Management of Dyslipidemia 2011
STATEMENT OF INTENT

This guideline was developed to be a guide for best clinical practice in the management of dyslipidaemia. It is based on the best available evidence at the time of development. Adherence to this guideline does not necessarily lead to the best clinical outcome in individual patient care. Thus, 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 was issued in 2011 and will be reviewed in 2016 or earlier if important new evidence becomes available.

CPG Secretariat
Health Technology Assessment Unit
Medical Development Division
Level 4, Block EI, Parcel E
Government Offices Complex
62590 Putrajaya, Malaysia

Available on the following websites:

http://www.malaysianheart.org
http://www.moh.gov.my
http://www.acadmed.org.my
SUMMARY

• Total cholesterol (TC) and High Density Cholesterol (HDL-C) can be measured in the fasting and non fasting states. Triglycerides (TG) is best measured in a fasting sample. Low Density Cholesterol (LDL-C) is calculated using the Friedwald’s equation. When TG > 2.3mmol/l, non HDL-C is a better indicator of total atherogenic burden.

• Dyslipidaemias may be primary or secondary.

• Target of therapy:
  • LDL-C should be the primary target of therapy I,A
  • Non HDL-C should be an alternative primary target of therapy in patients with TG > 4.5 mmol/l I,A
  • Individuals should be risk stratified. I,C (See Table 1, pg 3 and Fig 1A & B, 2A & B, pg 30-31)

• Diabetes is a Coronary Heart Disease (CHD) risk equivalent. I,A

• Target lipids levels will depend upon the individual’s global risk.
  – CVD and CHD risk equivalents
    – (High Risk): LDL-C < 2.6 mmol/L with an option of <2.0 mmol/L I,A
    – (Intermediate Risk): LDL-C < 3.4 mmol/L I,A
    – (Low Risk): LDL-C < 4.1 mmol/L IIa,C

• Therapeutic Lifestyle Changes (TLC) should be an integral component of lipid management in all patients. I,B (Table 3, pg 4)

• Individuals with Cardiovascular Disease (CVD) and CHD risk equivalents should be treated aggressively with drug therapy from the outset. I,A (Table 1&2, pg 3; Flowcharts I-IV, pg5-8)
  • Statins are the drug of choice for reducing LDL-C. I,A
  • Fibrates and nicotinic acid may be considered for increasing HDL-C and reducing TG after LDL-C treatment goal has been achieved. IIa, B
  • Some individuals may require combination therapy to achieve lipid target goals.

• Control of glycaemia alone is inadequate in preventing cardiovascular (CV) events. I,A Concomitant treatment of dyslipidaemia, hypertension and other metabolic abnormalities are also important. I,A
Table 1: Major Risk Factors for CVD (other than LDL Cholesterol)

**Positive Risk Factors**
- Male ≥ 45 years of age
- Female ≥ 55 years of age or premature menopause without hormonal replacement therapy
- Hypertension
- Current cigarette smoking
- Family history of myocardial infarction or sudden death prior to age 55 in a male parent or male first degree relative and prior to age 65 in a female parent or other female first degree relative
- HDL-C < 1.0 mmol/L

