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1. INTRODUCTION

Cardiovascular disease (CVD), particularly coronary heart disease (CHD), is the leading cause of medically certified deaths in Malaysia. Risk factors that contribute to the pathogenesis of this disease include smoking, hypertension, dyslipidaemia, diabetes and a family history of premature CHD.

Atherosclerosis begins in early adolescence appearing as fatty streaks. It progresses with age, the rate of progression being dependent on the presence and severity of the risk factors. Occasionally these plaques fissure and rupture giving rise to acute coronary syndromes and myocardial infarction. Factors that may contribute to this acute event include hypercholesterolemia, smoking, an elevated blood pressure and inflammation.

In the prevention of CVD, it is important to treat the individual as a whole and to reduce or eliminate all risk factors. Cessation of smoking, aggressive control of hypertension and diabetes, regular exercise and weight reduction are all important and have been shown to reduce CVD morbidity and mortality. Numerous clinical studies have also shown that aggressive cholesterol reduction results in stabilization and sometimes regression of the atherosclerotic plaque, resulting in a reduction in total mortality and CVD morbidity and mortality in individuals with heart disease and also in individuals without known heart disease.

This is the third edition of the clinical practice guidelines on dyslipidaemia. It incorporates the most recent clinical trial results. The strength of the recommendations have been graded using the following system.[1]

GRADING OF RECOMMENDATIONS ACCORDING TO LEVELS OF EVIDENCE	
GRADE A	Based on evidence from one or more randomized clinical trials
GRADE B	Based on evidence from high quality clinical trials but no randomized clinical trial data available
GRADE C	Based on expert committee reports and/or clinical experience of respected authorities but lacking in directly applicable studies of good quality

2. MEASUREMENT OF LIPID LEVELS

Serum lipid levels are affected by several factors:

- acute stress or illness, eg fever, surgery, acute myocardial infarction.
- drugs eg beta-blockers, thiazides, steroids.

Total cholesterol (TC) and high density cholesterol (HDL-C) can be measured in both fasting and non fasting states. Triglycerides (TG) should be measured after 10-12 hours of fasting. TG levels are influenced by alcohol intake in the preceding 24 hours and smoking during the fasting state. Low density cholesterol (LDL-C) is calculated using the Friedewald equation:

$$LDL\text{-}C \text{ (mmol/l)} = TC - HDL\text{-}C - TG/2.2$$

If TG > 4.5mmol/l, this formula is not valid.

More recent data suggest that when TG > 2.3mmol/l, LDL-C calculation using the above formula may not be accurate. Cholesterol rich remnant lipoproteins (small VLDL and IDL) are also significantly elevated [2,3]. In this situation, LDL –C measurement alone does not reflect the entire atherogenic lipoprotein fraction. Measurement of Non-HDL-C is more representative of all atherogenic lipoproteins. This can be calculated by the following formula:

$$Non\text{-}HDL\text{-}C\text{(mmol/l)} = TC - HDL\text{-}C$$

Non HDL-C levels can be calculated from a non-fasting serum.

Measurements made from whole blood differs slightly from that obtained from plasma or serum. Desktop machines for the measurement of TC, TG and HDL-C, can produce satisfactory results.

Lipid levels especially TG show biological variability. Because of this and laboratory variability more than one measurements are usually required, particularly in borderline cases.

3. CLASSIFICATION OF DYSLIPIDAEMIAS

Based on therapeutic considerations, dyslipidaemias may be classified as follows (Table 1):

Table 1: Classification of Dyslipidaemias

	Increased Concentration Of:	
	Lipoprotein	Serum Lipid
Hypercholesterolemia	LDL	Cholesterol
Mixed Hyperlipidaemia	LDL + VLDL*	Cholesterol and triglyceride
Hypertriglyceridemia	VLDL	Triglycerides

* *VLDL – Very Low Density Lipoprotein*

Dyslipidaemias may be primary or secondary in aetiology. (Tables 2 & 3)

In the following situations, secondary causes of dyslipidaemia should be considered :

- When TC exceeds 7.0 mmol/L, exclude conditions such as primary hypothyroidism, nephrosis, obstructive liver disease.

- When TG exceeds 4.5 mmol/L, exclude secondary causes such as alcoholism.

- When there is high TG with low HDL-C, insulin resistance syndromes such as type 2 Diabetes and impaired glucose tolerance have to be considered.

- Failure to respond to anti-lipid therapy.

- In patients with a family history of type 2 Diabetes or a past history of thyroid disease.

Table 2: Primary Dyslipidaemias

	Risk of CHD	Risk of Pancreatitis	Plasma Cholesterol	Plasma Triglyceride	Physical signs (if present)
Common ("polygenic") hypercholesterolaemia	↑		↑	N	Corneal Arcus Xanthelasma
Familial Combined Hyperlipidaemia	↑↑		↑ or	↑ or	Corneal Arcus Xanthelasma
Familial Hypercholesterolaemia	↑↑↑		↑↑↑	↑	Tendon xanthomata (finger extensor, Achilles' tendons) Corneal Arcus, Xanthelasma, Aortic stenosis
Remnant Hypercholesterolaemia	↑↑↑		↑↑↑	↑↑	Tuberous xanthomata, (elbows), striae xanthomata, (palm creases) tendon xanthomata
Chylomicronemia Syndrome	or ↑	↑↑↑	↑	↑↑↑	Eruptive xanthomata (buttocks, elbows) retinal lipaemia, hepatosplenomegaly
Familial Hypertriglyceridaemia	↑	↑↑	↑	↑↑	Eruptive xanthomata (buttocks, elbows) retinal lipaemia, hepatosplenomegaly
High HDL			↑		-

Table 3: <u>Causes of Secondary Dyslipidaemias</u>

Disorder	Cholesterol	Triglycerides	HDL Cholesterol
Metabolic/Endocrine Hypothyroidism Type 2 Diabetes Cushing's Syndrome **Renal** End stage renal disease Nephrotic syndrome **Hepatic** Obstructive liver disease Primary biliary cirrhosis **Drugs** Alcohol Thiazide diuretics Beta blockers			

4. DYSLIPIDAEMIA AS A RISK FACTOR FOR CHD

From available epidemiological and scientific data, dyslipidaemia has been identified as one of the main risk factors for CHD. Specific lipid abnormalities implicated are :

4.1 **Elevated LDL-C levels**

LDL-C has been shown to be atherogenic in epidemiological studies. There is a direct relationship between levels of LDL-C (or TC) and the rate of new onset CHD in men and women who were initially free from CHD [4,5,6,7]. In people with established CHD, elevated LDL-C correlates with recurrent cardiac events [8,9]. There is a near absence of clinical CHD in populations with very low levels of serum cholesterol throughout their life (TC < 3.89 mmol/L or LDL-C 2.6 mmol/L) [10,11]. The risk for CHD appears to increase progressively above these levels. At levels of LDL-C above 3.4 mmol/l, atherogenesis proceeds at a significant rate particularly in the presence of other major risk factors [12].

LDL-C should be the primary target for cholesterol therapy. Clinical trials have shown that reducing LDL-C by 1 % reduces CHD risk by 1 % .

