MOH CLINICAL PRACTICE GUIDELINES 2/2016

LIPIDS
EXECUTIVE SUMMARY

Chapter of Family Medicine
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Singapore Cardiac Society

Endocrine & Metabolic Society of
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EXECUTIVE SUMMARY OF RECOMMENDATIONS

Introduction

This is the executive summary of the MOH Clinical Practice Guidelines (CPG) on Lipids. It is intended to be used with reference to the full version of the CPG which is freely available on the MOH website at this link:

https://www.moh.gov.sg/content/moh_web/healthprofessionalsportal/doctors/guidelines/cpg_medical.html

Cardiovascular disease, especially coronary artery disease (CAD) is a very important health problem in Singapore today, and 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.

Target audience

These guidelines are developed for all healthcare professionals, in particular, primary care physicians, as an evidence-based resource to provide up-to date information and guidance on the diagnosis, and management of dyslipidemia.

How to use this document

All recommendations made in the CPG are summarised in this document.

Please note the following:

a. The page numbers of the full CPG document where each recommendation is explained are provided.
b. Each recommendation has a corresponding Grade of Recommendation and Level of Evidence (refer to back cover page for details).

Key recommendations are highlighted in light blue.

Commonly used abbreviations

The following is a list of abbreviations commonly used in this set of guidelines (arranged in alphabetical order), and a description of what they represent:

- ALT   Alanine transaminase
- ApoA1   Apolipoprotein A1
- ApoB   Apolipoprotein B
- AST   Aspartate transaminase
- BNP   B-type natriuretic peptide
- CAD   Coronary artery disease
- DHA   Docosahexaenoic acid
- eGFR   Estimated glomerular filtration route
- EPA   Eicosapentaenoic acide
- HDL   High density lipoprotein
- HMG-CoA   3-hydroxy-3-methyl-glutaryl-CoA
- IDL   Intermediate density lipoprotein
- LDL   Low density lipoprotein
- Lp(a)   Lipoprotein(a)
- NT-proBNP   N-terminal prohormone of brain natriuretic peptide
- TC   Total cholesterol
- TG   Triglyceride
- VLDL   Very low density lipoprotein
- FH   Familial Hypercholesterolemia

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, HDL cholesterol and TG are used for risk stratification (Chapter 5) and for making decisions on treatment (Chapter 7).

Classification & 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 glycaemia 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;
d. A family history suggestive of familial hyperlipidemia.

Dyslipidemia can be classified as hypercholesterolemia, mixed (combined) dyslipidemia, hypertriglyceridemia, and severe hypertriglyceridemia (Table 1).

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 (1.7-4.5mmol/L [150-99mg/dL])
Hypertriglyceridemia	VLDL	TG (1.7-4.5mmol/L [150-99mg/dL])
Severe Hypertriglyceridemia	Chylomicrons	TG (≥4.5mmol/L [400mg/dL])

