These guidelines have been withdrawn

MOH clinical practice guidelines are considered withdrawn five years after publication unless otherwise specified in individual guidelines. Users should keep in mind that evidence-based guidelines are only as current as the evidence that supports them and new evidence can supersede recommendations made in the guidelines.

CLINICAL PRACTICE GUIDELINES

Lipids

Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grades of recommendation

Grade	Recommendation
A (evidence levels Ia, Ib)	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B (evidence levels IIa, IIb, III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.
C (evidence level IV)	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

CLINICAL PRACTICE GUIDELINES

Lipids

MOH Clinical Practice Guidelines   2/2006

Abbreviations

CHD	=	Coronary heart disease
TC	=	Total cholesterol
LDL-C	=	Low density lipoprotein cholesterol
HDL-C	=	High density lipoprotein cholesterol
TG	=	Triglyceride

4S	=	Scandinavian Simvastatin Survival Study
CARE	=	Cholesterol and Recurrent Events
LIPID	=	Long Term Intervention with Pravastatin in Ischaemic Disease
WOSCOPS	=	West of Scotland Coronary Prevention Study
AFCAPS/TexCAPS	=	Air Force/Texas Coronary Atherosclerosis Prevention Study
HPS	=	Heart Protection Study
PROSPER	=	Prospective Study of Pravastatin in the Elderly at Risk
PROVE-IT	=	Pravastatin or Atorvastatin Evaluation and Infection Therapy
TNT	=	Treating to New Targets
IDEAL	=	Incremental Decrease in End Points Through Aggressive Lipid Lowering
CARDS	=	Collaborative Atorvastatin Diabetes Study
VA-HIT	=	Veterans Affairs High Density Lipoprotein Intervention Trial
FIELD	=	Fenofibrate Intervention and Event Lowering in Diabetes
SPARCL	=	Stroke Prevention by Aggressive Reduction in Cholesterol Levels

Conversion from mmol/L to mg/dl

- Total cholesterol, LDL cholesterol and HDL cholesterol in mmol/L x 38.6 = mg/dL
- Triglyceride in mmol/L x 88.5 = mg/dL

Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Foreword

The Singapore 2004 National Health Survey (NHS) has shown decreases in the prevalence of high cholesterol levels in both sexes and across the three major ethnic groups in Singapore, compared to the NHS in 1998. Nevertheless, coronary heart disease (CHD) is still the second leading cause of death here, and as dyslipidaemias are important risk factors for CHD, there remains a need for these guidelines on managing lipid disorders.

This review of the MOH Clinical Practice Guidelines on Lipids, first published in 2001, is a timely update that incorporates the best available evidence from the scientific literature, appraised by the comprehensive expertise of the expert workgroup that revised the guidelines. They have interpreted the evidence in our local context and drafted practical recommendations on managing patients with lipid abnormalities.

These guidelines address important issues in diagnosis and managing patients with dyslipidaemia according to the individual's co-existing risk factors for CHD. A key change is the addition of recently developed risk score tables to estimate 10-year CHD risk in individuals with two or more risk factors. Cost-effectiveness is an important factor that has been considered by the workgroup in making recommendations.

I hope these guidelines will assist all doctors, particularly primary care physicians, to provide the most appropriate treatment to their individual patients.

PROFESSOR K SATKU
DIRECTOR OF MEDICAL SERVICES

Contents

Details of recommendations can be found in the main text at the pages indicated.

Laboratory lipid measurements

A lipid profile consisting of total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglyceride (TG) should be obtained in the following individuals:

A Patients with coronary heart disease (CHD), cerebrovascular or peripheral artery disease (pg 16).

Grade A, Level Ib

A Patients with diabetes mellitus (pg 16).

Grade A, Level Ib

A Individuals with a family history or clinical evidence of familial hyperlipidaemia (pg 16).

Grade A, Level Ib

A Individuals with other risk factors for CHD (pg 16).

Grade A, Level Ib

Goal lipid levels

For the prevention of coronary heart disease, the first priority is the **optimization of LDL-C level**.

A The recommended LDL-C goal level for the **High Risk Group** is < 2.6 mmol/L (100 mg/dL) (pg 27).

Grade A, Level Ib

C The recommended LDL-C goal level for the **Intermediate Risk Group** is < 3.4 mmol/L (130 mg/dL), with an LDL-C level of < 2.6 mmol/L (100 mg/dL) being an option (pg 27).

Grade C, Level IV

C The recommended LDL-C goal level for the **Low Risk Group** is < 4.1 mmol/L (160 mg/dL), with an LDL-C of < 3.4 mmol/L (130 mg/dL) being an option (pg 27).

Grade C, Level IV

C In **very high risk patients** (e.g. patients with established CHD and diabetes mellitus or multiple other risk factors) an "optional goal" of LDL-C < 2.1 mmol/L (80 mg/dL) may be considered by the physician, who, however, must balance the benefits against the cost and potential side effects of high doses of medication or combination therapy which are often required to achieve very low LDL-C levels (pg 28).

Grade C, Level IV

GPP The goal TG level for all three risk groups is < 2.3 mmol/L (200 mg/dL) (pg 29).

GPP

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 for this reason. In these patients, the first priority is to reduce the TG level to prevent acute pancreatitis (pg 29).

Grade C, Level IV

C The goal HDL-C level for all three risk groups is ≥ 1.0 mmol/L (40 mg/dL) (pg 29).

Grade C, Level IV

Lifestyle changes

A Lifestyle changes are an integral part of overall management. They are the mainstay in population based primary prevention strategies. In addition, it is very important to continue these lifestyle changes in patients who have been started on drug therapy (pg 30).

Grade A, Level Ib

A Patients who smoke should be advised to stop smoking immediately (pg 30).

Grade A, Level Ib

A Weight reduction is achieved mainly by dietary therapy and exercise (pg 30).

<div align="right">**Grade A, Level Ib**</div>

C It is recommended that individuals engage in at least 30 minutes of moderate intensity physical activity most days of the week. For individuals who have difficulty exercising, they should be encouraged to engage in less strenuous physical activity (pg 30).

<div align="right">**Grade C, Level IV**</div>

Drug therapy

A The appropriate drug must be chosen for the particular type of dyslipidaemia, e.g statins for lowering high LDL-C levels and fibrates for lowering TG levels or for elevating low HDL-C levels (pg 32).

<div align="right">**Grade A, Level Ib**</div>

C The cost of therapy should be considered in the choice of a particular lipid medication (pg 32).

<div align="right">**Grade C, Level IV**</div>

C Generic formulations cost less than non-generic drugs and can be considered if they meet prescribed standards (pg 33).

<div align="right">**Grade C, Level IV**</div>

Recommended drugs for Hypercholesterolaemia

A HMG-CoA reductase inhibitors (statins) are the preferred drugs for hypercholesterolaemia (pg 34).

<div align="right">**Grade A, Level Ia**</div>

Ezetemide when added to a statin will produce a further 18% lowering of the LDL-C.

C Check serum transaminases before and 8 to 12 weeks after starting statin therapy. If they are normal, consider repeating this test at least once annually (especially when the dosages of the drugs are increased or when combination therapy is initiated) (pg 35).

<div align="right">**Grade C, Level IV**</div>

C Monitoring of serum creatine kinase is also advisable in patients with renal disease, when high dosages of statins are used or when statins are combined with fibrates or nicotinic acid. Patients should be advised to report promptly to their doctors if they have muscle pain, tenderness or weakness (pg 35).

Grade C, Level IV

C 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 the liver function has returned to normal (pg 35).

Grade C, Level IV

C Elevation of serum creatine kinase greater than 5 to 10 times the upper limit of the normal range, 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 (pg 35).

Grade C, Level IV

Recommended drugs for Hypertriglyceridaemia

In all individuals in whom a fibrate is recommended, nicotinic acid can also be considered.

A Fibrates are the drugs of choice in the treatment of hypertriglyceridaemia (pg 36).

Grade A, Level Ib

A In severe hypertriglyceridaemia (e.g. TG >10 mmol/L [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 to 12 gm per day (pg 36).

