

**5<sup>th</sup>**

Edition of  
Clinical Practice Guidelines

# Management of Dyslipidaemia 2017





## STATEMENT OF INTENT

This guideline was developed to be a guide for best clinical practice in the management of dyslipidaemia, based on the best available evidence at the time of development. Specific attempts were made to use local data and publications to ensure local relevance. Adherence to this guideline does not necessarily lead to the best clinical outcome in individual patient care. Every health care provider is responsible for the management of his/her unique patient based on the clinical presentation and management options available locally.

## REVIEW OF THE GUIDELINE

This guideline is issued in 2017 and will be reviewed in about 5 years or earlier if important new evidence becomes available.

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Available on the following websites:

<http://www.moh.gov.my>

<http://www.acadmed.org.my>

This is an update to the Clinical Practice Guidelines on Management of Dyslipidaemia published in 2011. This CPG supersedes the previous CPG.

**MESSAGE FROM THE DIRECTOR GENERAL OF HEALTH**

Dyslipidaemia remains a significant problem in Malaysia, with the National Health and Morbidity survey in 2015 reporting an estimated 47% of the adult population having hypercholesterolaemia. In the main, dyslipidaemia is asymptomatic but its associations with serious vascular conditions such as acute myocardial infarction and stroke is well known.

The previous edition of the National Clinical Practice Guidelines (CPGs) were launched in 2011. Since then, the evidence base on this subject has grown and new treatments now available. In addition, more clinical information on dyslipidaemia has emerged from Malaysia and the region. Therefore, this edition, which is the 5<sup>th</sup> Edition of the CPG on the Management of Dyslipidaemia, is timely.

Accessing this CPG, and others endorsed by the Ministry of Health, by healthcare providers is now easier, with the advent of modern telecommunications – downloading a soft copy of this CPG should be a seamless affair. I anticipate the readership of this and other such CPGs to grow and the information provided be useful for healthcare providers in their day to day management of patients.

I would like to congratulate the multidisciplinary team for working together for many months to produce this CPG. Members of the this CPG Expert Panel consist of experts from both the private and public sectors, from primary to tertiary care centres, and from across the country. Under the capable and enthusiastic leadership of Dr Robaayah Zambahari, supported by Dr Jeyamalar Rajadurai, the Expert Panel regularly met to ensure the most recent and relevant information are incorporated into this CPG. I also thank members of the Panel of External Reviewers for their efforts.

Finally, I hope elements of this CPG will be put into practice on a daily basis, to tackle the problem of dyslipidaemia in this country, and eventually result in a drop in mortality and morbidity associated with vascular disease. I am sure this 5<sup>th</sup> Edition of the CPG on the Management of Dyslipidaemia (2017) will go a long way towards achieving this.

A handwritten signature in black ink, appearing to read 'Hisham', written in a cursive style.

**Datuk Dr Noor Hisham Abdullah**  
**Director General of Health Malaysia**

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## RATIONALE AND PROCESS OF GUIDELINE DEVELOPMENT

### Rationale:

In Malaysia, cardiovascular disease (CVD) is the leading cause of death in both men and women<sup>1</sup>. CVD includes coronary heart disease (CHD), cerebrovascular disease and peripheral arterial disease. CHD is a spectrum ranging from stable angina to acute coronary syndromes (ACS).

The prevalence of the common cardiovascular (CV) risk factors – dyslipidaemia, hypertension, diabetes, smoking and overweight/obesity have been on an increasing trend. Malaysians develop heart disease (ACS) at a younger age when compared to people in Thailand, mainland China and western countries. Our local NCVD-ACS Registry (2011-2013), showed that most patients (96.8%) had at least one established CV risk factor – hypertension (65%), dyslipidaemia (37%) and/or diabetes (46%)<sup>2</sup>.

In preventing CVD, efforts should be aimed at reducing global risks. This Clinical Practice Guideline (CPG) is on management of dyslipidaemia. The last CPG (4<sup>th</sup> edition) was published in 2011. Thus the need for an update.

### Objectives:

The objective of this clinical practice guideline is to review:

- The clinical evidence linking dyslipidaemia and atherosclerosis. Atherosclerosis affects the entire vascular tree. However, evidence for a causal link is strongest for CVD (heart disease and strokes).
- Strategies for assessing CV risk that is most applicable to our local population.
- Evidence based management of dyslipidaemia, utilising existing healthcare resources wherever possible.

### Process:

This CPG has been drawn up by a committee appointed by the National Heart Association of Malaysia, Ministry of Health and the Academy of Medicine. It comprises cardiologists, endocrinologists, general physicians, pharmacists and dieticians from the government and private sectors as well as from the Universities.

Literature search was carried out using the following electronic databases – PubMed and Cochrane Database of Systemic Reviews. The following MeSH terms or free text terms were used either singly or in combination:

“Hyperlipidaemia”; “Dyslipidaemia”; “Hypercholesterolemia”; “Cholesterol”; “LDL-cholesterol” “HDL-cholesterol”; “Triglycerides”; “Diabetic dyslipidaemia”

The search was filtered to clinical trials and reviews, involving humans and published in the English language. The relevant articles were carefully selected from this huge list. In addition, the reference lists of all relevant articles retrieved were searched to identify further studies. The search was conducted from August 2010 (date of last review for previous CPG) till 31<sup>st</sup> August 2016.

Local guidelines were also studied. Experts in the field were also contacted to obtain further information. International guidelines mainly that from the American Heart Association/ American College of Cardiology (AHA/ACC) and the European Society of Cardiology were used as main references.

After much discussion, the draft was then drawn up by the members of the Expert Panel and submitted to the Technical Advisory Committee for Clinical Practice Guidelines, Ministry of Health Malaysia and key health personnel in the major hospitals of the Ministry of Health and the Private Sector for review and feedback.

The clinical questions were divided into major subgroups and members of the Expert Panel were assigned individual topics. The group members met several times throughout the development of the guideline. All retrieved literature was appraised by individual members and subsequently presented for discussion during group meetings. All statements and recommendations formulated were agreed collectively by members of the Expert Panel. Where the evidence was insufficient the recommendations were derived by consensus of the Panel. The draft was then sent to local external reviewers for comments. It was also sent to the American College of Cardiology and the European Society of Cardiology for feedback.

The level of recommendation and the grading of evidence used in this guideline was adapted from the American Heart Association and the European Society of Cardiology (ACC/ESC) and outlined on page 10. In the text, this is written in black on the left hand margin.

#### **Clinical Questions Addressed:**

There were several topics and subtopics that were formulated using the PICO method, addressing diagnosis and therapy of dyslipidaemia.

For **diagnosis**:

- Does measuring the lipid profile in the fasting as compared to the non-fasting state, result in a significant difference in the measured values?
- Does measuring the lipid profile in the fasting as compared to the non-fasting state, have an impact on cardiovascular risk estimation?



For **therapy**, the topics and subtopics were as follows:

## **P: Population-** Persons

- With heart disease (secondary prevention)
- Without heart disease (primary prevention)
- With diabetes
  - Type 2 diabetes
  - Type 1 diabetes
- With Chronic Kidney Disease
  - Not on renal replacement therapy
    - With co-existing cardiovascular disease
    - Without co-existing cardiovascular disease
  - On renal replacement therapy
    - Co-existing cardiovascular disease
    - Without co-existing cardiovascular disease
- With Heart Failure
  - With co-existing cardiovascular disease
  - Without co-existing cardiovascular disease ( dilated cardiomyopathy)
- With Specific Lipid Disorders
  - High TG
    - With co-existing cardiovascular disease
    - Without co-existing cardiovascular disease
  - Low HDL-C
    - With co-existing cardiovascular disease
    - Without co-existing cardiovascular disease
- Elderly
- Women
- Children and adolescents

## **I: Intervention:**

- Total and LDL-Cholesterol lowering
- HDL-Cholesterol raising
- Triglyceride lowering

## **C: Comparison:**

- Therapeutic lifestyle intervention vs placebo
- Pharmacological therapy vs lifestyle intervention

## **O: Outcome:**

- Reduction in Cardiovascular Disease- Events, vascular mortality
- Reduction in All cause mortality

**Type of Question-** Involves:

- Therapy – Lipid lowering
- Harm – Increase in Cardiovascular Event Rate, Adverse effects due to Lipid lowering and/or Pharmacotherapy
- Prognosis – Cardiovascular Risk Reduction
- Prevention of Cardiovascular Disease

**Type of Study**

- Systematic review and meta analysis
- Randomised Controlled Studies
- Cohort studies

Thus, there were numerous clinical questions formulated.

Examples of some of these Clinical Questions:

- In persons with heart disease, does Total and LDL-Cholesterol lowering with therapeutic lifestyle interventions alone lead to a reduction in cardiovascular event rate and cardiovascular mortality?
- In persons with heart disease, does Total and LDL-Cholesterol lowering with pharmacotherapy with statins lead to a reduction in cardiovascular event rate and cardiovascular mortality?
- In persons without heart disease, does Total and LDL-Cholesterol lowering with pharmacotherapy with statins lead to an increase in cardiovascular event rate and/or an increase in adverse effects?

The additional question was:

- How to assess CV risk and risk stratify our local population?

**Target Group:**

This guideline is directed at all healthcare providers involved in the management of dyslipidaemia – general practitioners, medical officers, pharmacists, general and family physician, cardiologists and endocrinologists.

**Target Population:**

Individuals with and without cardiovascular disease, those with diabetes, Chronic Kidney Disease, Heart Failure, Specific Lipid Disorders, Elderly, Women, Children and adolescents.

## **Period of Validity of the Guidelines:**

This guidelines needs to be revised at least every 5 years to keep abreast with recent developments and knowledge that is being learnt.

## **Applicability of the Guidelines and Resource Implications:**

This guideline was developed taking into account our local health resources. Blood chemistry for lipid profiles, liver and renal function tests can be done in all government health facilities. Almost all the medications recommended (except for the PCSK9 inhibitors) are approved for use in Malaysia and available in public hospitals as generics.

This guideline aims to educate health care professional on strategies to optimize existing resources in the management of dyslipidaemia.

## **Facilitators and Barriers:**

The main barrier for successful implementation of this CPG is the lack of knowledge of the:

- role of cholesterol (especially LDL-Cholesterol) in the pathogenesis of cardiovascular disease
- benefits of total cholesterol (especially LDL-Cholesterol) lowering
- safety profile of pharmacotherapy

## **Implementation of the Guidelines:**

The implementation of the recommendations of a CPG is part of good clinical governance. To ensure successful implementation of this CPG we suggest:

- Increasing public awareness of CVD in general and educating them on the importance of knowing their individual CV risk.
- Continuous medical education and training of healthcare providers on CV risk assessment tools and the implementation of appropriate preventative strategies depending on each individual's CV risk status. This can be done byroad shows, electronic media, and in house training sessions.

Clinical audit by individual hospitals, units and general practices to ensure compliance using the suggested performance measures in Section 13, pg. 80.

**GRADES OF RECOMMENDATION AND LEVEL OF EVIDENCE**

<b>GRADES OF RECOMMENDATION</b>	
I	Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful and/or effective.
II	Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure/therapy.
II-a	Weight of evidence/opinion is in favour of its usefulness/efficacy.
II-b	Usefulness/efficacy is less well established by evidence/opinion.
III	Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful.

<b>LEVELS OF EVIDENCE</b>	
A	Data derived from multiple randomised clinical trials or meta analyses.
B	Data derived from a single randomised clinical trial or large non-randomised studies.
C	Only consensus of opinions of experts, case studies or standard of care.

Adapted from the American College of Cardiology Foundation/American Heart Association and the European Society of Cardiology

(Available at: [https://professional.heart.org/idc/groups/ahamamah-public/@wcm/@sop/documents/downloadable/ucm\\_319826.pdf](https://professional.heart.org/idc/groups/ahamamah-public/@wcm/@sop/documents/downloadable/ucm_319826.pdf) and at [https://www.escardio.org/static\\_file/Escardio/Guidelines/ESC%20Guidelines%20for%20Guidelines%20Update%202010.pdf](https://www.escardio.org/static_file/Escardio/Guidelines/ESC%20Guidelines%20for%20Guidelines%20Update%202010.pdf)).

## CONTENTS

<b>ABBREVIATION</b>	13
<b>SUMMARY</b>	15
<b>1. INTRODUCTION</b>	23
<b>2. MEASUREMENT OF LIPIDS AND APOLIPOPROTEINS</b>	25
2.1. LDL-C	25
2.2. NON-HDL-C	25
2.3. FASTING VS NON-FASTING LIPID MEASUREMENT	25
<b>3. CLASSIFICATION OF DYSLIPIDAEMIA</b>	27
<b>4. DYSLIPIDAEMIA AS A RISK FACTOR FOR CVD</b>	30
4.1. ELEVATED LDL-C LEVELS	30
4.2. LOW HDL-C LEVELS	31
4.3. ELEVATED TG LEVELS	31
4.4. ELEVATED NON-HDL-C LEVELS	32
4.5. ATHEROGENIC DYSLIPIDAEMIA	32
4.6. LIPOPROTEIN (A)	33
<b>5. GLOBAL CARDIOVASCULAR RISK ASSESSMENT</b>	34
5.1. RISK STRATIFICATION	34
5.2. PREVENTION OF CVD	34
<b>6. TARGET LIPID LEVELS</b>	39
6.1. LDL-C GOALS	39
6.2. NON-HDL-C GOALS	40
<b>7. MANAGEMENT OF DYSLIPIDAEMIA</b>	41
7.1. THERAPEUTIC LIFESTYLE CHANGES AS THE FOUNDATION FOR CVD RISK-REDUCTION	41
7.2. LIPID MODIFYING DRUGS	47
7.3. PHARMACOECONOMICS OF LIPID LOWERING THERAPY	59
<b>8. PRIMARY PREVENTION</b>	61
<b>9. SECONDARY PREVENTION</b>	62
9.1. CORONARY HEART DISEASE (CHD)	62
<b>10. MANAGEMENT OF DYSLIPIDAEMIA IN SPECIFIC CONDITIONS</b>	65
10.1. ASYMPTOMATIC ATHEROSCLEROTIC DISEASE	65
10.2. HYPERTENSION	65
10.3. DIABETES MELLITUS	66

**CONTENTS**

10.4. HEART FAILURE	67
10.5. RENAL DISEASE	68
10.6. SPECIFIC LIPID DISORDERS	70
10.7. HIV	73
<b>11. MANAGEMENT IN SPECIFIC GROUPS</b>	<b>75</b>
11.1. WOMEN	75
11.2. CHILDREN AND ADOLESCENTS	75
11.3. ELDERLY	76
<b>12. ADHERENCE TO LIFESTYLE CHANGES AND MEDICATIONS</b>	<b>78</b>
<b>13. PERFORMANCE MEASURES</b>	<b>80</b>
<b>14. FAQs ON LIPIDS</b>	<b>81</b>
<b>REFERENCES</b>	<b>82</b>
<b>APPENDIX</b>	<b>102</b>
<b>ACKNOWLEDGEMENTS</b>	<b>105</b>
<b>DISCLOSURE STATEMENT</b>	<b>105</b>
<b>SOURCES OF FUNDING</b>	<b>105</b>

## ABBREVIATION

ABI	Ankle Brachial Index
ABV	Alcohol By Volume
ACS	Acute Coronary Syndromes
AIDS	Acquired Immune Deficiency Syndrome
ALA	$\alpha$ -Linolenic Acid
ALT	Alanine Transaminase
Apo B	Apolipoprotein B
ART	Anti-Retroviral Therapy
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CHD	Coronary Heart Disease
CHO	Carbohydrate
CIMT	Carotid Intima Media Thickness
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CPG	Clinical Practice Guideline
CT	Computed Tomography
CV	Cardiovascular
CVD	Cardiovascular Disease
DHA	Docosahexaenoic Acid
DM	Diabetes Mellitus
EPA	Eicosapentaenoic Acid
FH	Familial Hypercholesterolemia
FRS - General CVD	Framingham General CVD Risk Score
GFR	Glomerular Filtration Rate
GIT	Gastrointestinal Tract
HCS	Healthier Choice Symbol
HDL-C	High Density Lipoprotein -Cholesterol
HF	Heart Failure
HIV	Human Immuno-Deficiency Virus
HMG CoA	3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A Reductase
IDL	Intermediate-Density Lipoprotein
IGT	Impaired Glucose Tolerance
LDL-C	Low Density Lipoprotein-Cholesterol

**ABBREVIATION**

Lp(a)	Lipoprotein (a)
MHO	Metabolically Healthy Obesity
MI	Myocardial Infarction
MNT	Medical Nutrition Therapy
MTAC	Medication Therapy Adherence Clinic
MUFA	Monounsaturated Fatty Acids
NCVD-ACS	National Cardiovascular Disease – Acute Coronary Syndrome
NHMS	National Health And Morbidity Survey
NSTEMI	Non-ST Elevation Myocardial Infarction
PAD	Peripheral Arterial Disease
PCI	Percutaneous Coronary Intervention
PCSK9	Proprotein Convertase Subtilisin Kexin Type 9
PI	Protease Inhibitors
PPAR	Peroxisome Proliferator Activated Receptor
PUFA	Polyunsaturated Fatty Acid
SAMS	Statin-Associated Muscle Symptoms
SFA	Saturated Fatty Acids
SLE	Systemic Lupus Erythematosus
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
TFA	Trans Fatty Acid
TG	Triglycerides
TLC	Therapeutic Lifestyle Changes
UA	Unstable Angina
ULN	Upper Limit Normal
VLDL	Very Low-Density Lipoprotein



## SUMMARY

- Cardiovascular disease (CVD) has been the leading cause of death in Malaysia for over a decade.
- The common cardiovascular (CV) risk factors - dyslipidaemia, hypertension, diabetes, smoking, overweight/obesity – are on an increasing trend.
- Dyslipidaemia has been well established as a CV risk factor. It refers to the following lipid levels:
  - Total cholesterol (TC) > 5.2 mmol/L
  - High density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L (males) < 1.2 mmol/L (females)
  - Triglycerides (TG) > 1.7 mmol/L
  - Low density lipoprotein cholesterol (LDL-C) levels - will depend on the patient's CV risk - Table 4 & 5, pg. 20
- Numerous randomized clinical trials have consistently shown that reducing TC and LDL-Cholesterol (LDL-C) reduces vascular risk and prevents CVD.
- LDL-C is the primary target of therapy.
- Non-HDL-Cholesterol may be considered as a secondary target when treating individuals with:
  - combined hyperlipidaemias
  - diabetes
  - metabolic syndrome
  - chronic kidney disease
- In measuring lipid levels:
  - A standard lipid profile includes measurement of plasma or serum TC, LDL-C, HDL-Cholesterol (HDL-C) and triglycerides (TG).
  - LDL-C is usually calculated by the Friedewald equation which is not valid in the presence of elevated TG (TG > 4.5 mmol/L).
  - Both fasting and non-fasting samples may be used for lipid screening.
- Dyslipidaemias may be primary or secondary to nephrotic syndrome, obstructive liver disease, hypothyroidism, Cushing's syndrome, drugs, alcoholism and insulin resistance states such as T2DM and metabolic syndrome. Treatment of the underlying aetiology can lead to an improvement in the lipid profile.
- In management, the global CV risk of the individual should first be assessed. (Table 4, pg. 20)
  - Patients with established CVD, CKD and diabetes fall into the **Very High** and **High Risk** Categories.

