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CME ARTICLE

Ministry of Health Clinical Practice Guidelines: Lipids

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ABSTRACT The Ministry of Health (MOH) has updated the Clinical Practice Guidelines on Lipids to provide doctors and patients in Singapore with evidence-based treatment for lipids. This article reproduces the introduction and executive summary (with recommendations from the guidelines) from the MOH Clinical Practice Guidelines on Lipids, for the information of *SMJ* readers. Chapters and page numbers mentioned in the reproduced extract refer to the full text of the guidelines, which are available from the Ministry of Health website: http://www.moh.gov.sg/content/moh_web/healthprofessionalsportal/doctors/guidelines/cpg_medical.html.

INTRODUCTION

Cardiovascular disease, especially coronary artery disease (CAD), is a very important health problem in Singapore today. CAD is second only to cancer as a leading cause of mortality in this country. Dyslipidemia is one of the most important modifiable risk factors for CAD. Many studies have demonstrated the efficacy of treating dyslipidemia in the prevention of CAD.

1.1 Objectives and scope

The main aim of these guidelines is to assist physicians and other healthcare professionals in clinical decision making by providing well-balanced information on the management of patients with dyslipidemia, without restricting the physician's individual clinical judgement.

1.2 Target group

These guidelines are developed for all health care professionals, in particular, primary care physicians who are involved in the care of patients with dyslipidemia.

1.3 Guideline development

The workgroup, comprising cardiologists, endocrinologists, lipid specialists, public health specialists and family physicians, was appointed by the Ministry of Health (MOH) to develop these guidelines.

1.4 What's new in the revised guidelines

This revision of the guideline incorporates data from several recent randomised controlled trials that have been published since 2006. In doing so, the committee has tried to simplify the recommendations, wherever possible. The key revisions are in the following chapters:

1. The chapter on risk assessment (page 24) has been revised to:
   (a) Do away with the previous approach of counting risk factors as part of the algorithm for risk stratification. In its place is a two-step process that stratifies patients into one of four levels of risk of CAD (very high risk, high risk, intermediate risk and low risk).
   (b) Include clear guidelines for the diagnosis of familial hypercholesterolemia and recognise that patients with familial hypercholesterolemia are at very high risk of CAD and, therefore, should be treated aggressively.
   (c) Introduce chronic kidney disease as one of the risk factors to consider when stratifying patients by risk of future CAD.
   (d) Recognise that patients with diabetes mellitus may not necessarily experience the same risk as patients with established CAD. As such, patients with diabetes mellitus can be stratified into two levels of risk (very high or high risk) based on the presence or absence of chronic kidney disease.
   (e) Retain treat to target levels of low-density lipoprotein (LDL) cholesterol based on the risk of CAD in individual patients. However, there is also the option for physicians to increase the dose of statins to those used in randomised controlled trials, even when the LDL cholesterol targets have been achieved.
2. The chapter on lifestyle changes (page 36) has been extensively revised to focus on areas that are supported by the strongest evidence, including some food-based dietary recommendations (in addition to macronutrients) to help physicians support the dietary changes necessary for patients.
3. The chapter on drug therapy (page 40) has been revised to:
   (a) Emphasise that statins remain the primary lipid lowering drugs used to reduce CAD risk, and identify the dosage range of statins used in randomised clinical trials in various patient groups to guide the choice of statin and dose.
   (b) Clarify the role of other lipid lowering therapies, including fibrates, niacin and ezetimibe, and this

List of institutions in alphabetical order

Frontier Healthcare Group, Health Promotion Board, Lipid & Endocrine Practice, Low Cardiology Clinic, Ministry of Health, National Heart Centre, National University Heart Centre, National University Hospital, Saw Swee Hock School of Public Health, SingHealth Polyclinics, The Harley Street Heart and Cancer Centre, Yishun Junior College

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clinical practice guideline identifies situations where these drugs may be beneficial based on recent clinical trials.

(c) Provide information on over the counter preparations for lipid lowering that have the most clearly documented effects on blood lipids given that patients often consume such products. These are omega 3 fish oils, red yeast rice, and plant sterols and stanols (see chapter on lifestyle change).

4. The chapter on special considerations (page 49) has been revised to:

(a) Provide recommendations on how to diagnose familial hypercholesterolemia and greater clarity on drug therapy for children with familial hypercholesterolemia.

(b) Make special recommendations for the elderly to recognise the limited data supporting the use of high intensity statins in patients aged > 75 years and the need to consider the presence of other co-morbidities, multiple medications and altered pharmacokinetics and pharmacodynamics of drugs in these individuals. The decision to start a statin should also take into account the life expectancy and the quality of life of these patients.

1.5 Review of guidelines

Evidence-based clinical practice guidelines (CPGs) are only as current as the evidence that supports them. Users must keep in mind that new evidence could supersede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review five years after publication, or if new evidence appears that requires substantive changes to the recommendations. This CPG refers to the CPG on Screening for Cardiovascular Disease and Risk Factors (MOH CPG 1/2011). As such, revision of this CPG could be undertaken in the event of a revision to MOH CPG 1/2011.

EXECUTIVE SUMMARY OF RECOMMENDATIONS

Details of recommendations can be found on the indicated pages. Key recommendations are highlighted in grey.

Lipids in coronary artery disease

Blood lipid levels are important risk factors for CAD. The relationship between CAD and total cholesterol levels is continuous and curvilinear. In these guidelines, total cholesterol (TC), LDL cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride (TG) are used for risk stratification (Chapter 5) and for making decisions on treatment (Chapter 7).