Grade A, Level Ib

Recommended drugs for Mixed Dyslipidaemia

A A statin is recommended if the predominant lipid abnormality is an elevated LDL-C. If the TG remains unacceptably high or if the HDL-C remains low despite the statin, consider adding a fibrate (pg 37).

Grade A, Level Ib

C A fibrate is recommended if the TG is > 4.5 mmol/L (400 mg/dL). If the LDL-C remains elevated despite the fibrate, consider adding a statin (pg 37).

Grade C, Level IV

C The decision to combine a statin and a fibrate must be individualized and should be initiated only when it is strongly indicated (pg 37).

Grade C, Level IV

B 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 (pg 37).

Grade B, Level III

C In combination therapy: (i) start the second drug at a low dosage and increase the dose gradually until the goal level is achieved. High dosages of statins should be avoided, (ii) monitor serum transaminases and creatine kinase before and 6 to 8 weeks after initiation of the combination therapy. Thereafter, these 2 tests should be repeated at least once annually or whenever the dosages of the drugs are increased, (iii) patients should be advised to promptly report to their doctors if they have muscle pain, tenderness or weakness, (iv) consider doing serum creatine kinase in patients who complain of muscle pain (pg 37).

Grade C, Level IV

Treatment of Isolated Low HDL-C

A Based on the results of the recent VA-HIT Study, CHD patients whose primary lipid abnormality is a low HDL-C despite lifestyle changes can be given a fibrate to elevate the HDL-C level (pg 38).

Grade A, Level Ib

Referral of patients to specialist

GPP Patients who remain outside the target values despite dietary changes and maximal drug therapy should be referred to lipid specialists (pg 38).

GPP

Special considerations

Children, women, pregnancy, elderly

A Statins can be used in children, but proper monitoring is required (pg 39).

Grade A, Level Ib

C Resins can be added on to statin therapy in children if LDL-C targets are not achieved (pg 39).

Grade C, Leve1 IV

A In postmenopausal women as well as premenopausal women, the decision to start drug therapy should be based on the 10-Year CHD Risk Score (pg 40).

Grade A, Level Ib

GPP During pregnancy, treatment is indicated only in patients with severe hypertriglyceridaemia (e.g. TG >10 mmol/L [900 mg/dL]). The only drug recommended is omega 3 fish oils after intensive dietary therapy (pg 40).

GPP

C Statins are contraindicated in women who are pregnant or who are likely to be pregnant (pg 40).

Grade C, Level IV

A In the elderly, the decision to start drug therapy should be based on the 10-Year CHD Risk Score, the life expectancy as well as the quality of life of the patient. Age is not a contraindication to drug therapy if indicated (pg 40).

Grade A, Level Ib

Renal disease

GPP The starting dose of statins in chronic renal failure should be low. During therapy, serum creatine kinase and renal function should both be carefully monitored (pg 40).

<div align="right">**GPP**</div>

GPP Fibrates can be used if the renal failure is only mild or moderate but the dosages should be reduced, with appropriate monitoring for side effects, especially myopathy. When creatinine clearance is less than 10 ml/min, fibrates are contraindicated (pg 40).

<div align="right">**GPP**</div>

Liver disease

C Screen liver function (especially transaminases) on 2 consecutive occasions in patients with chronic liver disease due to either hepatitis B or alcoholic abuse. If the level of either of these 2 transaminases is elevated but < 1.5 times the upper limit of the normal range, statins can be given. If the level is ≥ 1.5 times but < 3 times the upper limit of the normal range, statins can still be given but with caution. In both situations, the starting dose of the statins should be low. Statins are contraindicated in those with acute liver disease and also in those with advanced or end stage parenchymal liver disease (pg 41).

<div align="right">**Grade C, Level IV**</div>

GPP Fibrates can be given in patients whose transaminase levels are elevated < 3 times the upper limit of the normal range, but again at a lower starting dosage. Careful monitoring of the serum transaminases and creatine kinase after commencement of either statin or fibrate therapy is recommended (pg 41).

<div align="right">**GPP**</div>

1   Guideline development and objectives

1.1   Guidelines development

The workgroup, comprising cardiologists, endocrinologists, lipid specialists, public health specialists, a neurologist and a family physician, was nominated by the National Committee on Cardiac Care and appointed by MOH to develop these guidelines on lipids.

1.2   Objectives

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

1.3   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 dyslipidaemia.

1.4   What's new in the revised guidelines

- The ranking of evidence and recommendations has been changed from a format from the American College of Cardiology/American Heart Association to the format based on the Scottish Intercollegiate Guidelines Network that has been adopted in all Ministry of Health Clinical Practice Guidelines.

- In Section 2, the epidemiology of lipids in Singapore has been updated based on data obtained from the 2004 National Health Survey.

- In Section 5, the classification of dyslipidaemia has been simplified.

- Section 8 on risk assessment has been revised. Three risk categories i.e. High Risk, Intermediate Risk and Low Risk groups have been identified. The Table of major risk factors for CHD has been updated.

For individuals with ≥ 2 risk factors, estimation of the 10-year CHD risk is recommended using new risk score tables which have been recently developed.

- In Section 9 on goal lipid levels, the Table on the goal levels of LDL-C, TG and HDL-C in the 3 risk category groups have been amended. Also in this section, an "optional goal" of LDL-C < 2.1 mmol/L (80 mg/dL) in very high risk patients has been added. Annex 2A and 2B have been deleted.

- In Section 11 on drug therapy, cost effectiveness issues of lipid therapy have been updated. Newly introduced drugs (e.g. rosuvastatin, ezetimibe and niaspan) have been added.

1.5 Review of guidelines

Evidence-based clinical practice guidelines 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 three years after publication, or if new evidence appears that requires substantive changes to the recommendations.

2   Introduction

Cardiovascular disease, especially coronary heart disease (CHD) is a very important health problem in Singapore today. Coronary heart disease is second only to cancer as a leading cause of mortality in this country.

Recent mega trials in the last 12 years have shown significant benefits on coronary risk when total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) levels are reduced by statin drugs in patients with and without pre-existing CHD.[1-7] A recent trial has also shown the benefit of raising high density lipoprotein cholesterol (HDL-C) in CHD patients with a normal LDL-C level but a low HDL-C level.[8]

2.1   Epidemiology

The **Singapore 2004 National Health Survey** (NHS)[9] found that the mean TC level of our adult population aged 18-69 years was 5.3 mmol/L (205 mg/dL). The prevalence of high blood cholesterol level, defined as a TC of ≥ 6.2 mmol/L (240 mg/dL) was 18.7%. Malays had the highest prevalence of high TC (22.8%) followed by Chinese (18.2%) and Indians (16.9%). Also, more males (19.8%) than females (17.5%) had high TC. A significant decrease in the prevalence of high TC was detected in both genders and in all three ethnic groups in the 2004 NHS compared to the 1998 NHS.

Similar to TC, the prevalence of high LDL-C, defined as a level of ≥ 4.1 mmol/L (160 mg/dL) has also declined from 26.5% in 1998 to 19.8% in 2004. Lastly, the prevalence of low HDL-C, defined as a level < 1.0 mmol/L (40 mg/dL) has also declined from 11.7% in 1998 to 5.5% in 2004. However, in the 2004 NHS, Indians had the highest prevalence of low HDL-C (19.1%), compared to Malays (7.3%) and Chinese (3.9%).

3 The role of lipids in CHD

Lipid disorders (dyslipidaemia) play a major role in the pathogenesis of CHD.[10]

3.1 Hypercholesterolaemia

The relationship between CHD and cholesterol levels is continuous and curvilinear. Clinically relevant risk of CHD begins with a TC level of around 3.9 mmol/L (150 mg/dL) and escalates sharply when the TC exceeds 5.2 mmol/L (200 mg/dL).[11] The fraction of cholesterol that has been shown to be the most important is the LDL-C.