## SUMMARY

- All other individuals should be risk stratified at the outset using the Framingham General CVD risk score to determine if they are at **High**, **Intermediate (Moderate)** or **Low Risk**. (Table 1 & 2 pg. 17 & 18) or online at <https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php>
- The intensity of risk factor reduction and target lipid levels will depend on the individual's CV risk. (Table 4 & 5, pg. 20)
- Therapeutic lifestyle changes i.e. adhering to a healthy diet, regular exercise, avoidance of tobacco smoking and maintenance of an ideal weight, remain a critical component of health promotion and CVD risk reduction. (Table 6, pg 21)
- The amount of CV risk reduction seen will depend on the absolute risk of the individual and the degree of LDL-C lowering that is achieved (level of LDL-C achieved and/or the percentage reduction).
- Statin treatment has been clearly documented to reduce CV events in all age groups and irrespective of the baseline LDL-C. (Table 7, pg. 22)
- An achieved on-treatment LDL-C level of < 1.8 mmol/L appears to significantly slow down progression of atherosclerosis.
- Lower levels of LDL-C have been shown to be associated with atherosclerotic regression.
- In most individuals at **Low** and **Intermediate (Moderate)** risk, therapeutic lifestyle changes alone should suffice. Occasionally drug therapy may be necessary to achieve target lipid levels. Only statins have been studied in these individuals.
- In individuals at **Very High** and **High** CV risk, drug therapy with statins should be initiated at the outset in conjunction with therapeutic lifestyle changes.
- In patients with hypertension, diabetes, chronic kidney disease and combined hyperlipidaemias, the primary target of therapy is still LDL-C – the target level will depend on the individual's CV risk. (Table 5, pg. 20)

# Management of Dyslipidaemia 2017

**Table 1A: Estimation of 10 Year CVD Points for MEN  
(Framingham Point Scores)<sup>3</sup>**

Points	Age, y	HDL-C	TC	SBP (not treated)	SBP (treated)	Smoker	Diabetes
-2		1.6+		<120			
-1		1.3-1.6					
0	30-34	1.2-<1.3	<4.2	120-129	<120	No	No
1		0.9-<1.2	4.2-<5.2	130-139			
2	35-39	<0.9	5.2-<6.3	140-159	120-129		
3			6.3-<7.4	160+	130-139		Yes
4			>7.4		140-159	Yes	
5	40-44				160+		
6	45-49						
7							
8	50-54						
9							
10	55-59						
11	60-64						
12	65-69						
13							
14	70-74						
15	75+						
Points allotted							

Grand Total: \_\_\_\_\_ points

**Table 1B: CVD Risk for Men<sup>3</sup>**

Total Points	10 year Risk %	Total Points	10 year Risk %
≤-3	<1	8	6.7
-2	1.1	9	7.9
-1	1.4	10	9.4
0	1.6	11	11.2
1	1.9	12	13.2
2	2.3	13	15.6
3	2.8	14	18.4
4	3.3	15	21.6
5	3.9	16	25.3
6	4.7	17	29.4
7	5.6	18+	>30

**Table 2A: Estimation of 10 Year CVD Points for WOMEN  
(Framingham Point Scores)<sup>3</sup>**

Points	Age, y	HDL-C	TC	SBP (not treated)	SBP (treated)	Smoker	Diabetes
-3				<120			
-2		1.6+					
-1		1.3-1.6			<120		
0	30-34	1.2-<1.3	<4.2	120-129		No	No
1		0.9-<1.2	4.2-<5.2	130-139			
2	35-39	<0.9		140-149	120-129		
3			5.2-<6.3		130-139	Yes	
4	40-44		6.3-<7.4	150-159			Yes
5	45-49		>7.4	160+	140-149		
6					150-159		
7	50-54				160+		
8	55-59						
9	60-64						
10	65-69						
11	70-74						
12	75+						
Points allotted							

Grand Total: \_\_\_\_\_ points

**Table 2B: CVD Risk for Women<sup>3</sup>**

Total Points	10 year Risk %	Total Points	10 year Risk %
≤-2	<1	10	6.3
-1	1.0	11	7.3
0	1.2	12	8.6
1	1.5	13	10.0
2	1.7	14	11.7
3	2.0	15	13.7
4	2.4	16	15.9
5	2.8	17	18.5
6	3.3	18	21.5
7	3.9	19	24.8
8	4.5	20	28.5
9	5.3	21+	>30

**Table 3A: Heart Age/ Vascular Age for Men<sup>3</sup>**

Points	Heart age, y
<0	<30
0	30
1	32
2	34
3	36
4	38
5	40
6	42
7	45
8	48
9	51
10	54
11	57
12	60
13	64
14	68
15	72
16	76
≥17	>80

**Table 3B: Heart Age/ Vascular Age for Women<sup>3</sup>**

Points	Heart age, y
<1	<30
1	31
2	34
3	36
4	39
5	42
6	45
7	48
8	51
9	55
10	59
11	64
12	68
13	73
14	79
15+	>80

**Table 4: Risk Stratification of Cardiovascular Risk**

<ul style="list-style-type: none"> <li>• <b>Very High Risk</b> individuals are those with:             <ul style="list-style-type: none"> <li>➤ Established CVD</li> <li>➤ Diabetes with proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia</li> <li>➤ CKD with GFR &lt; 30 ml/min<sup>-1</sup>/1.73 m<sup>2</sup> (≥ Stage 4)</li> </ul> </li> <li>• <b>High Risk</b> Individuals include:             <ul style="list-style-type: none"> <li>➤ Diabetes without target organ damage</li> <li>➤ CKD with GFR ≥ 30 - &lt; 60 ml/min<sup>-1</sup>/1.73 m<sup>2</sup> (Stage 3)</li> <li>➤ Very high levels of individual risk factors (LDL-C &gt; 4.9 mmol/L, BP &gt; 180/110 mmHg)</li> <li>➤ Multiple risk factors that confer a 10-year risk for CVD &gt; 20% based on the Framingham General (FRS) CVD Risk Score</li> </ul> </li> <li>• <b>Intermediate (Moderate) Risk</b> Individuals:             <ul style="list-style-type: none"> <li>➤ Have a FRS-CVD score that confer a 10-year risk for CVD of 10-20%</li> </ul> </li> <li>• <b>Low Risk</b> Individuals:             <ul style="list-style-type: none"> <li>➤ Have a FRS-CVD score that confer a 10-year risk for CVD &lt; 10%</li> </ul> </li> </ul>
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**Table 5: Target LDL-C Levels**

Global Risk	LDL-C Levels to Initiate Drug Therapy (mmol/L)	Target LDL-C Levels (mmol/L)	Non HDL-C Level corresponding to LDL-C targets in individuals with TG > 4.5 mmol/L
<b>Low CV Risk*</b>	clinical judgement**	< 3.0	< 3.8
<b>Intermediate (Moderate) CV Risk*</b>	> 3.4 **	< 3.0	< 3.8
<b>High CV risk</b> >20% 10-year CVD risk diabetes without target organ damage CKD with GFR 30-<60 ml/min <sup>-1</sup> /1.73m <sup>2</sup>	> 2.6	≤ 2.6 or a reduction of > 50% from baseline***	≤ 3.4 or a reduction of > 50% from baseline***
<b>Very high CV risk</b> established CVD, diabetes with proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia CKD with GFR <30 ml/min <sup>-1</sup> /1.73m <sup>2</sup> but not dialysis dependent)****	> 1.8	< 1.8 or a reduction of > 50% from baseline***	< 2.6 or a reduction of > 50% from baseline***

\*Low and Intermediate (Moderate) CV risk is assessed using the Framingham General CVD Risk Score

\*\*After a therapeutic trial of 8-12 weeks of TLC and following discussion of the risk: benefit ratio of drug therapy with the patient

\*\*\*whichever results in a lower level of LDL-C

\*\*\*\*In dialysis dependent patients, drug therapy is not indicated for primary prevention of CVD.

**Table 6: Recommendations for Therapeutic Lifestyle Changes**

Nutrition	Comments	Grade of Recommendation Level of Evidence
Total fats	20 – 25% with an upper limit of 30% of total energy	I,B
Saturated fat (SFA)	<10% of total calories. SFA should be replaced by: <ul style="list-style-type: none"> <li>➢ PUFA</li> <li>➢ MUFA or</li> <li>➢ complex CHO e.g. whole grain, oatmeal</li> </ul>	I,B IIa,B IIA,b
Trans Fat	<1% of total calories	I,A
Dietary cholesterol*	Keep to <200 mg per day.* High cholesterol foods also contain high levels of SFA (e.g. meat, organ meats, full cream dairy products and some processed foods).	IIa,B
Carbohydrates (CHO)	Total CHO 50 – 60% of total calories intake with emphasis on whole grains. To reduce intake of refined CHO foods e.g. white rice. In the presence of High TG and low HDL-C, CHO intake should be lower.	I,B I,B
Protein	15 - 20% of total calories intake with emphasis on vegetable protein.	I,B
Omega-3 fatty acids*	2 - 4 g per day from food and/or supplements in patients with hypertriglyceridemia.	IIa,B
Dietary fibre	Incorporate fibre-rich foods that contribute at least 20 to 30 g of fibre per day. Emphasis should be on soluble fibre sources (7 to 13 g) such as fruits**, vegetables**, whole grains, high-fibre cereals, oatmeal, legumes and beans.	I,B
Plant sterols and stanols	2 – 3 g per day. These include fortified milk, wheat germ, wheat bran, peanuts, vegetable oils (corn, sesame, canola and olive oil), oats***, almonds and food supplements.	IIa,B
Weight reduction	Achieve Body Mass Index (BMI) <23 kg/m <sup>2</sup> or at least 5-10% reduction in body weight over 1-2 years Maintain waist circumference at: <ul style="list-style-type: none"> <li>▪ &lt; 90 cm for men</li> <li>▪ &lt; 80 cm for women</li> </ul>	I,B
Exercise	150 minutes a week of moderate aerobic or 75 minutes a week of vigorous aerobic exercise.	I,B
Smoking	Make efforts to stop smoking completely and avoid passive smoke.	I,B

\*this applies to patients with Very High and High CV risk.

\*\*Juicing removes fibre from whole fruits and vegetables, thus it is not recommended

\*\*\*Adding ≥3 g OBG/d to the diet reduces LDL and total cholesterol by 0.25 mmol/L and 0.30 mmol/L, respectively, without changing HDL cholesterol or triglycerides.<sup>4</sup>

**Table 7: Lipid Modifying Therapy for Dyslipidaemia**

**The Primary Target of Therapy is LDL-C:**  
**The target will depend on the Individuals' CV Risk (Table 4 & 5, pg. 20)**

Pharmacotherapy		Indication	Grade of Recommendation, Level Of Evidence
Statins		Very High and High CV Risk	I,A
		Intermediate (Moderate) and Low CV risk *	I,A
Statins	+ ezetimibe	Failure to achieve LDL-C goals	IIa,B
Statins	+ PCSK-9 inhibitors	Familial hypercholesterolemia	I,A
		Failure to achieve LDL-C goals	IIa,B
Statins	+ fibrates	Diabetic patients on maximally tolerated statins who have achieved the LDL-C target but have low HDL-C and high TG	IIb,B
Ezetimibe		Statin intolerance	IIa,C
PCSK-9 inhibitors		Very High and High CV risk with statin intolerance	IIa,B
Fibrates		Very High TG despite therapeutic lifestyle changes	IIa,C

\* After Therapeutic Lifestyle changes



## 1. Introduction

Cardiovascular disease (CVD) has been the leading cause of mortality in both Malaysian men and women for more than a decade<sup>1,5</sup>. CVD includes coronary heart disease (CHD), cerebrovascular disease (strokes) and peripheral arterial disease (PAD).

According to the National Health and Morbidity Surveys (NHMS) the prevalence of the common cardiovascular (CV) risk factors among adults  $\geq 18$  years had been on an increasing trend.<sup>6-8</sup> (Table 8, pg. 24). The prevalence of hypercholesterolemia had risen by 46% over the 4 years, 2011 – 2015<sup>7,8</sup>. Almost 1 in 5 adults in the 18-19 year age group had hypercholesterolemia.<sup>8</sup> The prevalence increased with age, from 22.0% in the 18-19 year age group, reaching a peak of 68.8% among adults aged 55-59 years. The prevalence was the same in both rural and urban areas. A similar survey carried out recently among 13-year old students from both urban and rural public schools, found that almost 23% of them had total cholesterol  $>5.2$  mmol/L.<sup>9</sup>

Although atherosclerosis affects the entire vascular tree- coronary, cerebral and peripheral vessels- the causal link between hypercholesterolemia and CVD (heart disease and strokes) has been most well established. (Section 4, pg. 30).

Data from the National Cardiovascular Disease – Acute Coronary Syndrome (NCVD-ACS) Registry 2011-2013, indicated that Malaysians developed acute coronary syndrome (ACS) at a younger age than that seen in neighbouring countries.<sup>2</sup> The mean age was 58.5 years and the peak incidence was in the 51-60 year age group.<sup>2</sup> This is younger than that noted in Thailand (63.5 years)<sup>10</sup> and Singapore (median: 68.3-69.2 years).<sup>11</sup> About 6.6% of our patients admitted with ACS were  $<40$  years<sup>2</sup>.

In the prevention of CVD, efforts should be aimed at reducing global risks. This guidelines emphasize:

- A multifactorial approach that addresses all risk factors. This is because the benefits of modifying several risk factors simultaneously are synergistic.
- That preventing CVD should be directed at global CVD burden rather than CHD alone.

There already exists clinical practice guidelines (CPG) addressing specific CV risk factors. The objectives of this CPG on the Management of Dyslipidaemia are to:

- Critically review the role of dyslipidaemia as a CV risk factor.

- Provide treatment strategies for managing dyslipidaemia, utilising and optimising existing health resources, in the following:
  - High risk individuals – these include those who have established CVD, diabetes, multiple CV risk factors and/or chronic kidney disease (CKD) (ie secondary prevention).
  - Individuals who are otherwise healthy (ie primary prevention).
- Provide strategies for the successful implementation and dissemination of the recommendations.

Dyslipidaemia refers to the following lipid levels:

- Total cholesterol (TC) > 5.2 mmol/L
- HDL-C < 1.0 mmol/L (males) < 1.2 mmol/L (females)
- TG > 1.7 mmol/L
- LDL-C levels - will depend on the patient's CV risk - Table 4 & 5, pg. 20

Decision making however, should be individualised and based on sound clinical judgement.

**Table 8: Prevalence of Cardiovascular Risk Factors Among Adults > 18 Years of Age in Malaysia**

Risk Factor	NHMS III (2006) <sup>b</sup>	NHMS IV (2011) <sup>c</sup>	NHMS V (2015) <sup>d</sup>
Hypercholesterolemia*	20.7%	35.1%	47.7%
Hypertension**	32.2%	32.7%	30.3%
Diabetes***	11.5%	15.2%	17.5%
Smoking****	21.5%	23.1%	22.8%
Overweight /Obesity BMI >25 kg/m <sup>2</sup>	43.1%	44.5%	54.4%

\* total cholesterol  $\geq$  5.2 mmol/L by finger prick test

\*\*BP > 140/>90mmHg

\*\*\*fasting blood glucose  $\geq$  6.1 mmol/L by finger prick

\*\*\*\*current smokers  $\geq$  15 years of age

#### Key Message:

- Cardiovascular disease (CVD) is an important cause of morbidity and mortality in both Malaysian men and women for more than a decade.
- The prevalence of the common cardiovascular (CV) risk factors among adults  $\geq$  18 years has been on an increasing trend.

#### Recommendation:

- In the prevention of CVD, efforts should be aimed at reducing global risks and all CV risk factors should be targeted.

## 2. Measurement of Lipids and Apolipoproteins

A standard lipid profile includes measurement of:

- plasma or serum total cholesterol (TC)
- LDL-Cholesterol (LDL-C)
- HDL-Cholesterol (HDL-C)
- triglycerides (TG)

TC, HDL-C and TG are measured directly.

### 2.1 LDL-C

LDL-C is usually calculated by the Friedewald equation. This equation is not valid in the presence of elevated TG (TG > 4.5 mmol/L). In this situation, LDL-C will have to be measured directly. The method of measurement is not standardized and thus, this is not routinely performed.