Classification and screening for dyslipidemia

The screening for dyslipidemia should be carried out in accordance with MOH CPG 1/2011 Screening for Cardiovascular Disease and Risk Factors, where risk factors for CAD include: (a) diabetes mellitus; (b) multiple CAD risk factors (e.g. tobacco use, hypertension, impaired fasting glycemia or impaired glucose tolerance); (c) a family history of cardiovascular disease before age 50 years in male relatives or before age 60 years in female relatives; and (d) a family history suggestive of familial hyperlipidemia.

Dyslipidemia can be classified as hypercholesterolemia, mixed (combined) dyslipidemia, hypertriglyceridemia and severe hypertriglyceridemia (Table 1). Secondary dyslipidemia may occur in various conditions and should be excluded in any patient presenting with dyslipidemia (Table 2).

Table 1. Classification of dyslipidemia (CPG pg. 22).

Types of dyslipidemia	Increased concentration	
	Lipoprotein	Serum lipid
Hypercholesterolemia	LDL	TC & LDL cholesterol*
Mixed (combined) dyslipidemia	LDL & VLDL	TC, LDL cholesterol* & TG (1.7–4.5 mmol/L [150–399 mg/dL])
Hypertriglyceridemia	VLDL	TG (1.7–4.5 mmol/L [150–399 mg/dL])
Severe hypertriglyceridemia	Chylomicrons	TG (≥ 4.5 mmol/L [400 mg/dL])

* LDL cholesterol (mmol/L) = TC – (HDL cholesterol + TG/2.2)

Table 2. Common causes of secondary dyslipidemia (CPG pg. 23).

Disorder	Lipid abnormalities
Diabetes mellitus	↑ TG and ↓ HDL cholesterol
Chronic kidney disease	↑ TG
Nephrotic syndrome	↑ TC
Hypothyroidism	↑ TC
Alcohol abuse	↑ TG
Cholestasis	↑ TC
Pregnancy	↑ TG
Drugs e.g. diuretics, beta-blockers, oral contraceptives, corticosteroids, retinoids, anabolic steroids, progestins related to testosterone	↑ TG and/or TC, ↓ HDL cholesterol

Who should be screened for lipid disorders?

B Clinicians should routinely screen men and women aged 40 years and older for lipid disorders.
(Grade B, Level 2^{++}, CPG pg. 19)

GPP Clinicians can routinely screen younger adults (men and women aged 18 years and older) for lipid disorders if they have other risk factors for CAD.
(CPG pg. 19)

GPP For individuals with screening results within the LDL cholesterol target levels (see Table 3 CPG pg. 8) and have low TG levels, screening should be repeated at three yearly intervals unless they are at very high or high risk of CAD, in which case screening should be repeated annually.
(CPG pg. 20)

What should a lipid profile include?

D A lipid profile should include TC, TG, LDL cholesterol and HDL cholesterol. These should be obtained after 10–12 hours of fasting, which is required for the measurement of TG.

(Grade D, Level 4, CPG pg. 21)

D Routine ApoB and ApoA1 determination is not recommended.

(Grade D, Level 4, CPG pg. 17)

C Lp(a) determination is not recommended for routine cardiovascular disease screening. However, further to a global cardiovascular risk assessment, Lp(a) measurements may be useful in individuals with strong family history of premature cardiovascular disease.

(Grade C, Level 2^{+}, CPG pg. 18)

Recent illnesses

Recent illnesses may affect lipid levels, and lipid tests may need to be deferred or repeated in these circumstances.

GPP Physicians and patients may wish to defer lipid tests for at least two weeks after a febrile illness, as blood lipids may be abnormal after an acute illness such as an infection.

(CPG pg. 20)

D Patients who suffer myocardial infarction may have depressed cholesterol levels that do not require treatment. These patients should have their blood lipids repeated three months after a myocardial infarction.

(Grade D, Level 3, CPG pg. 20)

Risk assessment of CAD in dyslipidemia

A basic principle in the prevention of CAD is that the intensity of risk reduction therapy should be adjusted to a person's risk of developing future coronary events. The steps taken for risk stratification are illustrated in Fig. 1. First, very high risk and high risk patients can be identified based on whether they have existing CAD, atherosclerotic cerebrovascular disease, aortic aneurysm, peripheral arterial disease, diabetes mellitus, chronic kidney disease, or familial hypercholesterolemia. If the patient is not in the very high risk or high risk strata, his/her ten-year CAD risk can be estimated using Tables A-1 to A-4 (CPG pg. 21–24).

Target lipid levels

While it was noted that randomised controlled trials used fixed doses of statins, physicians in Singapore involved in treating patients at risk of CAD with lipid lowering therapy were of the view that there was sufficient evidence for a causal link between LDL cholesterol and the risk of CAD, such that a strategy to treat patients to achieve target lipid levels (i.e. treat to target strategy) remains relevant today. Table 3 shows the recommended LDL cholesterol target levels in the four risk group categories.

B Table 3. LDL cholesterol target levels in the four risk categories. (Grade B, Level 1^{++}, CPG pg. 34–36).

Risk group category	LDL cholesterol target level
Very high risk group	< 2.1 mmol/L (80 mg/dL)
High risk group	< 2.6 mmol/L (100 mg/dL)
Intermediate risk group	< 3.4 mmol/L (130 mg/dL)
Low risk group	< 4.1 mmol/L (160 mg/dL)

B The recommended LDL cholesterol target level for the intermediate risk group is < 3.4 mmol/L (130 mg/dL), with an LDL cholesterol level of < 2.6 mmol/L (100 mg/dL) being an option if the physician feels that the benefits of more intensive therapy outweigh the risks.