3.2 HDL Cholesterol

High density lipoprotein cholesterol (HDL-C) has a powerful protective effect against CHD.[12-14] Therefore, a low HDL-C is an important independent risk factor for CHD. HDL cholesterol is decreased with obesity, cigarette smoking and a sedentary lifestyle, but is increased with exercise and alcohol intake.

3.3 Triglyceride

The association between triglyceride (TG) and CHD is not as well proven as for LDL-C and HDL-C. Nevertheless, hypertriglyceridaemia is important when it is associated with diabetes mellitus, in patients with pre-existing CHD and in individuals whose TC/HDL-C ratio is ≥ 5.[15]

4   Risk factors for CHD

Risk factors for CHD are as follows:

Non-Modifiable	Modifiable
- Increasing age	- Dyslipidaemia
- Male gender	- Hypertension
- Family history of premature CHD	- Diabetes mellitus
- Indian ethnicity	- Cigarette smoking
	- Obesity
	- Sedentary lifestyle
	- Stress

Risk factors are additive in their effect. Therefore, in the assessment and management of coronary risk in any individual, it is essential to adopt a global approach consisting of an evaluation and treatment of all existing risk factors.

4.1   Age

Increasing age is probably the most important risk factor for CHD.[16]

4.2   Gender

The incidence of CHD is approximately 3 to 4 times higher in men compared to pre-menopausal women.[16] However, after the onset of menopause, the risk of women developing CHD increases rapidly.

4.3   Smoking

Smoking approximately doubles the risk of CHD, which is directly related to the number of cigarettes smoked.[17]

4.4   Hypertension

Both elevated systolic and diastolic blood pressures increase the risk of CHD and strokes.[18] The prevalence of hypertension (BP $\geq$ 140/90 mmHg) in our adult population aged 30-69 years is 24.9%.

4.5 Diabetes mellitus

Diabetes mellitus (especially type 2) greatly increases the risk of CHD. Diabetic patients without previous myocardial infarction have as high a risk of suffering an acute myocardial infarction compared to non-diabetic patients with previous myocardial infarction.[19] Insulin resistance or the metabolic syndrome also increases the risk for CHD in non-diabetic patients.

4.6 Family history of premature CHD

A positive family history of premature CHD is an important risk factor for CHD.[20]

4.7 Ethnicity

Indians are at an increased risk of CHD partly because of a higher prevalence of diabetes mellitus and for other reasons which are at present not entirely clear.[21]

4.8 Obesity

Obesity significantly increases the risk for CHD.[22]

4.9 Other risk factors

The other risk factors that have been implicated for CHD are:
- Sedentary life-style[23]
- Stress[24]
- Elevated C-reactive protein levels[25]
- Elevated homocysteine levels[26]
- Elevated lipoprotein(a) levels[27]
- Elevated fibrinogen levels[28]

5 Classification of dyslipidaemia

Dyslipidaemias may be inherited (e.g. familial hypercholesterolaemia) or acquired (e.g. polygenic hypercholesterolaemia). Table 1 shows a classification of lipid disorders.

Hypercholesterolaemia, Mixed (Combined) Dyslipidaemia and Hypertriglyceridaemia are the 3 commonest dyslipidaemias. The HDL-C level is usually inversely related to the TG level and is therefore frequently low in both mixed (combined) dyslipidaemia and hypertriglyceridaemia. In severe hypertriglyceridaemia, the TG levels are extremely high, e.g. >10 mmol/L (900 mg/dl), due to the presence of chylomicrons. The main complication here is acute pancreatitis.

Table 1   Classification of dyslipidaemia

Type of Dyslipidaemia	Increased Concentration	
	Lipoprotein	Serum Lipid
1. **Hypercholesterolaemia** - polygenic, familial hypercholesterolaemia	LDL	Cholesterol
2. **Mixed (Combined) Dyslipidaemia** - polygenic, familial combined hyperlipidaemia	LDL & VLDL	Cholesterol & Triglyceride
3. **Hypertriglyceridaemia**	VLDL	Triglyceride
4. **Severe Hypertriglyceridaemia**	Chylomicrons	Triglyceride

LDL = low density lipoprotein
VLDL = very low density lipoprotein

Secondary dyslipidaemia may occur in the various conditions listed in Table 2. These conditions should be excluded in any patient presenting with dyslipidaemia.

Table 2   Common causes of secondary dyslipidaemia

Disorder	Lipid abnormalities
Diabetes mellitus[29]	↑ TG and ↓ HDL-C
Chronic renal failure[30]	↑ TG
Nephrotic syndrome[31]	↑ TC
Hypothyroidism[32]	↑ TC
Alcohol abuse[33]	↑ TG
Cholestasis[33]	↑ TC
Pregnancy[34]	↑ TG
Drugs[35] e.g. diuretics, beta-blockers, oral contraceptives, corticosteroids, retinoids, anabolic steroids, progestins related to testosterone	↑ TG and /or TC, ↓ HDL-C

6 Laboratory lipid measurements

6.1 Recommendations for testing

A lipid profile consisting of TC, LDL-C, HDL-C and TG should be obtained in the following individuals:

A Patients with CHD, cerebrovascular or peripheral artery disease.[6]

Grade A, Level Ib

A Patients with diabetes mellitus.[36]

Grade A, Level Ib

A Individuals with a family history or clinical evidence of familial hyperlipidaemia.[37]

Grade A, Level Ib

A Individuals with other risk factors for CHD.[38]

Grade A, Level Ib

With regard to routine screening of lipids in the population, the reader is advised to refer to the Ministry of Health Clinical Practice Guidelines on Health Screening.[39]

Serum TC and HDL-C levels can be measured at any time of the day in the non-fasting state. However, TG levels must be obtained after 10 to 12 hours of fasting. TC, HDL-C and TG are measured directly.

LDL cholesterol is usually calculated using the Friedwald formula[40] which is as follows:

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

This formula cannot be used if the TG is ≥ 4.5mmol/L (400 mg/dL). Direct measurement of LDL-C is now available in some laboratories in Singapore.

6.2   Precautions to be taken

- 10 to 12 hours of fasting is necessary for the estimation of TG.
- Defer tests for at least 2 weeks after a febrile illness.
- For patients suffering from acute myocardial infarction, the cholesterol level may be depressed between 24 hours to about 3 months after the infarction.

Table 3   Classification of total, LDL and HDL cholesterol and triglyceride levels

Total Cholesterol (mmol/L [mg/dL])	
< 5.2 (200)	Desirable
5.2- 6.1 (200-239)	Borderline high
≥ 6.2 (240)	High
LDL Cholesterol (mmol/L [mg/dL])	
< 2.6 (100)	Optimal
2.6-3.3 (100-129)	Desirable
3.4- 4.0 (130-159)	Borderline high
4.1- 4.8 (160-189)	High
≥ 4.9 (190)	Very high
HDL Cholesterol (mmol/L [mg/dL])	
< 1.0 (40)	Low
1.0-1.5 (40-59)	Desirable
≥ 1.6 (60)	High
Triglyceride (mmol/L [mg/dL])	
< 1.7 (150)	Optimal
1.7-2.2 (150-199)	Desirable
2.3- 4.4 (200-399)	High
≥ 4.5 (400)	Very high

7   Strategies for primary and secondary prevention of CHD

Prevention of CHD is of crucial importance. Primary prevention implies preventing CHD in hitherto normal individuals, and secondary prevention implies prevention of future coronary events in individuals with pre-existing CHD. Coronary heart disease, stroke and peripheral artery disease patients share many similar risk factors. Strategies aimed at preventing CHD have also been shown to reduce cerebrovascular events.[41] Since risk factors are additive in their effect, it is important to treat not only dyslipidaemia but also all other risk factors such as hypertension, diabetes mellitus, cigarette smoking, obesity, etc., if these are present.[38]

7.1   Primary prevention

The approach to primary prevention must be both population-based as well as individual-based.

Population-based strategies aim at community education of the public on the risk factors, the various clinical presentations of CHD and the importance of healthy lifestyle practices.

Individual-based primary prevention involves the identification of healthy individuals who are at an increased risk of developing CHD because of diabetes mellitus or multiple risk factors.

