) PUFAs from vegetable oil has

been shown to reduce LDL-C and CV risk, and may cause regression of atherosclerosis.[55]

Observational evidence indicates that twice-weekly consumption of fish providing omega-3 fatty acids (EPA and DHA) may reduce the risk of CV death and stroke.[5] CVD reduction is greater with consumption of polyunsaturated than with monounsaturated fats, but both are preferable to saturated fats.[55]

#### 8.1.2.2 Saturated fats

Saturated fats are predominantly solid and include both animal and vegetable solid fats (e.g., visible fat on meat and chicken, lard and dairy cream; coconut, palm and palm kernel) and food products that have vegetable fats as an ingredient (e.g., non-dairy creamer). Because saturated fat is an integral component of fats and oils in varying quantities, most dietary products contain some saturated fat. Even sunflower oil and olive oil contain saturated fat, but in smaller quantities than in the foods mentioned above. Therefore, a diet that is high in fat, or which is associated with an increase in total fat consumption, will also be associated with higher intake of saturated fat.

Saturated fatty acids are the dietary fats with the greatest impact on LDL-C (0.02 - 0.04 mmol/L LDL-C increase for every additional 1% energy coming from saturated fat).[5]

Randomised controlled trials have shown that reducing intake of dietary saturated fat and replacing it with polyunsaturated vegetable oil can reduce CVD by ~30%, similar to that achieved by statin treatment.[55]

#### 8.1.2.3 Trans unsaturated fatty acids

*Trans* unsaturated fatty acids are monounsaturated or polyunsaturated fatty acids containing at least one double bond in the trans configuration. They occur naturally in the meat and milk of ruminant animals (e.g., cattle, sheep) and are also produced commercially for use in partially hydrogenated vegetable oils. These industrial *trans* fatty acids are inexpensive, have a long shelf-life and are able to withstand repeated heating. Consequently, they are widely used in production of processed foods, including margarines, baked goods and commercial deep-fried foods. Clinical trials have consistently demonstrated adverse health effects associated with industrial *trans* fatty acids, which include raising LDL-C, apolipoprotein B, TG and lipoprotein(a) (Lp(a)), as well as lowering HDL-C and apolipoprotein A1 and increasing the risk of CHD.[55,59] The use of *trans* fats in foodstuffs is regulated in SA.[60]

#### 8.1.2.4 Dietary cholesterol

Animal products provide cholesterol similarly in all muscle tissue and more so in organ meat and eggs. However, the effects of dietary cholesterol on blood cholesterol vary markedly from person to person and dietary cholesterol has less of an impact on blood cholesterol than saturated fats, which are consistently adverse. It should be noted that because saturated fat increases both LDL-C and HDL-C levels, the TC/HDL-C ratio will not be greatly affected despite an adverse change in LDL-C.

It should be noted that the dietary recommendations provided here aim to provide general guidance on a sustainable, healthy intake of fats, assuming maintenance of an ideal body weight. For detailed information about dietary fats and nutrition in general, readers are referred to the South African Food-Based Dietary Guidelines available at: http://www.adsa.org.za/Portals/14/Documents/FoodBasedDietaryGuidelinesforSouthAfrica.pdf.[44] Readers should also refer to the appropriate treatment guidelines when providing dietary guidance to patients with specific nutritional needs (e.g., diabetes mellitus, CKD, weight loss).

#### 8.1.2.5 Supplements

Epidemiological and interventional studies support the role of healthy dietary choices to help reduce the risk of cardiovascular events. However, it is important to emphasise that, as far as possible, nutrient intake should come from foods and there is insufficient evidence to recommend the use of dietary supplements in patients with dyslipidaemia. While some dietary supplements have been shown to influence plasma lipids, there are no outcome data that show reduction in CV events. Conversely, there is evidence that some supplements may be harmful to health and may interact with prescription medicines.[61,62] Consumers should be aware of unsubstantiated advertising claims relating to long-term health benefits.

Although there are no known risks associated with its use, the routine use of coenzyme Q10 to reduce statin-related myalgia or myopathy is not supported by systematic reviews.[63,64]

### 8.1.3 Tobacco smoking and vaping

Tobacco smoking and passive smoking are harmful to cardiovascular health in both adults and children.[65-66] All current smokers should be advised to stop smoking.

Although electronic cigarettes (e-cigarettes, vaping) are considered to be less harmful than cigarettes and may be a less unhealthy replacement for traditional smoking, especially in those who are trying to cut down or quit smoking, the long-term health effects of vaping are unknown. Non-smokers should be encouraged to remain so and young people in particular should be advised against starting smoking.[67,68]

## 8.2 Statin therapy

### 8.2.1 Benefits of statin therapy

A wealth of evidence from both observational and large randomised controlled clinical trials (RCTs) support the use of statins in a wide variety of patients with hypercholesterolaemia. The absolute benefit of treatment depends on the individual's absolute risk of CVD and the absolute reduction of LDL-C achieved, but evidence from RCTs shows that for every year of statin therapy after the first year, the risk of major coronary events (i.e. coronary deaths or myocardial infarctions and coronary revascularisation procedures) is reduced by approximately one-quarter for each 1 mmol/L reduction in LDL-C. Not only do the benefits accrue with ongoing statin use, but they are also persistent in the long term.[31,34]

### 8.2.2 Adverse effects of statins

Statins are remarkably safe drugs and the benefits of cardiovascular protection far outweigh the risks of therapy. However, patients should be encouraged to make and sustain healthy lifestyle choices and the lowest dose of statin necessary to achieve LDL-C target should be used (and a 50% reduction in LDL-C if baseline LDL-C is between 1.8 and 3.5 mmol/L in individuals at very high risk or between 2.5 and 5.2 mmol/L in those at high risk; see Table 5).

The only noteworthy serious adverse events associated with long-term statin therapy are myopathy, new onset diabetes and haemorrhagic stroke. However, these adverse effects are relatively uncommon with incidences of 5, 50 - 100 and 5 - 10 per 10 000 patients treated for 5 years, respectively. Although in routine clinical practice symptomatic adverse events (e.g., myalgia, or muscle weakness) are reported to occur in up to 50 - 100 per 10 000 patients treated for 5 years, placebo-controlled RCTs indicate that almost all of these incidences are incorrectly attributed to the statin and are more likely to be due to another cause.[34] It is not necessary

**Table 7. Practical guide to initiating statins depending on baseline LDL-C and target LDL-C values*†**

| Starting LDL-C (mmol/L) | Goal: <1.8 mmol/L | | Goal: <2.5 mmol/L | | Goal: <3.0 mmol/L | |
|---|---|---|---|---|---|---|
| | % Reduction required | Statin dose | % Reduction required | Statin dose | % Reduction required | Statin dose |
| >6.2 | >70‡ | Rosuvastatin 40 mg<br>Atorvastatin 80 mg | >60† | Rosuvastatin 40 mg<br>Atorvastatin 80 mg | >55 | Rosuvastatin 40 mg<br>Atorvastatin 80 mg |
| 5.2 - 6.2 | 65 - 70‡ | Rosuvastatin 40 mg<br>Atorvastatin 80 mg | 50 - 60 | Rosuvastatin 20 mg<br>Atorvastatin 40 mg | 40 - 55 | Rosuvastatin 10 mg<br>Atorvastatin 20 mg |
| 4.4 - 5.2 | 60 - 65‡ | Rosuvastatin 40 mg<br>Atorvastatin 80 mg | 40 - 50 | Rosuvastatin 10 mg<br>Atorvastatin 20 mg<br>Simvastatin 40 mg | 30 - 45 | Rosuvastatin 5 mg<br>Atorvastatin 10 mg<br>Simvastatin 20 mg<br>Lovastatin 40 mg<br>Fluvastatin 80 mg |
| 3.9 - 4.4 | 55 - 60 | Rosuvastatin 40 mg<br>Atorvastatin 80 mg | 35 - 40 | Rosuvastatin 5 mg<br>Atorvastatin 10 mg<br>Simvastatin 20 mg<br>Lovastatin 40 mg<br>Fluvastatin 80 mg | 25 - 30 | Rosuvastatin 5 mg<br>Atorvastatin 10 mg<br>Simvastatin 10 mg<br>Lovastatin 20 mg<br>Pravastatin 40 mg<br>Fluvastatin 80 mg |
| 3.4 - 3.9 | 45 - 55 | Rosuvastatin 10 mg<br>Atorvastatin 40 mg | 25 - 35 | Rosuvastatin 5 mg<br>Atorvastatin 10 mg<br>Simvastatin 10 mg<br>Lovastatin 20 mg<br>Pravastatin 40 mg<br>Fluvastatin 80 mg | 10 - 25 | Any statin at lowest dose |
| 2.9 - 3.4 | 35 - 45 | Rosuvastatin 5 mg<br>Atorvastatin 10 mg<br>Simvastatin 20 mg<br>Lovastatin 40 mg<br>Fluvastatin 80 mg | 10 - 25 | Any statin at lowest dose | <10 | Any statin at lowest dose |
| 2.3 - 2.9 | 22 - 35 | Rosuvastatin 5 mg<br>Atorvastatin 10 mg<br>Simvastatin 10 mg<br>Lovastatin 10 mg<br>Pravastatin 20 mg<br>Fluvastatin 40 mg | <10 | Any statin at lowest dose | - | |
| 1.8 - 2.3 | <22 | Rosuvastatin 5 mg<br>Atorvastatin 10 mg<br>Simvastatin 10 mg<br>Lovastatin 10 mg<br>Pravastatin 20 mg<br>Fluvastatin 40 mg | - | | - | |

LDL-C = low-density lipoprotein cholesterol.
*Adapted from 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 2016[5] and Weng T-C, et al., J Clin Pharm Ther 2010;35:139-151.[70]
†Based on weighted average of pooled analysis at starting dose. Dose should be titrated according to response.
‡Maximum LDL-C reduction achievable with high-dose statin monotherapy is 50 - 60%. To achieve a reduction in LDL-C of >60%, another cholesterol-lowering agent in addition to statin therapy may be required. Addition of ezetimibe can increase lipid lowering by ~20% and addition of a PCSK9 inhibitor can increase lipid lowering by ~50 - 70%.

to test muscle enzymes (creatine kinase (CK)) and liver functions (alanine aminotransferase (ALT)) in all patients before initiating treatment with a statin. Consider testing CK at baseline in patients who report unexplained muscle pain or report statin-associated muscle symptoms in the past. ALT should be tested in patients with a past history of hepatic abnormalities or when there is a high clinical suspicion of liver disease (e.g., non-alcoholic fatty liver disease in obese patients, high alcohol intake).

An algorithm for the management of muscle symptoms in statin-treated patients is shown in Appendix 5.