Friedewald equation:

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

*(If TG > 4.5 mmol/L, this formula is not valid.)*

### 2.2 Non- HDL-C:

Measurement of Non-HDL-C:

- Estimates the total amount of atherogenic lipoproteins (VLDL, VLDL remnants, IDL, LDL-C and lipoprotein(a) {Lp(a)}) present in plasma
- Can be used to evaluate CV risk when TG is > 4.5 mmol/L<sup>12</sup>
- Can be used to predict CV risk<sup>13-16</sup>

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

(It is a target of therapy in patients with TG > 4.5 mmol/L)

If non-HDL-C is used as a treatment target, the value is 0.8 mmol/L higher than the corresponding LDL-C target level.

### 2.3 Fasting vs Non-Fasting Lipid Measurement

Non-fasting lipid testing is acceptable.<sup>15,17-22</sup> The difference in the values between a fasting and non-fasting sample is small and has been shown to have no impact on CV risk estimation even in diabetics.<sup>18,21,22</sup>

The maximal mean changes between fasting and non-fasting samples at 1–6 h after habitual meals are +0.3 mmol/L for TG; -0.2 mmol/L for TC; -0.2 mmol/L for LDL-C; +0.2 mmol/L for calculated remnant cholesterol; -0.2 mmol/L calculated non-HDL-C. Concentrations of HDL-C, apolipoprotein A1, apolipoprotein B (Apo B), and Lp(a) are not affected by fasting/non-fasting status.<sup>21</sup>

The use of a non-fasting sample for lipid analysis simplifies blood sampling, improves compliance to testing, helps workflow in laboratories and facilitates clinical decision making.<sup>20,21</sup> Numerous population studies and major trials have used random non-fasting blood sampling for measurement of plasma or serum lipids.<sup>21</sup>

Fasting lipid profile should be considered or preferred:

- if the non-fasting TG is > 4.5 mmol/L
- in cases of familial hyperlipidaemia/hypertriglyceridemia
- following recovery from hypertriglyceridemic pancreatitis
- when initiating medication(s) that may cause hypertriglyceridemia (e.g. steroids, anti-retroviral therapy)
- when other tests that are requested require fasting or morning samples (e.g. fasting glucose)

Other lipid measures that can be considered include Lp(a)<sup>23</sup> and Apo B<sup>16</sup>.

Apo B is found in each of the atherogenic lipoprotein particles -chylomicrons, very low density lipoprotein cholesterol (VLDL-C), intermediate density lipoprotein cholesterol (IDL-C), LDL-C and Lp(a). It is thus a better measure of the total atherogenic burden of an individual.<sup>24,25</sup> It has however not been used as a treatment target in any intervention trial. Apo B can be used as an alternative to non-HDL-C measurement. It is however, not routinely measured.

#### Key Messages

- A standard lipid profile includes measurement of plasma or serum total cholesterol (TC), LDL cholesterol (LDL-C), HDL-cholesterol (HDL-C) and triglycerides (TG).
- LDL-C is usually calculated by the Friedewald equation which is not valid in the presence of elevated TG (TG > 4.5 mmol/L).
- The difference in the values between a fasting and non-fasting sample is small and has been shown to have no impact on CV risk estimation.

#### Recommendation:

- Both fasting and non-fasting samples may be used for lipid measurement.

## 3. Classification of Dyslipidaemia

Dyslipidaemias may be primary (due to genetic causes) or secondary. (Table 9 & 10, pg. 28 & 29).

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, and cholestatic liver disease. Hypothyroidism is more prevalent in the elderly in whom a high index of suspicion may be necessary for diagnosis.<sup>26,27</sup>
- Cushing's syndrome (including subclinical disease) can lead to lipid abnormalities in 40-70% of patients.<sup>28</sup> Patients on exogenous steroids may also develop secondary dyslipidaemias.
- When TG exceeds 4.5 mmol/L, exclude secondary causes such as alcoholism.
- When there is high TG with low HDL-C, insulin resistance states such as type 2 diabetes mellitus (T2DM) and metabolic syndrome have to be considered.
- Failure to respond to anti-lipid therapy.
- In patients with a family history of T2DM or a previous history of thyroid disease.
- The effect of drugs on lipid levels is generally small and insignificant except for anabolic steroids that can lead to almost a 50% reduction in levels of HDL-C and Lp (a).<sup>29-31</sup>

Treatment of the underlying aetiology can lead to an improvement in the lipid profile.

**Table 9: Effects of Secondary Causes of Dyslipidaemias**

CAUSES	CHOLESTEROL	TRIGLYCERIDES	HDL-CHOLESTEROL
<b>Lifestyle factors</b>			
Alcohol	↔	↑↑	↑
Saturated fat/ trans-fat	↑	↑	↓
Cardio metabolic risk	↔	↑↑	↓
Smoking	↔	↔	↓
Physical inactivity	↔	↑	↓
<b>Metabolic / Endocrine</b>			
Hypothyroidism	↑↑	↔	↔
Type 2 Diabetes (T2DM)	↑	↑↑	↓
Cushing's Syndrome	↑	↑↑	↓
<b>Renal</b>			
End stage renal disease	↔ or ↓	↑	↓
Nephrotic syndrome	↑↑	↑↑	↓
<b>Hepatic</b>			
Obstructive liver disease	↑↑	↔	↓
Primary biliary cirrhosis	↑↑	↔	↑
<b>Drugs*</b>			
Thiazide diuretics	↔	↑↑	↓
Beta blockers <sup>29</sup>	↔	↑	↓
Anabolic steroids <sup>30</sup>	↔	↑	↓↓
Glucocorticoids <sup>31</sup>	↔	↔	↓* ↑**

\* &lt; 60 years

\*\* ≥ 60 years

**Table 10: Primary (Genetic) Dyslipidaemias**

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

**Key messages:**

- Dyslipidaemias may be primary or secondary to nephrotic syndrome, cholestatic liver disease, hypothyroidism, Cushing's syndrome, drugs, alcoholism and insulin resistance states such as T2DM and metabolic syndrome.

**Recommendation:**

- Treatment of the underlying aetiology can lead to an improvement in the lipid profile.

## 4. Dyslipidaemia as a Risk Factor for CVD

Dyslipidaemia is a major risk factor for CVD. According to the NHMS V, 47.7% of adult Malaysians over the age of 18 have hypercholesterolemia (TC > 5.2 mmol/L)<sup>8</sup>. In the most recent National Cardiovascular Disease Database-Percutaneous Coronary Intervention (NCVD-PCI) Registry 2010-2012, 72.6% of patients had a known history of hypercholesterolemia (TC > 5.2 mmol/L) at the time of percutaneous coronary intervention (PCI)<sup>32</sup>.

Specific lipid abnormalities implicated are:

### 4.1 Elevated LDL-C levels

LDL-C has been shown to be atherogenic in epidemiological studies.<sup>33-43</sup> 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.<sup>44-47</sup> In people with established CHD, elevated LDL-C correlates with recurrent cardiac events.<sup>48,49</sup>

Mendelian disorders resulting from mutations in the genes involved in cholesterol metabolism, highlight the strong and causal relationship between LDL-C and CVD.<sup>50</sup> In familial hypercholesterolemia (FH), a mutation in the LDL-C receptor results in very high levels of LDL-C and premature CVD.

It has been postulated that LDL-C levels of 1.3 to 1.8 mmol/L are physiologically normal in man.<sup>51</sup> There is a near absence of clinical CHD in populations with very low levels of serum cholesterol throughout their life (TC < 3.9 mmol/L or LDL-C < 2.6 mmol/L).<sup>52,53</sup> The risk of CHD appears to increase progressively above these levels. In the Atherosclerosis Risk In Communities (ARIC) Study the lowest incidence of CHD was seen in individuals at the lowest quartile of LDL-C suggesting that optimal values for both gender is < 2.6 mmol/L (100 mg/100 ml).<sup>54</sup>

A recent analysis of selected observational studies suggests that there is an inverse relationship between levels of LDL-C and all-cause mortality in the elderly (> 60 years)<sup>55</sup>. Many of the studies that were included in this analysis however, were small and with a wide variation in the adjustment of confounding factors. This raises concern over the conclusion of this analysis.



Furthermore, epidemiological evidence indicates an association between TC (and LDL-C) with atherosclerosis and CVD and not necessarily with all-cause mortality.<sup>56</sup> An earlier larger systemic review of 900,000 adults showed a clear relationship between levels of TC and vascular mortality in all age groups.<sup>57</sup>

Randomized controlled trials have repeatedly shown that lowering of LDL-C reduces CVD events in both primary and secondary prevention in both gender.<sup>58-66</sup> Patients with established disease have greater absolute benefit from LDL-C reduction. There appears to be a dose-dependent reduction in CVD with LDL-C lowering; the greater the LDL-C reduction, the greater the CV risk reduction.<sup>58-66</sup>

Studies have also shown that LDL-C particle concentration and size are important predictors of CVD.<sup>67-69</sup> However measurement of these are not widely available and are not standardized.

For these reasons, LDL-C should be the primary target for cholesterol therapy. A 1 mmol/L reduction in LDL-C reduces CV mortality by 22%.<sup>70</sup> A meta regression analysis showed that the use of statin and non-statin therapies that act via upregulation of LDL receptor expression (i.e. diet, bile acid sequestrants, ileal bypass, and ezetimibe) lead to similar reduction in major CV events per 1 mmol/L reduction in LDL-C.<sup>71</sup>

Statins have consistently been shown to reduce CV events, are safe, well-tolerated and cost effective.

## 4.2 Low HDL-C levels

There is substantial epidemiological evidence linking low HDL-C levels (< 1.0 mmol/L) with increased risk of CHD.<sup>15,72</sup> A 1% decrease in HDL-C, in epidemiological studies, has been associated with 2-3% increase in CHD risk.<sup>15</sup>

Clinical trials using pharmacotherapy to increase HDL-C levels have, however, not shown any CV benefit.<sup>73-76</sup>

## 4.3 Elevated TG levels

The role of TG as a CV risk factor is controversial and not as robust as is with LDL-C.<sup>14,77-80</sup> It is now widely believed that TG is not directly atherogenic but remains a biomarker of CV risk via its association with remnant lipoproteins and ApoCIII.<sup>14</sup>

Two studies have suggested that non-fasting TG measurements are more predictive of CV risk than fasting TG.<sup>17,81</sup> Non-fasting TG more accurately reflects the presence of atherogenic remnant lipoproteins compared to fasting TG measurements. There is however a lack of a standardized protocol for quantitation of post-prandial hypertriglyceridemia. This limits its clinical applicability.

Recent clinical trials with pharmacotherapy (fibrates and niacin) that were specifically directed at reducing TG levels have not however, shown any benefit in reducing CV events.<sup>76,82–85</sup>

#### 4.4 Elevated Non-HDL-C levels

Non-HDL-C reflects the concentration of cholesterol within all lipoprotein particles considered atherogenic. Studies have demonstrated that non-HDL-C is a better predictor of CV risk than is LDL-C and may be especially true in statin-treated patients.<sup>16,86–92</sup> A prospective study demonstrated that non-HDL-C levels conferred a similar risk of future major adverse cardiac events (MACE) as LDL-C in patients with clinically manifest cerebrovascular, coronary artery or polyvascular diseases.<sup>89</sup>

Achieved non-HDL-C levels seem more closely associated with coronary atheroma progression than LDL-C.<sup>93</sup> Among statin-treated patients, on-treatment levels of LDL-C, non-HDL-C, and apo B were each associated with risk of future major CV events, but the strength of this association was greater for non-HDL-C than for LDL-C and apoB.<sup>16</sup>

Non-HDL-C has however, not been used as a target of therapy in either primary or secondary prevention clinical trials.

#### 4.5 Atherogenic Dyslipidaemia

This consists of low HDL-C, raised TG and small dense LDL particles.<sup>94,95</sup> The LDL-C levels are usually normal but there is a higher proportion of small dense LDL particles which are more atherogenic.

Although epidemiological data indicates that the ratio of TC/HDL-C is a CV risk marker, there have been no outcome studies to support using this as a target of therapy. Its use is thus not recommended.

## 4.6 Lipoprotein Lp(a)

The association of Lp(a) to CV risk is continuous and independent of LDL-C or non HDL-C levels.<sup>23,96</sup> However, there is no data as yet that reducing Lp(a) leads to an improvement in CV outcomes.

For this reason, Lp(a) is not recommended to be routinely measured.

### Key messages

- There is strong and consistent evidence of LDL-C as a CV risk factor.
- LDL-C lowering has been to reduce the risk of cardiovascular disease in individuals with CVD (secondary prevention) and without CVD (primary prevention).
- Patients with established disease have greater absolute benefit from LDL-C reduction.
- There appears to be a dose-dependent reduction in CVD with LDL-C lowering; the greater the LDL-C reduction, the greater the CV risk reduction.
- Statins have consistently been shown to reduce CV events, safe, well-tolerated and cost effective.

### Recommendation:

- LDL-C should be the primary target of therapy.
- The greater the LDL-C reduction, the greater the CV risk reduction

## 5. Global Cardiovascular Risk Assessment

### 5.1 Risk Stratification

Based on the Malaysian NHMS V data, about 1 in 5 young adults (aged 18-19 years) have TC > 5.2 mmol/L.<sup>8</sup> All the CV risk factors- diabetes, hypertension, hypercholesterolemia, overweight/obesity and smoking- stratified by age, showed a sharp increase in prevalence from the age group 25-29 years.<sup>8</sup>

I, C As such, the committee advocates screening all adults > 30 years of age. These individuals should have a complete lipid profile (TC, LDL-C, HDL-C and TG). The presence of other CV risk factors (blood sugar, blood pressure (BP), weight, smoking status, physical inactivity) should also be determined and the individual counselled appropriately.

Individuals who are at high risk of developing CVD should have a lipid profile earlier in life (> 18 years of age). This includes individuals with a family history of premature CVD, genetic dyslipidaemias, metabolic syndrome, diabetes mellitus (DM) and abdominal obesity.

### 5.2 Prevention of CVD

Individuals at highest risk of CVD can be categorized as (Table 4, pg 20):

- Very High Risk, or
- High Risk

**Very High Risk** individuals include those with (Table 4, pg. 20):

- Established CVD
  - Patients who already had a CV event are at highest risk for a recurrent event.
    - After an ACS, the 6-month risk of CV death and major CV event rate was 5-8% and 15-20% respectively in the Global Registry of Acute Coronary Events (GRACE) registry.<sup>97</sup>
    - In patients with stable CHD, the 1-year rate of CV death was 1.9% and the rate of CV death, myocardial infarction (MI) or stroke was 4.5%.<sup>98</sup>
    - Following a stroke, the risk of a recurrent stroke was 8-11%<sup>99,100</sup> and the risk of death 24.5%.<sup>99</sup>
  - It also includes individuals with:
    - Atherosclerosis in other vascular beds - aorta including atherosclerotic aortic aneurysms, carotid, cerebral and peripheral vessels

# Management of Dyslipidaemia 2017

- Asymptomatic significant atherosclerotic plaques detected on computed tomography (CT) coronary angiogram and carotid ultrasound.(Section 10.1, pg 65)
- Diabetes with proteinuria<sup>101-103</sup> or with a major risk factor such as smoking, hypertension or dyslipidaemia
- Chronic Kidney Disease (CKD) – Glomerular Filtration Rate (GFR) <30  $\text{ml}/\text{min}^{-1}/1.73 \text{ m}^2$  (Stage 4 & 5)
  - There is an independent, graded association between reduced GFR and the risk of death, CV events, and hospitalization.<sup>101,104</sup>
  - The risk begins to increase with  $\text{GFR} < 60 \text{ ml}/\text{min}^{-1}/1.73 \text{ m}^2$  and escalates as the GFR drops below  $< 30 \text{ ml}/\text{min}^{-1}/1.73 \text{ m}^2$ .<sup>104</sup>
  - It is still controversial whether CKD itself is a causal factor for CVD or if it just a CV risk marker.<sup>101,105,106</sup>

**High Risk** individuals include those with (Table 4, pg. 20):

- Chronic Kidney Disease (CKD) -  $\text{GFR} \geq 30 - < 60 \text{ ml}/\text{min}^{-1}/1.73 \text{ m}^2$  (Stage 3)
- Diabetes without target organ damage<sup>107</sup>
- Very high levels of individual risk factors (e.g.  $\text{LDL-C} > 4.9 \text{ mmol/L}$  or  $\text{BP} \geq 180/110 \text{ mmHg}^{61}$ )
- Multiple risk factors that confer a 10-year risk for CVD >20% based on the Framingham General CVD Risk Score<sup>3</sup>

Individuals who belong to the above **Very High Risk** and **High Risk** categories, should be encouraged to have a healthy lifestyle (stop smoking, regular exercise and a healthy diet) in addition to pharmacotherapy, to ensure that all their risk factors are treated to targets.

I, A These individuals derive the greatest benefit from risk factor reduction and lipid lowering statin therapy.<sup>108,109</sup>

In all otherwise healthy individuals, their global CV risk should first be determined to help guide the intensity of risk factor reduction efforts. Based on their CV risk, they may be categorized as:

- Intermediate (Moderate) Risk
- Low Risk

CV risk refers to the likelihood of an individual developing a CV event, fatal or non-fatal, over a defined time period.

The relative risk reduction of lipid lowering therapy is similar in all individuals irrespective of their CV risk status. However, in low risk individuals the absolute benefit may be less.<sup>108-111</sup>

There are several risk equations that may be used to determine CV risk. (Appendix 1, pg. 102). The cut-off points that are used in these risk models to define risk categories are in part arbitrary. They are based on the risk levels at which benefit was demonstrated in clinical trials.