7.2   Secondary prevention

Secondary prevention involves individuals who already have CHD. Since this group of individuals has the highest risk of subsequent coronary events, an aggressive approach is essential. The benefits of cholesterol reduction in patients with established CHD have been clearly demonstrated in a few recent landmark trials.[1,2,6,41]

8   Risk assessment

8.1   Assessment of risk status

A basic principle in the prevention of CHD is that the intensity of risk-reduction therapy should be adjusted to a person's risk of developing future coronary events. As such, the first step to be taken is the assessment of the individual's risk status.

The **3 risk group categories** are[42,43]:
- High risk (10-year CHD risk >20%)
- Intermediate risk (10-year CHD risk 10-20%)
- Low risk (10-year CHD risk <10%)

For the purpose of risk assessment, **the 10-year CHD risk** refers to the risk of having **myocardial infarction** or **coronary death** in the next 10 years.

The **following 3 steps** are recommended for risk stratification (see Figure 1, page 22).

Step 1

Identify the following individuals who automatically fall into the High Risk Group:
(1) Individuals with established CHD
(2) Individuals with CHD Risk Equivalents defined as:
    (a) diabetes mellitus
    (b) atherosclerotic cerebrovascular disease, peripheral artery disease or abdominal aortic aneurysms

(Estimation of the 10-Year CHD Risk Score in these individuals is not necessary).

Step 2

For all other individuals, count how many risk factors they have using **Table 4** (page 20).

If the individual has 0-1 risk factor, this person automatically falls into the Low Risk Group.

(Estimation of the 10-Year CHD Risk Score in these individuals is not necessary).

Step 3

If the individual has ≥ 2 risk factors, estimation of the **10-Year CHD Risk Score** using **Tables 5 and 6** (pages 23-26) is recommended.
Based on this risk score, the risk status of the individual is classified as follows:

(1) > 20% - high risk
(2) 10 to 20% - intermediate risk
(3) < 10% - low risk.

Table 4   Major risk factors for coronary heart disease[44]

> • Total cholesterol ≥ 6.2 mmol/L (240 mg/dL) or
>   LDL cholesterol ≥ 4.1 mmol/L (160 mg/dL)
>
> • Cigarette smoking
>
> • Hypertension (BP ≥ 140/90 mmHg or on anti-hypertensive medication)
>
> • Low HDL cholesterol (< 1.0 mmol/L [40 mg/dL])
>
> • Family history of premature CHD (CHD in male first degree relative < 55 years; CHD in female first-degree relative < 65 years)
>
> • Age (men ≥ 45 years; women ≥ 55 years)
>
> • Indian ethnicity

Source: Modified from Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001.
Diabetes mellitus is not included in the above as it is already regarded as a CHD risk equivalent.

Tables 5 and 6 show the 10-Year CHD Risk Score for Chinese, Malay and Indian males and females in Singapore. These risk scores are derived from the Framingham-based NCEP ATP III 10-Year Risk Score Tables[44] which have been modified taking into account the Singapore cardiovascular epidemiological data. This modification was

carried out as part of a collaboration between investigators at the Singapore Ministry of Health, Singapore General Hospital, National University of Singapore and Prof. Ralph B D'Agostino from the Framingham Heart Study, USA.

Since there are insufficient data for other ethnic minorities, it is recommended that the 10-Year CHD Risk Score (as shown in tables 5 and 6) for the lowest risk group (i.e. Chinese) be used for these individuals.

Figure 1 - The 3 Steps for Risk Stratification

Step 1

Identify individuals with:
  (1) Established CHD
  (2) CHD Risk Equivalents, defined as:
      (a) Diabetes mellitus
      (b) Atherosclerotic cerebrovascular disease, peripheral artery disease or abdominal aortic aneurysm

Yes → **No**

Step 2
Count the Number of Risk Factors the individual has using Table 4 (page 20)

→ ≥ 2 Risk Factors

→ 0-1 Risk Factor

Step 3
Estimate the individual's 10-Year CHD Risk Score using Tables 5 and 6 (pages 23-26)

| 10-year CHD Risk > 20% | 10-year CHD Risk 10-20% | 10-year CHD Risk < 10% |

High Risk

Intermediate Risk

Low Risk

Table 5.1   Estimation of 10-Year Coronary Heart Disease Risk for Men

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

Allocate points based on person's age, total and HDL cholesterol levels, smoking status and systolic blood pressure (BP). Check the total points against table 5.2 for estimate of that person's 10-year CHD 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	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	0	1
130-139	1	2
140-159	1	2
≥ 160	2	3

Table 5.2   Estimation of 10-Year Coronary Heart Disease Risk for Men

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 6.1 Estimation of 10-Year Coronary Heart Disease Risk for Women

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

Allocate points based on person's age, total and HDL cholesterol levels, smoking status and systolic blood pressure (BP). Check the total points against table 6.2 for estimate of that person's 10-year CHD 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 6.2   **Estimation of 10-Year Coronary Heart Disease Risk for Women**

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

9 Goal lipid levels

Table 7 shows the recommended lipid goal levels in the three risk group categories. For the prevention of coronary heart disease, the first priority is the **optimization of LDL-C level**. It is important to note that the higher the risk category, the lower will be the goal LDL-C level.[4-6]

Table 7   Lipid goal levels in the three risk group categories

	High Risk Group	Intermediate Risk Group	Low Risk Group
LDL Cholesterol mmol/L (mg/dL)	< 2.6 (100)	< 3.4 (130)	< 4.1 (160)
Triglyceride mmol/L (mg/dL)	< 2.3 (200)	< 2.3 (200)	< 2.3 (200)
HDL Cholesterol mmol/L (mg/dL)	≥ 1.0 (40)	≥ 1.0 (40)	≥ 1.0 (40)

A The recommended LDL-C goal level for the **High Risk Group** is < 2.6 mmol/L (100 mg/dL).[6,44]

Grade A, Level Ib

C The recommended LDL-C goal level for the **Intermediate Risk Group** is < 3.4 mmol/L (130 mg/dL), with an LDL-C level of < 2.6 mmol/L (100 mg/dL) being an option.[38,42,43]

Grade C, Level IV

C The recommended LDL-C goal level for the **Low Risk Group** is < 4.1 mmol/L (160 mg/dL), with an LDL-C level of < 3.4 mmol/L (130 mg/dL) being an option.[42,43]

Grade C, Level IV

Recently, the results of two large trials comparing the lowering of LDL-C to < 2.6 mmol/L (100 mg/dL) versus very low LDL-C of around 2.1 mmol/L (80 mg/dL) in patients with pre-existing CHD were announced.

The **Treating to New Targets Study (TNT)** compared 80 mg with 10 mg of atorvastatin in patients with CHD. There was an absolute risk reduction of 1.3% in non-fatal myocardial infarction and 0.8% in stroke in the 80 mg atorvastatin group compared to the 10 mg atorvastatin group. However, the total mortality was similar in both groups. The on-treatment mean LDL-C level was 2.0 mmol/L (77 mg/dL) in the 80 mg atorvastatin group and 2.6 mmol/L (101 mg/dL) in the 10 mg atorvastatin group.[41]

In the **Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL)** study, 80 mg of atorvastatin was compared to 20-40 mg of simvastatin in patients with previous acute myocardial infarction. There was an absolute risk reduction of 1.2% in non-fatal myocardial infarction and 3.7% in coronary revascularization in the 80 mg atorvastatin group compared to the 20-40 mg simvastatin group. However, the total mortality was similar in both groups. The on-treatment mean LDL-C level was 2.1 mmol/L (81 mg/dL) in the 80 mg atorvastatin group and 2.7 mmol/L (104 mg/dL) in the 20-40 mg simvastatin group.[45]

C In **very high risk patients** (e.g. patients with established CHD and diabetes mellitus or multiple other risk factors) an "optional goal" of LDL-C < 2.1 mmol/L (80 mg/dL) may be considered by the physician, who, however, must balance the benefits against the cost and potential side effects of high doses of medication or combination therapy which are often required to achieve very low LDL-C levels.[46]

Grade C, Level IV

The results of the **Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)** study was presented at a recent European Stroke Conference.[47] This study compared 80 mg of atorvastatin with placebo in patients with previous ischaemic stroke or transient ischaemic attack and with no known history of CHD. There was a significant reduction in the primary end point of fatal or non-fatal stroke but a small increase in haemorrhagic stroke in the 80 mg atorvastatin group compared to the placebo group. Final recommendations of goal LDL-C level in patients with ischaemic stroke due to atherosclerotic cerebrovascular disease must await the full publication of the SPARCL study. Meanwhile however, the Workgroup believes that it is reasonable to continue the

previous recommendation of regarding these patients as being CHD risk equivalents with a goal LDL-C level of < 2.6 mmol/L (100 mg/dL).