(Grade B, Level 1^{++}, CPG pg. 35)

B The recommended LDL cholesterol target level for the low risk group is < 4.1mmol/L (160 mg/dL), with an LDL cholesterol level of < 3.4 mmol/L (130 mg/dL) being an option if the physician feels that the benefits of more intensive therapy outweigh the risks.

(Grade B, Level 1^{++}, CPG pg. 36)

GPP In patients with two consecutive values of LDL cholesterol levels < 1.03 mmol/L (40 mg/dL), decreasing the statin dose may be considered.

(CPG pg. 37)

It is also notable that in 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) released a guideline on the treatment of blood cholesterol in which treatment initiation and statin dose were driven primarily by CAD risk status and not by LDL cholesterol level. The 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults recommended: (a) high intensity statin therapy, e.g. atorvastatin 40–80 mg, or its equivalent, in very high risk patients with clinical atherosclerotic cardiovascular disease; and (b) moderate intensity statin therapy, e.g. simvastatin 20–40 mg, or its equivalent, in high risk patients with diabetes mellitus without established chronic CAD or chronic kidney disease.

High intensity statin therapy is defined as the ability to lower LDL cholesterol by more than 50%. This is a property of the specific statin at the dose indicated.

The ACC/AHA recommendation is based on randomised controlled trials of lipid lowering for the prevention of CAD, which used fixed doses of statins, as opposed to treating patients to a specific target as many other guidelines recommended. However, this view is not universally accepted by physicians at this time. Other guidelines continue to recommend targets for treatment of dyslipidemia.

Physicians may consider increasing the statin therapy to the doses recommended in ACC/AHA guidelines, if tolerated, even after the LDL cholesterol goal is achieved on a lower dose of statin, especially if the patient is not on other lipid lowering therapy. However, when doing so, the physician and the patient must

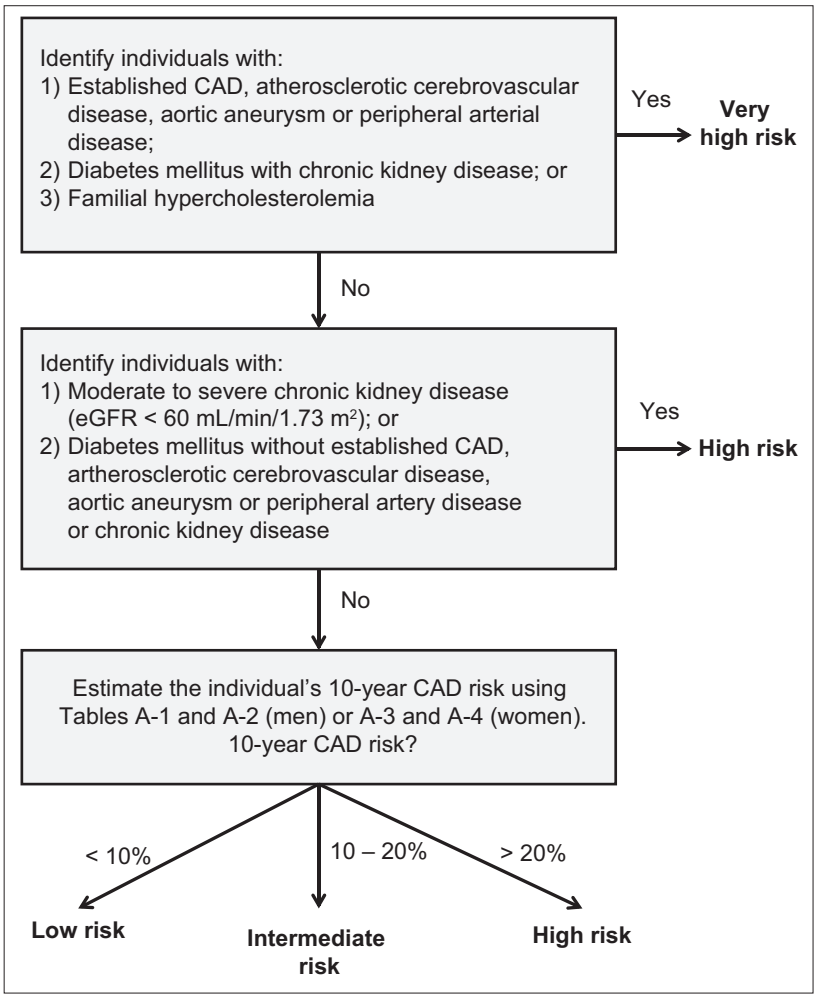

Fig. 1 Risk Stratification (CPG pg. 28).

balance the benefits against the cost and potential side effects of high doses of medication.

Patients with high TG levels

C Individuals with very high levels of TG, e.g. > 4.5 mmol/L (400 mg/dL) or especially > 10 mmol/L (900 mg/dL), have an increased risk of acute pancreatitis and should be treated to reduce the risk of pancreatitis. In these patients, the first priority is to reduce the TG level to prevent acute pancreatitis.

(Grade C, Level 2+, CPG pg. 36)

B Fibrates (but not gemfibrozil) can be considered as add-on therapy to statins in very high or high risk patients when TG is between 2.3 mmol/L (200 mg/dL) and 4.5 mmol/L (400 mg/dL), in the presence of low HDL cholesterol (< 1.0 mmol/L or 40 mg/dL in males, < 1.3 mmol/L or < 50 mg/dL in females).

(Grade B, Level 1++, CPG pg. 36)

Lifestyle changes

Appropriate lifestyle changes are an integral part of dyslipidemia management. Lifestyle interventions can reduce risk of cardiovascular disease. The following lifestyle changes are recommended:

B Patients who smoke should be advised to stop smoking immediately.