All risk models have limitations and difficulty when extrapolated to our local population. Ideally, the CV risk model used should be based on data derived from our local population. Currently, we do not have such a CV risk score. Both Thailand and Singapore have their own CV risk score which is based on the older Framingham Risk Score (10-year risk of CHD deaths, Non-fatal MI only) adapted to the local populations.<sup>112,113</sup>

The risk score that is widely used in Malaysia is the Framingham General CVD risk score tool (FRS-General CVD) for primary care that assesses the 10-year risk of developing CVD (heart disease, strokes, PAD and heart failure).<sup>3</sup> (Tables 1 & 2 pg. 17-18) It can also be calculated online at <https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php>

The earlier version of the Framingham Risk Score CHD (2002) provided a risk estimate of “hard” CHD events only i.e. cardiac death and non-fatal MI.

The FRS – General CVD has the advantage of being derived from a population that had received no or little treatment at the start and during the study.<sup>114</sup> It is also simple and easy to use – an important feature if healthcare providers are to use it routinely.<sup>115</sup> In two local studies, the FRS-General CVD risk model was a better discriminator of CV risk in our local multi ethnic population.<sup>116,117</sup>

The new 2013 ACC / AHA risk calculator has the advantage that it is gender specific.<sup>118</sup> In a local study, however, this risk model overestimated CV risk in the Malaysian population.<sup>119</sup>

Individuals who belong to the **Very High Risk** and **High Risk** categories mentioned earlier in section 5.1 do not need to be risk stratified.

## Management of Dyslipidaemia 2017

All other apparently healthy individuals should be risk stratified using the FRS-General CVD Risk Score<sup>3</sup> (Tables 1 & 2 pg. 17-18) or online at <https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php>

The 10-year risk calculation is to be performed at the outset to help guide the intensity of lipid lowering therapy.

- It cannot be used to track changes in risk over time as risk factors are modified.
- In calculating the risk scores the TC and HDL-C should be the average of at least 2 measurements.
- The average baseline blood pressure (BP) should be obtained from an average of several readings.
- A "smoker" means any cigarette smoking in the past month.

Based on the 10-year CV risk, individuals may be:

- > 20% - **High CV Risk**
- 10-20 % - **Intermediate (Moderate) CV Risk**
- < 10% - **Low CV Risk**

Those individuals with a 10-year risk of CVD of > 20% are **High Risk**. (Section 5.1, pg 34) They should be treated aggressively from the outset with non-pharmacological measures and pharmacotherapy to achieve treatment targets.

Individuals who have a 10-year CVD risk of < 10% are **Low Risk**. Low-risk individuals should be given advice to help them maintain this status.

Many young individuals may fall into this category of low absolute risk of CVD but they may have a high lifetime risk if their individual risk factors are high. These include individuals with:

- BP > 180/110 mmHg
- LDL-C > 4.9 mmol/L

In these individuals, using Vascular Age (Table 3A & B, pg. 19)<sup>3</sup> may be helpful in defining CV Risk and guiding management strategies. This risk model has not been validated in our local population.

Individuals who have a 10-year CVD risk of 10-20% are **Intermediate (Moderate) Risk**. In these individuals, other risk factors not included in the FRS-General CVD Risk Score may influence treatment targets and the decision to initiate pharmacotherapy.

Additional factors that may support upgrading of CV risk include<sup>120</sup>:

- family history of premature CVD - males (father and/or brother(s)) < 55 years of age and females (mothers and/or sister(s)) < 65 years of age<sup>121-125</sup>
- ankle: brachial (ABI) index < 0.9 - this indicates PAD, the lower the index, the more severe the disease
- hs-CRP levels  $\geq 2$  mg/L<sup>120</sup>
- coronary artery calcium score of  $\geq 300$  Agatston units.<sup>120,126-129</sup> This is an indirect measure of disease burden.

III, B

Routine measurement of carotid intima media thickness (CIMT) for risk assessment is no longer recommended.<sup>130</sup>

These risk models help guide risk assessment and management. They do not replace sound clinical judgement in the assessment of global risk and management strategies. It has not as yet been demonstrated that with upgrading of the risk category of patients at **Intermediate (Moderate) Risk** and subjecting them to aggressive risk factor reduction, it would lead to reduction in CV risk and improvement in CV outcomes.<sup>131</sup>

The intensity of preventive actions should be tailored to the patient's total CV risk. The risks (side effects, costs etc.) should be weighed against the benefits of each intervention. In subjects who are at **Low or Intermediate (Moderate)** risk, the decision to initiate pharmacotherapy should be individualised following a mutual discussion with the patient.

**Key messages:**

- The intensity of LDL-C lowering should be tailored to the individual's global CV risk.

**Recommendations:**

- All individuals should be risk stratified. (Table 4, pg. 20)
- Patients with established CVD, CKD and diabetes fall into the **Very High** and **High Risk** Categories.
- All other individuals should be risk stratified at the outset using the Framingham General CVD risk score to determine if they are at **High, Intermediate (Moderate)** or **Low Risk**. (Tables 1 & 2, pg. 17-18)
- The intensity of risk factor reduction and target lipid levels will depend on their CV risk. (Table 4, pg. 20)



## 6. Target Lipid Levels

### 6.1 LDL-C Goals

I, A LDL-C is the primary target of therapy.<sup>108–111</sup>

I, A The target LDL-C level will depend on the individual's CV global risk. (Table 5, pg. 20, & 39)

Both the absolute on treatment LDL-C level and the percentage LDL-C reduction achieved have been found to correlate with the observed CV benefits<sup>70, 108, 109, 132–137</sup>

**Table 5: Target LDL-C levels**

Global Risk	LDL-C Levels to Initiate Drug Therapy (mmol/L)	Target LDL-C levels (mmol/L)
<b>Low CV Risk*</b>	clinical judgement**	< 3.0
<b>Intermediate (Moderate) CV Risk*</b>	> 3.4 **	< 3.0
<b>High CV risk</b> > 20% 10-year CVD risk > diabetes without target organ damage > CKD with GFR 30-< 60 ml/min <sup>-1</sup> /1.73 m <sup>2</sup>	> 2.6	≤ 2.6 or a reduction of >50% from baseline***
<b>Very high CV risk</b> > established CVD, > diabetes with proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia > CKD with GFR < 30 ml/min <sup>-1</sup> /1.73 m <sup>2</sup> but not dialysis dependent)	> 1.8	< 1.8 or a reduction of > 50% from baseline***

\*Low and Moderate CV risk is assessed using the Framingham General CVD Risk Score

\*\*After a therapeutic trial of 8-12 weeks of TLC and following discussion of the risk: benefit ratio of drug therapy with the patient

\*\*\*whichever results in a lower level of LDL-C

## 6.2 Non-HDL-C Goals

IIa, B

Non-HDL-C may be considered as a secondary target when treating patients with:

- combined hyperlipidaemias
- diabetes<sup>138</sup>
- cardio metabolic risk
- chronic kidney disease

The targets for non-HDL-C are < 2.6 mmol/L and < 3.4 mmol/L in subjects at high and very high CV risk respectively. The specific goal for non-HDL-C should be 0.8 mmol/L higher than the corresponding LDL-C goal.

Adjusting lipid lowering therapy to achieve these secondary goals may be considered after achieving LDL-C targets in patients with **Very High** and **High** CV risk. Although increases in HDL-C predict atherosclerosis regression and low HDL-C is associated with excess events in CHD patients, clinical trial evidence is lacking on the effectiveness of intervention.<sup>73-76</sup>

### Recommendations:

- Non-HDL-C may be considered as a secondary target when treating patients with combined hyperlipidaemias, diabetes, cardio metabolic risk and chronic kidney disease.

## 7. Management of Dyslipidaemia

### 7.1 Therapeutic Lifestyle Changes as the Foundation for CVD Risk-Reduction

Therapeutic lifestyle changes (TLC) i.e. adhering to a healthy diet, regular exercise, avoidance of tobacco smoking, alcohol restriction and maintenance of an ideal weight, remains a critical component of health promotion and CVD risk reduction efforts both prior to and after commencement of lipid lowering therapies in all individuals.

These measures should be promoted as a population based strategy for prevention of CVD.<sup>139</sup> A diet high in fibre, fruits and vegetable, wholegrain, low in salt and saturated/trans-fat is associated with lower CV risk and should be encouraged in all individuals.<sup>139</sup>

#### 7.1.1 Dietary Modification

This CPG focuses on dietary therapy for dyslipidaemia. There is limited randomized controlled trial (RCT) on dietary interventions and CV risk reduction, most of the data being derived from observational studies. For a more detailed discussion of nutrition for health and weight loss, refer to the Malaysian Clinical Practice Guidelines Primary and Secondary Prevention of Cardiovascular Disease, 1<sup>st</sup> Ed. 2017.<sup>139</sup>

TLC is an essential component of the treatment of dyslipidaemia from the initial diagnosis. It is especially important in obese individuals, smokers and those who lead a sedentary lifestyle. It should be emphasized in both primary and secondary prevention. (Table 6, pg. 21)

Dietary therapy is aimed at optimising lipid levels while maintaining a balanced diet. It is advised to refer to a dietician for medical nutrition therapy (MNT). Dietary therapy is continued to empower the individual to manage their stages of change to achieve their nutritional goal. To optimize outcomes, motivational interviews are beneficial.<sup>140</sup>

##### 7.1.1.1 Dietary Cholesterol

The role of serum cholesterol (especially LDL-C) in the pathogenesis of atherosclerosis and CVD is consistent and robust. (Section 4, pg. 30). The contribution of dietary cholesterol to blood cholesterol levels is however, more complex and controversial. The question is whether eating food high in cholesterol leads to high serum cholesterol and LDL-C, and whether limiting dietary cholesterol intake lowers serum LDL-C.<sup>141</sup>

Recent data indicate that the impact of dietary cholesterol on serum cholesterol levels is weak.<sup>131,142</sup> However, many high-cholesterol foods also contain high levels of saturated fats (SFA). This includes dairy products, meat and most processed foods. For this reason, international lipid guidelines recommend limiting dietary cholesterol to < 200 mg/day in secondary prevention.<sup>131,143</sup>

### 7.1.1.2 Total Fats, Saturated Fats and Unsaturated Fats

I, B

The recommended total fat intake is between 20 to 25% with an upper limit of 30% of total energy intake in all individuals.<sup>144,145</sup> (Table 6, pg. 21)

Fats in the diet consist of TG which is made up of three fatty acids and a glycerol backbone.<sup>146</sup> Fatty acids differ in the length of their aliphatic tails, ranging from short chain ( $\leq 5$ ) to very long chain ( $\geq 22$ ) fatty acids. Depending on the number of double bonds, fatty acids can be further categorized as:

- Saturated fatty acids (SFA) - no double bonds
- Unsaturated fats which may occur as either:
  - polyunsaturated fats (PUFA) - 2 or more double bonds
  - monounsaturated fatty acids (MUFA) - 1 double bond

Oils are mixtures of fatty acids. (Appendix 2, pg 100 for fatty acid composition of common dietary oils)

The predominant fatty acids present in the following oils are:<sup>144,147</sup>

- coconut oil, palm kernel oil, santan, palm oil, beef, pork, milk, yogurt, cheese - SFA
- corn oil, sunflower oil, soybean oil, tofu, tempeh, walnut - PUFA
- olive oil, peanut oil, canola oil (n=20), almond, peanut, hazelnut, palm oil - MUFA

Omega fatty acids are PUFA and include:

- omega-6 fatty acids - linoleic acid found in vegetable oils such as sunflower, safflower, soybean, corn, grapeseed, peanut and canola oils as well as nuts and seeds<sup>148</sup>
- omega-3 fatty acids which consists of:
  - $\alpha$ -linolenic acid (ALA)- found in plant oils, canola oil, flaxseed oil, soybean, chia seed, linseed and rapeseed oils, walnuts, and leafy green vegetables<sup>144,149,150</sup>
  - eicosapentaenoic acid (EPA) - found in marine oils<sup>151</sup>
  - docosahexaenoic acid (DHA) - found in marine oils<sup>151,152</sup>

The body can produce all the required fatty acids except for the essential fatty acids -linoleic acid and alpha-linolenic acid.<sup>153</sup> These have to come from the

diet e.g. corn, sunflower and soybean, flaxseed walnuts and dark leafy vegetables (e.g. spinach, kailan).

The rate of conversion of omega-6 fatty acids to omega-3 fatty acids in the body is low.<sup>149</sup> Thus it is also important to increase the intake of omega-3 fatty acids in the diet. Sources of omega-3 fatty acids (docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)) are fatty fish (e.g. salmon, ikan kembung, ikan jelawat, siakap, keli, patin, senangin, white pomfret).<sup>144,151,152</sup>

Excess intake of SFA has been implicated with an increased risk of CVD in several epidemiological studies.<sup>142</sup> A recent large meta-analysis however, found no association between SFA intake and all-cause mortality, CVD, CHD, ischemic stroke, or type 2 diabetes.<sup>154</sup> The authors however concluded that the evidence was heterogeneous with methodological limitations. They state that the review does not support recommendations to increase SFA intakes.<sup>154</sup>

III, B

I, A

The current recommendation is that the intake of SFA should not exceed 10% of energy intake.<sup>131,142,144</sup> (Table 6, pg. 21)

As the intake of SFA is reduced to even lower than 10% of total energy intake, there continues to be a favourable effect on lipoprotein profile.<sup>146</sup> There is little evidence however at present, that a reduction in SFA intake below 9% of total energy intake is associated with a reduced CVD risk.<sup>155</sup> With reduction in SFA intake, dietary cholesterol intake is also lowered since SFA and cholesterol often coexist in the same food.

A central issue in the relationship between SFA and CVD is the specific macronutrients that are used to replace it in the diet.<sup>142</sup> When SFA is replaced with:

I, B

- PUFA, there is consistent data that CV events and coronary mortality are reduced.<sup>142</sup>

IIa, B

- MUFA or CHO, the evidence is not that clear that it lowers CVD risk.<sup>140,142</sup>

IIb, B

- Excess CHO, it may, in fact, contribute to an atherogenic dyslipidaemia with small dense LDL, low HDL-C levels, insulin resistance and obesity.<sup>140,142</sup>

Taking PUFA or MUFA (e.g. 1 teaspoon of olive oil/ virgin coconut oil) without cutting down SFA intake will not confer CV benefit.

### 7.1.1.3 Trans Fats

Trans fat (TFA) may be:<sup>156</sup>

- "Industrially produced" TFA- these are man-made fats added to foods such as shortening and baked goods
- "Ruminant" TFA- these occur naturally in small amounts in foods such as butter and beef

Trans fats are created through a process of partial hydrogenation.<sup>156</sup> The presence of TFA make oils more solid and extend their shelf life.<sup>156</sup> Major sources of TFA are deep fried fast foods, margarines, commercially baked cookies, cakes, crackers, and some breads.<sup>156</sup> Repeated/ prolonged heating of MUFA and PUFA may convert them to trans fat.

Intake of TFA raises levels of LDL-C, reduces HDL-C and increases the ratio of TC to HDL-C.<sup>156</sup> Prospective cohort studies showed that TFA was also associated with an increase in the incidence of diabetes.<sup>157-159</sup>

TFA appears to increase the risk of CVD more than any other macronutrient on a per calorie basis.<sup>156</sup> Even at low levels of consumption of 1-3% of total energy intake, CV risk is substantially increased.<sup>156</sup> Total TFA fat intake was associated with all-cause mortality, CHD mortality and total CHD. Industrial, but not ruminant, TFA fats were associated with CHD mortality and CHD.<sup>146,160</sup>

A 2 percent increase in energy intake from trans fats was associated with a 23 percent increase in the incidence of CHD.<sup>161</sup> It was estimated that substituting 2% of energy from trans fats with saturated fat, MUFA and PUFA would reduce CV risk by 17%, 21% and 24% respectively.<sup>161</sup>

A more recent meta-analysis however, showed that only replacement of TFA fat with PUFA, MUFA or CHO resulted in more favourable lipoprotein profiles.<sup>162</sup> The effect was most consistent with PUFA. Replacement with SFA tended to lead to higher TC and LDL-C levels.<sup>162</sup>

There has been no consistent scientific evidence of a relationship between TFA with BP or cancer.<sup>163</sup>

I, A

TFA intake should be kept at less than 1% of total energy.<sup>131,142</sup> (Table 6, pg. 21 and Appendix 3, pg. 104)

## 7.1.1.4 Atherogenic Dyslipidaemia

Atherogenic dyslipidaemia comprises a triad of low HDL-C, high TG and increased levels of small dense LDL-C. In prospective cohort studies, the presence of a low HDL-C and a raised TG have been associated with increased CV events. The use of pharmacotherapy to lower TG and increase HDL-C however, have been, to date, either neutral or shown an increase in adverse outcomes.<sup>73–76,82–85</sup>

Dietary modification can result in an improvement in atherogenic dyslipidaemia. A low carbohydrate (CHO) diet (< 26% of total energy intake) results in a significant reduction in TG levels, an increase in HDL-C levels and a shift from small dense LDL-C to the larger buoyant LDL-C even in the presence of a high SFA diet and in the absence of weight loss.<sup>164–169</sup> The Low Fat diet, on the other hand, required weight loss for an improvement in the atherogenic profile.<sup>167</sup>

The effects of a low CHO diet on long term health are unknown.<sup>142, 170,171</sup>

## 7.1.2 Exercise

Regular exercise reduces the risk of all-cause and CVD mortality in both healthy individuals and patients with CVD by 20–30%.<sup>172–174</sup>

Studies show that regular aerobic exercise can:<sup>175,176</sup>

- increase HDL-C by 3–10% (up to 0.16 mmol/L)
- reduce TG by about 11% (up to 0.34 mmol/L)

Vigorous aerobic exercise improves HDL-C more than less-intense exercise.<sup>175</sup> The decrease in TG with exercise is acute and short-lived, becomes evident 12-18 hours after a single bout of exercise and lasts for 2-3 days.<sup>177</sup> It requires that a certain amount of energy (a threshold) be expended during exercise, independent of duration or intensity. More exercise above that threshold does not seem to result in greater reductions in plasma TG concentrations.<sup>177</sup>

The recommended duration of exercise for CVD prevention in healthy adults regardless of age is:<sup>173,174</sup>

- I, B
- at least 150 minutes a week of moderate intensity or
  - 75 minutes a week of vigorous intensity PA or an equivalent combination

- I, A
- For weight loss, increased physical activity of approximately 250 to 450 minutes of moderate-intensity physical activity per week, including strength training 2 to 3 times per week is required.<sup>178</sup> This should be accompanied with a calorie restricted diet.