4.2 **Low HDL-C levels**

There is substantial data linking a low HDL-C with increased risk of CHD [4, 13,14]. A 1 % decrease in HDL-C is associated with 2-3 % increase in CHD risk [14]. Clinical trial data suggests that raising HDL-C will reduce risk for CHD[15].

4.3 **Elevated TG levels**

Recent data show that raised triglycerides are independent risk factors for CHD [16,17]. This suggests that some TG-rich lipoproteins are atherogenic. Weight reduction and drug therapies reduce remnant lipoproteins (fibrates, nicotinic acid and statins) and are accompanied by reduced risk for CHD [18,19].

4.4 **Elevated Non-HDL-C levels**

At levels of TG > 2.3 mmol/L , VLDL-C is significantly raised and Non-HDL-C is a better representative of all atherogenic lipoproteins than LDL-C [20,21]. However, currently there is no clinical study identifying Non-HDL-C as a primary target of therapy.

4.5 **Atherogenic Dyslipidaemia**

This consists of low HDL-C, raised TG and small dense LDL particles [22,23]. The LDL-C levels are usually normal but there is a higher proportion of small dense LDL particles which are more atherogenic. This dyslipidaemia is usually found in persons with insulin resistance (metabolic syndrome) and type 2 Diabetes. It occurs commonly in persons with premature CHD [24].

Salient Point :

- LDL-C should be the primary target of therapy.

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5. <u>OTHER RISK FACTORS FOR CHD</u>

5.1 **Age**
The incidence of CHD increases with age [4.]

5.2. **Gender**
The incidence of CHD is about 3-4 times higher in men than women in the middle decades of life and approximately twice as high in the elderly [4].

5.3. **Hypertension**

Both elevated systolic and diastolic blood pressures are linked with increased CHD risk [25,26]. From epidemiological data, elevated systolic blood pressure appears to be more important when compared to diastolic blood pressure as a risk factor [27,28]. The presence of left ventricular hypertrophy is associated with increased CHD risk.

5.4. **Smoking**

This is an important risk factor in both men and women [29,30,31]. The incidence and mortality of CHD is twice as high in male cigarette smokers compared to non smokers. The risk of developing CHD is directly related to the number of cigarettes smoked. In individuals who discontinue smoking, the risk decreases within a year or two of stopping although it remains slightly higher compared to non smokers [32].

5.5. **Family History of Premature CHD**

Familial and genetic factors may play an important role in the determination of some major risk factors, especially hypertension, lipid abnormalities and glucose intolerance. In addition there appears to be a familial predisposition to CHD per se [33]. The presence of premature CHD in first degree male relatives below the age of 55 years or female relatives below the age of 65 years is a recognized independent risk factor for CHD [34]. This risk is greater when more family members are affected and the younger their age of onset of CHD.

5.6 **Others:**

It has been estimated that one or more of the major risk factors (High LDL –C, Low HDL-C, smoking, hypertension and diabetes) is present in less than 50% of patients with CHD. Other risk factors that have been implicated in CHD include:

5.6.1: **Lifestyle Risk Factors**

- Obesity - Risk for CHD is particularly increased in those with abdominal obesity (waist circumference greater than 102 cm in men and 88 cm in women) [35].
- Physical Inactivity - Numerous studies have shown that regular exercise is cardioprotective [36,37].

5.6.2: **Emerging Risk Factors**

- Lipoprotein Lp(a)- Levels of Lp(a) have been shown to be related to cardiovascular risk in some but not all studies [38].

- Hyperhomocysteinemia- Recent epidemiological evidence indicates that hyperhomocysteinemia may be an independent risk factor. [39]

- <u>Inflammatory markers:-</u> Pathological studies strongly support a role of inflammation in the pathogenesis of the early stages of atherosclerosis, plaque progression and rupture. One such acute phase reactant is high sensitivity C-reactive protein (hs-CRP). Data show that an elevated level of hs-CRP identifies healthy individuals who are at an increased risk of an initial[40] and recurrent cardiac event [41].

- <u>Hemostatic markers.-</u> An elevated level of fibrinogen has been associated with an increased risk for coronary events [42].

- <u>Evidence of subclinical atherosclerotic disease.</u> – Individuals with advanced subclinical atherosclerotic disease are at increased risk for major coronary events [43]. Subclinical atherosclerosis may be identified by the:

- presence of abnormalities in the resting and/or stress ECG
- measurement of the ankle/brachial blood pressure (ABI) (a level of less than 0.9 is significant
- measurement of carotid intima-medial thickness (IMT) by ultrasound (more than 75th percentile for age and sex)
- measurement of coronary calcium score by electron beam computed tomography (EBCT) – In accordance with recent reports there is insufficient evidence to recommend EBCT for indiscriminate screening for coronary calcium in asymptomatic individuals.
- non invasive imaging of the coronary arteries by EBCT, multislice computed tomography and magnetic resonance imaging (MRI). These tests allow determination of the extent of the atherosclerotic burden. They should not be used primarily to identify individuals for revascularization, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), nor to predict clinical outcomes in symptomatic patients. They should be used primarily to identify patients with subclinical atherosclerotic disease in whom a more aggressive preventive treatment strategy is necessary. Future advances in technology may make it possible for MRI to determine the characteristics of the plaque and measure plaque activity and their likelihood of rupture.

Routine measurement of these emerging risk factors is not advocated. They do not categorically modify LDL-C goals. In selected individuals, they however guide the intensity of risk reduction efforts.

Salient Point :

- Increasing age, male gender, hypertension, smoking and a family history of premature CHD are major independent risk factors for CHD. Diabetes is a CHD risk equivalent.

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6. GLOBAL CARDIOVASCULAR RISK ASSESSMENT

All adults (above the age of 20 years) should have a complete fasting lipid profile (TC, LDL-C, HDL-C, TG). The individual's level of risk in developing CHD should then be assessed.

Risk determinants besides LDL-C include the presence or absence of CHD or CHD risk equivalents and the presence of the major risk factors (Table 4). The intensity of risk reduction therapy is dependent on an individual's global risk of developing CHD.

Table 4: <u>Major Risk Factors for CHD (Other than LDL Cholesterol)</u>

Positive Risk Factors
- Male $\geq$ 45 years of age   - Female $\geq$ 55 years of age or premature menopause without hormonal replacement therapy   - Hypertension   - Current cigarette smoking   - Family history of myocardial infarction or sudden death prior to age 55 in a male parent or male first degree relative and prior to age 65 in a female parent or other female first degree relative   - HDL-C < 1.0 mmol/l
Negative Risk Factor**
HDL-C > 1.6 mmol/l is considered as a negative risk factor

**When determining risk status for CHD, if HDL-C > 1.6mmol/L subtract one risk factor.

In determining an individual's global risk for CHD, the following steps are taken :

- Count the number of major risk factors for CHD (see table 4).
- In individuals with more than 2 risk factors, calculate the 10-year CHD risk using the Framingham score sheets (See Figures 1 & 2).

Individuals with 0-1 risk factors almost always have a 10 year CHD risk < 10%.