(Grade B, Level 2++, CPG pg. 38)

A If body mass index is above 23 kg/m², weight reduction through diet modification and exercise is recommended.

(Grade A, Level 1+, CPG pg. 38)

A Persons with dyslipidemia should undertake 150 to 300 minutes per week (~ 30 to 60 minutes per day) of moderate intensity aerobic activity spread out over 5–7 days per week.

(Grade A, Level 1+, CPG pg. 39)

C For good overall health, individuals who do not currently drink should not start. For individuals who do drink, a maximum of two standard drinks per day for women and three per day for men is recommended. A standard drink is 10 g of alcohol, which is the equivalent of 2/3 can of 220 mL beer, one small 100 mL glass of wine or 1 nip (30 mL) of spirits.

(Grade C, Level 2+, CPG pg. 42)

Recommendations for dietary changes

Physicians may also wish to make the following recommendations for dietary changes for their patients:

A A diet rich in wholegrain foods, vegetables, fruit, legumes, nuts, fish and unsaturated oils, and low in saturated and trans fat, refined grains and cholesterol should be encouraged.

(Grade A, Level 1+, CPG pg. 39)

C Dietary fibre intake should be 25–30 g per day by increasing consumption of whole grains, fruit and vegetables, and reducing consumption of processed grains and sugar.

(Grade C, Level 2+, CPG pg. 40)

GPP Saturated fat intake should be reduced to < 7% of total calories and polyunsaturated fat intake should be around 10% of total calories. A total fat intake of 25%–35% of total calories will be most compatible with these targets.

(CPG pg. 40)

A Saturated fat should be replaced with mono- and polyunsaturated fats to lower TC and LDL cholesterol (without lowering HDL cholesterol) and lower risk of CAD.

(Grade A, Level 1+, CPG pg. 39)

A Trans fat intake should be limited to < 1% of total energy or < 2 g per day.

(Grade A, Level 1+, CPG pg. 39)

A Cholesterol intake should be reduced to < 300 mg per day, as this reduces serum LDL cholesterol levels.

(Grade A, Level 1++, CPG pg. 40)

C For patients with high TG levels, simple sugars (mono- and disaccharides) should be limited to < 10% of total calories.

(Grade C, Level 2+, CPG pg. 40)

Drug therapy

Choice of drugs

In considering the choice of drugs for dyslipidemia, there are three important principles:

A Statins are the first line drug for both hypercholesterolemia (elevated LDL cholesterol) and mixed hyperlipidemia when pharmacotherapy is indicated, except when TG is > 4.5 mmol/L (400 mg/dL).

(Grade A, Level 1++, CPG pg. 43)

D Since patients are at increased risk for acute pancreatitis when TG is > 4.5 mmol/L (400 mg/dL) and the risk is greater with higher TG level, fibrates are the first line drug to reduce the risk of pancreatitis when TG is > 4.5 mmol/L (400 mg/dL). Niacin and high intakes of omega 3 fish oils can also be considered for treatment of severe hypertriglyceridemia.

(Grade D, Level 3, CPG pg. 43)

D If LDL cholesterol remains elevated with fibrate therapy, a statin can be added.

(Grade D, Level 4, CPG pg. 43)

Statins

Statins are very effective in lowering both TC and LDL cholesterol. The approximate equipotency of the different statins is as follows: 10 mg atorvastatin = 5 mg rosuvastatin = 20 mg simvastatin = 40 mg lovastatin/pravastatin = 80 mg fluvastatin.

Some statins, including atorvastatin, simvastatin and lovastatin, are metabolised by the cytochrome P450 isoform 3A4. Drugs such as erythromycin, clarithromycin, azole antifungal agents and cyclosporine, which are also metabolised by the

Table 4. Examples of dietary measures for patients (CPG pg. 41).

Food	Suggested Change
Grains	Choose wholegrains instead of refined grains (e.g. brown rice, oats, wholegrain noodles and breads)
Fruit	At least two servings* per day
Vegetables	At least two servings† per day
Meat, fish and alternatives	Choose oily fish (such as mackerel, pomfret, scad) twice per week Choose lentils, chickpeas, beans, tofu and nuts, and fish in place of red meat Choose white meat such as chicken instead of red meat. If you do consume red meat (mutton, beef, pork) choose lean cuts of meat. Eat eggs (egg yolk) and shrimp/prawn in moderation
Dairy foods	Choose reduced or low fat dairy products
Butter and oils	Choose canola, olive, peanut, corn, safflower, sunflower, mustard and soybean oil Limit intake of butter, ghee, palm and coconut oil
Sweets and sweetened drinks	Limit intake of sweets, cakes, soft drinks, and sweetened teas, sports, and juice drinks
Cooking procedures	Limit intake of deep fried foods and dishes cooked with coconut cream/milk

*One serve of fruit is equivalent to a small apple/orange/medium banana or wedge of papaya or pineapple equal to 130 g. †One serve of vegetables is equivalent to 3/4 of a mug (100 g) cooked vegetables.

Table 5. Drugs that can be used for dyslipidemias (CPG pg. 44).

Dyslipidemia	Drugs of choice
Hypercholesterolemia	Statin, adding ezetimibe if lipids still not at target
Mixed dyslipidemia	Statin, adding ezetimibe, then fibrate or niacin if lipids still not at target
Hypertriglyceridemia (> 4.5 mmol/L or 400 mg/dL)	Fibrate, adding omega 3 fish oils or niacin if triglyceride > 4.5 mmol/L (400 mg/dL)
Severe hypertriglyceridemia (> 10 mmol/L or 90.0 mg/dL)	Fibrate and omega 3 fish oils, adding niacin if triglyceride > 4.5 mmol/L (400 mg/dL)

same enzyme pathway, may elevate the serum level of these statins when administered concomitantly, and therefore, may increase the risk of toxicity. Other statins such as pravastatin are not affected, as they are metabolised by other pathways.