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

Secondary dyslipidemia may occur in the various conditions and should be excluded in any patient presenting with dyslipidemia (Table 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 lipids 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 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 pg. 8) and have low TG levels, screening should be repeated at 3 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 to 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 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 2 weeks after a febrile illness as blood lipids may be abnormal after an acute illness such as an infection. **(CPG pg. 20)**
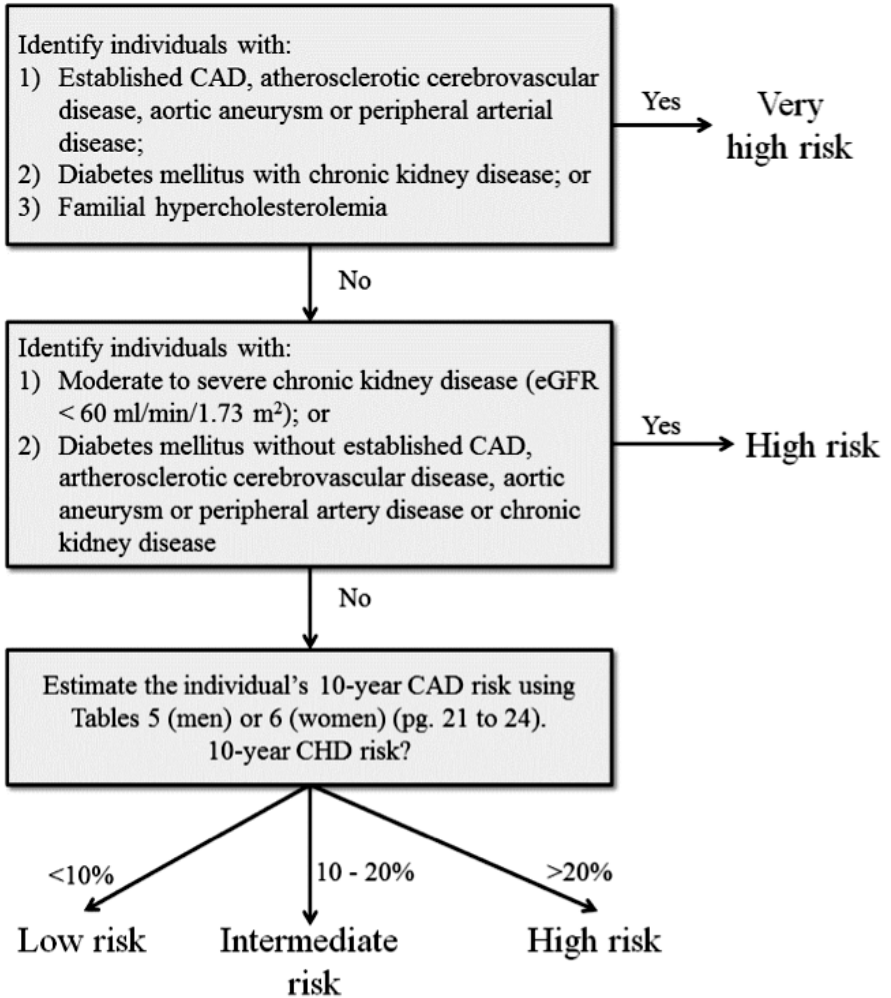
D Patients who suffer myocardial infarction may have depressed cholesterol levels that do not require treatment. These patients should have their blood lipids repeated 3 months after a myocardial infarction. **(Grade D, Level 3, CPG pg. 20)**

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 Figure 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, chronic kidney disease, or familial hypercholesterolemia. If the patient is not in the very high risk or high risk strata, his/her 10-year CAD risk can be estimated using Tables A-1 to A-4, pg. 21-24.

Figure 1 Risk Stratification (CPG pg. 28)

Identify individuals with:
1) Established CAD, atherosclerotic cerebrovascular disease, aortic aneurysm or peripheral arterial disease;
2) Diabetes mellitus with chronic kidney disease; or
3) Familial hypercholesterolemia

→ Yes → **Very high risk**

↓ No

Identify individuals with:
1) Moderate to severe chronic kidney disease (eGFR < 60 ml/min/1.73 m^2); or
2) Diabetes mellitus without established CAD, artherosclerotic cerebrovascular disease, aortic aneurysm or peripheral artery disease or chronic kidney disease

→ Yes → **High risk**

↓ No

Estimate the individual's 10-year CAD risk using Tables 5 (men) or 6 (women) (pg. 21 to 24).
10-year CHD risk?

<10% → **Low risk**

10 - 20% → **Intermediate risk**

>20% → **High risk**

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.

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 <3.4mmol/L (130mg/dL), with an LDL cholesterol level of <2.6mmol/L (100mg/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 (160mg/dL), with an LDL cholesterol level of <3.4mmol/L (130mg/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 2 consecutive values of LDL cholesterol levels less than 1.03mmol/L (40mg/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 was 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.