**Negative Risk Factors**
- HDL > 1.6 mmol/L

Table 2: Recommendations for Drug Therapy for Dyslipidaemia

<table>
<thead>
<tr>
<th>Medications</th>
<th>Grades of recommendation/ Levels of evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>I, A</td>
<td>Reduction of LDL-C. Increase dose till target levels are achieved or till tolerated</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>IIa, B Ila, C</td>
<td>As an addition to statins if target LDL-C is not achieved As monotherapy in statin intolerant individuals</td>
</tr>
<tr>
<td>Fibrates</td>
<td>IIa, B Ila, B</td>
<td>As monotherapy to increase HDL-C and/or lower TG in individuals with mildly raised LDL-C As part of combination therapy with statins to increase HDL-C and lower TG after LDL-C target is achieved or almost achieved</td>
</tr>
<tr>
<td>Nicotinic Acid</td>
<td>IIa, B Ila, B</td>
<td>As monotherapy to increase HDL-C and/or lower TG in individuals with mildly raised LDL-C As part of combination therapy with statins to increase HDL-C and lower TG after LDL-C target is achieved or almost achieved</td>
</tr>
<tr>
<td>Table 3 : Recommendations for Therapeutic Lifestyle Changes</td>
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<tr>
<td>---------------------------------</td>
<td>---------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td><strong>Grade of Recommendation</strong></td>
<td><strong>Level of Evidence</strong></td>
<td><strong>Comments</strong></td>
</tr>
<tr>
<td><strong>Diet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturated Fats and Trans-fatty acids</td>
<td>I, B</td>
<td>&lt; 7% of calorie intake</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>I,B</td>
<td>&lt; 200 mg /day</td>
</tr>
<tr>
<td>Monounsaturated fats</td>
<td>I,B</td>
<td>Up to 10% of calories</td>
</tr>
<tr>
<td>Polyunsaturated fats</td>
<td>I,B</td>
<td>Up to 20% of calories</td>
</tr>
<tr>
<td>Dietary Fiber</td>
<td>I,B</td>
<td>20-30 gm/day</td>
</tr>
<tr>
<td>Plant stanols</td>
<td>IIb, B</td>
<td>2-3 gm /day</td>
</tr>
<tr>
<td>Soy protein</td>
<td>IIb, B</td>
<td>25-50 gm/day</td>
</tr>
<tr>
<td>Omega 3 fatty acids</td>
<td>IIa, B</td>
<td>A dose of 3-9 gm/day to lower TG levels</td>
</tr>
<tr>
<td></td>
<td>IIb,B</td>
<td>A dose of 0.75-1 gm/day as secondary prevention to prevent sudden death</td>
</tr>
<tr>
<td>Total fats</td>
<td>I,B</td>
<td>25-35% of calories</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>I,B</td>
<td>50-60% of calories</td>
</tr>
<tr>
<td>Proteins</td>
<td>I,B</td>
<td>About 15% of calories</td>
</tr>
<tr>
<td>Anti-oxidants</td>
<td>III,A</td>
<td>Avoid</td>
</tr>
<tr>
<td><strong>Weight Reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goal: BMI : 18.5-&lt;23 kg/m2</td>
<td>I,C</td>
<td>Assess BMI and waist circumference at each visit. Encourage a weight reduction of 0.5-1kg/week in the overweight and obese. The initial goal should be to reduce body weight to &lt; 10% of baseline.</td>
</tr>
<tr>
<td>Waist circumference &gt;90 cm in males and &lt; 80 cm in females</td>
<td>I,B</td>
<td></td>
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<tr>
<td><strong>Exercise</strong></td>
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<tr>
<td>Goal: 30-45 min per session, at least 5 times a week</td>
<td>I,B</td>
<td>Encourage aerobic exercises such as brisk walking, jogging, cycling and swimming</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goal: Complete cessation</td>
<td>I,B</td>
<td>Enquire about smoking status at each visit and encourage complete cessation. Avoid exposure to environmental tobacco smoke at work and at home</td>
</tr>
<tr>
<td></td>
<td>I,C</td>
<td></td>
</tr>
</tbody>
</table>
In these high risk individuals the recommended LDL-C goal is < \( 2.6^{1,A} \) mmol/L with an optional goal < 2.0 mmol/L\(^{1,A}\).

TLC – Therapeutic Lifestyle Changes
* Start statins to achieve LDL-C target goal < 2.0 mmol/L\(^{1,A}\)
** Consider LDL-C target goal < 2.0 mmol/L in very high risk individuals eg individuals with ACS, recurrent cardiac events, CHD with T2DM and those with multiple poorly controlled risk factors\(^{1,A}\)
*** Other therapeutic options include increasing the dose of statin, changing to high intensity statin or combination therapy, intensifying diet therapies, weight reduction, exercise or adding drugs to lower TG and / or increase HDL-C.
The LDL-C goal is < 3.4 mmol/L. Drugs can be considered after a trial of TLC if the LDL-C level is ≥ 3.4 mmol/L.

TLC – Therapeutic Lifestyle Changes

The LDL-C goal is < 3.4 mmol/L. Drugs can be considered after a trial of TLC if the LDL-C level is ≥ 3.4 mmol/L.