Statins have been associated with a small increased risk of dysglycaemia, new onset diabetes mellitus and a minor, clinically irrelevant elevation of glycated haemoglobin (HbA1c). The number needed to treat (NNT) to cause one new case of diabetes mellitus is estimated at 255 over 4 years, although the risk may be greater with high doses of more potent statins, in the elderly and in individuals with other risk factors for diabetes, such as overweight or insulin resistance. Overall, in high-risk individuals, the absolute reduction in CVD events with statins outweighs the possible risk of diabetes.[6]

### 8.2.3 High-dose simvastatin treatment

In comparison with maximum doses of atorvastatin and rosuvastatin, high doses of simvastatin carry greater risk of both myopathy and clinically significant interactions with other drugs. Therefore,

it is recommended that patients who do not reach their LDL-C goal with 40 mg simvastatin, or who need to start taking another drug that may interact with simvastatin, should be switched to an appropriate alternative statin, such as rosuvastatin or atorvastatin. If it is necessary to co-prescribe simvastatin with other drugs, do not exceed 10 mg simvastatin with amiodarone, verapamil or diltiazem, and do not exceed 20 mg simvastatin with amlodipine. Simvastatin is contraindicated with azole antifungals, macrolide antibiotics, HIV protease inhibitors, gemfibrozil, cyclosporine and danazol.[69]

#### 8.2.4 Scheme for introducing statin treatment

- First evaluate the Framingham risk in primary prevention, or identify the patient as deserving of secondary prevention.
- Involve the patient in CV risk management decisions.
- Identify the appropriate LDL-C target.
- Calculate percentage reduction in LDL-C required to reach target.
- Choose the statin (and dose) able to achieve the desired reduction (Table 7).
- Choice of statin should also be appropriate considering comorbidities, concomitant drug therapy, tolerability and affordability.
- The dose of statin should be up-titrated to achieve the LDL-C target (and a 50% reduction in LDL-C if baseline LDL-C is between 1.8 and 3.5 mmol/L in individuals at very high risk or between 2.5 and 5.2 mmol/L in those at high risk (Table 5), unless adverse effects prohibit further dose modification).
- If target is not reached at maximal dose, consider a more potent statin or add a lipid-lowering drug from another class.

### 8.3 Ezetimibe

In the IMPROVE-IT study, the cholesterol absorption inhibitor ezetimibe in combination with a statin was shown to incrementally reduce LDL-C and to reduce the incidence of myocardial infarction (MI), coronary revascularisation, ischaemic stroke and cardiovascular mortality in patients who had been hospitalised for acute coronary syndrome.[28] Reducing LDL-C to levels as low as 1.4 mmol/L was safe and well tolerated and the reduction in events was consistent with the magnitude of LDL-C achieved and those reported in other studies.[31]

Ezetimibe is recommended:

- as second-line treatment in combination with a statin when the LDL-C target is not achieved with the highest tolerated statin dose
- when there is intolerance to statins
- when there is a contraindication to a statin.

### 8.4 PCSK9 inhibitors

The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a new class of lipid-lowering drugs. Under normal conditions, PCSK9 binds to LDL receptors and prevents them from recycling to the cell surface after internalisation. Inhibition of PCSK9 therefore facilitates recycling of the receptor leading to increased expression of LDL receptors on the surface of hepatocytes, which significantly enhances clearance of circulating LDL.[71] In a range of patients, including those with diabetes or pre-existing atherosclerotic disease, a PCSK9 inhibitor administered subcutaneously once every 2 or 4 weeks reduced LDL-C levels by ~50 - 70%. There was a consistent relationship between lower achieved LDL-C and lower risk of CV events that was significant within the first year of treatment. Treatment with the PCSK9 inhibitor was safe and well tolerated, including patients reaching LDL-C levels <0.2 mmol/L.[29,72-78] To date, two PCSK9 inhibitors, evolocumab and alirocumab, have been licensed by EU and US medicines regulatory authorities.

Patients for whom a PCSK9 inhibitor might be considered are listed in Table 8. Groups 1 and 2 are at the highest risk of CVD events and would therefore gain the most benefit from drug treatment, and therefore should be prioritised where cost prohibits wider use.

We would recommend that a national registry be established for such high-risk patients, including those with a formal diagnosis of FH, and that use of the PCSK9 inhibitors be restricted to patients enrolled in this national database.

### 8.5 Management of hypertriglyceridaemia

Pharmacotherapy for management of hypertriglyceridaemia should be considered in patients at high and very high risk of CVD and/or pancreatitis and with TG >2.3 mmol/L. Unless hypertriglyceridaemia exceeds 10 mmol/L, the preferred treatment is a statin. There is uncertainty as to the best management approach when TG remain >2.3 mmol/L despite optimal statin therapy, but, based on a retrospective analysis of the ACCORD study, addition of fenofibrate may be considered.[80,81] Unless there is a specific indication to justify their use, other combination therapies are discouraged.

Although n-3 fatty acids reduce TGs, their effects on other lipoproteins are negligible and, at present, there is insufficient evidence to recommend them for routine management of hypertriglyceridaemia.

Severe hypertriglyceridaemia (TG >10 mmol/L) is associated with a significant risk of pancreatitis and preventative strategies should be implemented as a matter of urgency. Patients may require admission to hospital with careful monitoring of TG levels and, where appropriate, investigation for a secondary cause. Dietary calories and fat content (10 - 15% recommended) should be restricted, alcohol is forbidden, and diabetes, a frequent precipitant, should be treated aggressively (start or intensify insulin) if it is present. Fibrate therapy (fenofibrate) should be initiated either as monotherapy or in combination with n-3 fatty acids (2 - 4 g/day) or nicotinic acid. Where it is necessary, plasmapheresis may be considered, and causes rapid reduction in TG levels.

### 8.6 Pharmacotherapy affecting high-density lipoprotein cholesterol

While low levels of HDL-C are predictive of CVD risk, pharmacotherapy aimed exclusively at modifying HDL-C has not been shown to be of any benefit in reducing atherosclerotic events. Statins and fibrates increase HDL-C levels to a similar degree, but the efficacy of fibrates may be attenuated in people with type 2 diabetes.

### 8.7 Bile acid sequestrants

Bile acid sequestrants and nicotinic acid have cholesterol-lowering properties. They may occasionally be useful alone or in combination with statin therapy. However, their side-effects limit wider application and their use is discouraged. Bile acid sequestrants are not readily available in SA.

## 9. Approach to primary prevention

Risk factor scoring has its limits and in primary prevention may over- or underestimate actual risk. Furthermore, there are currently insufficient numbers of primary prevention trials to make strong recommendations about the use of statins in populations with intermediate Framingham risk scores.[82] Under these circumstances, where a patient is considered to be at moderate risk and where there is uncertainty about whether to initiate drug therapy, the use of novel biomarkers of CVD (e.g. high-sensitivity C-reactive protein (hsCRP)) and imaging technologies (e.g.

**Table 8. Patients who may be appropriate for a PCSK9 inhibitor[79]**

| | |
|---|---|
| 1. Patients with atherosclerotic CVD (CAD, symptomatic PAD, ischaemic stroke) at very high risk who have substantially elevated LDL-C levels despite maximally tolerated statin with or without ezetimibe therapy, and thus are considered at particularly high risk of an adverse CV outcome. | A) LDL-C >3.6 mmol/L |
| | B) LDL-C >2.6 mmol/L and with additional indices of risk severity, including:<br>• FH<br>• diabetes mellitus with target organ damage or a major risk factor (e.g., marked hypertension)<br>• severe and/or extensive atherosclerotic CVD (e.g., severe polyvascular disease or extensive coronary disease*) |
| 2. FH patients without clinically diagnosed ASCVD, at high or very high cardiovascular risk, and with substantially elevated LDL-C levels despite maximally tolerated statin plus ezetimibe therapy. | A) No additional indices of risk severity and LDL-C >4.5 mmol/L |
| | B) LDL-C >3.6 mmol/L with additional indices of risk severity:<br>• diabetes mellitus with target organ damage or a major risk factor (e.g., marked hypertension)<br>• Lp(a) >50 mg/dL (>125 nmol/L)<br>• major risk factors: smoking, marked hypertension<br>• premature CVD in first-degree relative<br>• imaging indicators of extensive atherosclerosis (e.g., carotid artery ultrasound; CTA*) |
| 3. Patients with atherosclerotic CVD and at very high risk who do not tolerate appropriate doses of at least three statins and who have elevated LDL-C levels despite alternative lipid-lowering therapies, such as ezetimibe. | |

PCSK9 = proprotein convertase subtilisin/kexin type 9; CVD = cardiovascular disease; CAD = coronary artery disease; PAD = peripheral artery disease; LDL-C = low-density lipoprotein cholesterol; FH = familial hypercholesterolaemia; ASCVD = atherosclerotic cardiovascular disease; Lp(a) = lipoprotein(a); CTA = computed tomography angiography.
*Markers of high risk with coronary computed tomography angiography (CTA):
1. Global high-risk markers: left main disease, proximal left anterior descending disease, 3-vessel coronary disease
2. Focal high-risk markers: stenosis severity >50% luminal obstruction, lesion composition: mixed or non-calcified (reflecting earlier, unstable atherosclerosis).

coronary calcium scoring, carotid intima-media thickness) might be helpful to refine risk assessment.[5] However, it should be borne in mind that their role is in supporting a decision to treat rather than to justify not treating. Modalities include the following:

### 9.1 Lipoprotein(a)

Recent studies have identified elevated lipoprotein(a) (Lp(a)) as a causal and independent risk factor for CVD.[83] Lp(a) concentration is genetically determined and is stable over time. Risk is considered important when Lp(a) is >50 mg/dl (>125 nmol/L). Screening is not recommended for the general population, but may be considered for reclassification of subjects falling on a borderline between moderate and high risk. Lp(a) screening can also be considered for selected individuals at high CVD risk, including those with premature CVD, FH, a family history of premature CVD and/or elevated Lp(a), recurrent CVD despite optimal lipid-lowering treatment, and risk ≥15% on the 10-year Framingham risk tables.

### 9.2 Lipoprotein particle size

The metabolic syndrome is associated with small dense LDL that, in conjunction with mild hypertriglyceridaemia and low HDL-C levels, indicates higher CVD risk (Table 9).[84] Although subclasses of LDL may contribute differently to risk estimation and may be of benefit in risk assessment at the border of risk level for decision of drug prescription, there are no studies that have prospectively evaluated this approach. Measurement of LDL particle size is not part of the diagnostic criteria for the metabolic syndrome and is therefore not recommended, but may help to identify patients with dysbetalipoproteinaemia or lipoprotein X.

### 9.3 High-sensitivity C-reactive protein

hsCRP is a nonspecific inflammatory marker that may be elevated in many infectious or non-infectious inflammatory conditions. In the absence of other causes, elevated hsCRP may signify an increased risk of CVD. Ideally, hsCRP should be <1 mg/L, whereas hsCRP >3 mg/L signifies high risk of CVD and hsCRP >10 mg/L is likely to be due to another inflammatory cause. In selected individuals where there is uncertainty regarding initiation of statin treatment, hsCRP >2 mg/L supports revising the risk assessment upward.[85] hsCRP is included in the Reynolds risk score assessment (Appendix 2).