Individuals with 2 or more risk factors can fall into one of the following risk categories for developing CHD over 10 years:

- >20%
- 10-20 %
- <10%

Figure 1:Estimation of 10 year CHD Risk for MEN (Framingham Point Scores)

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

Total Cholesterol (mmol/l)	Points at age 20-39	Points at age 40-49	Points at age 50-59	Points at age 60-69	Points at age 70-79
< 4.1	0	0	0	0	0
4.1- 5.1	4	3	2	1	0
5.1- 6.2	7	5	3	1	0
6.2- 7.2	9	6	4	2	1
>7.2	11	8	5	3	1

	Points at age 20-39	Points at age 40-49	Points at age 50-59	Points at age 60-69	Points at age 70-79
Non smoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL mmol/l	Points
>1.6	-1
1.3-1.6	0
1.1-1.3	1
<1.1	2

Systolic BP	Untreated	Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
160	2	3

Total Points	10 year Risk	Total Points	10 year Risk	Total Points	10 year Risk
< 0	<1%	6	2%	13	12%
0	1%	7	3%	14	16%
1	1%	8	4%	15	20%
2	1%	9	5%	16	25%
3	1%	10	6%	17	30%
4	1%	11	8%		
5	2%	12	10%		

Figure2:<u>Estimation of 10 year CHD Risk for WOMEN (Framingham Point Scores)</u>

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

Total Cholesterol (mmol/l)	Points at age 20-39	Points at age 40-49	Points at age 50-59	Points at age 60-69	Points at age 70-79
< 4.1	0	0	0	0	0
4.1- 5.1	4	3	2	1	1
5.1- 6.2	8	6	4	2	1
6.2- 7.2	11	8	5	3	2
>7.2	13	10	7	4	2

	Points at age 20-39	Points at age 40-49	Points at age 50-59	Points at age 60-69	Points at age 70-79
Non smoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL mmol/l	Points
>1.6	-1
1.3-1.6	0
1.1-1.3	1
<1.1	2

Systolic BP	Untreated	Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
160	4	6

Total Points	10 year Risk	Total Points	10 year Risk	Total Points	10 year Risk
< 9	<1%	15	3%	22	17%
9	1%	16	4%	23	22%
10	1%	17	5%	24	27%
11	1%	18	6%	25	30%
12	1%	19	8%		
13	2%	20	11%		
14	2%	21	14%		

Those individuals with a 10-year risk of developing CHD of > 20% have a very high risk and are therefore considered as CHD risk equivalents. (see 6.1)

Determining an individual's global CHD risk will guide LDL target goal and management strategies. (Table 5)

The 10 year risk scores (Figures 1& 2) are adapted from the ATPIII guideline [44] which in itself is derived from the Framingham database. The primary endpoint for 10 year risk assessment is "hard CHD" ie myocardial infarction + CHD death. The 10 year risk calculation is to be performed at the outset to help guide the intensity of cholesterol lowering therapy. It cannot be used to track changes in risk over time as risk factors are modified.

In calculating the risk scores (Figures 1 & 2), the TC and HDL-C should be the average of at least 2 measurements. The average baseline blood pressure (BP) must be obtained from an average of several readings. If the individual is on anti hypertensive medication, a point is added beyond points for BP readings. A "smoker" means any cigarette smoking in the past month.

6.1. CHD And CHD Risk Equivalents

Individuals with CHD and CHD risk equivalents belong to the highest risk category.

The CHD risk equivalents are:

- Other clinical forms of atherosclerotic disease – (peripheral vascular disease, abdominal aortic aneurysm, symptomatic carotid artery disease)
- Diabetes mellitus
- Multiple risk factors that confer a 10 year risk for CHD > 20%

6.2. Diabetes mellitus and Dysglycaemia as CHD risk equivalents

Patients with diabetes mellitus (DM) and impaired glucose tolerance (IGT) have an increased risk of cardiovascular events[45]. These patients have higher mortality and a higher incidence of recurrent cardiac events[46].

The two main types of DM (type 1 and type 2) have different patterns of dyslipidaemia. Type 2 diabetes is associated with the insulin resistance syndrome (metabolic syndrome).

The metabolic syndrome includes any 3 or more of the following[44] :

- Obesity (especially central/visceral obesity)
  Waist circumference :
  > females > 88 cm;
  > males   > 102 cm

  and / or,
  BMI > 27 Kg/m^2
- Hypertension $\geq$ 130 / $\geq$ 85 mmHg
- Dyslipidaemia :
  TG > 1.7 mmol/L
  HDL-C <1.3 mmol/L (female) or
  > < 1.0 mmol/L (male)
- Disorders of glycaemia
  type 2 diabetes, or
  impaired glucose tolerance, or
  > (Fasting blood sugar < 7.0 mmol/l
  > 2 hours after 75gm glucose load : 7.8 – 11.1 mmol/l)

  impaired fasting glucose (IFG)
  > (Fasting blood sugar : 6.1 – 7.0 mmol/l)

Proatherogenic features like elevated Lp(a), prothrombotic features eg. raised PAI-1, increased fibrinogen and endothelial dysfunction are found in insulin resistance and contribute to the increased CHD risk. These features of insulin resistance can be present for up to 10 years before detection of the glycaemic disorder.

Patients with type 1 diabetes are more likely to have elevated TC, with rise in LDL-C and increased TG. Patients with type 2 diabetes, however have the atherogenic dyslipidaemia. Some studies show better correlation of Non-HDL-C than LDL-C to coronary mortality[22] (see 4.4. & 4.5).

6.3   **Target Lipid Levels**

LDL-C is the primary target for therapy. The target LDL-C level will depend on the individual's global risk. (see Table 5)

Table 5: Target LDL-C levels

Global Risk	Target LDL –C levels (mmol/l)	LDL-C levels to initiate Drug therapy
0 -1 risk factor*	$\leq$4.1	>4.1 ***
2 or more risk factors**	$\leq$3.4	3.4 ***
CHD and CHD risk Equivalents	$\leq$2.6	>2.6

*   Almost all individuals with 0-1 risk factor have a 10 year risk <10%, thus 10 year risk assessment in these individuals with 0-1 risk factor is not necessary.
**   These include individuals with multiple risk factors but a 10 year risk of CHD of <20%
*** After 8-12 weeks of TLC

Salient Points :

- Individuals should be risk categorized (Table 4 and Figures 1 & 2).
- Target lipids levels will depend upon the individual's global risk (Table 5).
- Diabetes mellitus and individuals with multiple risk factors that confer a 10 year risk for CHD > 20% are considered CHD risk equivalents.
- Individuals with CHD and CHD risk equivalents should be treated aggressively with drug therapy (Table 5).

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7. PREVENTION OF CHD

Prevention can be divided into :

- Primary prevention is the prevention of the occurrence of CHD events in people without CHD.

- Secondary prevention is the prevention of progression of CHD and its complications in people with established CHD or CHD risk equivalents.