Precautions in diabetes mellitus

GPP In patients with pre-diabetes mellitus/impaired fasting glucose/impaired glucose tolerance, closer monitoring of glycemic control is recommended upon initiation of statin therapy.

(CPG pg. 46)

Myopathy and rhabdomyolysis

D Due to the risk of myopathy and rhabdomyolysis, high dosages of statins should be prescribed with caution, especially in elderly patients, in those with impaired renal function and when a statin is combined with a fibrate or niacin.

(Grade D, Level 4, CPG pg. 46)

D When using simvastatin, the highest dose should be 40 mg. However, in patients who have been taking 80 mg for more than 12 months without any evidence of myopathy or other side effects, it is acceptable to continue the dose.

(Grade D, Level 4, CPG pg. 46)

Monitoring for side effects of statins

Baseline measurements of serum aspartate/alanine transaminase and creatine kinase are recommended to establish the patient's baseline prior to starting statin therapy. However, routine repeat measurements are not needed for patients who are well and asymptomatic. Monitoring of creatinine kinase is necessary only in patients with muscle symptoms (e.g. pain, tenderness, cramping, weakness).

D When using statins, monitor creatinine kinase in patients with muscle symptoms (e.g. pain, tenderness, cramping, weakness).

(Grade D, Level 4, CPG pg. 47)

D When using statins, monitor ALT and AST in patients developing symptoms suggestive of hepatotoxicity (e.g. fatigue, weakness, loss of appetite, jaundice).

(Grade D, Level 4, CPG pg. 47)

D When using statins, patients should be advised to report promptly to their doctors if they develop any of the above liver or muscle symptoms.

(Grade D, Level 4, CPG pg. 47)

Indications for stopping statins

D Elevation in the levels of serum transaminases above three times the upper limit of the normal range is an indication to stop statins. The drugs can be reintroduced at a lower dose when liver function has returned to normal.

(Grade D, Level 4, CPG pg. 48)

D Elevation of serum creatine kinase greater than 5–10 times the upper limit of the normal range, when associated with muscle pain is an indication to stop statins. Patients who are troubled by muscle pain, even in the absence of a raised serum creatine kinase, may benefit from either: (i) stopping the statin therapy or (ii) reducing the dosage.

(Grade D, Level 4, CPG pg. 48)

Some patients who experience muscle symptoms without elevations of creatine kinase may experience a reduction in symptoms when switched to an alternative statin.

Ezetimibe

A Ezetimibe can be used as an add-on drug in association with statins when the therapeutic target is not achieved at the maximum tolerated statin dose, or as an alternative to statins in patients who are intolerant of statins or with contraindications to statins.

(Grade A, Level 1^{++}, CPG pg. 49)

Resins (bile acid sequestrants)

Resins (e.g. cholestyramine) are effective in lowering TC and LDL cholesterol. However, they are infrequently used because of side effects.

Fibrates

D Addition of fenofibrate to a statin may benefit certain patients with Type 2 diabetes mellitus, with both high TG and low HDL cholesterol dyslipidemic pattern, particularly those with microvascular complications.

(Grade C, Level 2^{+}, CPG pg. 49)

Niacin

A When a patient's LDL cholesterol remains above target despite being on the maximum tolerated dose of statin, or in cases of severe hypertriglyceridemia (TG ≥

4.5 mmol/L or 400 mg/dL) when statin therapy is not indicated as first line therapy, niacin can be considered.
(Grade A, Level 1+, CPG pg. 50)

Omega 3 fish oils

A In severe hypertriglyceridemia (e.g. TG > 10 mmol/L or 900 mg/dL), where fibrates alone may not adequately lower the markedly elevated TG levels, omega 3 fish oils should be added in dosages of 3–12 g per day, which contains 1–4 g of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).
(Grade A, Level 1+, CPG pg. 50)

Omega 3 fish oils can lower TC (due to lowering of TG) but has no effect on LDL cholesterol and cardiovascular mortality. Thus, they should not be used as a substitute for statins.

Use of combination therapy with statins

D The decision to combine a statin and another lipid lowering agent must be individualised and should be initiated only when it is strongly indicated. When statin therapy fails to achieve LDL target on the maximum tolerated dose, consideration should be given to use either ezetimibe or resin as an add-on drug to achieve the LDL target level for the patient.
(Grade D, Level 4, CPG pg. 51)

C Fibrates can be considered as add-on therapy to a statin in very high or high risk patients when TG is between 2.3 mmol/L (200 mg/dL) and 4.5 mmol/L (400 mg/dL), in the presence of low HDL cholesterol (< 1.0 mmol/L or 40 mg/dL in males, < 1.3 mmol/L or < 50 mg/dL in females).
(Grade C, Level 2+, CPG pg. 51)

D When a fibrate is combined with a statin, fenofibrate is recommended. Gemfibrozil should not be given because it significantly increases the level of most statins and this may increase the risk of complications.
(Grade D, Level 3, CPG pg. 51)

D When combination therapy is used, (i) patients should be advised to promptly report to their doctors if they have muscle pain, tenderness or weakness, and (ii) physicians should consider ordering a serum creatine kinase test in patients who complain of muscle pain.
(Grade D, Level 4, CPG pg. 51)

Cost-effectiveness of lipid therapy

D Generic formulations cost less than non-generic drugs and can be considered if they meet prescribed standards.
(Grade D, Level 4, CPG pg. 52)