### 9.4. Coronary artery calcium score

Coronary artery calcium (CAC) indicates atherosclerosis and its extent relates to total plaque burden. It is considered to be the most robust predictor of CV events in asymptomatic patients, allowing improved accuracy and personalisation of CV risk, especially among those with intermediate risk based on risk factor scoring.[86]

CAC is most commonly quantified by the Agatston method (Table 10). A CAC score of 0 is consistently associated with low (~ 1%) 10-year CVD risk, regardless of risk factor status. Conversely, a CAC score >400 is considered justification for modification of an intermediate CVD risk factor score.[5,86]

CAC does not predict degree of atherosclerotic stenosis or soft plaque and is of no value in symptomatic patients, or those who are already on treatment. Serial CAC scans do not add significantly to risk prediction and are not recommended. However, in a patient with an initial CAC score of 0 and who is not on statin therapy, a repeat scan may be considered after 5 years, when a second CAC score of 0 is highly predictive and reassuring of very low CVD risk.[87]

### 9.5 Carotid ultrasound

There is a correlation between the severity of atherosclerosis in one arterial territory and the involvement of other arteries. Carotid ultrasound is commonly used to establish the presence of atherosclerosis

and may be used to measure both intima-medial thickness (cIMT) and the presence and characteristics of atherosclerotic plaques. cIMT is a measure of both early atherosclerosis and smooth muscle hypertrophy/hyperplasia and a value >0.9 mm is considered abnormal. However, the risk of stroke or cardiac events associated with cIMT is non-linear, with risk increasing more rapidly at lower cIMTs and clinical studies have been unable to demonstrate any additional benefit of cIMT over Framingham risk analysis in predicting CVD risk. Therefore, routine measurement of cIMT is not recommended for risk assessment for a first atherosclerotic vascular event.

In contrast, the presence of carotid plaque is a stronger and more accurate predictor of CVD risk. Plaque is defined as a focal structure of the inner vessel wall at least ≥0.5 mm (or ≥50% thickening of IMT), or any cIMT measurement ≥1.5 mm that protrudes into the lumen. CVD risk increases incrementally with increasing number of plaques, and with plaque volume, area and thickness. Therefore, in selected individuals, carotid artery plaque assessment may be considered a risk modifier, where identification of carotid plaque places the individual in the high or very high risk category.[6,88,89]

# 10. Special patient populations

## 10.1 Screening and statin therapy in children younger than 16 years of age

Atherosclerosis begins at an early age. In autopsy studies, fatty streaks were observable in the aorta of all and in the coronary arteries of 50% of children aged between 2 and 15 years of age. Approximately 20% and 8% already had raised fibrous plaque lesions in the aorta and coronary arteries, respectively. The severity of atherosclerosis increased significantly with increasing number of CV risk factors (body mass index, BP, TC, TG, LDL-C, HDL-C, smoking).[90] Accordingly, assessment of cardiovascular risk factors and dietary and lifestyle intervention for CVD needs to begin at an early age in all children. Cholesterol screening is appropriate from 8 years of age in children with family history of FH or any other reasons to be considered at high CVD risk. Children with CKD are of particular concern. Potentially modifiable CV risk factors (especially anaemia) are commonly present even in early CKD, and routine screening and timely intervention are essential to prevent progression of CVD and early mortality.[91]

When to begin statin therapy for children with FH or who are at high risk for CVD is a matter of clinical judgement, but is usually appropriate beginning from age 8 years, especially if additional risk factors are present.

**SI Units conversion**

**Cholesterol:**

mmol/L = mg/dL × 0.0259

mg/dL = mmol/L × 38.6

**Triglyceride:**

mmol/L = mg/dL × 0.0113

mg/dL= mmol/L × 88.5

## 10.2 Young adults

CV risk charts may underestimate risk in young people with high levels of risk factors, in that a low absolute risk may conceal a very high relative risk requiring intensive lifestyle advice. Consequently, showing the patient an estimate of their heart (vascular or relative risk) age and how that might be reduced by lifestyle change can be more effective in motivating lifestyle modification (Appendix 2). Heart age is independent of the CV endpoint used (i.e. CV mortality or total CVD events) and can be used in any population regardless of the baseline risk or secular changes in mortality. It is the age that corresponds to the age of a person with the same level of risk, but with ideal levels of risk factors. In people with CV risk factors, heart age can be substantially older than the individual's chronological age.[5,92,93]

## 10.3 HIV infection

SA has the largest HIV epidemic worldwide, with approximately one-fifth of all infected individuals and 270 000 new infections in 2016.[94,95] The phenotype of SA patients with HIV infection is different to that in developed countries, where the predominantly affected individuals are white males with an average age of 45 years, and both HIV infection and antiretroviral treatment, the latter partly because of treatment-induced dyslipidaemia, are independently associated with an increased risk of CV and cerebrovascular events.[95-98] In contrast, in SA, the prevalence of HIV is highest among black females aged 30 - 34 years and the rate of new infections among women aged 15 - 24 years is more than 4 times that of men of the same age.[99] Compared with HIV-negative individuals, significant cardiometabolic risk factors are not more common (and may be less common) in those with HIV infection and LDL-C levels are usually not elevated. Furthermore, although ART may be associated with small changes in the lipid profile, severe lipid abnormalities that require evaluation and treatment are uncommon.[100-103]

Consequently, considering their age and the low prevalence of other CVD risk factors, HIV-positive SA patients are considered to be at low risk for CVD events and recommendations for lipid management and indications for lipid-lowering drugs in HIV-positive patients are the same as for HIV-negative individuals. There is no validated risk score for HIV-infected black South Africans and the Framingham risk tables may be used to aid decision-making.

Nevertheless, with the exception of those who have severe risk factors for CVD (e.g. FH), it is currently unknown how to accurately predict risk for individuals with HIV. At least in some populations, it is likely that conventional risk tables underestimate CV risk.[104] Diet and lifestyle modification should always be advised and other CV risk factors must be addressed.

A full lipogram should be performed before initiating ARV treatment. It should be repeated at 3 months after starting treatment with a protease inhibitor and thereafter periodically while on therapy. In patients with high lipid levels who are already on ARV treatment, switching to an alternative ARV and cautious use of a statin or fibrate should be

**Table 9. Diagnostic criteria for metabolic syndrome[84]**

| At least 3 of: | |
|---|---|
| 1. Elevated waist circumference | Men ≥94 cm; women ≥80 cm |
| 2. Elevated TG* | ≥1.7 mmol/L or on TG-lowering therapy |
| 3. Reduced HDL-C | Men <1.0 mmol/L; women <1.3 mmol/L |
| 4. Elevated BP* | Systolic ≥130 and/or diastolic ≥85 mmHg or on antihypertensive therapy |
| 5. Elevated fasting glucose* | ≥5.6 mmol/L or on treatment for type 2 diabetes |

TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; BP = blood pressure.
*Criterion is regarded as positive if the patient is on treatment directed at this variable.

**Table 10. Agatston classification of coronary artery calcification (CAC)[86]**

| Total calcium score | Classification |
|---|---|
| 0 | no CAC |
| 1 - 10 | minimal CAC |
| 11 - 100 | mild CAC |
| 101 - 400 | moderate CAC |
| >400 | severe CAC |
| >1 000 | very severe CAC |

considered as necessary. Atorvastatin is the statin of choice in patients with HIV. Because of a high risk of drug interactions with ARVs, simvastatin is contraindicated and rosuvastatin is not recommended.[105]

Before prescribing, it is recommended that clinicians refer to the detailed and interactive information about drug-drug interactions between lipid-lowering agents and ARVs available from www.hiv-druginteractions.org.

### 10.4 The older adult

CVD is a common cause of both morbidity and mortality among adults older than 75 years of age, who are also frequently affected by comorbidities, including diabetes mellitus, hypertension, hyperlipidaemia and renal dysfunction. Because the absolute risk of CV events is very high in this group, even a small relative benefit from treatment may be clinically significant. However, evidence for lipid-lowering therapy in older individuals, and data on choice of statin and dose, are limited. In primary and secondary prevention studies, statin therapy was associated with a reduction in myocardial infarction and stroke and, in secondary prevention studies also with a reduction in cardiovascular mortality.[106-110] Statins may also reduce cognitive decline.[111-113] The ongoing Australian STAREE randomised trial of atorvastatin among adults aged ≥70 years is expected to provide further guidance on statin use in this population.[114]

Age, comorbidity and polypharmacy increase the risk of drug-drug interactions, side-effects and myopathy, and adherence to medication among older patients is often poor. The Framingham risk estimates are unreliable in older individuals who will be placed in the high-risk categories merely based on age and gender. Risk tables for older patients have been developed based on the SCORE tables, but these have not been validated in a South African population.[115] Therefore, clinical judgement should be used to guide treatment decisions and avoid side-effects and overmedication. Unless there is a specific reason to stop, patients who are already on a statin should continue with treatment into older age. Decisions on whether to initiate new therapy should be made jointly by the clinician and patient and/or their family, with careful consideration of pre-existing dementia, disability and dependence on caregivers.

Where statins are prescribed, it would seem prudent to start at a low dose with agents that do not commonly interact with other drugs and cautiously titrate the statin to achieve target lipid levels.

### 10.5 Chronic kidney disease

Chronic kidney disease (CKD) is associated with dyslipidaemia, which worsens with decreasing GFR. The initial stages of CKD are characterised by elevated TG and low HDL-C, whereas TC and LDL-C levels are also raised in end-stage renal disease (ESRD), with a shift towards an excess of small, dense LDL particles. Individuals with a GFR of 30 - 59 mL/min/1.73 $m^2$ or <30 mL/min/1.73 $m^2$ are considered to be at high and very high CV risk, respectively, and do not require Framingham risk scoring.

The safety of statins in CKD has been well established. A statin with or without ezetimibe is recommended for management of dyslipidaemia in patients with non-dialysis-dependent CKD.

Statins should not be initiated in patients with dialysis-dependent CKD who are free of atherosclerotic CVD, but where a statin and/or ezetimibe has been initiated before dialysis, they should be continued if dialysis is required. For detailed information about lipid management in patients with CKD, readers are referred to the KDIGO lipid management guidelines (www.kdigo.org).[116]

## 11. Secondary prevention

In patients presenting with acute coronary syndrome (ACS), a lipid profile should be obtained at the time of admission. Regardless of initial LDL-C values, they should be treated with high-intensity lipid-lowering therapy during their acute care, which should be continued after discharge. The dose of lipid-lowering therapy at discharge is based on lipid values at admission and the patient's target values. All patients with proven atherosclerotic disease require a target LDL-C concentration <1.8 mmol/L and a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L. Lipids should be re-evaluated 4 - 6 weeks after discharge to determine whether target levels have been achieved and to evaluate any safety issues. Doses should be adjusted accordingly. If the LDL-C target is not reached with the highest tolerable statin dose, consider addition of ezetimibe and, if necessary and appropriate, a PCSK9 inhibitor.

Routine short pre-treatment or loading (on the background of chronic therapy) with high-dose statins before percutaneous coronary intervention (PCI) should be considered in elective PCI or in non-ST segment elevation ACS.

## 12. Residual risk

Partly because of the significant levels of atherosclerotic disease that are already present before treatment is initiated, even with the best therapy, and despite therapy, there remains a significant residual CV event rate.[28,29,72-74] Patients who appear to be at LDL-C goal, yet still experience recurrent events must be considered for even lower target lipid levels. Research into ameliorating residual risk is ongoing, including use of fibrates, omega-3 fatty acids, more intense lowering of LDL-C, as well as anti-inflammatory therapies.

Clinicians and their patients must be open to aggressive management of all risk factors, including hypertension, plasma glucose, healthy eating habits and exercise, as well as meticulous adherence to prescribed interventions. Where it is appropriate and indicated, antithrombotic therapy should also be considered.