Strategy of primary prevention

The strategy is based on :

- Population based strategy

This strategy is aimed at educating the public concerning CHD, its presentation and complications, cardiac risk factors, and the importance of maintaining a healthy lifestyle, which is a healthy diet, weight control, increased physical activity and the avoidance or cessation of smoking. These measures should be started early in life. Mass screening for dyslipidaemia is not advocated as it is not cost-effective and there may be inadequate follow-up and counseling.

- Individual based strategy

The aim is to identify individuals at risk of developing CHD and modifying their risk factors. This would include individuals with 0 – 2 risk factors and a 10- year CHD risk of < 20%.

Strategy of secondary prevention.

This is aimed at individuals with established CHD or with CHD risk equivalents. In these high-risk persons, drug therapy should be initiated together with therapeutic lifestyle changes (TLC).

8. MANAGEMENT OF DYSLIPIDAEMIA

8.1 THERAPEUTIC LIFESTYLE CHANGES

Introduction

Therapeutic lifestyle changes (TLC) refer to dietary modification, weight reduction, regular physical activity, cessation of smoking and alcohol restriction. TLC is an integral component of the treatment of dyslipidaemia. It should precede or be initiated together with drug therapy and is directed especially at individuals who are obese, who smoke and who seldom exercise. For patients without CHD or CHD risk equivalents, emphasis should be placed on TLC.

8.1.1 **Dietary Modification**

This is aimed at optimizing lipid levels while maintaining a balanced diet.
It is encouraged to refer an individual to a dietician for medical nutrition therapy. Dietary therapy can lower TC by 10-15%. Dietary therapy is continued indefinitely. (see Appendix 1)

Grade B

The intake of food high in cholesterol content must be reduced[47] .High intake of saturated fatty acids (SFA) [48,49] and trans fatty acids raise LDL-C[50] levels while monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) lower LDL-C[51]. Thus both PUFA and MUFA should be encouraged in place of SFA.

Grade A

A high intake of carbohydrate (> 60% of total caloric intake) results in a reduction in HDL-C and a rise in TG levels[51,52]. In individuals with the metabolic syndrome a lower carbohydrate intake is important.

Grade A

The use of viscous (soluble) forms of dietary fibre (oats, pectin, guar and psyllium) of at least 5 – 10 gm per day is encouraged as they have been shown to reduce LDL-C levels[53].

Grade A

Plant stanol/sterol esters (2 – 3 gm/day) also have an LDL-C lowering effect[54].

Grade A

High intake of soy protein (25 - 50 gm/day) can cause small reductions in LDL-C[55] . Its role is mainly to help reduce the intake of animal food products containing animal fats.

Grade B

8.1.2 **Weight Reduction**

This is of special importance in overweight and obese patients particularly those with metabolic syndrome. Weight reduction helps to lower TG and increase HDL-C, in addition to enhancing the cholesterol (TC and LDL-C) lowering effects of dietary modification.

A weight reduction of 0.5-1.0 kg per week is recommended. According to the Asia Pacific World Health Organization, the recommended BMI is < 23 kg/m^2 and a waist circumference < 95 cm for males and < 80 cm for females.

Grade B

8.1.3 **Physical Activity**

Increase in physical activity and weight reduction enhances the lipid-lowering effects of dietary therapy. It also improves cardiovascular fitness, lowers BP, increases insulin sensitivity, increases HDL-C and decreases TG[56,57]. Such activities include aerobic exercises such as brisk walking, jogging, cycling, swimming. Exercise needs to be regular and adequate (at least 30-45 minutes per session 3x a week).

Grade B

8.1.4 **Cigarette Smoking**

Smoking is one of the major risk factors for CHD and must be stopped. Even passive smokers are at high risk of developing CHD. The decline in CHD risk begins a few months after smoking cessation.

8.1.5 **Alcohol**

Restriction of alcohol is advised in patients with hyperlipidaemia as it increases plasma TG levels. Moderate alcohol consumption (not more than 14 units for males and 7 units for female per week) increases HDL-C and apoprotein A-I and is associated with a reduction in all cause mortality[58]. Over-consumption is however associated with a higher mortality rate. High intake of alcohol elevates BP and can precipitate acute pancreatitis in individuals with high TG levels. Non-drinkers should therefore not be encouraged to start alcohol consumption to improve their dyslipidaemia.

Grade B

(1 unit of alcohol is equivalent to 250ml of beer, 100ml of wine and 30ml of whisky)

8.1.6 **Miscellaneous**

Omega–3 polyunsaturated fatty acids are useful in individuals with high TG and can be considered in addition to fibrates or nicotinic acid. For lowering TG, a dose of 3-9 gm/day of omega 3 fatty acids is required. In patients with CHD, omega-3 fatty acids (dose of 0.75 gm-1 gm/day) has been shown to reduce sudden cardiac death, CHD mortality and total mortality[59,60].

Grade B

The importance of the following in treating hyperlipidaemia remains uncertain : - trans-fatty acids, essential fatty acids (linoleic acid, linolenic acid), and lecithin.

Grade B

The use of anti–oxidants (such as vitamin C, E, beta carotene, bioflavonoids, selenium, Coenzyme Q-10) has not been shown to be effective in preventing or treating CHD. Some studies have shown that garlic[61] and Guggulipid reduce TC transiently but these effects are not sustained long term.

Grade C

8.1.7 **Assessing response to TLC**

The lipid profile should be measured 6-8 weeks after initiating TLC. Generally, TLC may reduce lipid levels (at best) up to 20%. For individuals who attain target lipid levels, they should continue these lifestyle changes life-long to maintain these effects. They can be assessed every 6 months with a full lipoprotein analysis. If, on the other hand, these levels are not achieved, patient compliance should be re-assessed and TLC intensified. They are then reassessed after 6-8 weeks. There is a genetically determined inter-individual variability in the

response to diet. Thus poor response to TLC is not always due to non-compliance.

For individuals at low risk, failure to achieve a defined target value for LDL-C does not necessarily mean that dietary therapy be replaced by drug therapy. Whatever reduction that is achieved will help lower the risk of CHD especially with the concomitant adoption of a healthy lifestyle.

When a decision has been made to start drug therapy, TLC must still be continued indefinitely[62] because it provides substantial additive LDL-C lowering effects.

Grade A

Salient Points:

- Therapeutic lifestyle changes (TLC) remain the cornerstone in managing dyslipidaemia.

- A multifactorial lifestyle approach is recommended to reduce the risk of CHD.

- In patients without CHD or CHD risk equivalents, a period of at least 3 months is given to assess the effectiveness of TLC before considering drug therapy.

8.2   DRUG THERAPY

TLC forms an integral component in the management of dyslipidaemia. In secondary dyslipidaemia, efforts should be made to correct the underlying cause. In those with established CHD and CHD risk equivalents, drug treatment will need to be initiated from the outset in conjunction with TLC (see table 5).

There are 5 major groups of anti-lipid drugs in use (Table 6). They are:

8.2.1 :HMG CoA Reductase Inhibitors (Statins)

HMG CoA reductase inhibitors are highly effective in reducing LDL-C. They are suitable first-line agents in familial hypercholesterolaemia. They have moderate effect in lowering TG and in elevating HDL-C.