For a more detailed discussion on weight loss, refer to the Clinical Practice Guidelines Primary and Secondary Prevention of Cardiovascular Disease, 1<sup>st</sup> ed, 2017.<sup>139</sup>

### 7.1.3 Smoking

Smoking is a strong and independent risk factor for CVD.<sup>179,180</sup> It accelerates coronary plaque development and may lead to plaque rupture.<sup>180</sup>

Smoking has:<sup>181</sup>

- An adverse effect on TG - heavy smokers had a significantly higher concentration.
- The concentration of HDL-C was inversely related to smoking, non-smokers having the highest concentration.

The concentrations of TC, fasting blood glucose and uric acid were correlated with body mass index (BMI) rather than smoking.<sup>181</sup>

Cigarette smoking cessation increases serum levels of HDL-C, especially in women, but has no effect on TC, LDL-C, and TG.<sup>182,183</sup> This improvement in HDL-C levels may be offset by the weight increase that occurs after quitting.<sup>184,185</sup> Strategies should be taken to minimise the weight gain following smoking cessation.

There is significant reduction in CV morbidity within the first 6 months of smoking cessation.<sup>179</sup> The risks of CVD decreases gradually after smoking cessation and reaches that of non-smokers after 10-15 years.<sup>179</sup> This benefit occurs independent of its effect on lipids.

I, B

Smoking should be discouraged<sup>179</sup> and individuals referred to the MQuit Services. More information is available at [www.JomQuit.com.my](http://www.JomQuit.com.my)

#### Key message:

- Therapeutic lifestyle changes (TLC) remain a critical component of CVD risk reduction efforts both prior to and after commencement of lipid lowering therapies in all individuals.



## Recommendations:

- The recommended total fat intake for healthy adults is between 20 to 25% with an upper limit of 30% of total energy intake.
- The intake of SFA should not exceed 10% of energy intake.
- TFA intake should be kept at less than 1% of total energy.
- The duration of exercise for CVD prevention in healthy adults regardless of age is:
  - at least 150 minutes a week of moderate intensity or
  - 75 minutes a week of vigorous intensity PA or an equivalent combination.
- Smoking should be discouraged and individuals referred to the MQuit Services.

## 7.2 Lipid Modifying Drugs

I, C TLC form an integral component in the management of dyslipidaemia. In secondary dyslipidaemia, efforts should be made to correct the underlying cause.

Most individuals at **Low Risk** and **Intermediate (Moderate) Risk** can be managed by TLC alone. Occasionally, lipid modifying agents may be necessary to achieve target lipid levels. Only statins have been studied in primary prevention.

In those at **Very High** and **High CV Risk**, it is recommended that drug treatment be initiated simultaneously with TLC. There are five major groups of lipid modifying drugs. (Table 11, pg. 49)

Not all lipid modifying drugs/interventions mentioned in this CPG are available in the MOH hospitals/Malaysia.

### 7.2.1 HMG CoA Reductase Inhibitors (Statins)

Statins are inhibitors of HMG CoA reductase, the rate limiting enzyme in hepatic cholesterol synthesis.

LDL-C reduction with statin treatment remains the cornerstone of lipid lowering therapy to reduce risk of CVD.<sup>108–111</sup> They are the drugs of choice in reducing LDL-C because of the consistent results of numerous randomized primary and secondary prevention clinical trials.<sup>108–111</sup>

The amount of CV risk reduction seen will depend on the absolute risk of the individual and the degree of LDL-C lowering that is achieved (level of LDL-C achieved and/or the percentage reduction).<sup>70,108,109,132–137</sup> Depending on the on treatment level of LDL-C level achieved, lipid modifying agents can slow the progression or even promote regression of coronary atherosclerotic plaques.<sup>132–134,186,187</sup> An achieved treatment LDL-C level of <1.8 mmol/L appears to significantly slow down progression of atherosclerosis.<sup>132–134,186,187</sup>

Statins have moderate effect in lowering TG and in elevating HDL-C. (Table 11, pg. 49)

Treatment is initiated at the recommended starting dose with the evening meal or at bed time especially with simvastatin.<sup>188</sup> Small short term clinical studies indicated that the LDL-C fell significantly by 5-8% when simvastatin was taken in the evening rather than in the morning.<sup>189–193</sup>

Since cholesterol is biosynthesized in the early morning hours, statins with shorter half-lives (lovastatin 2 hours, simvastatin <5 hours, and fluvastatin <3 hours) should be administered in the evening. In contrast, statins with longer half-lives (atorvastatin 14 hours, rosuvastatin 19 hours, and pravastatin 22 hours) can be administered during the day.<sup>188,194</sup>

III, C

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

**Table 11: Major Lipid Modifying Drug Classes<sup>#</sup>**

Drug Class	Lipid Effects	Side Effects	Contraindications
HMG-CoA Reductase Inhibitors (Statins)	LDL-C ↓ 21-55% HDL-C ↑ 2-10% TG ↓ 6-30%	<ul style="list-style-type: none"> <li>• Myopathy</li> <li>• Increased liver enzymes</li> </ul>	<p><u>Absolute:</u></p> <ul style="list-style-type: none"> <li>• Active or chronic liver disease</li> </ul> <p><u>Relative:</u></p> <ul style="list-style-type: none"> <li>• Concomitant use of certain drugs*</li> </ul>
Fibric-Acid Derivatives (Fibrates)	LDL-C ↓ 20-35% (fenofibrate) HDL-C ↑ 6-18% Primarily TG ↓ 20-35%	<ul style="list-style-type: none"> <li>• Dyspepsia</li> <li>• Cholelithiasis</li> <li>• Myopathy</li> </ul>	<p><u>Absolute:</u></p> <ul style="list-style-type: none"> <li>• Severe hepatic disease</li> <li>• Severe renal disease</li> </ul> <p><u>Relative:</u></p> <ul style="list-style-type: none"> <li>• Concomitant use of certain drugs**</li> </ul>
Proprotein convertase subtilisin/ kessin type 9 (PCSK 9) inhibitors	LDL-C ↓ 48-71% Non- HDL-C ↑ 49-58% TC ↓ 36-42%	<ul style="list-style-type: none"> <li>• Injection site swelling or rash</li> <li>• Nasopharyngitis</li> <li>• Limb pain</li> <li>• Fatigue</li> </ul>	<p><u>Absolute</u></p> <ul style="list-style-type: none"> <li>• Hypersensitivity</li> </ul>
Bile-Acid Sequestrants (Anion exchange resins)	LDL-C ↓ 15-25% HDL-C ↑ 3-5% TG ↔ / ↑	<ul style="list-style-type: none"> <li>• GIT distress</li> <li>• Constipation</li> <li>• Reduce absorption of folic acid and fat-soluble vitamins (A, D &amp; K)</li> <li>• ***Decreased absorption of certain drugs</li> </ul>	<p><u>Absolute:</u></p> <ul style="list-style-type: none"> <li>• Dysbetalipoproteinemia</li> <li>• TG &gt;4.5 mmol/L</li> </ul> <p><u>Relative:</u></p> <ul style="list-style-type: none"> <li>• TG &gt;2.3 mmol/L</li> </ul>
Nicotinic Acid (Niacin)	LDL-C ↓ 10-25% HDL-C ↑ 10-35% TG ↓ 20-30%	<ul style="list-style-type: none"> <li>• Flushing</li> <li>• Hyperglycaemia</li> <li>• Hyperuricemia (or gout)</li> <li>• Upper-GIT distress</li> <li>• Hepatotoxicity (rare but may be severe)</li> </ul>	<p><u>Absolute:</u></p> <ul style="list-style-type: none"> <li>• Chronic-liver disease</li> <li>• Severe gout</li> </ul> <p><u>Relative:</u></p> <ul style="list-style-type: none"> <li>• Diabetes (high doses only)</li> <li>• Peptic Ulcer Disease</li> </ul>
Cholesterol Absorption Inhibitors****	Primarily LDL-C ↓ 10-18% (monotherapy) In combination with (a) statins: Additional ↓ 25% (b) fenofibrate: ↓ 20-22%	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Abdominal pain</li> <li>• Diarrhoea</li> </ul>	

<sup>#</sup>Adapted from American Association of Clinical Endocrinologists 2017<sup>195</sup>

\*cyclosporin, macrolide antibiotics, antifungal agents, protease inhibitors and cytochrome P-450 inhibitors (fibrates and nicotinic acid should be used with appropriate caution)

\*\*gemfibrozil and repaglinide<sup>196</sup>

\*\*\*Paracetamol, NSAIDs, anticoagulant, valproate, digitalis, thiazides, thyroxine, raloxifene, propranolol and tricyclic antidepressants.

\*\*\*\*usually used in combination with statins.

These data are derived from short-term clinical trials meant for drug registration. In real life long term use, the amount of lipid change achieved may be less than this.

### 7.2.1.1 Monitoring Statin Therapy

It should be stressed that these individuals will be on lifelong therapy. It is therefore important to assess them on a regular basis to monitor for:

- Response to therapy and achievement of lipid targets.
  - The degree of LDL-C reduction is dose dependent and varies between the different statins.<sup>197</sup>
  - There is considerable inter-individual variation in LDL-C reduction with the same dose of drug.<sup>198</sup>
  - Inadequate response to statin treatment may be due to poor compliance and/or genetic variations of cholesterol and statin metabolism in the liver.<sup>199,200</sup>
- Adverse effects

#### A) Response to Therapy

Lipid profile should be measured at 1 to 3 months following initiation and following a change in the dose of statin therapy. The dose is then adjusted accordingly to achieve LDL-C levels.

If LDL-C targets have been achieved, the same dose of statin should be maintained. The drug should not be stopped. The lipid profile can be repeated at 6 to 12 month intervals.

If LDL-C target is not achieved, the dose of statin can be uptitrated to the maximal tolerated dose. If target level still not achieved, then a non-statin drug can be added. (Table 7, pg. 22)

The frequency of repeat testing while on stable lipid therapy, will depend on the individual adherence to therapy and lipid profile consistency; if adherence is a concern or the lipid profile is unstable, then more frequent assessment may be necessary.<sup>195</sup>

#### B) Safety/Adverse Effects

##### B.1. Liver Function

- Hepatic transaminases should be measured at baseline and at 1 to 3 months after starting treatment and/or following a change in dose.
- If levels are elevated prior to therapy, other causes (e.g. fatty liver, hepatitis) should be excluded. If due to fatty liver, lipid lowering therapy is not contraindicated.
- Mild elevation of alanine transaminase (ALT) occurs in < 3% of patients on statin treatment, more commonly with potent statins or high doses.<sup>201</sup>

- Mild elevation of ALT has not been shown to be associated with true hepatotoxicity or changes in liver function.
- When transaminase levels (especially ALT) are > 3 times the upper limit of normal (ULN) on 2 occasions, the drug should be stopped. Reversal of transaminase elevation is frequently noted with reduction of the dose or cessation of the drug.
- Cautious reintroduction of therapy may be considered under close monitoring after ALT values have returned to normal.
- Progression to liver failure is exceedingly rare. Routine monitoring of ALT during long term statin treatment is no longer recommended.<sup>202</sup>

## B.2. Muscle Symptoms

- In clinical practice and registries, 10-30% of patients report statin-associated muscle symptoms (SAMS).<sup>203,204</sup> This includes myalgia (normal creatine kinase (CK)), myositis (CK > ULN) and rhabdomyolysis (CK > 10X of ULN).
  - The incidence of SAMS is much lower in clinical trials, and only differs slightly from placebo.<sup>205-207</sup> In observational studies, the frequency varies between 10 and 15%.<sup>208-209</sup> In a study by Parker designed specifically to study the effects of statins on muscle symptoms, the frequency of muscle-related complaints was approximately 9%.<sup>210</sup>
  - Myalgia (without CK elevation) occurs in 5-10% of patients in clinical practice.<sup>210</sup> If the symptoms are not tolerable or are progressive, the dose of statin should be reduced or the drug stopped.
  - The incidence of myopathy (myositis and rhabdomyolysis) is low and is more likely to occur in persons with complex medical problems (in particular CKD) and/or who are taking multiple medications, or in elderly persons, especially women.
- Creatine Kinase (CK) is not routinely measured unless myositis is suspected. If the level is more than five times the ULN on two occasions, the drug should be discontinued.
- There is no uniform definition for statin intolerance. In certain trials; 'statin intolerant' patients are defined as patients unable to tolerate at least two different statins because of unexplained skeletal muscle-related symptoms (pain, aches, weakness, or cramping) that began or increased during statin therapy and returned to baseline when statin therapy was discontinued.<sup>205</sup>
- When a statin myopathy is suspected, typically the first step is statin discontinuation for 2-3 weeks.
  - If symptoms have not resolved, it is unlikely to be statin related and the patient should be continued on the same dose of statin
  - If symptoms have resolved, then the following strategies may be considered:
    - Lowering the dose or decreasing the frequency to less than daily.<sup>211</sup>
    - An alternative dosing such as every other day or twice a week with atorvastatin or rosuvastatin<sup>212</sup> can be used

- Treatment with the highest tolerable dose of statin in combination with a cholesterol absorption inhibitor (ezetimibe),
- If indicated, a PCSK9 inhibitor may be considered.<sup>213,214</sup>

92% of statin intolerant patients do well with a second statin.<sup>211</sup>

73% will tolerate a re-challenge with a third statin.<sup>211</sup>

- An alternative approach is to consider co-enzyme Q10 to alleviate the symptoms of myalgia. The relationship between co-enzyme Q10 and statin related muscle symptoms is circumstantial. However, the risk of side effects from co-enzyme Q10 is low. Thus a trial of co-enzyme Q10 in patients with possible statin related muscle side effects may be considered. The response rate is variable.<sup>215–217</sup>
- The routine use of co-enzyme Q10 together with statins is unproven and therefore not recommended.<sup>215–217</sup>

III, C

IIa, B

Care should be taken when prescribing high doses of simvastatin (>20 mg/daily) together with certain other medications that inhibit the cytochrome P450 pathway. It has the potential of increasing the risk of muscle injury.<sup>218,219</sup>

### B.3. Diabetes

- Statins have been associated with a slight increase in new-onset diabetes (9-12%)<sup>220,221</sup>. It occurs with all statins and may be dose related.
- The CV reduction benefits seen with statins far outweigh the risk of developing diabetes. In fact statins have been proven to prevent CV events in persons with diabetes with no overt CVD.<sup>59,109,222</sup>
- Screening for diabetes should be considered at 6 - 12 monthly intervals in patients at high risk of developing diabetes. These include the following individuals/conditions:
  - Elderly
  - Metabolic syndrome
  - Obesity or signs of insulin resistance
  - Family history of DM (parents and siblings)

I, A

## B.4. Kidney Effects

- An increased frequency of proteinuria has been reported for all statins, more so for rosuvastatin.
- The proteinuria induced by statins is of tubular origin and is due to reduced tubular reabsorption and not to glomerular dysfunction.<sup>223</sup>
- In clinical trials the frequency of proteinuria is in general, low and in most cases is not higher than for placebo.<sup>224</sup>
- III, B • As such, we do not recommend routine monitoring of renal function or proteinuria.<sup>224</sup>

## B.5. Neurocognitive function

- Regulatory bodies have required that a statement be added to the drug label for all statins indicating that there is a potential for cognitive side-effects (such as memory loss and confusion).<sup>225</sup>
- Clinical studies designed to assess the effect of statins on cognitive function have, however, found little to no evidence that statins are associated with adverse effects on memory or cognition.<sup>226,227</sup>

## B.6. Others

- There is no evidence that patients on statins have increased risk of non-CV mortality (e.g. cancers, suicides).

### 7.2.1.2 Optimising Statin Therapy

The therapeutic doses of statins used in clinical practice should be similar between Asian and Caucasian populations. Studies conducted among Asian and Caucasian subjects concluded that systemic exposure to atorvastatin did not differ between the two groups.<sup>228,229</sup>

I, A

- High-intensity statin therapy produces a greater percentage LDL-C reduction and thus reduces CV events more than moderate-intensity statin therapy.<sup>108-111</sup>(Table 12, pg. 54)

I, A

- Lower-intensity statin therapy has also been shown to reduce CV events, but to a lesser degree.<sup>108-111</sup>

I, A

- **Very High Risk and High Risk** individuals should be treated with the maximum appropriate intensity of a statin that does not cause adverse effects.<sup>108,109,132-137</sup>

**Table 12: Recommended Doses of Statin Therapy<sup>#</sup>**

<b>High-Intensity Statin Therapy*</b> Daily dose lowers LDL-C on average, by approximately ≥50%	<b>Moderate-Intensity Statin Therapy</b> Daily dose lowers LDL-C on average, by approximately 30% - <50%	<b>Low-Intensity Statin Therapy**</b> Daily dose lowers LDL-C on average, by <30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin 40 mg bid Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

<sup>#</sup>Adapted from: Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S76-S99<sup>20</sup>

\*High intensity statin therapy is for patients who are at **Very High** and **High Risk**

\*\*Low intensity statin therapy is generally used for primary prevention after TLC and following a discussion with the patient of the risk: benefit ratio

### 7.2.1.3 Adhering to Statin Therapy

- The importance of LDL-C lowering to prevent CVD is strongly emphasized. There appears to be a dose-dependent reduction in CVD with LDL-C lowering; the greater the LDL-C reduction, the greater the CV risk reduction.<sup>60,108,109,231</sup>
- The benefits related to LDL-C reduction are not specific for statin therapy.<sup>66,71,135</sup> No level of LDL-C below which benefit ceases or harm occurs has been defined.
- CV risk reduction should be individualised, and this can be more specific if goals are defined. The use of goals can also aid patient-doctor communication and facilitate adherence to treatment.
- We therefore advocate LDL-C treatment goals and where applicable percentage LDL-C reduction. (Table 4, pg. 20)

I, A

### 7.2.2 Cholesterol Absorption Inhibitors

Cholesterol absorption inhibitors selectively blocks intestinal absorption of both dietary and biliary cholesterol and other phytosterols. This leads to a reduction in hepatic cholesterol delivery - a mechanism which complements the action of statins.