## 13. Adherence to therapy

Adherence to prescribed therapy declines over time. It has been reported that as many as three-quarters of patients receiving statins for primary prevention discontinue their medication within 2 years. However, this is not unique to statins and applies to all drugs prescribed for CVD. The nonadherence rates are significantly greater for medicines prescribed for primary than for secondary prevention.[117-119] In contrast, the benefit of statin treatment increases incrementally with duration of therapy.[34]

Shared decision making, with frank and open discussion of the benefits and risks of both treating and not treating, may facilitate decisions on how to proceed and adherence to the chosen management strategy.[120]

## 14. Public health

### 14.1 Dyslipidaemia is a prescribed minimum benefit

In South Africa, dyslipidaemia is classified under section 29(1) of

the Medical Schemes Act as a prescribed minimum benefits (PMB) condition. Consequently, it is mandatory for medical schemes to cover the related costs of diagnosis and treatment.

### 14.2 New government treatment recommendations

In contrast to the recommendations of this guideline to treat to a predefined, patient-specific target with ongoing monitoring and adjustment of therapy, new government recommendations for the treatment of dyslipidaemia in South Africa advocate aiming for 1 mmol/L reduction in LDL-C in all patients regardless of baseline LDL-C with a 'fire and forget' approach (personal communication, Ms K Jamaloodien, National Department of Health, 4 November 2017). Furthermore, the general recommendation is to prescribe 10 mg simvastatin, which will not be sufficient to achieve even a 1 mmol/L reduction of LDL-C in many patients.

It is the opinion of SA Heart and LASSA that this overly generalised approach is clinically irresponsible and will not be cost effective, considering the potential costs of managing dyslipidaemia appropriately as set out in this guideline versus those related to management of patients who survive a cardiovascular event.

## 15. When to refer

The following patients should be referred for specialist assessment:

- high risk individuals who do not achieve target lipid levels despite optimised treatment
- unexplained cutaneous or tendinous lipid deposits (xanthomata)
- very premature vascular disease
- dyslipidaemia associated with endocrine, metabolic, or neurological disorders
- unusually low TC (<2.5 mmol/L) in untreated patients
- unusually high TG (>10 mmol/L), TC (>15 mmol/L), LDL-C (>10 mmol/L) or HDL-C (>3.0 mmol/L).

## 16. Conclusions: Implementation of the 2018 guidelines

To implement the guidelines, we propose a risk assessment chart based on the Framingham risk tables (Appendix 1). The chart is a guide to management only and should not replace an individualised assessment and treatment plan based on the clinical judgement of the doctor. We encourage the reader to read the 2016 European guidelines in full, which may be accessed on the ESC website www.escardio.org/guidelines. We hope that dissemination of these guidelines will go some way towards helping to reduce the burden of CVD in SA.

## 17. Mechanism of guideline preparation

In November 2017, a broad-based group of participants from the medical and allied health community, medical funders, pharmaceutical companies, the Department of Health and the Board of Health Funders met in Johannesburg to examine and discuss the joint ESC/EAS dyslipidaemia guidelines. The following day, a writing committee met to construct the South African Consensus Document, which was revised and finalised by the same committee over the ensuing 3 months.

In addition to the writing committee, delegates attending the Dyslipidaemia Guidelines Meeting Discussion Group were Dr C Badenhorst (cardiologist, SASCI), Mrs G Bartlett (Universal Care), Ms M Campbell (Discovery Health), Dr J Carapinha (Carapinha & Company), Mrs T Celliers (MSD), Mrs C de la Motte (Sandoz), Mr D Craythorne (Cipla), Prof. JA Dave (endocrinologist, University of Cape Town), Mrs E Fourie (Mediscor), Dr N Habangana (MSD), Mrs S Hassan (Medscheme), Ms C Henning (Amgen), Ms K Jamaloodien (National Department of Health), Prof. SZ Kalula (geriatrician, University of Cape Town), Mr G Kumalo (Aspen), Dr E Lai (Sanofi), Dr D Makgai (Pfizer Laboratories), Prof. E Makotoko (cardiologist, University of the Free State), Dr P Masopha (Sanlam Health Management), Dr N Mohamed (endocrinologist, University of the Witwatersrand and SEMDSA), Mr K Mungar (Pharma Dynamics), Dr P Naidoo (Sanofi), Dr V Ndungane-Tlakula (Amgen), Mr A Nicolson (MSD), Prof. M Ntsekhe (cardiologist, University of Cape Town), Dr R Patel (BHF), Ms N Ramushi (Abbott Laboratories), Mrs E Schaafsma (SA Heart), Dr D Segal (paediatric endocrinologist), Mr F Smuts (Abbott Laboratories), Prof. N Wearne (nephrologist, University of Cape Town) and Mrs T Woodman (Pharma Dynamics).

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**Author contributions.** This South African Consensus Document was authored exclusively by the writing committee listed below. All authors participated in the guidelines workshop and discussion meetings, contributed to content and reviewed and edited the initial and final drafts of the manuscript. The additional delegates listed above did not contribute to the writing of the document and the companies who provided unconditional grants had no influence over the content of the Consensus Document.

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1. De Backer G, Ambrosioni E, Borch-Johnson K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2003;24:1601-1610. https://doi.org/10.1016/j.atherosclerosis.2016.05.037
2. South African Medical Association and Lipid and Atherosclerosis Society of Southern Africa Working Group. Diagnosis, management and prevention of the common dyslipidaemias in South Africa - Clinical Guideline, 2000. S Afr Med J 2000;90:164-178.
3. Reiner Ž, Catapano AL, De Backer G, et al, for the Task Force for the management of dyslipidaemias of the European Society for Cardiology (ESC) and the European Atherosclerosis Society (EAS). ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 2011;32:1769-1818. https://doi.org/10.1093/eurheartj/ehr158
4. South African Heart Association (SA Heart) and the Lipid and Atherosclerosis Society of Southern Africa (LASSA). SA Dyslipidaemia Consensus Guidelines Statement. S Afr Med J 2012;102:177-188.
5. Catapano AL, Graham I, De Backer G, et al, The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 2016;37:2999-3058. https://doi.org/10.1093/eurheartj/ehw272
6. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37(29):2315-2381. https://doi.org/10.1093/eurheartj/ehw106
7. Steyn K, Sliwa K, Hawken S, et al, for the INTERHEART Investigators in Africa. Risk factors associated with myocardial infarction in Africa: the INTERHEART Africa study. Circulation 2005;112:3554-3561. https://doi.org/10.1161/CIRCULATIONAHA.105.563452.
8. Yusuf S, Hawken S, Ôunpuu S. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. Lancet 2004;364(9438):937-952. https://doi.org/10.1016/s0140-6736(04)17018-9
9. Sliwa K, Acquah L, Gersch BJ, et al. Impact of socioeconomic status, ethnicity, and urbanization on risk factor profiles of cardiovascular disease in Africa. Circulation 2016;133:1199-1208. https://doi.org/10.1161/CIRCULATIONAHA.114.008730
10. Mayosi BM, Flisher AJ, Lalloo UG, et al. The burden of non-communicable disease in South Africa. Lancet 2009;374:934-947. https://doi.org/10.1016/S0140-6736(09)61306-4
11. The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. Epidemiology of type 2 diabetes. In 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. J Endocrinol Metabol Diab 2017;21(1)(Supplement 1):S1-S196.
12. Blom DJ. Familial hypercholesterolaemia. J Endoccrinol Metabol Diab 2011;16(1):17-24.
13. Akioyamen LE, Genest J, Shan SD, et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: A systematic review and meta-analysis. BMJ Open 2017;7:e016461. https://doi.org/10.1136/ bmjopen-2017-016461
14. Steyn K. Heart disease in South Africa. Media data document. Heart and Stroke Foundation South Africa, July 2007.
15. Mayosi BM, Benatar SR. Health and healthcare in South Africa – 20 years after Mandela. N Engl J Med 2014;371(14):1344-1353. https://doi.org/10.1056/NEJMsr1405012
16. Norman R, Bradshaw D, Steyn K, et al. Estimating the burden of disease attributable to high cholesterol in South Africa in 2000. S Afr Med J 2007;97:708-715.
17. US Preventative Services Task Force. Screening for lipid disorders in children and adolescents. US Preventive Services Task Force Recommendation Statement. JAMA 2016;316(6):625-633. https://doi.org/10.1001/jama.2016.9852
18. Nordestgaard BG. A test in context: Lipid profile, fasting versus non-fasting. J Am Coll Cardiol 2017;70(13):1637-1646. https://doi.org/10.1016/j.jacc.2017.08.006
19. Nordestgaard BG, Langsted A, Mora S, et al. Fasting is not routinely required for determination of a lipid profile: Clinical and laboratory implications including flagging at desirable concentration cut-points – joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. Eur Heart J 2016;37:1944-1958. https://doi.org/10.1093/eurheartj/ehw152
20. Batki AD, Nayyar P, Thomason HL. Buyer's guide: Point-of-care testing for cholesterol measurement. http://www.healthcheck.nhs.uk/Library/pointofcare_testing_for_cholesterol_measurement.pdf. (accessed 26 October 2011).
21. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: A HuGE prevalence review. Am J Epidemiol 2004;160(5):407-420. https://doi.org/10.1093/aje/kwh236
22. Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Br Med J 1991;303(6807):893-896. https://doi.org/10.1136/bmj.303.6807.893
23. Scientific Steering Committee on behalf of the Simon Broome Register Group. Mortality in treated heterozygous familial hypercholesterolaemia: Implications for clinical management. Atherosclerosis 1999;142:105-112.
24. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women 2011 update: A guideline from the American Heart Association. Circulation 2011;123:1243-1262. https://doi.org/10.1161/CIR.0b013e31820faaf8
25. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743-753. https://doi.org/10.1161/CIRCULATIONAHA.107.699579
26. The Cholesterol Treatment Trialists (CTT) Collaboration. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-1278. https://doi.org/10.1016/S0140-6736(05)67394-1
27. Cholesterol Treatment Trialists (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010; 376: 1670-1681. https://doi.org/10.1016/S01406736(10)613505
28. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387-2397. https://doi.org/10.1056/NEJMoa1410489
29. Giugliano RP, Pedersen TR, Park JG, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: A prespecified secondary analysis of the FOURIER trial. Lancet 2017;390(10106):1962-1971. https://doi.org/10.1016/S0140-6736(17)32290-0
30. Koskinas KC, Siontis GCM, Piccolo R, et al. Effect of statins and non-statin LDL-lowering medications on cardiovascular outcomes in secondary prevention: A meta-analysis of randomized trials. Eur Heart J 2017;39(14):1172-1180. https://doi.org/10.1093/eurheartj/ehx566 https://doi.org/10.1093/eurheartj/ehx566
31. Soran H, Dent R, Durrington P. Evidence-based goals in LDL-C reduction. Clin Res Cardiol 2017;106:237-248. https://doi.org/10.1007/s00392-016-1069-7
32. Cholesterol Treatment Trialists (CTT) Collaboration. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: Meta-analysis of individual data from 27 randomised trials. Lancet 2012;380(9841):581-590. https://doi.org/10.1016/S0140-6736(12)60367-5
33. Cholesterol Treatment Trialists (CTT) Collaboration. Efficacy and safety of LDL-lowering therapy among men and women: Meta-analysis of individual data from 174 000 participants in 27 randomised trials. Lancet 2015;385(9976):1397-1405. https://doi.org/10.1016/S0140-6736(14)61368-4
34. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016;388:2532-2561. https://doi.org/10.1016/50140-6736(16)31357-5
35. Schwingshackl L, Bogensburger B, Hoffman G. Diet quality as assessed by the Healthy Eating Index, Alternate Healthy Eating Index, Dietary Approaches to Stop Hypertension Score, and Health Outcomes: An updated systematic review and meta-analysis of cohort studies. J Acad Nutr Diet 2018;118:74-100. https://doi.org/10.1016/j.jand.2017.08.024
36. Jones NRV, Forouhi NG, Khaw KT, et al. Accordance to the Dietary Approaches to Stop Hypertension diet pattern and cardiovascular disease in a British, population-based cohort. Eur J Epidemiol 2018;33(2):235-244. https://doi.org/10.1007/s10654-017-0354-8
37. Fitzgerald KC, Chiuve SE, Buring JE, et al. Comparison of associations of adherence to a Dietary Approaches to Stop Hypertension (DASH)-style diet with risks of cardiovascular disease and venous thromboembolism. J Thromb Haemost 2012;10(2):189-198. https://doi.org/10.1111/j.1538-7836.2011.04588.x
38. Salehi-Abarqouei A, Maghsoudi Z, Shriani F, Azadbakht L. Effects of Dietary Approaches to Stop Hypertension (DASH)-style diet on fatal or nonfatal cardiovascular diseases incidence: A systematic review and meta-analysis on observational prospective studies. Nutrition 2013;29(4):611-618. https://doi.org/10.1016/j.nut.2012.12.018
39. Sureda A, Bibiloni MDM, Julibert A, et al. Adherence to the Mediterranean Diet and inflammatory markers. Nutrients 2018;10(1):E62. https://doi.org/10.3390/nu10010062
40. Vicinanza R, Troisi G, Cangemi R, et al. Aging and adherence to the Mediterranean Diet: Relationship with cardiometabolic disorders and polypharmacy. J Nutr Health Aging 2018;22(1):73-81. https://doi.org/10.1007/s12603-017-0922-3
41. Rosata V, Temple NJ, La Vecchia C, Castellan G, Tavani A, Guercio V. Mediterranean diet and cardiovascular disease: A systematic review and meta-analysis of observational studies. Eur J Nutr 2017. https://doi.org/10.1007/s00394-017-1582-0
42. Grosso G, Marventano S, Yang J, et al. A comprehensive meta-analysis on evidence of Mediterranean diet and cardiovascular disease: Are individual components equal? Crit Rev Food Sci Nutr 2017;57(15):3218-3232. https://doi.org/10.1080/10408398.2015.1107021
43. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368(14):1279-1290. https://doi.org/10.1056/NEJMoa1200303
44. Vorster HH, Badham JB, Venter CS. An introduction to the revised food-based dietary guidelines for South Africa. S Afr J Clin Nutr 2013;26(3):S1-S164.
45. Gardner CD, Trepanowski JF, Del Gobbo LC, et al. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: The DIETFITS randomized clinical trial. JAMA 2018;319:667-679. https://doi.org/10.1001/jama.2018.0245
46. Davis NJ, Tomuta N, Schechter C, et al. Comparative study of the effects of a 1-year dietary intervention of a low-carbohydrate diet versus a low-fat diet on weight and glycemic control in type 2 diabetes. Diabetes Care 2009;32(7):1147-1152. https://doi.org/10.2337/dc08-2108
47. Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360(9):859-873. https://doi.org/10.1056/NEJMoa0804748
48. Sofi F, Dinu M, Pagliai G, et al. Low-calorie vegetarian versus Mediterranean diets for reducing body weight and improving cardiovascular risk profile: CARDIVEG study (Cardiovascular Prevention With Vegetarian Diet) Circulation 2018;137:1103-1113. https://doi.org/10.1161/CIRCULATIONAHA.117.030088
49. Kelemen LE, Kushi LH, Jacobs DR, Cerhan JR. Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. Am J Epidemiol 2005;161(3):239-249. https://doi.org/10.1093/aje/kwi038
50. Trichopoulou A, Psaltopoulou T, Orfanos P, et al. Low-carbohydrate-high-protein diet and long-term survival in a general population cohort. Eur J Clin Nutr 2007;61(5):575-581. https://doi.org/10.1038/sj.ejcn.1602557
51. Lagiou P, Sandin S, Weiderpass E, et al. Low carbohydrate-high protein diet and mortality in a cohort of Swedish women. J Intern Med 2007;261(4):366-374. https://doi.org/10.1111/j.1365-2796.2007.01774.x
52. Fung TT, van Dam RM, Hankinson SE, et al. Low carbohydrate diets and all-cause and cause-specific mortality. Two cohort studies. Ann Intern Med 2010;153(5):289-298. https://doi.org/10.7326/0003-4819-153-5-201009070-00003
53. Levine ME, Suarez JA, Brandhorst S, et al. Low protein intake is associated with a a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. Cell Metab 2014;19(3):407-417. https://doi.org/10.1016/j.cmet.2014.02.006
54. Noto H, Goto A, Tsujimoto T, Noda M. Low-carbohydrate diets and all-cause mortality: A systematic review and meta-analysis of observational studies. PLoS ONE 2013;8(1): e55030. https://doi.org/10.1371/journal.pone.0055030