Grade A

Table 6: <u>Major Anti Lipid Drug Classes</u> *Adapted from ATPIII* [44]

Drug Class	Lipid Effects	Side Effects	Contraindications
HMG-CoA reductase Inhibitors (statins)	LDL-C ↓ 18-55% HDL-C ↑ 5-15% TG ↓ 7-30%	-Myopathy -Increased liver enzymes	<u>Absolute:</u> -Active or chronic liver disease <u>Relative:</u> -Concomitant use of certain drugs*
Fibric-Acid Derivatives (Fibrates)	LDL-C ↓ 5-20% HDL-C ↑10-35% TG ↓20-50%	-Dyspepsia -Gallstones -Myopathy	<u>Absolute:</u> -Severe hepatic disease -Severe renal disease
Bile-Acid Sequestrants (Resins)	LDL-C ↓15-30% HDL-C ↑ 3-5% TG ↔ / ↑	-GIT distress -Constipation -**Decreased absorption of certain drugs[63,64,65,66]	<u>Absolute:</u> -Dysbeta-lipoproteinemia -Tg > 4.5 mmol/l <u>Relative:</u> Tg > 2.3 mmol/l
Nicotinic Acid (Niacin)	LDL-C ↓ 5-25 HDL-C ↑15-35% TG ↓20-50%	-Flushing -Hyperglycemia -Hyperuricemia (or gout) -Upper-GIT distress -Hepatotoxicity	<u>Absolute:</u> -Chronic-liver disease -Severe Gout <u>Relative:</u> -Diabetes (high doses only) -Hyperuricemia -Peptic-Ulcer Disease
Cholesterol Absorption Inhibitors ***	LDL-C ↓ 18-25% HDL-C ↑3-5% TG ↓ 8-14%	-Headache -Abdominal pain -Diarrhea	

cyclosporin, macrolide antibiotics, various anti fungal agents and cytochrome P-450 inhibitors (fibrates and nicotinic acid should be used with appropriate caution)
*** Paracetamol, NSAIDs, anticoagulant, valproate, digitalis, thiazides, thyroxine, raloxifene, propranolol and tricyclic antidepressants.*
*** usually used in combination with statins.*

Treatment is initiated at the recommended starting dose with the evening meal or at bed time. The dose is then adjusted accordingly to achieve target levels. Serum lipids and alanine aminotransferase should be measured at 6-8 weeks after starting treatment and thereafter as necessary.

Statin therapy is contraindicated in pregnancy and lactation. It should not be prescribed to women of child bearing potential unless adequate contraception is taken.

Recommended Dosages for Statins:

Drug	Recommended initiating dose	Usual dose range
Lovastatin	20mg	10-80mg/day in single or divided doses
Pravastatin	20 mg	10-40 mg daily
Simvastatin	20mg	5-80 mg once daily
Fluvastatin	20mg	20-80mg/day single or divided doses
Atorvastatin	10mg	10-80 mg once daily

8.2.2 Fibric Acid Derivatives (Fibrates)

Fibric acid derivatives are particularly useful in individuals with combined (mixed) hyperlipidaemia and hypertriglyceridaemia as they reduce serum TG effectively, increase HDL-C substantially and can be used in mild to moderate hypercholesterolaemia. Treatment is initiated with the recommended optimal dosage. Serum alanine aminotransferase should be monitored.

Grade A

Recommended Dosages for Fibrates:

Drug	Recommended Dosage
Bezafibrate	200 mg daily increasing to a maximum dose of 200 mg tds (regular) or 400 mg daily (sustained release)
Fenofibrate	300 mg daily or in divided doses (regular) or 200 mg daily (micronised) or 160 mg daily (supra)
Gemfibrozil	600-1500 mg daily in divided doses (regular) or 900 mg daily (sustained release)
Ciprofibrate	100 mg daily
Etofibrate	500 mg daily

8.2.3 Bile Acid Sequestrants (Resins)

Bile acid sequestrants are effective in lowering LDL-C . Resins may increase TG and HDL-C slightly. Combination with a statin may be necessary in severe hypercholesterolaemia. Resins are not suitable as monotherapy in combined hyperlipidaemia.

Grade A

Recommended Dosages:

- cholestyramine   1 packet (4g) 1-6 times daily

Other medications should be taken 1 hour before and/or 4 hours after resins.

8.2.4 Nicotinic Acid (Niacin) and its derivatives

Nicotinic acid (Niacin) effectively lowers both serum cholesterol and TG levels but its side effects tend to limit compliance. Acipimox is a derivative of nicotinic acid which produces fewer side effects (esp. less cutaneous flushing) and does not worsen glucose tolerance.

Grade A

Recommended Dosages:

- Nicotinic acid (Niacin) is available as capsules of 100 mg or 500 mg, and sustained release form :
  - starting dose : 150-300 mg daily in divided doses, titration of dose up to 2-6 g/day (Usual dose)

- Acipimox (Olbetam)
  - starting dose : 500mg . Usual dose 500-750 mg daily in divided doses

8.2.5 Cholesterol Absorption Inhibitors

It inhibits the intestinal absorption of dietary and biliary cholesterol . It is used in combination with statins to further lower LDL-C.

Grade B

Recommended Dose:

- Ezetimibe 10mg daily

8.2.6. Hypertriglyceridaemia

Several drugs are available for the treatment of hypertriglyceridaemia (see section 9.1)

Recommended Dosages:

- HMG Co A reductase inhibitors   as above
- Fibric Acid Derivatives   as above
- Nicotinic Acid and Derivatives   as above   -

8.2.7. Recommended Drug Therapy for Dyslipidaemia

This will depend on the type of dyslipidaemia. (see Table 7)

Table 7**:** Suggested Drug Therapy for Dyslipidaemia

Lipid Values	Initial Drug	Suggested Addition (in order of preference)
LDL-C > 3.4 mmol/l TG < 2.3 mmol/l	Statins	Resin Ezetimibe Fibrates Nicotinic Acid
LDL-C ≥ 3.4 mmol/l TG : 2.3-4.5 mmol/l	Statins	Fibrates Nicotinic Acid

HDL-C < 1.0 mmol/l
TG   < 4.5 mmo/l
If:
     LDL-C < 2.6 mmol/l
 	
If:
     LDL-C > 2.6 mmol/l
	Fibrates
	
	Statins
		Statins
		Nicotinic Acid
		
		Fibrates
		Nicotinic Acid

TG > 4.5 mmol/l	Fibrates	Nicotinic Acid Statins

8.2.8 **Combination Drug Therapy**

If target lipid goals have not been achieved after 8-12 weeks of optimal monotherapy , combination therapy is suggested (Table 7). Occasionally it may be necessary to start with combination therapy to achieve target levels in severe mixed-dyslipidaemia. However combination therapy carries a potential for adverse effects, especially myositis although the incidence is still low. (0.5 - 2.5%). For monotherapy, the incidence of myopathy is 0.1 - 0.5%. [67,68]

8.2.9 **Monitoring and Duration of Therapy**

It should be stressed that these patients will be on lifelong therapy. It is therefore important to assess them on a regular basis, ie. in terms of response to treatment and to look out for possible side-effects related to the drugs. After starting drug therapy, LDL-C level should be measured   at 6-8 weeks and   drug doses

titrated if necessary. Once target lipid levels are achieved a 4-6 monthly follow up is recommended.