b) Moderate intensity statin therapy, e.g. simvastatin 20-40mg, 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 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. >4.5mmol/L (400mg/dL) or especially >10mmol/L (900mg/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 2.3mmol/L (200mg/dL) and 4.5mmol/L (400mg/dL), in the presence of low HDL cholesterol (<1.0mmol/L or 40mg/dL in males, <1.3mmol/L or <50mg/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/m^2, **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 to 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 drink per day for women and three per day for men** is recommended. A standard drink is 10g of alcohol which is the equivalent of 2/3 can of 220ml beer, one small 100ml glass of wine or 1 nip (30ml) 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 grams 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% 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 grams per day. **(Grade A, Level 1+, CPG pg. 39)**

A Cholesterol intake should be reduced to less than 300mg 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)**

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 130g
†One serve of vegetables is equivalent to ¾ of a mug (100g) cooked vegetables

Drug therapy

Choice of drugs

In considering the choice of drugs for dyslipidemia, there are 3 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 > 4.5mmol/L (400mg/dL). **(Grade A, Level 1++, CPG pg. 43)**

D Since patients are at increased risk for acute pancreatitis when TG is >4.5mmol/L (400mg/dL) and the risk is greater with higher TG level, fibrates are the first line drug to reduce the risk of pancreatitis when TG > 4.5mmol/L (400mg/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)**

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 (>4.5mmol/L or 400mg/dL)	Fibrate, adding omega 3 fish oils or niacin if triglyceride >4.5mmol/L (400mg/dL)
Severe hypertriglyceridemia (>10mmol/L or 900mg/dL)	Fibrate and omega 3 fish oils, adding niacin if triglyceride >4.5mmol/L (400mg/dL)

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 that are also metabolised by the 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

GPP In patients with pre-diabetes / 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 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 40mg. However, in patients who have been taking 80mg 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 patient's baseline prior to starting statin therapy. However, routine repeat measurement 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 3 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 to 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

C Addition of fenofibrate to a statin may benefit certain patients with Type 2 diabetes 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 ≥4.5mmol/L or 400mg/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 >10mmol/L [900mg/dL]), where fibrates alone may not adequately lower the markedly elevated TG levels, omega 3 fish oils should be added in dosages of 3 to 12 gm per day, which contains 1-4 gm 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 2.3mmol/L (200mg/dL) and 4.5mmol/L (400mg/dL), in the presence of low HDL cholesterol (<1.0mmol/L or 40mg/dL in males, <1.3mmol/L or <50mg/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, (ii) physicians should consider doing serum creatine kinase 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 specialist

GPP Patients who remain outside the LDL cholesterol target values or with TG levels persistently >4.5mmol/L (400mg/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 2 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 is 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 8 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 <4.0mmol/L (~160mg/dL), and for those older than 10 years <3.4mmol/L (~130mg/dL). Consider lower treatment targets in those with particular adverse family history of CAD or with 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 4 monthly thereafter. **(CPG pg. 54)**

Pregnancy

GPP During pregnancy, treatment is indicated only in patients with severe hypertriglyceridemia (e.g. TG >10mmol/L [900mg/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 2.1mmol/L (80mg/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. 2.6mmol/L or 100mg/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 80mg/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 to 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 2 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 the 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 to 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 the 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 the 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 specialists 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 2.1mmol/L (<80mg/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 age >75 years.

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

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

GPP **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 (2) Intermediate risk and low risk	 Lipid measurement every 12 months Lipid measurement every 3 years

In the management of an individual patient, good clinical judgment, 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 age > 75 years.

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-1 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
$\geq$ 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
$\geq$ 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
$\geq$ 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 7.5mmol/L (~290mg/dL) or LDL cholesterol above 4.9mmol/L (~190mg/dL) in an adult. - TC above 6.7mmol/L (~260mg/dL) or LDL cholesterol above 4mmol/L (~160mg/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 7.5mmol/L (~290mg/dL) or LDL cholesterol above 4.9mmol/L (~190mg/dL) in an adult. - TC above 6.7mmol/L (~260mg/dL) or LDL cholesterol above 4mmol/L (~160mg/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 7.5mmol/L (~290 mg/dL) in adult first or second degree relative or above 6.7mmol/L (~260mg/dL) in a child or sibling aged under 16 years.

Source: Identification and Management of Familial Hypercholesterolaemia (FH)

Levels of evidence and grades of recommendation

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.