GPP The goal TG level for all three risk groups is < 2.3 mmol/L (200 mg/dL).

GPP

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 for this reason. In these patients, the first priority is to reduce the TG level to prevent acute pancreatitis.[48]

Grade C, Level IV

C The goal HDL-C level for all three risk groups is ≥ 1.0 mmol/L (40 mg/dL).[14,43]

Grade C, Level IV

10 Lifestyle Changes

A Lifestyle changes are an integral part of overall management. They are the mainstay in population based primary prevention strategies. In addition, it is very important to continue these lifestyle changes in patients who have been started on drug therapy.

Grade A, Level Ib

10.1 Cigarette smoking

A Patients who smoke should be advised to stop smoking immediately.[49-51]

Grade A, Level Ib

10.2 Weight reduction

A Weight reduction is achieved mainly by dietary therapy and exercise.

Grade A, Level Ib

Clinicians should refer to the Ministry of Health Clinical Practice Guidelines for Obesity for more information on weight management best practice.[52]

10.3 Exercise

C It is recommended that individuals engage in at least 30 minutes of moderate intensity physical activity most days of the week.[53,54] For individuals who have difficulty exercising, they should be encouraged to engage in less strenuous physical activity.

Grade C, Level IV

10.4 Diet

The diet shown below emphasises intake of fruit, vegetables, grains, cereals and legumes as well as skinless poultry, fish, lean meats and low-fat dairy products. To lower TG, it is important, in addition to the above measures, to restrict the intake of alcohol and simple carbohydrates (e.g. glucose).[55]

Nutrient	Recommended Intake
Total fat	20 to 30% of total calories
Saturated fat*	< 7% of total calories
Polyunsaturated fat*	6 to 10% of total calories
Trans-fatty acid	< 1% of total calories
Carbohydrate	50 to 60% of total calories (mainly from complex carbohydrates)
Dietary fibre	20 to 30 gm per day
Protein	About 15% of total calories
Cholesterol	< 200 mg/day

Food Group	Recommended Intake
Fruit and vegetables	2 + 2 servings (≥ 400 gm) per day
Total calories	Enough to achieve and maintain a body mass index (BMI) of 18.5 to 23 kg/m^2

*Monounsaturated fat: Difference of Total fat minus Saturated and Polyunsaturated fat i.e. Total fat - (Saturated fat + Polyunsaturated fat).

For further information regarding dietary therapy, the reader is advised to refer to the Health Promotion Board publication (2003) entitled 'Dietary management and physical activity guidelines on cardiovascular diseases, diabetes mellitus, hypertension and hypercholesterolaemia', which is a part of the 'Patient Education Tool (PET) for Doctors'.

11   Drug Therapy

Table 8 shows the important contemporary drugs and their effects on lipid levels, and Table 9 shows the recommended drugs for the different dyslipidaemias.

11.1 Choice of drugs

In considering the choice of any drug, it is important to remember 2 important issues:

A The appropriate drug must be chosen for the particular type of dyslipidaemia, e.g. statins for lowering high LDL-C levels[1,6,41] and fibrates for lowering TG levels or for elevating low HDL-C levels.[8,56]

Grade A, Level Ib

C The cost of therapy should be considered in the choice of a particular lipid medication.[57]

Grade C, Level IV

Table 8   Percentage change with the various drugs

Drug	LDL-C	HDL-C	TG
Statins	↓18-55%	↑ 5-15%	↓ 7-30%
Resins	↓15-30%	↑ 3-5%	− / ↑
Fibrates	↓ 5-25%	↑10-20%	↓ 20-50%
Nicotinic Acid	↓ 5-25%	↑15-35%	↓ 20-50%

Table 9   Recommended drug therapy in the different dyslipidaemias

Dyslipidaemia	Drugs of Choice
Hypercholesterolaemia	Statin ± Ezetimibe
Mixed Dyslipidaemia	• Statin ± Fibrate* • Fibrate* ± Statin
Hypertriglyceridaemia	Fibrate*
Severe Hypertriglyceridaemia	Fibrate* + Omega 3 Fish Oil
Isolated low HDL-C	Fibrate*

*In all individuals in whom a fibrate is recommended, nicotinic acid can also be considered.[42,44]

11.2 Cost-effectiveness of lipid therapy

One of the factors influencing the choice of lipid modifying drugs is cost and cost-effectiveness. Recent studies have shown that statins and fibrates are cost effective when used for both secondary as well as primary prevention.[57-61] Importantly, most of these studies had been done in the countries at a time when generic drugs were not available. Today, with the wide availability of generic drugs, statin and fibrate therapy have become even more cost-effective.[62]

C Generic formulations cost less than non-generic drugs and can be considered if they meet prescribed standards.[57,61-63]

Grade C, Level IV

11.3   Recommended drugs for hypercholesterolaemia

A HMG-CoA reductase inhibitors (statins) are the preferred drugs for hypercholesterolaemia.[1,6,41]

Grade A, Level Ia

11.3.1   Statins

- Statins are very effective in lowering both TC and LDL-C. Recent mega-trials have shown that statins are beneficial for both secondary as well as primary prevention of CHD.[1-7,36,41,64]

- Recommended daily dosages: atorvastatin 10-80 mg, fluvastatin 20-80 mg, lovastatin 20-80 mg, pravastatin 10-40 mg, rosuvastatin 5-40 mg* and simvastatin 10-80 mg.[65-67]
(*In rare cases where rosuvastatin at doses higher than 20 mg is indicated, initiation of therapy should be under close specialist supervision.[67])

- The approximate equipotency of the different statins is as follows: 5 mg rosuvastatin = 10 mg atorvastatin = 20 mg simvastatin = 40 mg lovastatin / pravastatin = 80 mg fluvastatin.[65,66]

- The incidence of side effects is low, consisting mainly of a rise in the liver enzymes (especially the transaminases - alanine aminotransferase and aspartate aminotransferase) and myopathy.[1,67,68]

Myopathy and rhabdomyolysis

Myopathy and the considerably rarer but much more serious complication of rhabdomyolysis are both more likely to occur with high dosages of statins.[68] High dosages of statins should therefore be prescribed with caution, especially in elderly patients, in those with impaired renal function and when a statin is combined with a fibrate or nicotinic acid.

Some statins (except pravastatin, rosuvastatin and fluvastatin) are metabolized by the cytochrome P_{450} isoform 3A4. Drugs such as erythromycin, clarithromycin, azole antifungal agents and

cyclosporine that are also metabolized by the same enzyme pathway may elevate the serum level of these statins when administered concomitantly and therefore may increase the risk of toxicity.[69]

Monitoring for side effects of statins

C Check serum transaminases before and 8 to 12 weeks after starting statin therapy. If they are normal, consider repeating this test at least once annually (especially when the dosages of the drugs are increased or when combination therapy is initiated).[67,70-73]

Grade C, Level IV

C Monitoring of serum creatine kinase is also advisable in patients with renal disease, when high dosages of statins are used or when statins are combined with fibrates or nicotinic acid. Patients should be advised to report promptly to their doctors if they have muscle pain, tenderness or weakness.[67,71,73]

Grade C, Level IV

Indications for stopping statins

C 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 the liver function has returned to normal.[67,70]

Grade C, Level IV

C Elevation of serum creatine kinase greater than 5 to 10 times the upper limit of the normal range, 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.[67,74]

Grade C, Level IV

11.3.2   Ezetimibe

Ezetimibe is a new class of lipid lowering agents that selectively inhibits the intestinal absorption of cholesterol and related plant sterols. When added to a statin (e.g. simvastatin), 10 mg of ezetimibe will produce a further 18% lowering of the LDL-C. This effect is

similar to increasing the dose of the statin by about 8 times (e.g. increasing 10 mg simvastatin to 80 mg).[75] Ezetimibe is also available as a combination tablet consisting of ezetimibe and simvastatin (Vytorin).