Monitoring of ALT is necessary if statins are used for treatment. Liver function test should be carried out before and within 1-3 months of starting treatment. Statins should be discontinued if transaminase levels rises to and persist at 3 times the upper limit of normal. If the levels are elevated but are less than 3 times the upper limit of normal, the trend should be monitored at monthly intervals. If the levels are normal, they only need be checked periodically or if the dose of statin or fibrate is increased.

If myositis is suspected, then creatine kinase levels should be measured. If the level is more than 10 times the upper limit of normal, then the drug should be discontinued.

8.3 **LDL-C APHERESIS**

Patients with homozygous familial hypercholesterolemia (FH) do not response satisfactory to drug therapy. In these patients, LDL-C apheresis should be considered.[69] This form of treatment may also be considered in individuals with severe heterozygous FH who do not achieve target lipid levels with maximal drug therapy.

Grade B

Salient Points :

- Therapeutic lifestyle changes (TLC) should precede or be initiated concomitantly with drug therapy.
- The choice of lipid lowering drug therapy depends on the individual's lipid profile (see Table 7).

9.TREATMENT OF SPECIAL CONDITIONS

9.1 Specific Lipid Disorders

9.1.1 Elevated TG

Very high serum TG (>5.7 mmol/l) can give rise to acute pancreatitis and needs urgent and definitive treatment. High(2.3-5.7 mmol/l) and borderline high levels (1.7-2.3mmol/l) of TG are a common association with low HDL cholesterol, small

dense LDL particles and insulin resistance. There is evidence of a strong association between TG levels and CHD[70]. This may in part be due to association with the other risk factors found in the metabolic syndrome, and in part be due to a raised level of TG being a marker for atherogenic dyslipidaemia and remnant lipoproteins eg in dysbetalipoproteinaemia.

9.1.1.1 **Targets of therapy**

In individuals with elevated TG, the primary target of therapy is to achieve LDL-C goals depending upon the individual's global risk. (Table 5) In individuals where the TG >2.3 mmol/l, Non HDL-C is more representative of all atherogenic lipoproteins than LDL-C. (see also section 2 and 4.4) In these individuals, the secondary target of therapy is Non HDL-C as listed in Table 8. Another secondary target of therapy is TG < 1.7 mmol/l.

Table 8: <u>Targets of LDL-C and Non HDL-C</u>

Global Risk	Target LDL –C levels (mmol/l)	Non HDL-C levels corresponding to LDL-C goals(mmol/l)
1 risk factor	≤ 4.1	< 4.9
2 or more risk factors*	≤ 3.4	≤ 4.1
CHD and CHD risk Equivalents	≤ 2.6	≤ 3.4

These include individuals with multiple risk factors but a 10 year risk of CHD of <20%

9.1.1.2 **Classification of TG (see Table 9)**

With reference to Table 9:

* *Secondary causes of elevated TG include: diabetes mellitus,chronic renal failure, nephrotic syndrome, Cushing's disease, lipodystrophy, pregnancy and various drugs (corticosteroids,beta-blockers,retinoids,oral estrogens (not transcutaneous estrogen),tomoxifen, protease inhibitors for AIDS.*

Table 9: Classification of TG *(Adapted from ATPIII)* [44]

Classification of serum TG	Causes of elevated TG	Clinical significance
Normal TG (<1.7mmol/l)		
Borderline High TG (1.7-2.3mmol/l)	• Acquired causes -Overweight and obesity -Physical inactivity -cigarette smoking -excess alcohol intake -high carbohydrate intake (>60% of total energy) • Secondary causes* • Genetic causes -various genetic polymorphism	• Marker for atherogenic dyslipidemia -elevated small LDL particles -Low HDL-C • Marker for the metabolic syndrome -elevated BP -insulin resistance and glucose intolerance -prothrombotic state -proinflammatory state
High TG (2.3-5.7mmol/l)	• Acquired causes -same as for borderline high TG (usually combined with foregoing causes) • Secondary causes* • Genetic causes -familial combined hyperlipidemia -familial hypertriglyceridemia -polygeneic hypertriglyceridemia -familial dysbetalipoproteinemia	• Elevated atherogenic remnant lipoproteins • Marker for other components of atherogenic dyslipidaemia (see above) • Marker for the metabolic syndrome (see above)
Ver high TG (≥5.7mmol/L)	• Usually combined causes -same as for high TG • Familial lipoprotein lipase deficiency • Familial apolipoprotein C-11 deficiency	• Metabolic syndrome, Type 2 diabetes and increased risk for CHD • Increased risk for acute pancreatitis • Chylomicronemia syndrome -eruptive skin xanthomas -hepatic steatosis -lipaemia retinalis -mental changes -high risk for pancreatitis

9.1.1.3   **Management of elevated TG**

<u>a) Very high TG > 5.7 mmol/L:</u>

When TG is very high, treatment is an emergency to prevent acute pancreatitis.

Suggested treatment:

- Start with a fibrate or nicotinic acid (Avoid in diabetics as nicotinic acid worsens glycaemic control). Gemfibrozil and Fenofibrate lower TG by about 70%. Nicotinic acid is effective at doses of above 2 gm per day.
- In patients with diabetes, insulin therapy should be started to lower blood glucose.
- Diet therapy should consist of a low fat (< 15% total calories) and a low carbohydrate diet.
- Fish oils which contain long chain omega-3 polyunsaturated fatty acids are also effective in lowering TG. Doses of 3 - 9 gm per day can lower TG by up to 50%.
- Statins are not useful in this situation.
- Lifestyle changes such as stopping alcohol, weight reduction, exercise and a low carbohydrate diet, should be reinforced.

In these individuals, it is difficult to achieve target values of TG (< 1.7 mmol/L). Levels of TG < 2.3 mmol/L are acceptable.

<u>b) High TG (2.3 – 5.7 mmol/L)</u>

In individuals with high TG, suggested treatment :

- Institute lifestyle changes as outlined above.
- Ensure diabetes if present is controlled, and emphasize a low carbohydrate diet.
- Drug therapy:
    - If LDL-C or Non HDL-C levels are high, use statins. Statins lower LDL-C and VLDL-C.
    - If TG is high and HDL-C is low, use a fibrate or nicotinic acid. Fibrates and nicotinic acid both lower VLDL-C and VLDL-TG. Nicotinic acid worsens glycaemic control.
    - If the target lipid values are not achieved, combination therapy should be considered (See Table 7).

<u>c) Borderline high TG (1.7 – 2.3 mmol/L)</u>

A target value of TG< 1.7 mmol/L can usually be achieved by:

- Lifestyle changes of weight reduction, low carbohydrate diets, control of diabetes or insulin resistance, exercise, reduction of alcohol and cessation of smoking.
- Medications are rarely required.