Referral of patients to specialists

GPP Patients who remain outside the LDL cholesterol target values or have TG levels persistently > 4.5 mmol/L (400 mg/dL), despite dietary changes and maximum tolerated drug therapy, should be referred to lipid specialists.
(CPG pg. 52)

Special considerations

Children

GPP Routine screening for dyslipidemia is not recommended in children. However, screening can be carried out from the age of two years in children who have a first degree relative diagnosed with familial hypercholesterolemia, as this gives the opportunity to teach good eating habits.
(CPG pg. 53)

D Dietary management and physical activity are the mainstay of treatment for dyslipidemia in children.
(Grade D, Level 4, CPG pg. 53)

D Drug therapy should be considered only in children aged eight years and older with severe familial hypercholesterolemia, whose LDL cholesterol target cannot be achieved with diet and exercise. The serum LDL cholesterol target for children 8–10 years should be < 4.0 mmol/L (~160 mg/dL), and for those older than 10 years < 3.4 mmol/L (~130 mg/dL). Consider lower treatment targets in those with particular adverse family history of CAD or other major cardiovascular risk factors.
(Grade D, Level 4, CPG pg. 54)

A If drug therapy is required, a statin is the drug of choice for use in children with dyslipidemia.
(Grade A, Level 1+, CPG pg. 54)

B Resins can be added on to statin therapy in children if LDL cholesterol targets are not achieved.
(Grade B, Level 1+, CPG pg. 54)

GPP Children are more vulnerable and may be less likely to report symptoms or side effects accurately. Hence, creatine kinase and transaminases should be measured before initiation of statins or after changes in the regime, and monitored four monthly thereafter.
(CPG pg. 54)

Pregnancy

GPP During pregnancy, treatment is indicated only in patients with severe hypertriglyceridemia (e.g. TG > 10 mmol/L or 900 mg/dL). The only drug recommended is omega 3 fish oils after dietary therapy.
(CPG pg. 55)

D Statins are contraindicated in women who are pregnant, likely to be pregnant, or who are still breastfeeding.
(Grade D, Level 4, CPG pg. 55)

Elderly

The elderly (age > 75 years) often have co-morbidities, take multiple medications, and have altered pharmacokinetics and pharmocodynamics. In very high risk elderly patients (> 75 years), more intensive therapy (achieving LDL cholesterol in the range of 2.1 mmol/L or 80 mg/dL) has not shown benefit over less intensive therapy. Treatment for such patients should be individualised, and special precautions need to be taken when instituting pharmacotherapy for hyperlipidemia in elderly patients.

D In the elderly (age > 75 years), the decision to start treatment should take into account the potential risk reduction associated with treatment, risk of adverse effects, drug-drug interactions and patient preferences.

(Grade D, Level 4, CPG pg. 55)

GPP In very high risk elderly patients (> 75 years), physicians may wish to consider less intensive targets (e.g. 2.6 mmol/L or 100 mg/dL). When used, lipid lowering medications in the elderly (age > 75 years) should be started at the lowest dose and then titrated to achieve optimal LDL cholesterol levels, in order to avoid statin-associated side effects.

(CPG pg. 56)

GPP For patients on treatment with a statin and LDL cholesterol < 2.1mmol/L or 80 mg/dL when they turn 75 years of age, there is no need to reduce therapy, if the treatment is well tolerated without any adverse effects.

(CPG pg. 56)

Renal disease

In patients with end stage chronic kidney disease on dialysis, statins did not significantly improve cardiovascular outcomes. The decision whether to start or continue statin therapy in these patients must balance the benefits against the cost and potential side effects of statins in this group of patients.

GPP The starting dose of statins in chronic kidney disease should be low. During therapy, serum creatine kinase and renal function should both be carefully monitored.

(CPG pg. 56)

GPP Fibrates can be used in patients with chronic kidney disease in stage 1–3, but the dosages should be reduced with appropriate monitoring for side effects, especially myopathy. When creatinine clearance is less than 30 mL/min (stage 4 or 5), fibrates are contraindicated.

(CPG pg. 57)

Liver disease

D Screen liver function (especially transaminases) on two consecutive occasions in patients with dyslipidemia and chronic liver disease.

(Grade D, Level 4, CPG pg. 57)

D In patients with dyslipidemia and chronic liver disease, if the level of the two transaminases (ALT and AST) is elevated but < 1.5 times the upper limit of the normal range, statins can be given but the starting dose should be low. Careful monitoring of serum transaminases and creatine kinase after commencement is recommended.

(Grade D, Level 4, CPG pg. 57)

D In patients with dyslipidemia and chronic liver disease, if the level of the two transaminases (ALT and AST) is between 1.5–3 times the upper limit of the normal range, statins can still be given but with caution, and the starting dose should be low. Careful monitoring of serum transaminases and creatine kinase after commencement is recommended.

(Grade D, Level 4, CPG pg. 57)

GPP Fibrates can be given in patients whose transaminase levels are elevated < 3 times the upper limit of the normal range, but at a lower starting dosage. Careful monitoring of serum transaminases and creatine kinase after commencement is recommended.

(CPG pg. 58)

Familial hypercholesterolemia

Familial hypercholesterolemia (FH) is a group of inherited genetic defects resulting in severely elevated serum cholesterol concentrations. Clinical diagnosis of FH can be made by applying any one of several validated sets of criteria, including the Simon Broome Trust diagnostic criteria provided in Table B-1. For patients with definite FH, primary care physicians can initiate therapy based on the guidelines or refer patients to a specialist to initiate and stabilise the patient on therapy. For patients with possible FH, primary care physicians may want to refer patient to a specialist to make a recommendation on the need for therapy and to initiate therapy if required.