There are no clinically significant effects of age, sex or race on ezetimibe pharmacokinetics, and no dosage adjustment is necessary in patients with mild hepatic impairment or mild to severe renal insufficiency.

No major adverse effects have been reported; the most frequent adverse effects are moderate elevations of liver enzymes and muscle pain.



It is used in combination with any dose of any statin to further lower LDL-C if targets are not achieved.

**Ila, B** When used in combination with a statin, it was found to have CV benefits in individuals with CKD.<sup>232</sup>

**I, B** More recent clinical trials showed CV benefits when ezetimibe was used in combination with statins in patients with CHD.<sup>66,134</sup>

**Ila,C** It may be considered as monotherapy in patients who cannot tolerate statins.

#### **Recommended Dose:**

- Ezetimibe 10 mg daily

### **7.2.3 PCSK9 Inhibitors**

This is a new class of lipid-lowering drug that target the proprotein convertase subtilisin kexin type 9 (PCSK9). It works by inhibiting the binding of PCSK9 to the LDL-receptors. This interaction decreases the degradation of the LDL-receptors, resulting in higher LDL-receptors density at the cell surface. The higher expression of LDL-receptors at the cell surface leads to increased clearance with resulting decrease in LDL-C levels.<sup>233,234</sup>

Currently, monoclonal antibodies have been developed against PCSK9 that have been shown to reduce LDL-C levels by about 50%, irrespective of the background lipid-lowering therapy.<sup>135,213,214,235–237</sup> No major changes were reported on HDL-C or plasma TG levels.

A recent study indicated that the PCSK9-inhibitor, evolocumab, when administered in addition to high dose statins to patients with CVD who had not achieved an LDL-C < 1.8 mmol/L, reduced the risk of major CV events.<sup>238</sup>

Currently, it is only available as an injection administered subcutaneously at 2-4 weeks intervals. Common side effects are injection-site swelling, flu-like symptoms, nausea and joint pains. Neurocognitive effects were reported in less than 1% and this requires further rigorous assessments. A recent trial did not show any increase in neurocognitive side effects.<sup>239</sup>

Possible indications for this group of drugs as add on therapy are:

**Ila, B** • individuals with high CV risk who have persistently elevated LDL-C despite optimum lipid-modifying therapy<sup>238</sup>

**I, A** • those with familial hypercholesterolemia – heterozygous FH and to a lesser extent those with homozygous FH<sup>235–237</sup>

**IIa, B** Very High Risk and High Risk patients with true statin intolerance and persistently high levels of LDL-C may also be candidates for PCSK9 inhibitors.<sup>213,214</sup>

**Recommended Dose:**

- Dose of evolocumab: 140 mg SC every two weeks or 420 mg SC monthly
- Dose of alirocumab: 75-150 mg SC every two weeks

**7.2.4 Fibric Acid Derivatives (Fibrates)**

Fibrates are Peroxisome Proliferator Activated Receptor (PPAR) –  $\alpha$  agonist which have an important role in fatty acid oxidation. They reduce serum TG effectively and increase HDL-C modestly.

Fibrates have not been shown to reduce CVD events in the secondary prevention trials.<sup>82,85,240</sup>

**IIa,C** Its use is limited to the treatment of patients with very high TG levels who do not respond to non-pharmacological measures.<sup>241</sup> (Table 13, pg. 56)

**IIb, B** In persons with diabetes already on maximally tolerated statins, and who have low HDL-C ( $\leq 0.88$  mmol/L) and high TG ( $\geq 2.3$  mmol/L), fibrates may be considered to reduce CV events.<sup>242</sup>

Doses of fibrates need to be adjusted in the presence of CKD. Serum ALT should be monitored when starting therapy or when doses are increased.

**Table 13: Recommended Dosages for Fibrates\***

Drug	Recommended Dosage
Fenofibrate	100mg TDS, 145 mg daily (nanoparticles), 160mg daily (micronized)
Gemfibrozil**	600-1200 mg daily in divided doses 30 minutes before meal (Max:1.5g/day)
Bezafibrate	200 mg daily increasing (gradually over 5-7 days) to a maximum dose of 200 mg tds (regular) or 400 mg daily (sustained release)
Ciprofibrate	100 mg daily

\*As stated in MIMS, (2016-2017) Malaysia

\*\*not recommended for use in combination with statins

## 7.2.5 Bile Acid Sequestrants (Anion exchange resins)

Bile acid sequestrants bind to bile acids to promote their secretion into the intestines. They are effective in lowering LDL-C. Resins may increase TG and HDL-C slightly. Its use is discouraged in patients with TG  $\geq 3.4$  mmol/L.<sup>243</sup>

Ila, B Monotherapy has a modest effect on CHD in primary prevention.<sup>45,46,244</sup>

Gastrointestinal adverse effects are often present with this drugs even at low doses, which limit their practical use. Other medications should be taken 1 hour before and/or 4 hours after resins.

### Recommended Dose:

Cholestyramine: 4 g/d increased by 4g at weekly intervals to 12-24 g/day in 1-4 divided doses, Max: 24 g/day

## 7.2.6 Nicotinic Acid (Niacin) and Its Derivatives

Nicotinic acid decreases mobilization of free fatty acids from adipose tissues. It increases HDL-C and lowers TG levels. Its effect on TC reduction is modest.

Ila, B An earlier trial showed mortality benefits with niacin during long term follow up.<sup>83</sup> More contemporary clinical studies, however, have not shown any CV benefits.<sup>76,245</sup>

Ila, C It may be considered as an alternative therapy to fibrates in individuals with elevated TG not responsive to non-pharmacological methods.

### Recommended Dosages:

- Nicotinic acid (Niacin) is available as tablets of 50mg, capsules of 100 mg and 250 mg
- Starting dose: 150-300 mg daily in divided doses, titration of dose up to 2 g/day (usual dose). It should be taken with meals to reduce gastrointestinal side effects.

## 7.2.7 Combination therapy

Ila, B There is sufficient evidence to show that the addition of non-statin therapies to statins is both safe and effective in further lowering LDL-C and improving CV outcomes<sup>66,134,232,238</sup>

Combination therapy is used when LDL-C targets are not achieved despite optimal statin dose or maximally tolerated statin dose.

#### A. Achieving LDL-C Target

The combinations that may be used are:

I, B

- Statin + cholesterol absorption inhibitors (ezetimibe)<sup>66,134,232</sup>

IIa,C

- Statin + bile acid exchange resins<sup>243</sup>

IIa, B

- Statin + PCSK-9 inhibitors<sup>135,213,214,235–239</sup>

#### B. Low HDL-C, High TG After LDL-C Target is Achieved

I, A

Achieving LDL-C target is the priority.

IIb, B

Occasionally combination therapy may be used if LDL-C target is achieved but HDL-C is low and TG is high.

- There is no data that drug therapy in this subset of individuals will reduce CV events.
- Subgroup analysis suggest a small benefit with the addition of fibrates to statins.<sup>242</sup>

When using a combination of statin and fibrates, the following should be considered:

- Fibrates increase the risk of myopathy with statins, and the risk is highest for gemfibrozil.
- The risk with gemfibrozil is 15 times higher when compared to fenofibrate.<sup>246,247</sup>
- The combination of statins and gemfibrozil is discouraged.
- The risk of myopathy when combining statins with fenofibrate seems to be small.<sup>248</sup>
- Fibrates should preferably be taken in the morning and statins in the evening to minimize peak dose concentrations and decrease the risk of myopathy.
- No increased risk has been seen with a statin and a nicotinic acid combination.<sup>245</sup>

## 7.3 Pharmacoeconomics of Lipid Lowering Therapy

Therapeutic lifestyle changes (TLC) are the most cost-effective options available for primary CVD prevention.

Cost effective analysis of major lipid lowering trials have shown that although direct short term cost may be higher, the incremental cost effectiveness ratio (derived from the ratio of cost over quality adjusted life years) is favourable for generic and even for patented lipid modifying agents.<sup>249</sup>

In a Malaysian study, both atorvastatin and simvastatin scored consistently high total utility score even before drug cost were included.<sup>250</sup>

The economic implication of treating dyslipidaemia should not be judged only by the direct out of pocket cost. Dyslipidaemia leads to major CV events which have economic implications. The incidence of CVD and CKD in the country is on the rise and so is the cost associated with it. As such the economic implication of treating dyslipidaemia must be looked at from the perspective of total cost (direct and intangible cost) instead of just direct out of pocket cost.

A substantial proportion of statin acquisition cost was offset by reduction in health care resource use as a consequent of lesser CV events. Even taking into consideration the cost of patented statin, statin use is cost effective even in primary prevention of medium risk individuals.<sup>251</sup>

There are generics available for almost all lipid modifying agents. It is important that these generic lipid modifying agents undergo bioequivalence studies with periodic quality control.

### 7.3.1 LDL-C Apheresis

Ila, B LDL-C apheresis is indicated in patients with homozygous FH who do not respond satisfactorily to maximum multiple drug therapy.<sup>252–255</sup>

Ilb, C This form of treatment may also be considered in individuals with severe heterozygous FH and progressive coronary artery disease (CAD) who do not achieve target lipid levels with maximal drug therapy (high intensity statin at maximal dose with ezetimibe/PCSK9).

In some patients with very high LDL-C levels, despite aggressive treatment with medications plus LDL-C apheresis, progression of atherosclerosis may occur but at a lesser extent.

**Key messages:**

- Statins are the drug of choice for reducing LDL-C in a wide range of individuals with dyslipidaemia.
- Some individuals may require combination therapy to achieve LDL-C goals.

**Recommendations:**

- Individuals should be on lifelong therapy.
- They should be assessed on a regular basis for:
  - Response to therapy and achievement of lipid targets.
    - Lipid profile should be measured at 1 to 3 months following initiation and following a change in the dose of statin therapy. The dose is then adjusted accordingly to achieve LDL-C levels.
  - Adverse effects
    - Hepatic transaminases should be measured at baseline and at 1 to 3 months after starting treatment and/or following a change in dose.
    - CK is measured if myositis is suspected.
    - Should there be an adverse effect, the dose of the drug should be reduced or it should be temporarily discontinued. Following an improvement and normalization of symptoms and/or biochemical parameters, the drug can be reintroduced at a lower dose. If the adverse effect recurs, then the drug should be discontinued and an alternative form of treatment used.

## 8. Primary Prevention

Primary prevention is prevention of the occurrence of CVD in people without CVD. It is directed at healthy individuals without any CV event.

### Strategies of Primary Prevention

The strategy is based on a:

- *Population based strategy*  
This is aimed at educating the public concerning CVD, 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 counselling.

- *Individual based strategy*  
The aim is to identify individuals at risk of developing CVD and modifying their risk factors. Based on the NHMS V, this would include individuals above the age of 30 years. Individuals who are at high risk of developing CVD should have a lipid profile earlier in life (> 18 years of age).

In these individuals, the emphasis should be on TLC. (Table 6, pg 21) The majority will be in the **Low Risk** and **Intermediate (Moderate) Risk** Categories. Refer to the Malaysian Clinical Practice Guidelines on Primary and Secondary Prevention of Cardiovascular Disease, 1<sup>st</sup> Ed, 2017.<sup>139</sup>

#### Key messages:

- Maintaining a healthy lifestyle- a healthy diet, weight control, increased physical activity and the avoidance or cessation of smoking - plays an important role in the prevention of CVD.

#### Recommendation:

- Maintaining a healthy lifestyle should be started early in life.
- All individuals above the age of 30 years should have a full lipid profile.
- Individuals who are at high risk of developing CVD should have a lipid profile earlier in life (> 18 years of age).

## 9. Secondary Prevention

### 9.1 Coronary Heart Disease (CHD)

Patients with CHD may present as stable angina or as acute coronary syndromes (ACS). ACS is a spectrum of disease ranging from unstable angina (UA), non- ST elevation myocardial infarction (NSTEMI) to ST elevation myocardial infarction (STEMI) depending on the acuteness and severity of the coronary occlusion.

#### 9.1.1 Stable CAD

Stable CAD refers to stable angina, asymptomatic MI and coronary atherosclerosis detected by coronary or CT Angiogram.

I, A Statin therapy should always be considered for individuals with stable CAD. (Table 2, pg. 18) Irrespective of the LDL-C level, one should aim for on target treatment LDL-C level of <1.8 mmol/L or a 50% reduction in baseline LDL-C (whichever is lower). At these levels, clinical studies have showed that progression of atherosclerosis is significantly reduced.<sup>132-135,137,186,187</sup>

I, A Individuals with stable CAD should be treated with optimal medical therapy using a combination of antiplatelet agents, statins,  $\beta$ -blockers and angiotensin converting enzymes inhibitors.<sup>256</sup>

##### 9.1.1.1 Acute Coronary Syndromes (ACS)

I, A Early initiation or continuation of high dose statin therapy soon after admission for ACS is safe and improves outcome regardless of baseline LDL-C levels.<sup>63,257-261</sup>

In our local NCVd-ACS Registry, the mean LDL-C on admission was 3.3 mmol/l in males and 3.1 mmol/l in females.<sup>2</sup> This indicates that in these **Very High Risk** patients, a much lower LDL-C is necessary.

**Lipid management includes:**

I, C Assessment of a lipid profile for patients who had no previous lipid measurements. This should be done within 24 hours of hospitalization since levels will drop after 24 hours of an ACS.



I, A Statins, in the absence of contraindications, should be initiated soon after admission and continued indefinitely to provide lifelong benefits.<sup>108,109</sup> Statin treatment should not be delayed until lipid levels are available or management of other modifiable risk factors.

Lipids should be re-tested about 1 to 3 months after ACS.

I, A LDL-C level should be targeted <1.8 mmol/L or a reduction of at least 50%.<sup>132-135,137,186,187</sup>

## 9.1.1.2 Post PCI

IIa, B Pre-treatment with statins 7 days prior to elective PCI has been shown to reduce post-procedure MI.<sup>262</sup>

IIa, B A loading dose of high intensity statins (atorvastatin, rosuvastatin) pre-procedure has also been shown to reduce post-procedure MI in individuals who are statin-naïve and those already on regular statins.<sup>263-267</sup>

I, A All cardiac patients post-revascularization (coronary artery bypass grafting (CABG), PCI) should be on long term statin therapy, the dose being adjusted to achieve a target lipid levels of < 1.8 mmol/L.<sup>132-135,186,187</sup> (Table 4, pg. 20)

### Recommendations:

- All patients with CHD should receive high intensity statins as an integral component of optimal medical therapy.
- High intensity statin therapy should be started (irrespective of their baseline cholesterol levels):
  - on admission in all individuals with ACS
  - prior to PCI and CABG and continued indefinitely

### 9.1.2 Stroke

Studies have shown an association between raised serum lipids and risk of ischaemic stroke.<sup>268,269</sup>

I, B Statins have been shown to prevent ischaemic stroke in high risk individuals.<sup>270,271</sup>

I, B Individuals with ischaemic stroke or transient ischaemic attacks benefit from lipid modifying therapy.<sup>270–272</sup>

High intensity statins have been found to prevent recurrent non cardioembolic ischaemic stroke.<sup>271</sup>

**Recommendations:**

- Lipid lowering therapy with statins should be considered in all individuals with previous non cardioembolic ischaemic stroke or transient ischaemic attack.

## 10. Management of Dyslipidaemia in Specific Conditions

### 10.1 Asymptomatic Atherosclerotic Disease

Asymptomatic atherosclerotic disease includes:

- Positive stress test at low to moderate work load ( $\leq 6$  METS)
- Significant plaques ( $> 50\%$  narrowing) seen during CT coronary angiography
- Calcium score:  $\geq 400$  Agatston units
- Ankle Brachial Index:  $< 0.9$  or  $> 1.40$
- Significant plaques on carotid ultrasonography (CIMT excluded)

The goal of management in this group of patients is the prevention of CV events. All risk factors should be treated to target.

I, A

High dose statin therapy should be initiated to achieved an LDL-C level of  $< 1.8$  mmol/L or at least 50% reduction from baseline.<sup>132–134,137,186,187</sup>

#### Recommendation:

- Patients with asymptomatic atherosclerotic disease should be on high intensity statins to achieve an LDL-C level of  $< 1.8$  mmol/L or at least 50% reduction from baseline.

### 10.2 Hypertension

The use of lipid lowering drugs (particularly statins) is well established in patients with high CV risk with or without hypertension.<sup>61,108–111</sup>

For primary prevention in hypertensive patients, the results have been mixed.