11.3.3 Bile acid sequestrants (Resins)

Bile acid sequestrants (e.g. cholestyramine) are effective in lowering TC and LDL-C. However, they are infrequently used because of side effects.

11.4 Recommended drugs for hypertriglyceridaemia

A Fibrates are the drugs of choice in the treatment of hypertriglyceridaemia.[56]

Grade A, Level Ib

11.4.1 Fibrates

The two most frequently prescribed fibrates are fenofibrate and gemfibrozil.[76] With regard to equipotency, 300 mg fenofibrate = 1200 mg of gemfibrozil.

Side effects of fibrates: (i) elevation of liver enzymes (transaminases) (ii) myopathy and (iii) gallstones.

11.4.2 Nicotinic acid

Nicotinic acid lowers LDL-C and TG effectively and is especially useful for elevating HDL-C. The main side effect is flushing, which is less with prolonged release preparations of nicotinic acid (e.g. Niaspan).[77] In all individuals in whom a fibrate is recommended, nicotinic acid can also be considered.

11.4.3 Omega 3 fish oils

A In severe hypertriglyceridaemia (e.g. TG > 10 mmol/L [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 to 12 gm per day.[78]

Grade A, Level Ib

11.5　Recommended drugs for mixed dyslipidaemia

A A statin is recommended if the predominant lipid abnormality is an elevated LDL-C. If the TG remains unacceptably high or if the HDL-C remains low despite the statin, consider adding a fibrate.[79,80]

Grade A, Level Ib

C A fibrate is recommended if the TG is > 4.5 mmol/L (400 mg/dL).[48] If the LDL-C remains elevated despite the fibrate, consider adding a statin.

Grade C, Level IV

C The decision to combine a statin and a fibrate must be individualized and should be initiated only when it is strongly indicated.[67,81,82]

Grade C, Level IV

B 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.[83,84]

Grade B, Level III

C In combination therapy: (i) start the second drug at a low dosage and increase the dose gradually until the goal level is achieved. High dosages of statins should be avoided, (ii) monitor serum transaminases and creatine kinase before and 6 to 8 weeks after initiation of the combination therapy. Thereafter, these 2 tests should be repeated at least once annually or whenever the dosages of the drugs are increased, (iii) patients should be advised to promptly report to their doctors if they have muscle pain, tenderness or weakness, (iv) consider doing serum creatine kinase in patients who complain of muscle pain.[67,73,85]

Grade C, Level IV

11.6 Treatment of isolated low HDL-C

A Based on the results of the recent VA-HIT Study, CHD patients whose primary lipid abnormality is a low HDL-C despite lifestyle changes can be given a fibrate to elevate the HDL-C level.[8]

Grade A, Level Ib

11.7 Referral of patients to specialist

GPP Patients who remain outside the target values despite dietary changes and maximal drug therapy should be referred to lipid specialists.

GPP

12 Special Considerations

12.1 Diabetes mellitus

Patients with diabetes mellitus are regarded as CHD Risk Equivalents because they have a high risk of future coronary events which is equal to that of non-diabetic patients with pre-existing CHD.[19] Diabetic patients usually have an elevated TG and a low HDL-C level. Although the level of LDL-C may be normal, there are qualitative changes in the LDL-C, with a predominance of the highly atherogenic small dense LDL-C particles.[86]

A high proportion of diabetic patients have the **metabolic syndrome**, which can be diagnosed if any 3 of the following criteria are present.[87]

- Waist circumference: > 90 cm in males, > 80 cm in females
- TG ≥ 1.7 mmol/L (150 mg/dL)
- HDL < 1.0 mmol/L (40 mg/dL) in males and < 1.3 mmol/L (50 mg/dL) in females
- BP ≥ 130/85 mmHg or on treatment for hypertension
- Fasting glucose ≥ 6.1 mmol/ L (110 mg/dL) or known diabetes mellitus on treatment

12.2 Children

Drug therapy should be considered only in children aged 12 years and older with severe familial hypercholesterolaemia after dietary intervention has failed to lower the LDL-C to < 4.9 mmol/L (190 mg/dL).[88,89]

A Statins can be used in children, but proper monitoring is required.

Grade A, Level Ib

C Resins can be added on to statin therapy in children if LDL-C targets are not achieved.

Grade C, Level IV

12.3 Women

A In postmenopausal women as well as premenopausal women, the decision to start drug therapy should be based on the 10-Year CHD Risk Score.[90,91]

Grade A, Level Ib

12.4 Pregnancy

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

GPP

C Statins are contraindicated in women who are pregnant or who are likely to be pregnant.[67]

Grade C, Level IV

12.5 Elderly

A In the elderly, the decision to start drug therapy should be based on the 10-Year CHD Risk Score, the life expectancy as well as the quality of life of the patient. Age is not a contraindication to drug therapy if indicated.[64]

Grade A, Level Ib

12.6 Renal disease

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

GPP

GPP Fibrates can be used if the renal failure is only mild or moderate but the dosages should be reduced, with appropriate monitoring for side effects, especially myopathy. When creatinine clearance is less than 10 ml/min, fibrates are contraindicated.

GPP

12.7 Liver disease

C Screen liver function (especially transaminases) on 2 consecutive occasions in patients with chronic liver disease due to either hepatitis B or alcoholic abuse. If the level of either of these 2 transaminases is elevated but < 1.5 times the upper limit of the normal range, statins can be given. If the level is ≥ 1.5 times but < 3 times the upper limit of the normal range, statins can still be given but with caution. In both situations, the starting dose of the statins should be low. Statins are contraindicated in those with acute liver disease and also in those with advanced or end stage parenchymal liver disease.[72]

Grade C, Level IV

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

GPP

13 Quality Indicators for Lipid Management

The goal LDL cholesterol levels are:

A High Risk Group: LDL-C < 2.6 mmol/L (100 mg/dl).[6,44]

Grade A, Level Ib

C Intermediate Risk Group: LDL-C < 3.4 mmol/L (130 mg/dl).[42,43]

Grade C, Level IV

C Low Risk Group: LDL-C < 4.1 mmol/L (160 mg/dl).[42,43]

Grade C, Level IV

Table 10 **GPP** Process Indicators and Recommended Frequency

Performance Parameter	Recommended Review Frequency
All patients who are on lipid modifying drug therapy	Lipids at least every 6-12 months
Patients who are not on lipid modifying drug therapy (goal LDL cholesterol levels as stated above achieved): (1) High Risk Group (2) Intermediate Risk Group (3) Low Risk Group	Lipids every 1 year Lipids every 2 years Lipids every 3 years
Patient education	At diagnosis and regular intervals according to risk level

GPP

It should be emphasized that the ultimate objective of treatment of dyslipidaemia is not to lower cholesterol per se but to reduce overall morbidity and mortality risk, which is also influenced by other concomitant risk factors.

In the management of an individual patient, good clinical judgement should be exercised in every situation.

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After reading the Clinical Practice Guidelines, you can claim one CME point under Category III (Self-Study) of the SMC Online CME System. Before you login to claim the CME point, we encourage you to evaluate whether you have mastered the key points in the Guidelines by completing this set of multiple choice questions. This is an extension of the learning process and is not intended to "judge" your knowledge and is not compulsory. The answers can be found at the end of the questionnaire.

Instruction: Choose the most appropriate answer.