9.1.2 **Low HDL-C and High TG** :

Low HDL-C and high TG are seen in insulin resistance (metabolic syndrome) and very high carbohydrate intakes[15].

Treatment of this dyslipidaemia in individuals with CHD or CHD risk equivalents is aimed at lowering LDL-C to target[71] . The choice of anti lipid drug will depend upon the level of LDL-C (Table 7)[72,73,74,75]. If the HDL-C is still low despite adequate TLC then consider,

Grade A

- LDL-C is < 2.6mmol/L use fibrates
- LDL-C is >2.6mmol/L but <3.4mmol/L, use either a statin, a fibrate or nicotinic acid.

In patients with 0 to 1 risk factor and a 10 year CHD risk of $\leq$20%, emphasis should be on TLC. If the LDL-C target goals have still not been achieved, then either fibrates or statins may be used.

9.1.3. **Isolated Low HDL-C**

Individuals with isolated low HDL –C have HDL-C < 1.0 mmol/l and TG < 1.7 mmol/l. The major causes are obesity, physical inactivity, cigarette smoking and genetic factors.

Low HDL-C is an independent major risk factor for CHD[14]. The statin trials have showed that lowering LDL-C in persons with isolated low HDL-C, significantly reduces CHD risk [76,77]. Furthermore, there was no difference in the magnitude of benefit due to LDL-C lowering, in individuals with high HDL-C as compared to those with low HDL-C. Fibrates have also been shown to reduce major CVD events in persons with isolated low HDL-C[75]. This benefit has been attributed in part to the HDL-C raising effects of fibrates.

9.1.3.1 **Management**

In persons with CHD and CHD risk equivalents;

- The primary target of therapy is to achieve LDL-C goals (<2.6mmol/l).
- TLC is an important component of therapy.

- Drug therapy:
  - consider use of fibrates or nicotinic acid. The latter raises HDL-C 2-3 times more than fibrates.
  - If LDL-C goal is not achieved, consider combination therapy of a statin and fibrate or statin and nicotinic acid.

In persons with isolated low HDL-C and 0-2 risk factors and 10 year CHD risk of ≤ 20%:

- The first line of therapy is TLC.
- LDL-C lowering with statins has been shown to reduce CHD risk in primary prevention.[77]

Salient Points:

- In patients with elevated TG, low HDL-C and elevated TG and isolated low HDL-C, the primary goal of treatment is lowering LDL-C to target.
- The secondary targets of therapy are lowering Non HDL-C (if TG >2.3mmol/l) to target, maintaining TG<1.7mmol/l and HDL-C > 1.0mmol/l.

9.2 Diabetes Mellitus

Diabetes is a CHD risk equivalent. Control of hyperglycaemia in type 2 diabetes has not been associated with a significant decrease of CVD events except in over weight diabetics who were given metformin therapy[78,79]. However the UKPDS Extended Study showed that 1% reduction in HbA1c conferred a 14% reduction in CHD risk[80]. Despite this, the risk still remains high when compared to non-diabetics. Thus efforts must also be directed to control of hypertension, lipids[81] and other abnormalities.

Optimal Lipid values in Diabetics are :

- Primary target : LDL-C < 2.6 mmol/l
- Secondary target:
  - Non-HDL-C < 3.4 mmol/L (when TG > 2.3mmol/L)
  - HDL-C >1.0 mmol (male) and >1.2 mmol/l(female)
  - TG < 1.7 mmol/L

These targets are usually not achievable by TLC or glucose control per se. Lipid lowering drug therapy is indicated early (See Table 10).

Table 10: <u>Drug Therapy In Diabetics</u>

Lipid Goal	Initial Drug	Suggested Addition In order of preference
Lower LDL –C	Statins	Resins Fibrates
Increase HDL -C	Fibrates or, Nicotinic Acid *	
Lower TG	Fibrates	Statins **
Treat Combined Hyperlipidaemia	Statins **	Fibrates Resins + Fibrates Nicotinic Acid

with careful monitoring and keeping the dose < 1.5 gm /day.
*** high doses may be required.*

In patients with very high TG, reduction of carbohydrate intake is emphasized. Treatment of hyperglycaemia per se will not reduce lipid levels but post prandial lipaemia will be reduced.

Salient Points:

- Treatment of glycemia per se is inadequate in preventing cardiovascular events.
- Concomitant treatment of dyslipidaemia, hypertension and other metabolic abnormalities are important.
- Target LDL-C goal in diabetics is $\leq$ 2.6 mol/l.

9.3. Coronary Heart Disease

9.3.1 Acute Coronary Syndromes (ACS)

ACS is a spectrum of clinical presentations for coronary artery disease due to a common underlying pathophysiological mechanism.[82] It includes Unstable Angina (UA), Non ST segment Elevation Myocardial Infarction (NSTEMI), and ST segment Elevation Myocardial Infarction (STEMI)[83]. It is associated with a high mortality and morbidity in the period immediately following the event.[84]

Studies have shown that statin therapy started soon after an ACS is safe. Morbidity and the need for revascularisation are reduced[85]. These benefits may be independent of the lipid lowering effects of statins.

Grade A

9.3.2 Post Revascularizations

All cardiac patients post-revascularizations (CABG[86], PCI[87,88]) should be on long term statin therapy, the dose adjusted to achieve target lipid levels.

Grade A

Salient Points:

- Statins should be started in patients with ACS, while still in hospital, irrespective of their cholesterol levels.
- Statins should be started on all post revascularised patients, irrespective of the cholesterol levels.

9.4 Hypertension

Hypertension is defined as a BP $\geq$140 mmHg systolic and / or $\geq$90 mmHg diastolic[89]. Systolic hypertension defined as systolic BP >140 mmHg[90] confers a greater relative risk for CHD than diastolic BP[91]. Hypertension[92] and high cholesterol are both independent risk factors for CHD. These two conditions often co-exist and synergistically increase the risk of CHD[93].

Though there are conflicting data on benefits of treating high cholesterol in hypertensive patients[94,95], both these conditions should be treated aggressively especially in individuals with CHD[96].

The choice of anti-lipid drug therapy will depend upon the patient's lipid profile (Table 8). In one large trial in hypertensive patients with TC $\leq$ 6.5 mmol/l and TG $\leq$ 4.5 mmol/l, statin therapy was found to be beneficial[95].

The choice of antihypertensive agents should be individualized. Certain antihypertensive agents may have an adverse effect on lipid levels eg high dose

thiazide increases TC, LDL-C and TG levels, beta-blockers with no intrinsic sympathetic activity reduce HDL and increase serum TG. These effects are modest and should not affect the selection of an antihypertensive agent[89,90,44].

Salient Points:

- Hypertension and elevated cholesterol levels often coexist and synergistically increase the risk of developing CHD.
- Treatment of both conditions reduces CHD and CVD events.

9.5 Stroke

Stroke is the 3rd leading cause of mortality in Malaysia[97]. Evidence for the role of elevated serum cholesterol in the pathogenesis of stroke is lacking [98,99]. Fibrates[75] and statins[76,100,101] are safe and should be considered in all patients presenting with strokes or transient ischaemic attacks
.