55. Sacks FM, Lichtenstein AH, Wu JHY, et al; on behalf of the American Heart Association. Dietary fats and cardiovascular disease: A presidential advisory from the American Heart Association. Circulation 2017;136(3):e1-e23. https://doi.org/10.1161/CIR.0000000000000510
56. Sacks F, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360(9):859-873. https://doi.org/10.1056/NEJMoa0804748
57. Epstein DE, Sherwood A, Smith PJ, et al. Determinants and consequences of adherence to the Dietary Approaches to Stop Hypertension Diet in African-American and white adults with high blood pressure: Results from the ENCORE Trial. J Acad Nutr Diet 2012;112(11):1763-1773. https://doi.org/ https://doi.org/10.1016/j.jand.2012.07.007
58. Anderson CAM. Dietary patterns to reduce weight and optimize cardiovascular health. Persuasive evidence for promoting multiple, healthful approaches. Circulation 2018;137(11): 1114-1116. https://doi.org/10.1161/CIRCULATIONAHA.117.031429
59. Smuts CM, Wolmarans P. The importance of the quality or type of fat in the diet: A food-based dietary guideline for South Africa. S Afr J Clin Nutr 2013;26(3)(Supplement):S87-S99.
60. Department of Health. Foodstuffs, Cosmetics and Disinfectants Act, 1972. (Act No 54 of 1972). Regulations relating to trans-fat in foodstuffs. No. R. 127. Government Gazette; 17 February 2011. https://extranet.who.int/ncdccs/Data/ZAF_B17_Regulationtransfatfoodstuffs.pdf. (accessed 20 February 2018).
61. Violil F, Pignatelli P, Basili S, et al. Nutrition, supplements and vitamins in platelet functions and bleeding. Circulation 2010;121(8):1033-1044. https://doi.org/10.1161/CIRCULATIONAHA.109.880211
62. Mursu J, Robien K, Harnack LJ, et al. Dietary supplements and mortality rate in older women. The IOWA Women's Health Study. Arch Intern Med 2011;171(18):1625-1633. https://doi.org/10.1001/archinternmed.2011.445
63. Marcoff L, Thompson PD. The role of coenzyme Q10 in statin-associated myopathy. A systematic review. J Am Coll Cardiol 2007;49(23):2231-2237. https://doi.org/10.1016/j.jacc.2007.02.049
64. Schaars CF, Stalenhoef AFH. Effects of ubiquinone (coenzyme Q10) on myopathy in statin users. Curr Opin Lipidol 2008;19(6):553-557. https://doi.org/10.1097/MOL.0b013e3283168ecd
65. Metsios GS, Flouris AD, Angioi M, Koutedakis Y. Passive smoking and the development of cardiovascular disease in children: A systematic review. Cardiol Res Prac 2011;2011:587650. https://doi.org/10.4061/2011/587650
66. Whincup PH, Gilg JA, Emberson JR, et al. Passive smoking and risk of coronary heart disease and stroke: Prospective study with cotinine measurement. Br Med J 2004;329(7459):200-205. https://doi.org/10.1136/bmj.38146.427188.55
67. Schraufnagel DE, Blasi F, Drummond MB, et al; Forum of International Respiratory Societies. Electronic cigarettes. A position statement of the Forum of International Respiratory Societies. Am J Respir Crit Care Med 2014;190(6):611-618. https://doi.org/10.1164/rccm.201407-1198PP
68. Dinakar C, O'Connor GT. The health effects of electronic cigarettes. N Engl J Med 2016;375(14):1372-1381. https://doi.org/10.1056/NEJMra1502466
69. Egan A, Coleman E. Weighing the benefits of high-dose simvastatin against the risk of myopathy. N Engl J Med 2011;365(4):285-287. https://doi.org/10.1056/NEJMp1106689
70. Weng T-C, Kao Yang Y-H, Lin S-J, et al. A systematic review and meta-analysis on the therapeutic equivalence of statins. J Clin Pharm Ther 2010;35(2):139-151. https://doi.org/10.1111/j.1365-2710.2009.01085.x
71. Krysa JA, Ooi TC, Proctor SD, et al. Nutritional and lipid modulation of PCSK9: Effects on cardiometabolic risk factors. J Nutr 2017;147(4):473-481. https://doi.org/10.3945/jn.116.235069
72. Sabatine MS, Giugliano RP, Wiviott DS et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372(16):1500-1509. https://doi.org/10.1056/NEJMoa1500858
73. Bonaca MP, Nault P, Giugliano RP, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease. Insights from the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). Circulation 2017;137:338-350. https://doi.org/10.1161/CIRCULATIONAHA.117.032235
74. Sabatine MC, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: A prespecified analysis of the FOURIER randomised controlled trial. Lancet 2017;5(12):941-950. https://doi.org/10.1016/S2213-8587(17)30313-3
75. Robinson J, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372(16):1489-1499. https://doi.org/10.1056/NEJMoal501031
76. Kereiakes D, Robinson J, Cannon C, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study. Am Heart J 2015;169(6):906-915. https://doi.org/10.1016/j.ahj.2015.03.004
77. Kastelein J, Ginsberg H, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Eur Heart J 2015;36(43):2996-3003. https://doi.org/10.1093/eurheartj/ehv370
78. Ginsburg HN, Rader DJ, Raal FJ, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dL or higher. Cardiovasc Drugs Ther 2016;30(5):473-483. https://doi.org/10.1007/s10557-016-6685-y
79. Landmesser U, Chapman MJ, Stock JK, et al. 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. Eur Heart J 2018;39(14):1131-1143. https://doi.org/10.1093/eurheartj/ehx549
80. Ginsberg HN, Elam MB, Lovato LC, et al, The ACCORD Study group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362(17):1563-1574. https://doi.org/10.1056/NEJMoa1001282
81. Nair R, Zachry WM III, Hume AR, Clarke S. Statin-fenofibrate combination therapy in an ACCORD population: A retrospective analysis. Am J Pharm Benefits 2012;4(5):209-216.
82. Huesch MD. Association of baseline statin use among older adults without cardiovascular disease in the SPRINT trial. JAMA Int Med 2018;178(4):560-561. https://doi.org/10.1001/jamainternmed.2017.7844
83. Saeedi R, Frohlich J. Lipoprotein (a), an independent cardiovascular risk marker. Clin Diab Endocrinol 2016;2(1):7. https://doi.org/10.1186/s40842-016-0024-x
84. Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome. A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644
85. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129(25 Suppl 2):S49–S73. https://doi.org/10.1161/01.cir.0000437741.48606.98
86. Weber LA, Cheezum MK, Reese JM, et al. Cardiovascular imaging for the primary prevention of atherosclerotic cardiovascular disease events. Cur Cardiovasc Imaging Rep 2015;8(9):36. https://doi.org/10.1007/s12410-015-9351-z
87. Lehmann N, Erbel RA, Mahabadi AA, et al. Value of progression of coronary artery calcification for risk prediction of coronary and cardiovascular events: Result of the Heinz Nixdorf Recall (HNR) Study. Circulation 2018;137(7):665-679. https://doi.org/10.1161/CIRCULATIONAHA.116.027034.
88. Vlachopoulos C, Xaplanteris P, Aboyans V, et al. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. Atherosclerosis 2015;241:507-532. https://doi.org/10.1016/j.atherosclerosis.2015.05.007
89. Naqvi TZ, Lee MS. Carotid intima-media thickness and plaque in cardiovascular risk assessment. JACC Cardiovasc Imaging 2014;7(10):1025-1038. https://doi.org/10.1016/j.jcmg.2013.11.014
90. Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. N Engl J Med 1998;338(23):1650-1656.
91. Mudi A, Dickens C, Levy C, Ballot D. Cardiovascular risk factors and mortality in children with chronic kidney disease. S Afr Med J 2017;107(8):710-714. https://doi.org/10.7196/SAMJ.2017.v107i8.12271
92. D'Agostino RB Sr, Pencina MJ, Massaro JM, Coady S. Cardiovascular risk assessment: Insights from Framingham. Glob Heart 2013;8(1):11-23. https://doi.org/10.1016/j.gheart.2013.01.001
93. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham Heart Study. Circulation 2008;117:743-753. https://doi.org/10.1161/CIRCULATIONAHA.107.699579
94. UNAIDS. HIV and AIDS in South Africa. https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/south-africa. (accessed 26 January 2018).
95. UNAIDS. Global HIV and AIDS statistics. https://www.avert.org/global-hiv-and-aids-statistics. (accessed 26 January 2018).
96. UNAIDS. HIV and AIDS in Western Europe, Central Europe and North America. . https://www.avert.org/professionals/hiv-around-world/western-central-europe-north-america. (accessed 26 January 2018).
97. DAD study group. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med 2007;356(17):1723-1735.
98. Gutierrez J, Albuquerque ALA, Falzon L. HIV infection as vascular risk: A systematic review of the literature and meta-analysis. PLoS ONE 12(5):e0176686. https://doi.org/10.1371/journal.pone.0176686
99. Shisana O, Rehle T, Simbayi LC, et al. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. Cape Town: HSRC Press, 2014. http://heaids.org.za/site/assets/files/1267/sabssm_iv_leo_final.pdf. (accessed 30 January 2018).
100. Gaziano TA, Abrahams-Gessel S, Gomez-Olive FX, et al. Cardiometabolic risk in a population of older adults with multiple co-morbidities in rural South Africa: The HAALSI (Health and Aging in Africa: Longitudinal studies of INDEPTH communities) study. BMC Public Health 2017;17(1):206. https://doi.org/10.1186/s12889-017-4117-y
101. Dillon DG, Gurdasani D, Riha J, et al. Association of HIV and ART with cardiometabolic traits in sub-Saharan Africa: A systematic review and meta-analysis. Int J Epidemiol 2013;42(6):1754-1771. https://doi.org/10.1093/ije/dyt198
102. Dave JA, Levitt NS, Ross IL, et al. Anti-retroviral therapy increases the prevalence of dyslipidemia in South African HIV-infected patients. PLoS ONE 2016;11(3):e0151911. https://doi.org/10.1371/journal.pone.0151911
103. Strehlau R, Coovadia A, Abrams EJ, et al. Lipid profiles in young HIV-infected children initiating and changing antiretroviral therapy. J Acquir Immune Defic Syndr 2012;60(4):369-376. https://doi.org/10.1097/QAI.0b013e318243760b
104. Triant VA, Perez J, Regan S, et al. Cardiovascular risk prediction functions underestimate risk in HIV infection. Circulation 2018;137(21):2203-2214. https://doi.org/10.1161/CIRCULATIONAHA.117.028975
105. Meintjes G, Moorhouse MA, Carmona S, et al. Adult antiretroviral therapy guidelines 2017. S Afr J HIV Med 2017;18(1):a776. https://doi.org/10.4102/sahivmed.v18i1.776
106. Savarese G, Gotto AM, Paolillo S, et al. Benefits of statins in elderly subjects without established cardiovascular disease. J Am Coll Cardiol 2013;62(22):2090-2099. https://doi.org/10.1016/j.jacc.2013.07.069
107. Gränsbo K, Melander O, Wallentin L, et al. Cardiovascular and cancer mortality in very elderly post-myocardial infarction patients receiving statin therapy. J Am Coll Cardiol 2010;55(13):1362-1369. https://doi.org/10.1016/j.jacc.2010.01.013
108. Afilalo J, Duque G, Steele R, et al. Statins for secondary prevention in elderly patients: A hierarchical Bayesian meta-analysis. J Am Coll Cardiol 2008;51(1):37-45. https://doi.org/10.1016/j.jacc.2007.06.063
109. Deedwania P, Stone PH, Bairey Merz CN, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: Results of the Study Assessing Goals in the Elderly (SAGE). Circulation 2007;115(6):700-707.
110. Leya M, Stone NJ. Statin prescribing in the elderly: Special considerations. Curr Atheroscler Rep 2017;19(11):47. https://doi.org/10.1007/s11883-017-0683-9
111. Richard E, Gouw AA, Scheltens P, van Gool WA. Vascular care in patients with Alzheimer disease with cerebrovascular lesions slows progression of white matter lesions on MRI. The Evaluation of Vascular Care in Alzheimer's disease (EVA) Study. Stroke 2010;41:554-556. https://doi.org/10.1161/STROKEAHA.109.571281
112. Smith KB, Kang P, Sabbagh MN, et al. The effect of statins on rate of cognitive decline in mild cognitive impairment. Alzheimer's Dement 2017;3(2):149-156. https://doi.org/10.1016/j.trci.2017.01.001
113. Geifman N, Brinton RD, Kennedy RE, et al. Evidence for benefit of statins to modify cognitive decline and risk of Alzheimer's disease. Alzheimer's Res Ther 2017;9(1):10. https://doi.org/10.1186/s13195-017-0237-y
114. National Institutes of Health. A clinical trial of STAtin Therapy for Reducing Events in the Elderly (STAREE). https://clinicaltrials.gov/show/NCT02099123 (accessed 27 February 2018).
115. Cooney MT, Selmer R, Lindman A, et al. Cardiovascular risk estimation in older persons: SCORE O.P. Eur J Prev Cardiol 2016;23(10):1093-1103. https://doi.org/10.1177/2047487315588390
116. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. Kidney Inter 2013;3(3)(Suppl.):259-305. https://doi.org/10.1038/ki.2014.31.
117. Chodick G, Shalev V, Gerber Y, et al. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: A population-based retrospective cohort study in Israel. Clin Ther 2008;30(11):2167-2179. https://doi.org/10.1016/j.clinthera.2008.11.012
118. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA 2002;288(4):462-467. https://doi.org/10.1001/jama.288.4.462
119. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: Meta-analysis on 376,162 patients. Am J Med 2012;125(9):882-887.e1. https://doi.org/10.1016/j.amjmed.2011.12.013
120. Cushing A, Metcalfe R. Optimizing medicines management: From compliance to concordance. Ther Clin Risk Management 2007;3(6):1047-1058.
121. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: Impact on statin therapy – European Atherosclerosis Society consensus panel statement on assessment, aetiology and management. Eur Heart J 2015;36(17):1012-1022. https://doi.org/10.1093/eurheartj/ehv043