1. A lipid profile consisting of TC, LDL-C, HDL-C and TG should be obtained in patients with the following medical conditions EXCEPT:

   A) Known coronary artery disease
   B) Diabetes mellitus
   C) Heart palpitations
   D) Peripheral vascular disease

2. Which of the following statements about lipids is INCORRECT?

   A) HDL-C is decreased with obesity, cigarette smoking and a sedentary lifestyle.
   B) Clinically relevant risk of CHD escalates sharply when the TC exceeds 5.2 mmol/L (200mg/dL).
   C) LDL-C is the most important fraction of cholesterol.
   D) LDL-C is increased in chronic infections.

3. Risk factors for CHD include the following EXCEPT:

   A) Stress
   B) Obesity
   C) Sedentary life-style
   D) Thalassemia minor

4. Secondary dyslipidaemia may occur in the following EXCEPT:

   A) Diabetes mellitus
   B) Hyperthyroidism
   C) Patients on oral contraceptives, beta-blockers or diuretics
   D) Cholestasis

5. LDL-C goal level for patients with peripheral artery disease is less than

   A) 2.6 mmol/L (100 mg/dL)
   B) 2.8 mmol/L (110 mg/dL)
   C) 3.4 mmol/L (130 mg/dL)
   D) 4.1 mmol/L (160 mg/dL)

6. Which of the following statements about strategy for risk stratification based on the 10-Year CHD Risk Score is INCORRECT:

   A) All individuals with ≥ 2 risk factors without CHD or CHD Equivalents are recommended to have their 10-Year CHD Risk Score estimated.
   B) All individuals with 0-1 risk factor do not require their 10-Year CHD Risk Score to be estimated.
   C) A 65-year old Malay female non-smoker with a treated systolic blood pressure of 150 mmHg, total cholesterol of 6.2 mmol/L (240 mg/dL) and HDL-C of 0.9 mmol/L (36 mg/dL) has a 10-year CHD risk of > 20%.
   D) The 10-Year CHD Risk Score is a useful tool in assessing risk for a 60-year old male who was recently diagnosed to have diabetes mellitus.

7. Which of the following statements about cholesterol screening is CORRECT?

   A) There is no need to postpone screening of lipid status on account of a febrile illness.
   B) 8 hours of fasting is adequate when collecting a fasting blood specimen for lipid studies.
   C) The best time to assess the lipid level of a patient who just had an acute myocardial infarction is within 72 hours of the event.
   D) Serum TC and HDL-C can be tested in the non-fasting state.

8. Which of the following statements about statins is INCORRECT?

A) Drugs such as erythromycin, clarithromycin and azole antifungal agents may elevate the serum level of statins when administered concomitantly.
B) Elevation in the levels of serum transaminases above 3 times the upper limit of the normal range is an indication to stop statin therapy.
C) Patients who are troubled by muscle pain, even in the absence of a raised serum creatine kinase, may benefit from either stopping the statin therapy or reducing the dosage.
D) Statins are not contraindicated in women who are pregnant or who are likely to be pregnant.

9. The following statements are correct EXCEPT:

A) In severe hypertriglyceridaemia where fibrates alone may not adequately lower the markedly elevated TG levels, omega 3 fish oils should be added.
B) Fibrates can be given to elevate the HDL-C level in CHD patients whose primary lipid abnormality is a low HDL-C despite lifestyle changes.
C) In combination therapy for Mixed Dyslipidaemia, any fibrate can be used with a statin.
D) The only drug recommended in patients with severe hypertriglyceridaemia during pregnancy is omega 3 fish oils after intensive dietary therapy.

10. Which ONE of the following statements is INCORRECT?

A) Statins are the drugs of choice for lowering LDL cholesterol.
B) Ezetemibe will enhance the LDL cholesterol lowering by a further 18% when added to a statin.
C) Although effective for lowering LDL cholesterol, bile acid sequestrants (resins) are infrequently used because of their side effects.
D) Statins are more effective in elevating HDL cholesterol as compared to nicotinic acid.

Answers to multiple choice questions

1. C   (Pg 16)
2. D   (Pg 11)
3. D   (Pg 12)
4. B   (Pg 15)
5. A   (Pgs 19, 27)
6. D   (Pgs 19, 25, 26)
7. D   (Pgs 16, 17)
8. D   (Pgs 34, 35, 40)
9. C   (Pgs 36, 37, 40)
10. D   (Pgs 34-36)

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Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

Laboratory lipid measurements

A lipid profile consisting of total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglyceride (TG) should be obtained in the following individuals:

A Patients with coronary heart disease (CHD), cerebrovascular or peripheral artery disease (pg 16).

Grade A, Level Ib

A Patients with diabetes mellitus (pg 16).

Grade A, Level Ib

A Individuals with a family history or clinical evidence of familial hyperlipidaemia (pg 16).

<div align="right">**Grade A, Level Ib**</div>

A Individuals with other risk factors for CHD (pg 16).

<div align="right">**Grade A, Level Ib**</div>

Goal lipid levels

For the prevention of coronary heart disease, the first priority is the **optimization of LDL-C level**.

Table1   Lipid goal levels in the three risk group categories

	High Risk Group	Intermediate Risk Group	Low Risk Group
LDL Cholesterol mmol/L (mg/dL)	< 2.6 (100)	< 3.4 (130)	< 4.1 (160)
Triglyceride mmol/L (mg/dL)	< 2.3 (200)	< 2.3 (200)	< 2.3 (200)
HDL Cholesterol mmol/L (mg/dL)	≥ 1.0 (40)	≥ 1.0 (40)	≥ 1.0 (40)

A The recommended LDL-C goal level for the **High Risk Group** is < 2.6 mmol/L (100 mg/dL) (pg 27).

<div align="right">**Grade A, Level Ib**</div>

C The recommended LDL-C goal level for the **Intermediate Risk Group** is < 3.4 mmol/L (130 mg/dL), with an LDL-C level of < 2.6 mmol/L (100 mg/dL) being an option (pg 27).

<div align="right">**Grade C, Level IV**</div>

C The recommended LDL-C goal level for the **Low Risk Group** is < 4.1mmol/L (160 mg/dL), with an LDL-C level of < 3.4 mmol/L (130mg/dL) being an option (pg 27).

<div align="right">**Grade C, Level IV**</div>

C In **very high risk patients** (e.g. patients with established CHD and diabetes mellitus or multiple other risk factors) an "optional goal" of LDL-C < 2.1 mmol/L (80 mg/dL) may be considered by the physician, who, however, must balance the benefits against the cost and potential side effects of high doses of medication or combination therapy which are often required to achieve very low LDL-C levels (pg 28).

<div align="right">

Grade C, Level IV

</div>

GPP The goal TG level for all three risk groups is < 2.3 mmol/L (200 mg/dL) (pg 29).

<div align="right">

GPP

</div>

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 for this reason. In these patients, the first priority is to reduce the TG level to prevent acute pancreatitis (pg 29).

<div align="right">

Grade C, Level IV

</div>

C The goal HDL-C level for all three risk groups is ≥ 1.0 mmol/L (40 mg/dL) (pg 29).

<div align="right">

Grade C, Level IV

</div>

Lifestyle changes

Nutrient	Recommended Intake
Total fat	20 to 30% of total calories
Saturated fat*	< 7% of total calories
Polyunsaturated fat*	6 to 10% of total calories
Trans-fatty acid	< 1% of total calories
Carbohydrate	50 to 60% of total calories (mainly from complex carbohydrates)
Dietary fibre	20 to 30 gm per day
Protein	About 15% of total calories
Cholesterol	< 200 mg/day
Food Group	**Recommended Intake**
Fruit and vegetables	2 + 2 servings (≥ 400 gm) per day
Total calories	Enough to achieve and maintain a body mass index (BMI) of 18.5 to 23 kg/m^2

*Monounsaturated fat: Difference of Total fat minus Saturated and Polyunsaturated fat i.e. Total fat – (Saturated fat + Polyunsaturated fat).