GPP Screening of all first degree relatives of diagnosed familial hypercholesterolemia patients is recommended.

(CPG pg. 58)

GPP Due to the high risk of CAD, a more aggressive treatment target of LDL cholesterol of 2.1 mmol/L (< 80 mg/dL) is needed for familial hypercholesterolemia patients.

(CPG pg. 58)

Quality indicators for lipid management

The following clinical quality indicators for recommended LDL

cholesterol target levels (Table 6) and process indicators for review frequency (Table 7) are proposed for lipid management. However, measurement of attainment of these target levels should exclude those aged > 75 years.

In the management of an individual patient, good clinical judgement, which takes into account other factors that may influence overall morbidity or mortality risk, should be exercised in every situation. As such, aiming for 100% attainment of these targets is inappropriate. Furthermore, measurements of attainment of these targets should exclude those aged > 75 years.

Table 6. LDL cholesterol target levels (CPG pg. 60).

Risk group category	Recommended LDL cholesterol target levels
Very high risk	The recommended LDL cholesterol target level for the very high risk group is < 2.1 mmol/L (80 mg/dL)
High risk	The recommended LDL cholesterol target level for the high risk group is < 2.6 mmol/L (100 mg/dL)
Intermediate risk	The recommended LDL cholesterol target level for the intermediate risk group is < 3.4 mmol/L (130 mg/dL), with an LDL cholesterol level of < 2.6 mmol/L (100 mg/dL) being an option if the physician feels that the benefits of more intensive therapy outweigh the risks.
Low risk	The recommended LDL cholesterol target level for the low risk group is < 4.1 mmol/L (160 mg/dL), with an LDL cholesterol level of < 3.4 mmol/L (130 mg/dL) being an option if the physician feels that the benefits of more intensive therapy outweigh the risks.

Table 7. Process indicators and recommended frequency (CPG pg. 61).

Performance parameter	Recommended review frequency
All patients who are on stable lipid modifying drug therapy with LDL cholesterol target levels achieved.	Lipid measurement at least every 12 months
Patients who are not on lipid modifying drug therapy (with LDL cholesterol target levels achieved as stated above):	
(1) Very high risk and high risk	Lipid measurement every 12 months
(2) Intermediate risk and low risk	Lipid measurement every 3 years

WORKGROUP MEMBERS

The members of the workgroup, who were appointed in their personal professional capacity, are:

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APPENDIX 1

Table A-1 Estimation of 10-Year Coronary Artery Disease Risk for Men (CPG pg. 29)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

1. Estimate the individual's 10-year CAD risk by allocating points based on his age, total and HDL cholesterol levels, smoking status and systolic blood pressure (BP).
2. Check the total points against Table A-2 to estimate that individual's 10-year CAD risk.

Total Cholesterol mmol/L (mg/dL)	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
< 4.1 (160)	0	0	0	0	0
4.1-5.1 (160-199)	4	3	2	1	0
5.2-6.1 (200-239)	7	5	3	1	0
6.2-7.2 (240-279)	9	6	4	2	1
≥ 7.3 (280)	11	8	5	3	1

Smoker	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
No	0	0	0	0	0
Yes	8	5	3	1	0

HDL Cholesterol mmol/L (mg/dL)	Points
≥ 1.6 (60)	-1
1.3-1.5 (50-59)	0
1.0-1.2 (40-49)	1
< 1.0 (40)	2

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

Table A-2 Estimation of 10-Year Coronary Artery Disease Risk for Men (CPG pg. 30)

Total Points	10-Year Risk (%)		
	Chinese	Malay	Indian
-1	< 1	< 1	1
0	< 1	< 1	1
1	< 1	1	1
2	1	1	1
3	1	1	2
4	1	1	2
5	1	1	3
6	1	2	3
7	2	2	4
8	2	3	5
9	3	4	7
10	4	5	9
11	5	6	11
12	6	8	14
13	8	11	18
14	11	13	> 20
15	13	17	> 20
16	17	> 20	> 20
≥ 17	> 20	> 20	> 20

Table A-3 Estimation of 10-Year Coronary Artery Disease Risk for Women (CPG pg. 31)

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

1. Estimate the individual's 10-year CAD risk by allocating points based on her age, total and HDL cholesterol levels, smoking status and systolic blood pressure (BP).
2. Check the total points against Table A-4 to estimate that individual's 10-year CAD risk.

Total Cholesterol mmol/L (mg/dL)	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
< 4.1 (160)	0	0	0	0	0
4.1-5.1 (160-199)	4	3	2	1	1
5.2-6.1 (200-239)	8	6	4	2	1
6.2-7.2 (240-279)	11	8	5	3	2
≥ 7.3 (280)	13	10	7	4	2

Smoker	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
No	0	0	0	0	0
Yes	9	7	4	2	1

HDL Cholesterol mmol/L (mg/dL)	Points
≥ 1.6 (60)	-1
1.3-1.5 (50-59)	0
1.0-1.2 (40-49)	1
< 1.0 (40)	2

Systolic BP (mmHg)	Points	
	If untreated	If treated
< 120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥ 160	4	6

Table A-4 Estimation of 10-Year Coronary Artery Disease Risk for Women (CPG pg. 32)

Total Points	10-Year Risk (%)		
	Chinese	Malay	Indian
5	< 1	< 1	1
6	< 1	< 1	1
7	< 1	1	1
8	< 1	1	1
9	1	1	2
10	1	1	2
11	1	2	3
12	1	2	3
13	1	3	4
14	2	4	6
15	3	5	7
16	3	6	10
17	4	8	12
18	5	10	16
19	7	13	20
20	9	16	> 20
21	12	20	> 20
22	15	> 20	> 20
23	19	> 20	> 20
≥ 24	> 20	> 20	> 20