* In patients at intermediate risk of CVD, the presence of high risk features such as a family history of premature CVD, evidence of subclinical atherosclerosis or high hs-CRP may warrant statin therapy to lower LDL-C target < 2.6 mmol/L.
In these individuals the LDL-C goal is < 3.4 mmol/L. Drug therapy can be considered if LDL-C level is ≥ 4.1 mmol/L after a trial of TLC.

**FLOWCHART III: LOW RISK INDIVIDUALS**

**LIPID MANAGEMENT OF PERSONS WITH MULTIPLE (2+) RISK FACTORS, 10-YEAR RISK < 10 PERCENT**

*(Adapted and modified from ATPIII)*

In these individuals the LDL-C goal is < 3.4 mmol/L. Drug therapy can be considered if LDL-C level is ≥ 4.1 mmol/L after a trial of TLC.

**TLC** – Therapeutic Lifestyle Changes

* Patients at low risk of CVD with at least 2 other risk factors but with evidence of subclinical atherosclerosis, high hs-CRP or positive family history of premature CVD should be considered an LDL-C goal of < 2.6 mmol/L.
FLOWCHART IV: LOW RISK INDIVIDUALS

LIPID MANAGEMENT OF PERSONS WITH 0-1 RISK FACTOR
(Adapted and modified from ATPIII)¹³⁹

In these individuals, the LDL-C goal is < 4.1 mmol/L. Drug therapy can be considered if the LDL-C level is ≥ 4.9 mmol/L after a trial of TLC. If LDL-C is 4.1-4.9 mmol/L, drug therapy is optional depending on clinical judgment.

* Patients at low risk of CVD with 0 to 1 risk factor but with evidence of subclinical atherosclerosis should be considered for a lower LDL-C target < 2.6 mmol/L.
FOREWORD BY THE DIRECTOR-GENERAL OF HEALTH MALAYSIA

The medical profession has long been regarded, aptly, as the “noble” profession, and has consistently made its mission an altruistic one: “to cure sometimes, to relieve often and to comfort always”. Members of the medical profession have been given the societal mandate and trust, as experts in their field, to “do things in the best interest of the patient”, acting as their advocates and advisors, in the quest for better health and quality of life.

It is thus indeed an alarming situation for all Malaysians when we are faced with the sobering fact that various studies have demonstrated the ever-increasing prevalence of non-communicable diseases (NCD) and NCD risk factors. The National Strategic Plan for Non-Communicable Diseases (NSP-NCD), a multi-pronged strategy and action plan drawn up to combat this menace to the health of our public, emphasises primary prevention, early NCD risk factor identification as well as NCD risk factor intervention (also known as “clinical preventive services”). Behaviour modification for healthy living through continuing health promotion, is important in reducing the prevalence and incidence of NCDs. In addition, focus on those who have a higher risk of developing NCDs (for example, cardiovascular diseases) is also an important one. Dyslipidaemia is a major risk factor that needs to be seriously addressed in order for us to stop this NCD juggernaut in its tracks, from harming the lives of more Malaysians.

Since the publication of the 3rd edition of the Clinical Practice Guidelines (CPG) on the Management of Dyslipidaemia, much water has flowed under the bridge...it became evident, from new clinical information and data from clinical trials, that an update of these evidence-based guidelines was sorely needed. This CPG has an important role to play to assist clinicians and health care professionals in their decision-making in the management of this major risk factor for cardiovascular diseases. The panel of experts, comprising clinicians and academicians, that have reviewed the best available evidence and synthesised them into usable information to manage dyslipidaemia, are to be commended for their unifying endeavour to ensure that knowledge of how best to treat this condition is being disseminated to all health care professionals who are committed to enhancing the lives of their patients and loved ones.

It is my fervent hope that these evidence-based guidelines will be implemented effectively into action plans that are tailored to an individual patient’s unique needs. We need to “walk the talk” and ensure that our treatment plans are based on the recommendations found in these CPGs. Let our paths in this noble quest to reduce the incidence of cardiovascular diseases, be lit by many more Clinical Practice Guidelines such as these, so that many more Malaysians can live healthy and productive lives.