# Appendix 1
## Cardiovascular risk stratification

**Category 1: Individuals considered to be at very high or high risk who do not need scoring**

**Very high risk**

1. Established atherosclerotic disease, i.e.
   a. coronary artery disease
   b. cerebrovascular disease
   c. peripheral arterial disease.
2. Type 2 diabetes plus one or more other risk factors (smoking, hypertension, dyslipidaemia) or age >40 years.
3. Type 1 diabetes with micro-albuminuria or proteinuria.
4. Genetic dyslipidaemia, e.g. familial hypercholesterolemia (FH), dysbetalipoproteinaemia, individuals with total cholesterol (TC) >7.5 mmol/L and/or low-density lipoprotein cholesterol (LDL-C) >5 mmol/L.
5. Severe chronic kidney disease (CKD) (glomerular filtration rate (GFR) <30 mL/min/1.73 $m^2$).
6. Asymptomatic individuals with arterial plaque demonstrated on imaging modalities.

**High risk**

1. Markedly elevated blood pressure (BP) (systolic BP ≥180 mmHg and/or diastolic BP ≥110 mmHg).
2. Uncomplicated type 1 diabetes and type 2 diabetes aged <40 years without other risk factors.
3. CKD (GFR 30 - 59 mL/min/1.73 $m^2$).

**Goal:**†

- Very high risk: LDL-C <1.8 mmol/L *and* also a reduction of at least 50% if baseline LDL-C is between 1.8 and 3.5 mmol/L.
- High risk: <2.5 mmol/L *and* also reduction of at least 50% if baseline LDL-C is between 2.5 and 5.2 mmol/L.

**Category 2:[‡]Risk scoring required – use the Framingham Risk tables below.[§]**

**Framingham 10-year risk assessment chart for patients without diabetes or severe monogenic disorders (e.g. FH) indicates risk of total CVD (coronary heart disease, stroke, peripheral artery disease or heart failure).**

**Estimate of 10-year risk of CVD for men**

| Age (yrs) | Points |
|---|---|
| 30 - 34 | 0 |
| 35 - 39 | 2 |
| 40 - 44 | 5 |
| 45 - 49 | 6 |
| 50 - 54 | 8 |
| 55 - 59 | 10 |
| 60 - 64 | 11 |
| 65 - 69 | 12 |
| 70 - 74 | 14 |
| 75 years or older | 15 |

| Total cholesterol (mmol/l) | Points |
|---|---|
| <4.10 | 0 |
| 4.10 - 5.19 | 1 |
| 5.20 - 6.19 | 2 |
| 6.20 - 7.20 | 3 |
| >7.20 | 4 |

| HDL-cholesterol (mmol/l) | Points |
|---|---|
| ≥1.50 | -2 |
| 1.30 - 1.49 | -1 |
| 1.20 - 1.29 | 0 |
| 0.90 - 1.19 | 1 |
| <0.90 | 2 |

| Systolic BP – untreated (mmHg) | Points |
|---|---|
| <120 | -2 |
| 120 - 129 | 0 |
| 130 - 139 | 1 |
| 140 - 159 | 2 |
| ≥160 | 3 |
| | |

| Systolic BP – on antihypertensive treatment (mmHg) | Points |
|---|---|
| <120 | 0 |
| 120 - 129 | 2 |
| 130 - 139 | 3 |
| 140 - 159 | 4 |
| ≥160 | 5 |
| | |

| Smoker | Points |
|---|---|
| No | 0 |
| Yes | 4 |

**Estimate of 10-year risk of CVD for women**

| Age (yrs) | Points |
|---|---|
| 30 - 34 | 0 |
| 35 - 39 | 2 |
| 40 - 44 | 4 |
| 45 - 49 | 5 |
| 50 - 54 | 7 |
| 55 - 59 | 8 |
| 60 - 64 | 9 |
| 65 - 69 | 10 |
| 70 - 74 | 11 |
| 75 years or older | 12 |