A Lifestyle changes are an integral part of overall management. They are the mainstay in population based primary prevention strategies. In addition, it is very important to continue these lifestyle changes in patients who have been started on drug therapy (pg 30).

Grade A, Level Ib

A Patients who smoke should be advised to stop smoking immediately (pg 30).

Grade A, Level Ib

A Weight reduction is achieved mainly by dietary therapy and exercise (pg 30).

<div align="right">**Grade A, Level Ib**</div>

C It is recommended that individuals engage in at least 30 minutes of moderate intensity physical activity most days of the week. For individuals who have difficulty exercising, they should be encouraged to engage in less strenuous physical activity (pg 30).

<div align="right">**Grade C, Level IV**</div>

Drug therapy

Table 2   Percentage change with the various drugs

Drug	LDL-C	HDL-C	TG
Statins	↓18-55%	↑5-15%	↓7-30%
Resins	↓15-30%	↑3-5%	−/↑
Fibrates	↓5-25%	↑10-20%	↓20-50%
Nicotinic Acid	↓5-25%	↑15-35%	↓20-50%

A The appropriate drug must be chosen for the particular type of dyslipidaemia, e.g statins for lowering high LDL-C levels and fibrates for lowering TG levels or for elevating low HDL-C levels (pg 32).

<div align="right">**Grade A, Level Ib**</div>

C The cost of therapy should be considered in the choice of a particular lipid medication (pg 32).

<div align="right">**Grade C, Level IV**</div>

C Generic formulations cost less than non-generic drugs and can be considered if they meet prescribed standards (pg 33).

<div align="right">**Grade C, Level IV**</div>

Table 3   Recommended drug therapy in the different dyslipidaemias

Dyslipidaemia	Drugs of Choice
Hypercholesterolaemia	Statin ± Ezetimibe
Mixed Dyslipidaemia	• Statin ± Fibrate* • Fibrate* ± Statin
Hypertriglyceridaemia	Fibrate*
Severe Hypertriglyceridaemia	Fibrate* + Omega 3 Fish Oil
Isolated low HDL-C	Fibrate*

*In all individuals in whom a fibrate is recommended, nicotinic acid can also be considered.

Recommended drugs for Hypercholesterolaemia

A HMG-CoA reductase inhibitors (statins) are the preferred drugs for hypercholesterolaemia (pg 34).

Grade A, Level Ia

Ezetemide when added to a statin will produce a further 18% lowering of the LDL-C.

C Check serum transaminases before and 8 to 12 weeks after starting statin therapy. If they are normal, consider repeating this test at least once annually (especially when the dosages of the drugs are increased or when combination therapy is initiated) (pg 35).

Grade C, Level IV

C Monitoring of serum creatine kinase is also advisable in patients with renal disease, when high dosages of statins are used or when statins are combined with fibrates or nicotinic acid. Patients should be advised to report promptly to their doctors if they have muscle pain, tenderness or weakness (pg 35).

Grade C, Level IV

C 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 the liver function has returned to normal (pg 35).

Grade C, Level IV

C Elevation of serum creatine kinase greater than 5 to 10 times the upper limit of the normal range, 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 (pg 35).

Grade C, Level IV

Recommended drugs for Hypertriglyceridaemia

In all individuals in whom a fibrate is recommended, nicotinic acid can also be considered.

A Fibrates are the drugs of choice in the treatment of hypertriglyceridaemia (pg 36).

Grade A, Level Ib

A In severe hypertriglyceridaemia (e.g. TG > 10 mmol/L [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 to 12 gm per day (pg 36).

Grade A, Level Ib

Recommended drugs for Mixed Dyslipidaemia

A A statin is recommended if the predominant lipid abnormality is an elevated LDL-C. If the TG remains unacceptably high or if the HDL-C remains low despite the statin, consider adding a fibrate (pg 37).

Grade A, Level Ib

C A fibrate is recommended if the TG is > 4.5 mmol/L (400 mg/dL). If the LDL-C remains elevated despite the fibrate, consider adding a statin (pg 37).

Grade C, Level IV

C The decision to combine a statin and a fibrate must be individualized and should be initiated only when it is strongly indicated (pg 37).

<div align="right">**Grade C, Level IV**</div>

B 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 (pg 37).

<div align="right">**Grade B, Level III**</div>

C In combination therapy: (i) start the second drug at a low dosage and increase the dose gradually until the goal level is achieved. High dosages of statins should be avoided, (ii) monitor serum transaminases and creatine kinase before and 6 to 8 weeks after initiation of the combination therapy. Thereafter, these 2 tests should be repeated at least once annually or whenever the dosages of the drugs are increased, (iii) patients should be advised to promptly report to their doctors if they have muscle pain, tenderness or weakness, (iv) consider doing serum creatine kinase in patients who complain of muscle pain (pg 37).

<div align="right">**Grade C, Level IV**</div>

Treatment of Isolated Low HDL-C

A Based on the results of the recent VA-HIT Study, CHD patients whose primary lipid abnormality is a low HDL-C despite lifestyle changes can be given a fibrate to elevate the HDL-C level (pg 38).

<div align="right">**Grade A, Level Ib**</div>

Referral of patients to specialist

GPP Patients who remain outside the target values despite dietary changes and maximal drug therapy should be referred to lipid specialists (pg 38).

<div align="right">**GPP**</div>

Table 4 GPP **Process Indicators and Recommended Frequency**

Performance Parameter	Recommended Review Frequency
All patients who are on lipid modifying drug therapy	Lipids at least every 6-12 months
Patients who are not on lipid modifying drug therapy (goal LDL cholesterol levels as stated above achieved): (1) High Risk Group (2) Intermediate Risk Group (3) Low Risk Group	 Lipids every 1 year Lipids every 2 years Lipids every 3 years
Patient education	At diagnosis and regular intervals according to risk level

GPP

Risk Assessment

Table 5   Major risk factors for coronary heart disease[#]

- Total cholesterol ≥ 6.2 mmol/L (240 mg/dL) or
  LDL cholesterol ≥ 4.1 mmol/L (160 mg/dL)

- Cigarette smoking

- Hypertension (BP ≥ 140/90 mmHg or on anti-hypertensive medication)

- Low HDL cholesterol (< 1.0 mmol/L [40 mg/dL])

- Family history of premature CHD (CHD in male first degree relative < 55 years; CHD in female first-degree relative < 65 years)

- Age (men ≥ 45 years; women ≥ 55 years)

- Indian ethnicity

[#] *Modified from Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001.*
Diabetes mellitus is not included in the above as it is already regarded as a CHD risk equivalent.

The 3 Steps for Risk Stratification

Step 1

Identify individuals with:
1. Established CHD
2. CHD Risk Equivalents, defined as:
    (a) Diabetes mellitus
    (b) Atherosclerotic cerebrovascular disease, peripheral artery disease or abdominal aortic aneurysm

Yes   **No**

Step 2

Count the Number of Risk Factors the individual has using Table 5 (page 10 in this booklet)

≥ 2 Risk Factors   0-1 Risk Factor

Step 3

Estimate the individual's 10-Year CHD Risk Score using Tables 6 and 7 (pages 12-15 in this booklet)

10-year CHD Risk > 20%	10-year CHD Risk 10-20%	10-year CHD Risk < 10%

High Risk	Intermediate Risk	Low Risk

Table 6.1 Estimation of 10-Year Coronary Heart Disease Risk for Men

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

Allocate points based on person's age, total and HDL cholesterol levels, smoking status and systolic blood pressure (BP). Check the total points against table 6.2 for estimate of that person's 10-year CHD 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	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	0	1
130-139	1	2
140-159	1	2
≥ 160	2	3

Table 6.2   Estimation of 10-Year Coronary Heart Disease Risk for Men

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 7.1   Estimation of 10-Year Coronary Heart Disease Risk for Women

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

Allocate points based on person's age, total and HDL cholesterol levels, smoking status and systolic blood pressure (BP). Check the total points against table 7.2 for estimate of that person's 10-year CHD 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 7.2   **Estimation of 10-Year Coronary Heart Disease Risk for Women**

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