Dato' Dr. Hasan bin Abdul Rahman
MESSAGE FROM THE AMERICAN COLLEGE OF CARDIOLOGY

The American College of Cardiology heartily congratulates the National Heart Association of Malaysia along with the Ministry of Health of Malaysia and the Academy of Medicine for the creation of this important Clinical Practice Guideline for the management of dyslipidemias.

Appreciating that in Malaysia cardiovascular disease is the leading cause of death in both men and women and that dyslipidemia is both readily identifiable and treatable offers the ideal opportunity to translate known cardiovascular science to the “bedside”. This CPG focusing on lipid management should become a cornerstone for practitioners in Malaysia in their mission to combat cardiovascular disease. Seminal work by Ford reported in the New England Journal of Medicine points out that both primary risk factor modifications along with adherence to secondary prevention measures has markedly decreased mortality and morbidity of cardiovascular disease.1 Risk factor modification has a much greater impact on population health than invasive or interventional cardiac procedures. Evidence based lipid management is a major component of the worldwide success in decreasing mortality and morbidity of cardiovascular disease along with hypertension control, tobacco cessation, diabetic care along with increasing exercise and successful treatment of obesity.

I again congratulate my Malaysian colleagues and encourage enthusiastic application of this seminal work to improve the health of the great people of Malaysia.

Sincerely,

Ralph Brindis, MD, MPH, MACC, FSCAI
Immediate Past President, American College of Cardiology

Reference:
Members of the Expert Panel

Chairperson:
Dr Robayaah Zambahari Consultant Cardiologist, Institute Jantung Negara, Kuala Lumpur

Secretary:  
Dr R. Jeyamalar Consultant Cardiologist, Sime Darby Medical Center, Subang Jaya, Selangor

Members (in alphabetical order)
Dr Abdul Rashid Rahman Consultant Physician, Cyberjaya University College of Medical Sciences, Cyberjaya, Selangor
Dr Chan Siew Pheng Consultant Endocrinologist, Sime Darby Medical Center, Subang Jaya, Selangor
Dr Khoo Kah Lin Consultant Cardiologist, Pantai Medical Center
Dr Rosli Mohd Ali Consultant Cardiologist, Institute Jantung Negara, Kuala Lumpur
Dr Sree Raman Consultant Physician, Hospital Tuanku Jaafar, Seremban (HTA trained)
Dr Sim Kui Hian Consultant Cardiologist, Sarawak General Hospital, Kuching
Dr Wan Azman Consultant Cardiologist, University Malaya Medical Center
Dr Zanariah Hussein Consultant Endocrinologist, Hospital Putrajaya, Putrajaya
External Reviewers (in alphabetical order):

Pn Che Zuraini Sulaiman, Pharmacist
Universiti Malaya Medical Centre

Dr Chia Yook Chin, Consultant Primary Care Physician
Universiti Malaya Medical Centre

Dr Ghazali Ahmad Kutty, Consultant Nephrologist
Hospital Kuala Lumpur

Dr Hashim Noh, General Practitioner,
Klinik Young, Newton and Partners
Kuala Lumpur/Petaling Jaya

Dr Lee Chuey Yan, Consultant Cardiologist
Hospital Sultanah Aminah Johor

Dr Lee Fatt Soon, Consultant Geriatrician
Hospital Kuala Lumpur,
Kuala Lumpur

Dr Santha Kumari, Consultant Physician
Hospital Sultanah Rahimah, Klang

Dr V Paranthaman, Family Medicine Specialist,
Klinik Kesihatan Jelapang,
Ipoh, Perak

Dr Wan Mohamad Wan Bebakar, Consultant Endocrinologist
Hospital Universiti Sains Malaysia,
Kota Baru, Kelantan

Dr Wong Kai Fatt, General Practitioner,
LW Medical Associates
Kuala Lumpur

Dr Zurkarnai Yusof, Consultant Cardiologist
Hospital Universiti Sains Malaysia,
Kota Baru, Kelantan
RATIONALE AND PROCESS OF GUIDELINE DEVELOPMENT

Rationale:
In Malaysia, cardiovascular disease (CVD) is the leading cause of death in both men and women. 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).