| Total cholesterol (mmol/l) | Points |
|---|---|
| <4.10 | 0 |
| 4.10 - 5.19 | 1 |
| 5.20 - 6.19 | 3 |
| 6.20 - 7.20 | 4 |
| >7.20 | 5 |

| HDL-cholesterol (mmol/l) | Points |
|---|---|
| ≥1.50 | -2 |
| 1.30 - 1.49 | -1 |
| 1.20 - 1.29 | 0 |
| 0.90 - 1.19 | 1 |
| <0.90 | 2 |

| Systolic BP – untreated (mmHg) | Points |
|---|---|
| <120 | -3 |
| 120 - 129 | 0 |
| 130 - 139 | 1 |
| 140 - 149 | 2 |
| 150 - 159 | 4 |
| ≥160 | 5 |

| Systolic BP – on antihypertensive treatment (mmHg) | Points |
|---|---|
| <120 | -1 |
| 120 - 129 | 2 |
| 130 - 139 | 3 |
| 140 - 149 | 5 |
| 150 - 159 | 6 |
| ≥160 | 7 |

| Smoker | Points |
|---|---|
| No | 0 |
| Yes | 3 |

**Points total for men**

| Points total | 10-year risk (%) |
|---|---|
| -3 or less | <1 |
| -2 | 1.1 |
| -1 | 1.4 |
| 0 | 1.6 |
| 1 | 1.9 |
| 2 | 2.3 |
| 3 | 2.8 |
| 4 | 3.3 |
| 5 | 3.9 |
| 6 | 4.7 |
| 7 | 5.6 |
| 8 | 6.7 |
| 9 | 7.9 |
| 10 | 9.4 |
| 11 | 11.2 |
| 12 | 13.2 |
| 13 | 15.6 |
| 14 | 18.4 |
| 15 | 21.6 |
| 16 | 25.3 |
| 17 | 29.4 |
| 18 or more | >30 |

**Points total for women**

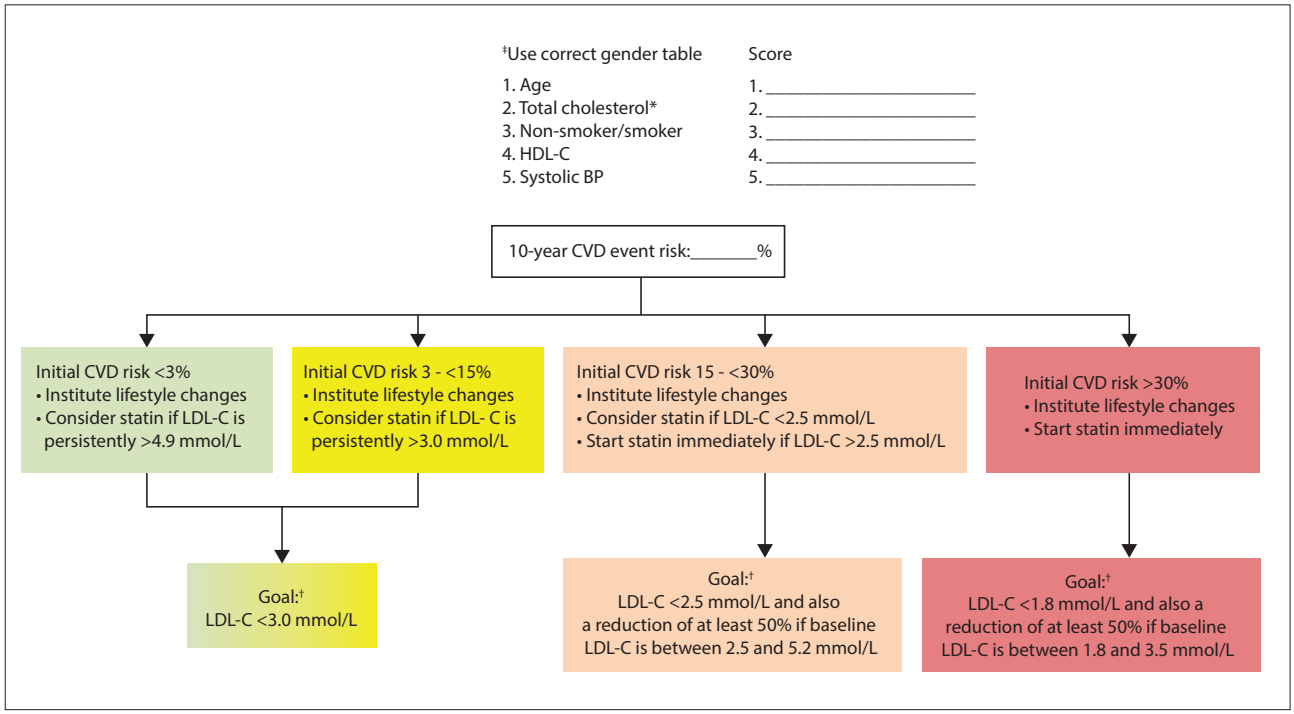
| Points total | 10-year risk (%) |
|---|---|
| -2 or less | <1% |
| -1 | 1.0 |
| 0 | 1.1 |
| 1 | 1.5 |
| 2 | 1.8 |
| 3 | 2.1 |
| 4 | 2.5 |
| 5 | 2.9 |
| 6 | 3.4 |
| 7 | 3.9 |
| 8 | 4.6 |
| 9 | 5.4 |
| 10 | 6.3 |
| 11 | 7.4 |
| 12 | 8.6 |
| 13 | 10.0 |
| 14 | 11.6 |
| 15 | 13.5 |
| 16 | 15.6 |
| 17 | 18.1 |
| 18 | 20.9 |
| 19 | 24.0 |
| 20 | 27.5 |
| 20 or more | >30 |

*Point totals indicate the 10-year risk of cardiovascular disease (coronary, cerebrovascular and peripheral arterial disease, and heart failure).

Low risk  Moderate risk  High risk  Very high risk

Adapted from Mosca L, *et al.*, Effectiveness-based guidelines for the prevention of cardiovascular disease in women 2011 update: A guideline from the American Heart Association. Circulation 2011;123:1243-1262[24] and D'Agostino RB, *et al.*, General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743-753.[25]

## Management and cholesterol goals according to Framingham risk score




*HDL-C = high-density lipoprotein cholesterol; BP = blood pressure; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.*

**Total cholesterol level is used to assign risk score and may be used for follow-up cholesterol measurement in patients on drug therapy, but LDL-C remains the target of treatment.*

*†Pharmacological treatment is required if LDL-C remains above these levels despite lifestyle modification. At present, statins are first-line drugs for lowering LDL cholesterol.*

*‡Secondary causes of dyslipidaemia should be excluded before progressing to risk assessment.*

*§See limitations of Framingham Risk Assessment Score listed below.*

*§ Limitations of the Framingham Risk Assessment Score Charts*

*1. Patients who are classified in the very high-risk category do not require further risk scoring for management decisions. Risk will also be underestimated in patients who have a markedly elevated single risk factor (e.g. severe hypertension: systolic BP >180 mmHg and/or diastolic BP >110 mmHg), or associated target organ damage.*

*2. Severe hypercholesterolaemia and hypertriglyceridaemia: The Framingham Risk Assessment Chart is only accurate up to TC values of 7.25 mmol/L and cannot be used for patients with TC levels above this value. It also does not apply to hypertriglyceridaemia (triglycerides >5 mmol/L).*

*3. Family history of early atherosclerotic disease is not considered. Clinicians should use their judgement in deciding whether to place a patient with an impressive family history in the high-risk category regardless of their Framingham Score, or avoid calculating risk in these patients.*

*4. Despite these factors being important risk factors for CVD, impaired glucose tolerance, abdominal obesity and lipoprotein(a) (Lp(a)) >50 mg/dL are not considered in the risk score.*

## Appendix 2

**Risk scoring applications for mobile devices**

| Application | Parameters required | Available from |
|---|---|---|
| SA Heart (recommended)* | Age, TC, HDL-C, systolic BP, antihypertensive treatment use, smoking status | App store: SADyslipidaemia |
| Framingham risk: 10- and 30-year CVD risk | Gender, age, systolic BP, blood pressure lowering medication use, smoking, diabetes status, BMI or lipids | https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/index.php |
| Heart (vascular) age (Framingham) | Gender, age, systolic BP, antihypertensive treatment use, smoking, diabetes status, BMI or lipids | https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/index.php |
| ESC relative risk | Smoking, BP, TC | https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts |
| AHA/ACC | Age, sex, race, TC, HDL cholesterol, systolic blood pressure, antihypertensive treatment use, diabetes status and smoking status | http://my.americanheart.org/cvriskcalculator |
| Reynold's risk score | Age, smoking status, systolic BP, TC, hsCRP, family history of premature CVD | http://www.reynoldsriskscore.org/ |
| Multi-Ethnic Study of Atherosclerosis (MESA) 10-year CHD risk | Gender, age, CAC, ethnicity, diabetes status, smoking status, family history of CVD, TC, HDL-C, systolic BP, lipid lowering medication use, blood pressure lowering medication use | https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx |
| MESA arterial age calculation from CAC score | CAC score, age, ethnicity | https://statcoder.wordpress.com/2011/07/27/mesa-arterial-age-from-coronary-calcium-score/ |
| UKPDS Risk Engine (non-insulin dependent diabetes)† | Age, duration of diabetes, HbA1c, systolic blood pressure, gender, TC, HDL-C, ethnicity, smoking status | https://www.dtu.ox.ac.uk/riskengine/download.php |
| Diagnosis of FH | Gender, age, presence of atherosclerosis, lipid-lowering medication use, clinical examination results, known DNA mutation, family history | http://www.circl.ubc.ca<br>An app (FH Diagnosis) is also available from the FH foundation: https://itunes.apple.com/us/app/fh-diagnosis/id543676258?mt=8 |

TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; BP = blood pressure; CVD = cardiovascular disease; BMI = mody mass index; ESC = European Society of Cardiology; AHA/ACC = American Heart Association/American College of Cardiology; hsCRP = high-sensitivity C-reactive protein; CHD = coronary heart disease; CAC = coronary artery calcification; UKPDS = UK Prospective Diabetes Study; HbA1c = glycated haemoglobin; FH = familial hyperholesterolaemia.
*The SA Heart application is based on these guidelines and it is recommended that clinicians refer to this risk score when corresponding with funders in SA.
†Risk calculators based on equations from the Framingham Heart Study tend to underestimate risks for people with diabetes, as this study included relatively few diabetic subjects. The UKPDS Risk Engine is a type 2 diabetes-specific risk calculator based on 53 000 patient years of data from the UKPDS, which also provides an approximate margin of error for each estimate.