- In the ALLHAT study high dose pravastatin failed to show any mortality and CV benefits in high risk hypertensive with mildly elevated blood pressure even after long term follow up.<sup>273</sup> The level of lipid lowering achieved was however very modest.
- In the ASCOT study low dose atorvastatin in medium risk hypertensive patients with moderately elevated BP showed significant reduction in CV events.<sup>61</sup> However in this study, there was no mortality benefits.<sup>61</sup> On long term follow up however, there was a reduction in all-cause mortality, suggesting a legacy effect.<sup>274</sup>
- A meta regression analysis showed that statin therapy effectively decreased CV morbidity and mortality to the same extent in hypertensive and non-hypertensive patients.<sup>275</sup>

**Recommendations:**

- Initiate statin therapy for primary prevention in patients with concurrent hypertension and elevated cholesterols.
- The target LDL-C level would depend upon the individual's CV risk (see Table 4 and 5, pg. 20)

**10.3 Diabetes Mellitus**

Patients with diabetes and impaired glucose tolerance (IGT) are at high risk of CVD.<sup>276,277</sup> These patients have higher mortality and a higher incidence of recurrent CV events.<sup>278</sup> This is especially in individuals with diabetes of more than 10 years duration.<sup>279,280</sup>

Dyslipidaemia is common in diabetes. In the National Diabetes Registry Report (NDR 2009 – 2012), only 28.5% of patients with diabetes in 2012 treated at public primary care clinics achieved TC < 4.5 mmol/L.<sup>281</sup> About 62.3% of diabetic patients treated at primary care clinics were receiving statins.<sup>281</sup>

Dyslipidaemia is one of the key risk factors contributing to CVD in patients with diabetes.

Lipid abnormalities differ in type 1 diabetes (T1DM) and T2DM.

- In T1DM, high TG is common. HDL-C levels are often normal and even high unless glycaemic control is poor or nephropathy is present.
- In T2DM high plasma TG concentration, reduced HDL-C and increased levels of small dense LDL particles is the usual pattern.

I, A

Statin therapy has been proven to reduce CV events in patients > 40 years with T2DM irrespective of the baseline LDL-C.<sup>59,60,70,108</sup>

IIa, B

Among individuals with T1DM without a history of CVD, registry data showed that statins are associated with a 22 - 44% reduction in risk of CVD and CV death.<sup>282</sup>

## Screening

In adult patients with diabetes, a lipid profile should be measured at least annually and more often if needed to achieve goals.<sup>283</sup>

In adults with low-risk lipid values (LDL-C <2.6 mmol/L, HDL-C >1.0 mmol/L in males and >1.3 mmol/L in females and TG <1.7 mmol/L), lipid assessments may be repeated every year.<sup>283</sup>

In adolescents with T2DM, screening for lipid disorders should be done at diagnosis after glycaemic control is achieved. If normal lipid values are obtained, screening should be repeated every 2 years.<sup>283,284</sup>

## Lipid Targets in Diabetes

I, A The primary target of therapy is LDL-C<sup>59,60,70,108</sup> (see Table 5, pg. 20).

I, A All persons with diabetes above the age of 40 should be on a statin.<sup>59,60,70,108</sup>

I, A All persons with diabetes and CVD should be on a high intensity statin from the time of the CV event.<sup>59,60,70,108</sup>

In patients who have achieved LDL-C targets, the following are secondary targets of therapy:<sup>262</sup>

- Non-HDL-C < 3.4 mmol/L (when TG > 4.5 mmol/L)
- HDL-C > 1.0 mmol/L for males, > 1.2 mmol/L for females
- TG < 1.7 mmol/L

### Recommendations:

- All patients with diabetes > 40 years should be treated with a statin regardless of baseline LDL-C levels
- The target LDL-C levels will depend upon their CV risk (Table 4 & 5, pg. 20)

## 10.4 Heart Failure

Heart failure (HF) is associated with a higher risk of CV death and recurrent hospital admissions.

In patients with CHD, cholesterol lowering with statin reduces the incidence of HF.<sup>243,285–287</sup>

Patients with chronic HF however usually have a low TC which is usually associated with a poorer prognosis.<sup>285</sup>

Most statin trials have excluded patients with HF.<sup>288</sup> Rosuvastatin showed a reduction in the rate of CV hospitalisation in patients with HF of ischemic aetiology.<sup>289</sup>

Ila, B All patients with HF due to CHD should be on statins.<sup>243,285–287</sup>

Ilb, B Routine use of cholesterol-lowering therapy with statins is not recommended in non-ischemic HF.<sup>289</sup>

**Recommendations:**

- All patients with HF due to CHD should be on statins
- Routine use of cholesterol-lowering therapy is not recommended in non-ischemic HF

## 10.5 Renal Disease

Individuals with chronic kidney disease (CKD) are at high risk for CV morbidity and mortality.<sup>101,104,290,291</sup> CVD is the most common cause of death in these patients. They should be screened for the traditional CV risk factors and treated appropriately.

Dyslipidaemia can occur in all stages of CKD, on dialysis, after renal transplantation and in nephrotic syndrome.

The main lipid abnormality in CKD is elevated TG and low HDL-C. TC is usually normal or low.<sup>292,293</sup>

In nephrotic syndrome, both TC and LDL-C are elevated. The lipid abnormalities may improve or resolve when the renal problem is successfully treated. If dyslipidaemia persists, drug therapy should be considered.

Caution must be exercised when starting lipid lowering therapy in patients with CKD.<sup>294,295</sup> The initiating dose of statin or fibrates should be lower. (Table 14, pg. 69)

**Table 14: Dosing modifications for lipid-lowering drugs in CKD**

Agent	GFR <60 ml/min/1.73m <sup>2</sup>
Atorvastatin	20
Fluvastatin	80
Lovastatin	Not studied
Pravastatin	40
Rosuvastatin	10
Simvastatin	40
Simvastatin/Ezetimibe	20/10

*From: KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. Kidney International Supplements 2013; volume 3 | issue 3<sup>296</sup>*

Statins significantly reduced the risk of all-cause mortality, CV mortality and non-fatal CV events in primary and secondary prevention.<sup>297,298</sup>

Ezetimibe/Simvastatin also showed significant reduction (17%) of major atherosclerotic events in patients with CKD Stage 3-5.<sup>232</sup>

End stage kidney disease patients on dialysis have not had similar benefits of lipid lowering therapy.<sup>299,300</sup>

**IIa, C** In patients with established CVD already on statins or an ezetimibe/statin combination at the time of initiation of dialysis, these drugs should be continued.

**III, B** Statin should not be commenced for primary prevention of CVD in patients on dialysis.<sup>299,300</sup>

Lipid modifying therapy has not been shown to retard the progression of CKD or reduce proteinuria.<sup>301,302</sup>

**Recommendations:**

- Lipid lowering therapy with statins or ezetimibe/simvastatin combination should be initiated in CKD patients for primary and secondary prevention of CVD.
- The target LDL-C levels will depend upon their CV risk (Table 4 & 5, pg. 20)
- Statins should not be commenced for primary prevention of CVD in patients on dialysis.
- In patients with established CVD already on statins or an ezetimibe/statin combination at the time of initiation of dialysis, these drugs should be continued.

## 10.6 Specific Lipid Disorders

### 10.6.1 Elevated TG

Hypertriglyceridemia has a modest association as a CVD risk factor<sup>14,77–80</sup>, but the association is far weaker than for hypercholesterolaemia.<sup>77</sup> Unfortunately, despite this correlation, there have been no randomized interventional trials with sufficient evidence to recommend specific targets for TG.

Data favour the role of TG-rich lipoproteins as the risk factor for CVD.<sup>303</sup> Data from large prospective studies have found that non-fasting TG predict CHD risk and mortality, more strongly than fasting TG<sup>77–80,304,305</sup>, indicative of insulin resistance and atherogenic remnant lipoproteins.

Associations were strongest with postprandial TG taken 2 to 4 h after the meal.

Unfortunately, the lack of standardization and reference ranges impedes the general implementation of nonfasting TG as target for control.<sup>306</sup>

At present, fasting TG > 1.7 mmol/L continue to be considered a marker of increased risk, but concentrations ≤ 1.7 mmol/L are not evidence-based target levels for therapy.

#### 10.6.1.1 Targets of Therapy

I, A In individuals with elevated TG, the primary target of therapy remains achieving LDL-C goal depending upon the individual's global risk.<sup>108–111</sup>

When TG levels are > 1.5 mmol/L, reported LDL-C levels do not reliably indicate LDL particle number.<sup>307</sup>

Individuals with a TG > 4.5 mmol/L should have a repeat lipid panel tested in the fasting state.

IIa, B 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.<sup>242,308</sup> (Table 6, pg. 21).



I, A In individuals where the TG > 4.5 mmol/L, non-HDL-C is the primary target of therapy.<sup>12</sup> (Table 6, pg 21).

## 10.6.1.2 Management of Elevated TG

I, A In individuals with mixed hyperlipidaemia, the primary target of therapy is to achieve LDL-C goal.<sup>108–111</sup>

In those individuals with:

IIa, B • TG between 2.3 and 4.5 mmol/L the secondary target of therapy is non-HDL-C<sup>242,308</sup>

I, A • TG > 4.5mmol/L, the primary target of therapy is non-HDL-C.<sup>12</sup>

### a) Mild-to-moderate Elevations in TG (>1.7–<10.0 mmol/L)

Treatment should include:

I, B • Lifestyle changes of weight reduction, low carbohydrate diet, control of diabetes or insulin resistance, exercise, reduction of alcohol intake and cessation of smoking.<sup>309–316</sup>

I, B • Ensure diabetes, if present is controlled.  
• Drug therapy should be considered in high risk individuals. There are two options to achieve targets:

I, A ➤ Intensifying statin therapy, especially if LDL-C target is not achieved.<sup>317</sup> Statins have significant effects on mortality as well as most CVD outcome parameters, these drugs are the first choice to reduce both total CVD risk and moderately elevated TG levels. More potent statins (atorvastatin, rosuvastatin, and pitavastatin) demonstrate a robust lowering of TG levels, especially at high doses.

IIb, B ➤ Adding fibrates as a combination therapy to statin.<sup>242,318,319</sup>

IIb, B ➤ Caution should be exercised when gemfibrozil is used in combination with statins because of the significant risk of rhabdomyolysis.<sup>246,247</sup>

There are no outcome data that show a reduction in CVD events with the use of drug therapy to reduce TG.<sup>76,82,245</sup>

**b) Severe Elevations in TG (> 10mmol/L)**

In asymptomatic individuals:

- repeat fasting TG measurement (after an interval of 5 days, but within 2 weeks) and
- review for potential secondary causes of hyperlipidaemia and seek specialist advice if the TG concentration remains above 10 mmol/L.<sup>20</sup>

In these individuals:

- The drug of choice is statins.

Ila, B

- Fish oil which contain long chain omega-3 polyunsaturated fatty acids can also lower TG. Doses of 3 to 4 gm per day can lower TG by 20-50%.<sup>316</sup>
- Very low carbohydrate and low fat diets ( $\leq 15\%$  of calorie intake) and lifestyle changes (See Section 7.1).<sup>309,316,320</sup>

In patients who have suspected pancreatitis, treatment includes:

- Fibrate or nicotinic acid

I, B

- Gemfibrozil and Fenofibrate lower TG by about 20-35%.<sup>195</sup>

I, B

- Nicotinic acid at doses of above 1.5 gm per day can reduce TG by 40%.<sup>321</sup>

I, B

- Severe hypertriglyceridemia associated with uncontrolled diabetes warrants initiation of intravenous (IV) insulin infusion. IV insulin stimulates intravascular lipoprotein lipase that helps to clear TG at a faster rate. The TG level will improve within 2-5 days, but may not normalize.

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

Low HDL-C and high TG are seen in insulin resistance states (e.g. T2DM, abdominal obesity), physical inactivity and high carbohydrate intakes. This lipid pattern is associated with small dense atherogenic LDL-particles. HDL-C < 1.0 mmol/L (men) and < 1.3 mmol/L (women) is considered a marker of increased CV risk.<sup>283</sup>

Treatment of this dyslipidaemia in individuals with high/very high CV risk is aimed at lowering LDL-C to target.<sup>322</sup>

Pharmacological manipulation of HDL-C has not improved CV outcomes. At present, there is inadequate data to recommend the use of additional lipid-modifying therapies beyond statins.<sup>76</sup>

**IIb, B** Results of a meta-analysis suggest a nominal benefit in the subgroup of patients with high TG/low HDL-C levels at baseline (heterogeneous populations from 5 trials).<sup>323</sup>

### 10.6.3 Low HDL-C

Recent studies have cast doubt on the causal role of HDL-C in CVD.<sup>324</sup>

**IIa, B** Modifying lifestyle with increased physical activity<sup>314,325</sup> and dietary modification (reduction in simple carbohydrate, sucrose/fructose consumption), weight reduction, smoking cessation<sup>326</sup>, rather than drug treatment, is recommended for increasing HDL levels.

#### **Recommendation:**

- In patients with high TG and/or low HDL-C, the primary goal of treatment is lowering LDL-C to target. (Table 2 pg. 18)

### 10.7 HIV

With the advent of good and effective therapy for Human Immuno-deficiency Virus (HIV), CVD has become an important cause of morbidity and mortality in these patients.<sup>327</sup> This may be due to:

- HIV infection itself which may produce a cardiometabolic type of syndrome,
- metabolic changes associated with anti-retroviral therapy (ART)
- Associated CV risk factors such as smoking and recreational drug use (e.g. cocaine)<sup>327–330</sup>

**I, A** When treating dyslipidaemia in patients with HIV, the following are important:

- LDL-C remains the primary target of therapy.<sup>331</sup> (Table 4, pg. 20)

**I, B**

- Suggested statin therapy:
  - Pravastatin has a good safety profile, has limited interaction with ART and is currently the longest used statin in these patients.<sup>331</sup>

- I, B
  - Rosuvastatin is recommended if a greater reduction in LDL-C levels is needed.<sup>332,333</sup>
- III, B
  - Lovastatin is contraindicated in patients on a protease inhibitor (PI)<sup>334</sup>.
- I, B
  - Atorvastatin can be used, but a lower dose (10-20 mg) is recommended especially in the presence of ART in combination with a booster in the form of cobisistat. This increases the effect of the atorvastatin. In other circumstance, a higher dosing is safe.
- IIa, B
  - If the patient is statin intolerant or LDL-C target has not been achieved despite maximally tolerated dose, ezetimibe can be considered.<sup>335</sup>
  - Monitoring for side effects is vital. Liver function test has to be done regularly. Symptoms of muscle soreness or myopathy, neurologic complications, blood sugar and diabetes should be routinely evaluated.
  - Hepatitis C co-infection is common in HIV patients, and care must be taken regarding the interactions between statins and Hepatitis C medication.

TG may be very high in these patients as a consequence of therapy.  
Suggested drug therapy:

- IIa, B
  - Fenofibrates are preferred because there is no significant interaction with ART
- IIa, B
  - Gemfibrozil may have a lower efficacy due to interaction with PI.
- IIa, B
  - Fish oils at a high dose of 4 g per day.<sup>336</sup>

**Recommendations:**

- In patients with HIV, LDL-C is the primary goal of treatment. (Table 4 pg. 20)
- Drug interactions with ART is common and monitoring for adverse effects is important.

## 11. Management in Specific Groups

### 11.1 Women

Women develop heart disease about 10 to 15 years later than men.<sup>337–339</sup> There are no gender differences in the risk factors that predispose to CVD although women with T2DM are at higher risk of CVD than men.<sup>340–343</sup> In premenopausal women, CVD tends to occur in those with T2DM and multiple CV risk factors.

In secondary prevention, women have similar benefits on CV outcomes as men.<sup>60,64,108,109</sup>

I, A Statins should be the drug of first choice.<sup>60,64,108,109</sup>

III, C Statins should not be used in women who are pregnant, intend to become pregnant or who are breastfeeding. However bile acid sequestrants may be considered.

I, B In primary prevention, the cornerstone of management is lifestyle modification with advice on a healthy diet and physical activity.

I, A Women at high risk who do not achieve their target LDL-C levels should be treated with statins for primary prevention.<sup>110,111,231</sup> Benefits are similar in both gender.

### 11.2 Children and Adolescents

Cholesterol levels, including LDL-C and non HDL-C are low at birth, increase in the first two years, peak prior to adolescence and reduce during adolescence (age <18).<sup>344</sup>

Risk factors for atherosclerosis in this age group include:

- Genetic dyslipidaemia such as familial hypercholesterolemia.<sup>345</sup>
- Overweight or obese
- Kawasaki's disease
- Nephrotic syndrome
- CKD
- Type 1 and 2 diabetes mellitus
- Chronic inflammatory diseases such as systemic lupus erythematosus (SLE)

- HIV
- Cigarette smoking

These high risk patients should have a full lipid profile.

The main approach is a healthy lifestyle with appropriate diet, maintenance of “desirable weight” and regular exercise.

Children whose lipid levels are significantly elevated may have a genetic dyslipidaemia and should be referred to specialists interested in this field.

Ia, B In patients with FH, statins are the drug of choice. All statins can be used as an adjunct to diet, in children >10 years of age.<sup>346,347</sup> Pravastatin can be used in > 8 years of age.<sup>346,347</sup>

When prescribing drugs in children, the need for life long therapy and its associated health risks and drug exposure during unplanned pregnancy in individuals of child bearing age need to be considered. Patients should be extensively counselled prior to initiation of drug therapy.

There has been increasing risk for T2DM in adolescents. Thus, the risk of new onset diabetes should also be considered when prescribing statins in children with risk factors for diabetes.<sup>348</sup>

### 11.3 Elderly

Increasing age is a major risk factor for CVD and death.

I, A For secondary prevention, the elderly derive a greater absolute benefit from lipid lowering therapy.<sup>108,109,349</sup> Thus, they should not be deprived from lipid lowering therapy solely on the basis of their age although there is limited clinical trial data in patients over the age of 80 years.

Ia, B In primary prevention, a meta-analysis of subjects > 65 years of age<sup>350</sup> showed that statin treatment reduced MI and stroke. Statin therapy should be considered in older adults free from CVD, particularly in the presence of hypertension, smoking, diabetes and dyslipidaemia.<sup>108,109,351</sup>

Ila, C

Since older people have co-morbidities and have altered pharmacokinetics, lipid lowering medication should be started at a lower dose and then titrated with caution to achieve target lipid levels.