Table B-1 Simon Broome Trust Diagnostic criteria for Familial hypercholesterolemia (CPG pg. 59)

Diagnosis	Criteria
Definite Familial hypercholesterolemia	- TC above 7.5 mmol/L (~290 mg/dL) or LDL cholesterol above 4.9 mmol/L (~190 mg/dL) in an adult. - TC above 6.7 mmol/L (~260 mg/dL) or LDL cholesterol above 4 mmol/L (~160 mg/dL) in a child aged under 16 years. PLUS - Tendon xanthomas in patient or a first degree relative (parent, sibling, child), or in a second degree relative (grandparent, uncle, aunt). OR - DNA-based evidence of an LDL receptor mutation, familial defective apoB-100, or a PCSK9 mutation.
Possible Familial hypercholesterolemia	- TC above 7.5 mmol/L (~290 mg/dL) or LDL cholesterol above 4.9 mmol/L (~190 mg/dL) in an adult. - TC above 6.7 mmol/L (~260 mg/dL) or LDL cholesterol above 4mmol/L (~160 mg/dL) in a child aged under 16 years. PLUS - Family history of myocardial infarction (MI): Before 50 years in a second degree relative or below age 60 in a first degree relative. OR - Family history of raised TC: Above 7.5 mmol/L (~290 mg/dL) in adult first or second degree relative or above 6.7 mmol/L (~260 mg/dL) in a child or sibling aged under 16 years.

Source: Identification and Management of Familial Hypercholesterolaemia (FH)

APPENDIX 2

Levels of evidence and grades of recommendations

Levels of evidence

Level	Type of Evidence
1^{++}	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

Grade	Recommendation
A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1^{++} and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

(Code SMJ 201703B)

These questions are based on the full text of the guidelines which may be found at http://www.moh.gov.sg/content/moh_web/healthprofessionalsportal/doctors/guidelines/cpg_medical.html

	True	False
Question 1. With regard to lipids in coronary artery disease (CAD):		
(a) Elevated levels of high-density lipoprotein (HDL) cholesterol are associated with increased risk of CAD.	☐	☐
(b) ApoB and ApoA1 assays should be routinely measured for use in global risk assessment.	☐	☐
(c) Further to a global cardiovascular risk assessment, lipoprotein(a) measurements may be useful in individuals with a strong family history of premature cardiovascular disease.	☐	☐
(d) The association between blood triglyceride (TG) and CAD is attenuated after adjustment for other lipids.	☐	☐
Question 2. With regard to screening for dyslipidemia:		
(a) It is strongly recommended that clinicians routinely screen all adults (men and women aged 18 years and older) for lipid disorders.	☐	☐
(b) Blood lipids may be abnormal after an acute illness such as an infection. As such, physicians and patients may wish to defer tests for at least two weeks after a febrile illness.	☐	☐
(c) Screening is recommended for men and women aged 18 and older in the presence of multiple CAD risk factors (e.g. tobacco use, hypertension).	☐	☐
(d) Patients who suffer a myocardial infarction and have low low-density lipoprotein (LDL) cholesterol levels that do not require treatment during this period should have their blood lipids repeated three months after a myocardial infarction.	☐	☐
Question 3. The following risk factors are considered in the assessment of risk status:		
(a) Gender.	☐	☐
(b) Alcohol consumption.	☐	☐
(c) Presence of chronic kidney disease.	☐	☐
(d) Occupation.	☐	☐
Question 4. With regard to target lipid levels:		
(a) The higher the risk category, the lower will be the target LDL cholesterol level.	☐	☐
(b) The recommended LDL cholesterol target level for the very high risk group is < 2.1 mmol/L (80 mg/dL).	☐	☐
(c) In individuals with very high levels of TG, e.g. > 4.5 mmol/L (400 mg/dL) or especially > 10 mmol/L (900 mg/dL), the first priority is to reduce the LDL cholesterol level to prevent acute hepatitis.	☐	☐
(d) The recommended LDL cholesterol target level for a diabetic patient with chronic kidney disease is < 3.4 mmol/L (130 mg/dL).	☐	☐
Question 5. With regard to management of dyslipidemias:		
(a) Statins are safe and not contraindicated in pregnancy or breastfeeding.	☐	☐
(b) When a fibrate is combined with a statin, fenofibrate is recommended. Gemfibrozil should not be given because it significantly increases the blood level of most statins and this may increase the risk of complications.	☐	☐
(c) Saturated fat should be replaced with mono- and polyunsaturated fats to lower total and LDL cholesterol (without lowering HDL cholesterol) and lower risk of CAD.	☐	☐
(d) Omega 3 fish oils can lower LDL cholesterol and cardiovascular mortality.	☐	☐

Doctor's particulars:

Name in full : _____

MCR number : _____ Specialty: _____

Email address : _____

SUBMISSION INSTRUCTIONS:

(1) Visit the SMJ website: http://www.smj.org.sg/current-issue and select the appropriate set of questions. (2) Provide your name, email address and MCR number. (3) Select your answers and click "Submit".

RESULTS:

(1) Answers will be published online in the SMJ May 2017 issue. (2) The MCR numbers of successful candidates will be posted online at the SMJ website by 2 May 2017. (3 Passing mark is 60%. No mark will be deducted for incorrect answers. (4) The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council. (5) One CME point is awarded for successful candidates.

Deadline for submission: (March 2017 SMJ 3B CME programme): 12 noon, 25 April 2017.