Salient Points:

- Statins have been shown to reduce the incidence of ischemic strokes when used in high risk individuals.

9.6 Renal disease

TC and TG are elevated in nephrotic syndrome. The lipid abnormality may improve or resolve following resolution of the nephrosis. If the dyslipidaemia still persists then drug therapy should be considered.

Chronic renal failure is associated with dyslipidaemia and hypertension. In patients on haemodialysis or CAPD, the main lipid abnormalities are elevated levels of TG and low levels of HDL-C.

Caution must be exercised when starting anti lipid drug therapy in patients with renal insufficiency. The use of fibrates in these individuals carries a higher risk of

myopathy. The initiating dose of some of this group of anti lipid drugs should be lower. (Table 11)

The immunosuppresive drugs used post renal transplants or for underlying renal disease are associated with dyslipidaemia . Patients receiving statins and fibrates in combination with cyclosporin should be closely monitored for myositis.

Table 11: Dose Adjustment in Renal Failure. *Adapted* [102]

Drugs	GFR>50ml/min	GFR 10-50ml/min	GFR <10ml/min
Bezafibrate	50% of usual dose	25% of usual dose	Avoid
Nicotinic Acid	No change	50% of usual dose	25%of usual dose
Gemfibrozil	No change	No change	No change
Statins	No change	No change	No change
Cholestyramine	No change	No change	No change

10. TREATMENT OF SPECIAL GROUPS

10.1   Women

The onset of CHD in women is delayed by 10 to 15 years when compared to men. All the risk factors for CHD mentioned earlier are equally important. In premenopausal women, premature CHD tends to occur in those with diabetes mellitus and multiple risk factors. Although it is generally believed that estrogens confer cardioprotection in women, recent studies however have shown that hormone replacement therapy (HRT) does not confer cardiovascular benefits[103,104,105]. In fact, some studies suggest that it may have slight deleterious effects during the initial 2 years. Clinical trials have shown that statin therapy protects women from cardiovascular events and that the magnitude of benefit closely parallels that observed in men[76]. For secondary prevention, treatment

Grade A

should be as for men. For primary prevention, while in general treatment should be similar, the delay in onset of CHD in women should be taken into consideration prior to instituting drug therapy.

10.2   Children & Adolescents

Atherosclerosis begins in childhood. Screening in young children is only recommended in those whose parents have genetic dyslipidaemia (Table 2). Children whose lipid levels are significantly elevated should be referred to specialists interested in this field.

Grade A

The main approach is a healthy lifestyle with appropriate diet. Bile acids sequestrants (resins) are the only lipid lowering drugs that have been approved for use in children but are generally not well tolerated. Statins while effective in adults is not presently approved for use in children.

Screening for lipids is recommended for those above the age of 20 years. Clinical evidence suggest that serum cholesterol in those at 22 years is predictive of CHD risk.

10.3   Elderly (>65 years)

Old age is one of the major risk factors for CHD events and death, as accumulation of atherosclerosis increases with age. Clinical trials have demonstrated that older persons with CHD, CHD risk equivalents and multiple risk factors to benefit from LDL-lowering therapy[76]. Thus, elderly persons should not be deprived from lipid lowering therapy solely on the basis of their age.

Grade A

The benefits of lipid lowering therapy for primary prevention in elderly persons with no other risk factors besides dyslipidaemia are less well established. Global risk assessment using standard risk factors as mentioned earlier is generally less reliable in older persons. Management of other risk factors such as smoking, hypertension and diabetes are also important. Clinical judgement and consideration of comorbid factors, co-existing disease and functional age become essential in deciding the need for drug therapy in this situation. (see Table 5)

11. ADHERENCE,COMPLIANCE AND QUALITY ASSURANCE

It has been well documented that there is a lack of adherence to cardiovascular preventive therapy. This is due to both doctor factors (not initiating treatment, not achieving treatment goals, not checking on drug compliance) and patient factors (non compliance).

Lack of adherence threatens the success of the guideline recommendation and implementation. Clinical trials have shown that the amount of risk reduction achieved is related to the level of adherence to treatment[106,107]. More importantly, lack of adherence leads to missed opportunity for the risk reducing benefits of the treatment, thus creating enormous costs to the health system for treating cardiovascular events that could have been prevented.

To improve adherence and compliance the following are recommended:

- **Patient factors**
  - Simplify medications regimens using wherever possible drugs
  - with a single daily or twice daily dosing.
  - Give clear instructions
  - Encourage the support of the family
  - Involve patients in their care through self-monitoring

- **Doctor Factors**
  - Teach physicians to implement lipid treatment guidelines
  - Educate patients to prompt preventive care
  - Remind patients of appointments and follow-up missed appointments

- **Health Delivery System**
  - Involve pharmacists and other health care deliverers in patient education
  - Use mass media for patient education
  - Disseminate clinical guidelines and clinical pathways to health care providers
  - Standardize reference values in all laboratories to recommended Malaysian guidelines

Adherence to therapy should be checked periodically. Some suggested indicators as audit for lipid lowering therapy are:

- Measurements of lipid value
- Risk categorization of patients
- Appropriate usage of drug therapy
- Achieving primary lipid target goals – LDL-C to target
- Achieving secondary lipid target goals – HDL-C and TG to target

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APPENDIX 1: <u>LIPID LOWERING DIET</u>

PRINCIPLE	AMOUNT	COMMENT
Decrease dietary cholesterol	<200mg/day	Not more than 2 egg yolks per week (including egg based products),organ meat (offal) eg liver, minimize intake of heart, brains, kidney. Limit to 3 oz once fortnightly. A small amount of prawn / crab / oysters / cockles may be taken once or twice a week if desired
Decrease total fat/oil	<30% of total energy	Modify cooking methods – grill / steam / boil / bake/ microwave to reduce use of oils and fats. Avoid oily /fatty food eg deep fat fried foods
Types: a) saturated fats	7-10% (not more than 10% of total calorie intake	Minimize the use of following – butter, hard margarine, full cream milk (including condensed milk) craem, high fat cheese, fatty meats, bacon and sausages, coconut oil, santan, products containing hydrogenated oil and some non dairy creamers.
b) mononunsaturated and polyunsaturated oils/margarine	Not more than 6 teaspoonsfuls per day to be used in cooking or as a spread	Choices may include the following: olive oil, sunflower oil, corn oil, palm oil, soybean oil, peanut oil and polyunsaturated margarine
Increase intake of complex carbohydrate and fiber	20-25gm fiber/ day Include 2-3 servings of fruit And 3-4 servings of vegetables (5-7 servings per day)	<u>Sources of complex carbohydrates</u>: rice, bread, pasta, noodles and tuber <u>Sources of Fiber</u>: fruits,. vegetables, pulses legumes and unrefined cereals
Choose food high in protein but low in saturated fat	2-3 servings per day	Choices may include: chicken without skin, fish. Legumes and pulse (tofu,

		dhal, green peas and beans),egg whites, lean meat, skim milk and milk products (low fat milk may be used but some low fat milk may contain up to 50% of its original fat.