Few areas in CVD prevention are more controversial than the mass use of statins in the elderly. There is no evidence of decreasing effectiveness of statins in patients >75 years of age.<sup>285</sup>

Evidence supporting effectiveness in individuals >80 years of age is very limited. A recent trial suggested no harm of stopping statins in the elderly with a limited life expectancy.<sup>352</sup> Taken together, the recommendations of cholesterol-lowering treatment in the elderly should be followed with caution and common sense, adverse effects should be monitored closely and treatment should be reconsidered periodically.

### **Recommendations:**

- The goals of lipid lowering therapy is similar in both gender and in the elderly. Target LDL-C levels will depend on the global CV risk (Table 2, pg 18)
- When prescribing lipid lowering therapy in the elderly, the presence of co-morbidities and altered pharmacokinetics should be considered. Lipid lowering medication should be started at a lower dose and then titrated with caution to achieve target lipid levels.
- Children whose lipid levels are significantly elevated may have a genetic dyslipidaemia and should be referred to specialists interested in this field.

## 12. Adherence to Lifestyle Changes and Medications

It has been well documented that there is a lack of adherence to CV preventive therapy. A number of scientific studies have shown that adherence among patients with chronic disease is only about 50%.<sup>353</sup>

Lack of adherence threatens the success of the guideline recommendation and implementation. The amount of risk reduction achieved is related to the level of adherence to treatment. Compared with poor adherence, good adherence was associated with lower mortality.<sup>354</sup> 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 CV events that could have been prevented.<sup>353</sup>

The reasons for the high discontinuation rate and missed doses are complex and multifactorial and may include both intentional and unintentional non-adherence.<sup>355–358</sup> These include:

- cost of medication
- affordability
- unclear label instructions
- patient forgetfulness
- adverse effects from medication that patient is too embarrassed to discuss with doctor
- patient does not like the idea of having to take medication
- patient does not understand the importance of a given medication for a condition for which he or she has no symptoms
- patient-practitioner relationship is suboptimal
- polypharmacy and complexity of regimen

To improve adherence and compliance the following are recommended:<sup>357,358</sup>

- **Patient factors**
  - Simplify medication 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
  - Remind patients that lipid lowering drugs are not a substitute for dietary and lifestyle interventions



# Management of Dyslipidaemia 2017

- **Physician 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, dieticians and other health care deliverers in patient education
  - Refer patients to medication therapy adherence clinic (MTAC)
  - 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

### 13. Performance Measures

In accordance with the National Strategic Plan on Non-Communicable Disease, performance indicators should be put in place. This CPG recommends the following audit parameters:

Primary Prevention - At Klinik Kesihatan (for follow up patients only)

- Was a CV risk stratification performed?
  - Numerator: number of adult > 30 years who were risk stratified
  - Denominator: number of adult > 30 years seen at that clinic session
- Was a lipid profile measured?
  - Numerator: number of adult > 30 years whose lipid profile was measured
  - Denominator: number of adult > 30 years seen at that clinic session
- Was the LDL-C target of the individual noted?
  - Numerator: number of adult > 30 years with the LDL-C target stated in the clinical notes
  - Denominator: number of adult > 30 years seen at that clinic session
- Did the individual attain the LDL-C target?
  - Numerator: number of adult > 30 years who achieved the LDL-C target
  - Denominator: number of adult > 30 years seen at that clinic session who had a lipid target stated < 6 months prior to current visit

Secondary Prevention - At follow up in cardiac clinic/general medical clinic (within 3 months of discharge after an admission for ACS/Stable CHD)

- Is the patient on a statin?
  - Numerator: number of patients who were discharged on statins
  - Denominator: number of patients seen at that clinic session who had ACS/Stable CHD
- Did the individual attain the LDL-C target?
  - Numerator: number of patients who achieved the LDL-C target
  - Denominator: number of patients seen at that clinic session who had ACS/Stable CHD

An initial audit should be performed to determine baseline performance indicators. Suggest an initial target of 60% with an incremental improvement in performance indicators when reassessed at yearly intervals.

Reasons for non-achievement of the above targets should also be determined. Following this corrective measures should be taken.

## 14. FAQs on Lipids

What is the role of non-statin therapy in dyslipidaemia	Evidence	Grade
<b>Cholesterol and heart disease</b>	<p>Is cholesterol an important cause of heart disease?</p> <ul style="list-style-type: none"> <li>The role of serum cholesterol in the pathogenesis of atherosclerosis and CVD is unequivocal and irrefutable.</li> <li>The question is whether eating food high in cholesterol leads to high serum cholesterol and LDL-C, and whether limiting dietary cholesterol intake lowers serum LDL-C.</li> <li>Recent data indicate that the impact of dietary cholesterol on serum cholesterol levels is weak.</li> </ul>	
<b>Statins safety</b>	Statins are safe. Its side effects are uncommon, self-limiting, are reversible, and have no long term sequelae	<b>I, A</b>
<b>Fish oil supplements</b>	<ul style="list-style-type: none"> <li>It may be useful in the treatment of elevated triglycerides.</li> <li>Fish oils is not a replacement for statins in the treatment of elevated LDL-C.</li> </ul>	<b>Ila, B III, A</b>
<b>Co-enzyme Q10</b>	No definitive evidence to support the use of Co-enzyme Q10 on the reduction of cholesterol level and primary prevention of CVD. <sup>359,360</sup>	<b>III, A</b>
<b>Complementary and alternative therapies:</b>		
<b>Estrogen and progestins</b>	Hormone replacement is not indicated for primary or secondary prevention of CVD	<b>III, A</b>
<b>Red yeast rice</b>	<ul style="list-style-type: none"> <li>Red yeast rice contains substances that are structurally identical to statins.</li> <li>Unlike statins, there is no data on its safety in long term use.</li> </ul>	<b>IIb, C</b>
<b>Garlic</b>	Natural Medicine Comprehensive Database recently downgraded garlic to a rating of "Possibly ineffective". Garlic can also cause drug interactions and increased risk of bleeding. <sup>361,362</sup>	<b>IIb, B</b>
<b>Apple cider vinegar</b>	There is no evidence at present for CV protection	<b>III, C</b>
<b>Virgin coconut oil, or coconut oil</b>	<ul style="list-style-type: none"> <li>Not supported by robust scientific evidence when taken on its own.</li> <li>It worsens the lipid profile.</li> <li>The saturated fatty acids in coconut oil increase total-C, LDL-C, and HDL-C.<sup>363</sup></li> <li>One tablespoon of coconut oil contains 12 g of saturated fat and 1 tablespoon of virgin coconut oil contains 13 g of saturated fat.<sup>364</sup></li> <li>Either would, therefore, contribute a significant portion of the recommended total daily saturated fat limit of &lt;10% of energy</li> <li>If coconut oil is used as part of a daily eating plan and/or in food preparation, it is recommended that it be used within the context of a healthy dietary pattern</li> </ul>	<b>III, B IIb, B</b>

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## APPENDIX

Appendix 1: Comparison of Global Coronary and Cardiovascular Risk

	Framingham	SCORE	PROCAM (Men)	Reynolds (Women)	Reynolds (Men)
Sample size	5,345	205,178	5,389	24,558	10,724
Age (y)	30 to 74; Mean: 49	19 to 80; Mean : 46	35 to 65; Mean: 47	> 45; Mean: 52	> 50; Mean: 63
Mean follow-up, y	12	13	10	10.2	10.8
Risk factors considered	Age, sex, total cholesterol, HDL cholesterol, smoking, systolic blood pressure, antihypertensive medications	Age, sex, total-HDL cholesterol ratio, smoking, systolic blood pressure	Age, LDL cholesterol, HDL cholesterol, smoking, systolic blood pressure, family history, diabetes, triglycerides	Age, HbA1C (with diabetes), smoking, systolic blood pressure, total cholesterol, HDL cholesterol, hsCRP, parental history of MI at < 60 y of age	Age, systolic blood pressure, total cholesterol, HDL cholesterol, smoking, hsCRP, parental history of MI at < 60 y of age
Endpoints	CHD (MI and CHD death)	Fatal CHD	Fatal/nonfatal MI or sudden cardiac death (CHD and CVD combined)	MI, ischemic stroke, coronary revascularization, cardiovascular death (CHD and CVD combined)	MI, stroke, coronary revascularization, cardiovascular death (CHD and CVD combined)
URLs for risk calculators	<a href="http://hp2010.nhlbihin.net/atp/iii/calculator.asp?usertype=prof">http://hp2010.nhlbihin.net/atp/iii/calculator.asp?usertype=prof</a>	<a href="http://www.heartscore.org/pages/welcome.aspx">http://www.heartscore.org/pages/welcome.aspx</a>	<a href="http://www.chdtaskforce.com/coronary_risk_assessment.html">http://www.chdtaskforce.com/coronary_risk_assessment.html</a>	<a href="http://www.reynoldsriskscore.org/">http://www.reynoldsriskscore.org/</a>	<a href="http://www.reynoldsriskscore.org/">http://www.reynoldsriskscore.org/</a>



## Appendix 2: Fatty acid composition of selected dietary fats and oils,<sup>365-370</sup>

Type of fats and oils	SFA	MUFA	PUFA	P/S ratio
Coconut oil	91.9	6.5	1.5	0.02
Palm kernel oil	84.2	13.7	2	0.02
Cocoa butter	60.4	35.6	2.9	0.05
Beef fat	50.6	42.1	2.8	0.06
Shea butter	46	48	5.1	0.11
Palm oil	44.9	43.4	10.8	0.24
Palm olein	42.4	44	11.8	0.28
Lard	38.7	48.2	11	0.28
Olive oil	18.8	68.2	14.6	0.78
Groundnut oil	9.6	71.2	18.2	1.89
Corn oil	14.2	27.8	57.1	4.02
Soybean oil	14.8	24.1	59.9	4.05
Canola oil	7.4	56	35.6	4.81
Sunflower oil	9.1	28.1	62.4	6.85
Safflower oil	9.2	11.6	79.2	8.6

Notes: values represent %/100 g edible fat

## Appendix 3: List of commonly eaten food and their Fatty acid content

Food categories	Total fat (g/100 g) <sup>a</sup>	TFA (g kg <sup>-1</sup> ) <sup>a</sup>	TFA g serving size <sup>b</sup>	Total fatty acid composition (%) <sup>a</sup>				Labelling adherence
				TFA	SFA	MUFA	PUFA	
<i>Confectionary</i>								
Cooking chocolate (n = 3)	33.1 (2.3–41.1)	0.5 (0.04–1.34)	0.3 (0–0.7)	1.27 (0.17–3.26)	80.7 (59.8–92.6)	15.64 (3.6–35.3)	2.0 (0.5–4.0)	None
Chocolate wafer (n = 22)	27.3 (7.0–44.3)	0.23 (0–783)	0.26 (0–2.74)	2.72 (0–28.2)	62.3 (28.7–97.6)	27.9 (0–59.4)	6.4 (0.48–17.6)	8
Chocolate candy (n = 3)	20.1 (17.0–23.0)	0.01 (0–0.01)	0	0.03 (0–0.06)	54.2 (40.0–62.2)	35.1 (32.8–39.1)	8.08 (2.9–17.6)	None
<i>Fats, oils, spreads, dressing</i>								
Ghee (n = 6)	99.8 (99.8–99.8)	1.04 (0.20–1.92)	0.16 (0.03–0.29)	1.04 (0.20–1.93)	61.5 (60.9–62.6)	29.7 (29.1–30.9)	3.3 (1.2–6.8)	None
Shortening (n = 2)	99.8 (99.5–100)	0.20 (0.19–0.21)	0.20 (0.19–0.21)	0.20 (0.19–0.21)	57.0 (52.2–61.8)	33.6 (30.2–37.0)	8.8 (7.3–10.2)	None
Butter (n = 8)	80.6 (79.0–81.5)	0.99 (0.07–3.23)	0.15 (0.01–0.49)	1.32 (0.11–3.85)	57.8 (36.4–66.9)	31.7 (25.5–44.8)	5.9 (1.9–16.1)	2
Margarine (n = 6)	77.0 (70.0–82.0)	0.27 (0.04–0.38)	0.04 (0.01–0.05)	0.36 (0.05–0.54)	46.5 (20.9–61.0)	36.3 (29.1–36.3)	16.8 (8.3–28.8)	Only one
Salad dressing (n = 6)	45.0 (21.7–72.2)	0.09 (0.02–0.20)	0.03 (0.01–0.06)	0.18 (0.05–0.27)	14.5 (13.6–15.8)	22.7 (21.4–24.0)	61.0 (58.6–62.5)	None
Vanaspati (n = 3)	99.8 (99.8–99.8)	0.43 (0.17–0.88)	0.06 (0.03–0.13)	0.43 (0.18–0.89)	50.6 (46.1–54.0)	37.9 (35.7–40.2)	10.7 (9.7–12.5)	None
Fat spread (n = 12)	73.4 (65.0–82.0)	0.16 (0.01–0.63)	0.02 (0–0.09)	0.22 (0.01–0.89)	36.3 (17.2–61.5)	39.4 (30.3–57.2)	23.2 (7.2–47.3)	Only one
Peanut butter (n = 9)	41.97 (30.0–53.7)	0.22 (0.02–0.67)	0.07 (0.01–0.21)	0.52 (0.04–1.42)	20.33 (12.6–41.0)	48.56 (41.9–52.0)	26.85 (13.9–37.0)	Only 6
<i>Dairy-based products</i>								
Ice cream (n = 6)	11.0 (8.4–18.14)	0.21 (0–0.61)	0.13 (0–0.37)	2.09 (0.03–5.47)	68.3 (49.9–83.0)	23.4 (10.9–38.4)	4.8 (0.27–11.0)	Only one
Cheese (n = 5)	21.5 (13.7–24.7)	0.18 (0.05–0.63)	0.04 (0.01–0.16)	0.78 (0.33–2.57)	59.8 (50.7–65.4)	31.6 (27.1–38.8)	4.6 (1.7–9.4)	2
Children's milk > 3 years (n = 4)	17.8 (13.0–27.2)	0.18 (0.08–0.39)	0.07 (0.03–0.13)	0.93 (0.60–1.42)	44.7 (18.0–58.4)	36.8 (27.4–44.6)	16.4 (1.9–37.6)	None
Children's milk < 1 year (n = 2)	27.4 (26.7–28.1)	0.04 (0.01–0.06)	0.01 (0–0.02)	0.14 (0.04–0.24)	39.6 (37.0–42.2)	40.7 (36.0–45.4)	18.3 (16.1–20.5)	None
Adult milk powder (n = 4)	25.6 (19.9–28.7)	0.44 (0.06–0.82)	0.14 (0.02–0.26)	1.65 (0.28–3.17)	58.9 (51.2–66.4)	30.8 (24.5–35.6)	5.2 (1.3–10.0)	Only one
<i>Snaps</i>								
Soup, concentrates (n = 3)	16.98 (11.0–22.3)	0.37 (0.02–0.59)	0.07 (0–0.11)	1.94 (0.17–3.37)	52.0 (49.3–55.1)	36.28 (35.7–37.1)	9.0 (6.0–11.5)	Only one
Soups, canned (n = 3)	45.8 (40.1–49.0)	0.004 (0.002–0.01)	0.01 (0–0.01)	0.09 (0.03–0.18)	10.7 (10.3–11.3)	54.6 (54.3–55.5)	32.3 (30.9–33.1)	None
<i>Snacks</i>								
Potato chips (n = 13)	32.7 (25.4–36.1)	0.08 (0.01–0.14)	0.02 (0–0.03)	0.24 (0.05–0.50)	38.3 (6.8–45.5)	45.3 (37.4–75.7)	15.1 (11.5–38.0)	None
French fries (n = 4)	2.55 (1.99–3.08)	0.01 (0–0.01)	0.01 (0–0.01)	0.26 (0.09–0.51)	51.3 (47.5–54.5)	36.9 (34.4–38.5)	10.8 (9.3–13.1)	2
Ethnic breads (n = 7)	9.1 (6.15–14.7)	0.06 (0–0.15)	0.04 (0–0.12)	0.64 (0.02–1.45)	52.1 (42.0–60.1)	34.3 (30.1–43.7)	12.2 (9.1–16.2)	None
Frozen dough (n = 13)	5.5 (2.36–12.1)	0.01 (0–0.06)	0 (0–0.02)	0.28 (0.06–1.0)	48.9 (42.2–58.0)	37.8 (28.5–43.0)	12.2 (10.5–13.9)	None
<i>Meat products</i>								
Nuggets (n = 7)	15.04 (12.5–16.8)	0.02 (0.01–0.03)	0.02 (0.01–0.03)	0.18 (0.07–0.36)	43.5 (40.4–46.5)	42.1 (40.6–45.0)	13.1 (9.4–14.0)	None
Burger patties (n = 2)	13.0 (13.0–13.0)	0.01 (0.01–0.01)	0.01 (0.01–0.01)	0.08 (0.06–0.09)	40.9 (39.2–42.5)	43.4 (42.9–43.9)	12.3 (8.0–16.7)	None
Sausages (n = 5)	13.75 (10.0–19.0)	0.01 (0–0.02)	0.01 (0–0.02)	0.15 (0.04–0.36)	31.1 (27.4–39.6)	45.9 (39.1–50.4)	21.3 (16.3–28.0)	None

Notes: TFA, trans fatty acid; MUFA, monounsaturated fatty acid.

<sup>a</sup>Values are mean (minimum to maximum) values for brands within categories.

<sup>b</sup>g/serving size on a fresh weight basis as referred to on the front-of-pack information.

Labelling adherence is determined as a declaration of TFA content as per the risk category defined by the Food Act and/or declaration of partially hydrogenated fat on the ingredient label.

From : Tilakavati Karupaiyah, Hui Kuen Tan, Wei Wen Ong, Choon Heen Tan & Kalyana Sundram (2014). Trans fatty acid content in Malaysian supermarket foods: a field-to-laboratory approach in assessing food risk, Food Additives & Contaminants: Part A<sup>37</sup>

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