## Appendix 3

### South African Heart Association/LASSA guidelines for lifestyle modification for patients with dyslipidaemia

1. Stop smoking and avoid exposure to tobacco products and second-hand smoke.
2. Increase physical activity to at least 30 minutes per day every day.
3. Achieve and maintain ideal body weight.
4. Drink sufficient clean, safe water in preference to carbonated drinks and fruit juices.
5. Eat a variety of foods with preference for fresh, unprocessed foods.
6. Reduce dietary intake of saturated fats, trans-fats and cholesterol.
7. Replace dietary saturated fats with unsaturated fats (mono- and polyunsaturated fats).
8. Avoid tropical oils (e.g., coconut and palm kernel oil).
9. Increase intake of fibre, especially soluble fibre.
10. Replace all refined carbohydrate types of foods with foods high in fibre.
12. People who consume alcohol should do so in moderation. Excessive alcohol consumption should be avoided. Patients with hypertriglyceridaemia should abstain completely.
11. Avoid foods that are naturally high in sugar, e.g. honey, syrups, fruit juices and foods with added sugar, fructose or corn syrup.
13. Reduce salt intake from all sources to <5 g salt or <2.4 g sodium, equivalent to 1 teaspoon of salt per day.
14. For dietary lifestyle intervention, all patients should ideally be referred to a registered dietitian.

# Appendix 4

**Dietary recommendations to lower low-density lipoprotein cholesterol and improve the overall lipoprotein profile**

1. Achieve and maintain ideal body weight.
2. Eat a variety of foods – preferably fresh, unprocessed foods.
3. Eat vegetables and fresh fruit every day – at least five portions per day.
4 . Eat whole wheat products and whole wheat cereal without added sugar.
5. Eat more legumes.
6. Eat fish, poultry and low-fat or fat-free dairy products.
7. Limit the intake of red meat.
8. Avoid/limit foods that are naturally high in sugar like honey, syrups and fruit juices and foods containing added sugar, fructose or corn syrup.
9. Use oils provided by non-tropical vegetable oil for example sunflower oil, canola oil, olive oil.
10. If you use alcohol, do so in moderation (men: 2 standard drinks per day; women: 1 standard drink per day). People with high triglyceride levels should abstain.
11. Drink sufficient clean, safe water in preference to carbonated drinks and fruit juices.

**Dietary recommendations to lower low-density lipoprotein cholesterol and improve the overall lipoprotein profile**

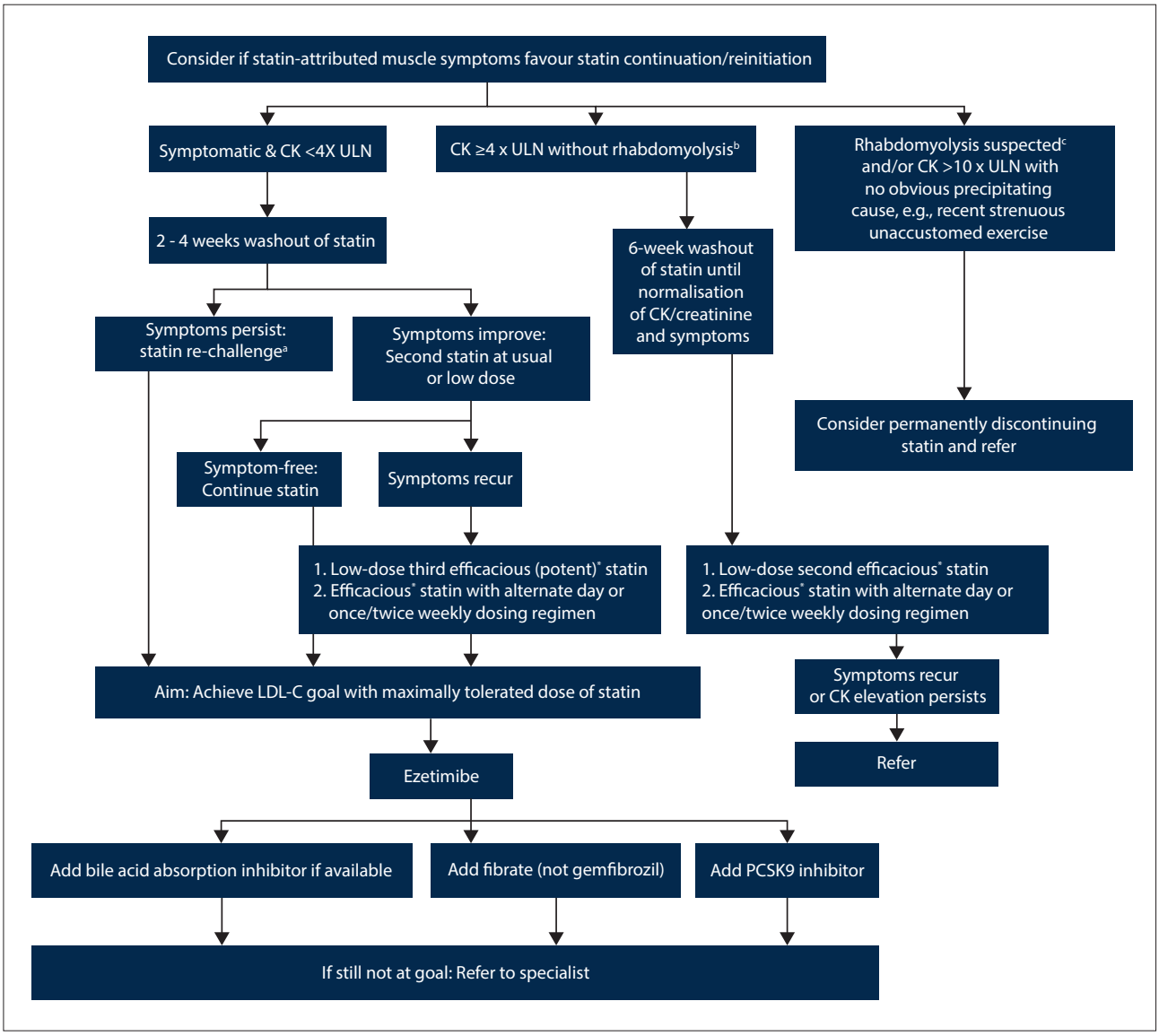
| | **Preferred foods – eat regularly** | **Use in moderation (1 - 3 times per week)** | **Best to avoid these foods (at most to be chosen occasionally in limited amounts)** |
|---|---|---|---|
| Vegetables and fruits (minimum 5 portions per day) | Raw and cooked vegetables<br>Choose colourful vegetables<br>Avocado, butternut, broccoli, cabbage, carrot, beetroot, green beans, peppers, pumpkin, spinach and other green leafy vegetables and herbs, tomatoes, etc.<br>Note: no added sugar and/or fat | Potato, sweet potato<br>Note: no added sugar and/or fat | Vegetables prepared in oil, fat, butter or cream<br>Deep fried potatoes ('slap chips'), potato crisps |
| | Fresh or frozen fruits (no added sugar) | Dried fruit, canned fruit (in natural juice) | Canned fruit (in sugar syrup), fruit juice, fruit prepared with added sugar e.g. fruit rolls |
| Whole-wheat grains and cereals | Brown/wild rice, buckwheat, barley, bulgur, quinoa, millet, whole-wheat couscous, cracked wheat, samp, oats, corn, whole spelt, unrefined maize meal, whole-grain breakfast cereal (with no added sugar), brown and whole-wheat bread, seed bread, popcorn (without added fat and/or sugar) | Wholewheat breakfast cereal with fibre and no added sugar, wholewheat pasta | Products made with white flour and added fat, such as pastries, muffins, pies, croissants, white bread, pasta, koeksisters, cake, biscuits, cookies, crackers, etc.<br>Breakfast cereal with added sugar, breakfast cereal with no fibre, white rice<br>Snacks high in fat, sugar and/or salt<br>Fast foods high in fat, suagr and/or salt |
| Legumes | Lentils, all dried beans (e.g. small white beans, haricot beans, Borlotti beans, black beans, Cannellini beans, sugar beans, red kidney beans, fava beans, black-eye beans, dhal beans, pinto beans, dried peas, chickpeas, canned baked beans, soybeans, cowpeas) | Soybean products with high salt content | |
| Meat, chicken and fish | Lean fish (hake, kingklip, etc.)<br>Oily fish (salmon, canned pilchards, sardines and salmon, mackerel, snoek)<br>Poultry without skin<br>Ostrich<br>Venison | Lean cuts of beef, lamb, pork or veal, seafood, shellfish<br>Lean cuts of cold meats<br>Liver (limit to 60 gram per week) | Sausages, salami, polony, bacon, spare ribs, hot dogs, organ meats, processed meat, skin of chicken, any fat on meat |
| Dairy food and eggs | Low-fat or fat-free dairy:<br>Skim milk and fat free yoghurt (unsweetened)<br>Low-fat milk and low-fat yoghurt (unsweetened)<br>Fat-free and low-fat cheese, e.g. fat-free and low-fat cottage cheese | Eggs | Regular cheese like cheddar, gouda, cream, whole milk and full cream yoghurt |
| Nuts and seeds | | All (except coconut), unsalted<br>Peanut butter (low salt) | Coconut |
| | | | ...continued |

**Dietary recommendations to lower low-density lipoprotein cholesterol and improve the overall lipoprotein profile (continued)**

| | **Preferred foods – eat regularly** | **Use in moderation (1 - 3 times per week)** | **Best to avoid these foods (at most to be chosen occasionally in limited amounts)** |
|---|---|---|---|
| Cooking fat and dressings | Sunflower oil, olive oil, avocado oil, canola oil<br>Plant stenol-/stanol-enriched soft margarine<br>Vinegar, mustard, fat-free dressings, tomato sauce (low-salt type) | Soft margarines, salad dressing, light/lite or low-fat mayonnaise | Trans fats and hard margarines, palm, palm kernel and coconut oils, butter, ghee, lard, beef tallow, beef or mutton shin, bacon fat |
| Limit sweets and sweeteners | Non-caloric sweeteners, stevia | | Cakes, ice creams, fructose, sugar-sweetened beverages, products containing high-fructose corn syrup, sugar, sucrose, honey, chocolate, candies |
| Limit intake of salt to <5 g (or <2 400 mg sodium), equivalent to 1 teaspoon) per day | Flavour food using:<br>lemon juice or vinegar;<br>herbs, e.g. Italian herbs mix, parsley, rosemary, oregano,<br>spices, e.g. curry powder, paprika, pepper, garlic, ginger, chilli, and onions | | Salty crackers, bacon, biltong, dried sausage<br>Note: Do not use salt or salty condiments at table |
| Cooking procedures | Grilling, boiling, steaming, stirfrying (use allowed oils)<br>Use less salt when cooking | Roasting | Frying, baking in fat and oil |

## Appendix 5

**General management recommendations for muscle symptoms on statin treatment**




*CK = creatine kinase; LDL-C: low-density lipoprotein cholesterol; ULN = upper limit of the normal range.*

** Efficacious statin, such as atorvastatin or rosuvastatin.*

*[a] Where muscle symptoms do not improve after statin discontinuation, causality is uncertain. Withdrawal of statin therapy followed by one or more re-challenges (after a washout) can often help in determining causality.*

*[b] In patients with CK >10× ULN for which no secondary cause can be found, statin therapy should be discontinued because of potential risk of rhabdomyolysis. If the CK level subsequently returns to normal, re-challenge with a lower dose of an alternative statin and careful monitoring of symptoms and CK may be considered.*

*[c] Rhabdomyolysis should be considered if there is severe muscular pain, general weakness and signs of myoglobinaemia or myoglobinuria. If rhabdomyolysis is suspected, statin should not be reintroduced and patient should be referred for evaluation of renal damage.*

*Recommendations adapted from: Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy – European Atherosclerosis Society Consensus Panel Statement on assessment, aetiology and management. Eur Heart J 2015;36(17):1012-1022. http://dx.doi.org/10.1093/eurheartj/ehv043.*[121]