Malaysians develop ACS at a younger age when compared to people in Thailand, mainland China and western countries. Our local NCVD-ACS Registry, showed that most patients (96.8%) had at least one established cardiovascular risk factor—hypertension (72.6%), dyslipidaemia (55.9%) and /or diabetes (55%)³.

In preventing CVD, efforts should be aimed at reducing global risks. The Clinical Practice Guideline (CPG) is on management of dyslipidaemia. The last CPG (3rd edition) was published in 2004. Thus the need for an update.

Objectives:
The objective of this CPG is to:
• provide guidance on the best treatment strategies for managing dyslipidemia utilizing and optimizing existing health resources.

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 and general physicians from the government and private sectors as well as from the Universities.

Process:
Evidence was obtained by systematic review of current medical literature on dyslipidaemia using the usual search engines – PubMed, Medscape and Ovid. The other international guidelines (American and European) on the subject were also studied. 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 were 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 15. In the text, this is written in black on the left hand margin. In the Summary and Key Recommendations, it is written as a superscript immediately after the therapeutic agent or at the end of the statement as applicable.

Clinical Questions Addressed:
• What is the current evidence on the management of patients with dyslipidaemia?
• Which management and recommendations are most applicable to our local setting?

Target Group:
This guideline is directed at healthcare providers including general practitioners, medical officers, pharmacists, general and family physicians, cardiologists and endocrinologists.

Target Population: All individuals.

Period of Validity of the Guidelines:
This guideline needs to be revised at least every 5 years to keep abreast with recent developments and knowledge.

Applicability of the Guidelines:
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. The medications recommended are approved for use in Malaysia.

This guideline aims to educate health care professional on strategies to optimize existing resources in the management of dyslipidemia.
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 and its prevention
- continuing medical education and training of healthcare providers.
- monitoring lipid levels in the population through National health surveys which will now be conducted every 5 years and through the NCVD ACS/PCI registry.
- clinical audit at hospital level- documentation of target LDL-C levels.

GRADES OF RECOMMENDATIONS AND LEVELS OF EVIDENCE

<table>
<thead>
<tr>
<th>GRADES OF RECOMMENDATION</th>
<th>II-b</th>
<th>II-a</th>
<th>II</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure/therapy.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Weight of evidence/opinion is in favor of its usefulness/efficacy.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Usefulness/efficacy is less well established by evidence/opinion</td>
<td>-</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>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.</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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</tbody>
</table>

LEVELS OF EVIDENCE

<table>
<thead>
<tr>
<th>LEVELS OF EVIDENCE</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data derived from multiple randomized clinical trials or meta analyses</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Data derived from a single randomized clinical trial or large non randomized studies</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Only consensus of opinions of experts, case studies or standard of care</td>
<td>-</td>
<td>-</td>
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Adapted from the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC)
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1. INTRODUCTION

In 2009, cardiovascular disease (CVD) was the leading cause of death in both men and women\(^1\). 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 peak incidence of ACS in Malaysia was in the 51-60 year age group and the male to female ratio was 3:1\(^2\). The mean age in the local NCVD-ACS Registry 2006 was 58.1 years.\(^3\) This is younger than that noted in neighbouring countries such as Thailand (65 years)\(^4\), China (63 years)\(^5\) and in the western population (GRACE Registry- 66 years\(^6\), Canada- 68 years\(^7\)).

In the NCVD-ACS Registry, most patients (96.8%) had at least one established cardiovascular risk factor – hypertension (72.6%), dyslipidaemia (55.9%) and/or diabetes (55%)\(^3\).

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

- 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.

In the management of dyslipidaemia the following changes have been made:

- identification of those at high risk – this includes individuals with established CVD, diabetes, multiple risk factors and established renal disease.
- emphasizes the importance of a family history of premature CVD and familial dyslipidaemia
- treatment targets.

The objectives of this CPG is to:

- provide guidance on the best treatment strategies for managing dyslipidemia utilizing and optimizing existing health resources.
2. MEASUREMENT OF LIPIDS AND APOLIPOPROTEINS

Serum lipid levels are affected by several factors:
- acute stress or illness, eg fever, surgery, acute myocardial infarction.
- drugs eg beta-blockers, thiazides, steroids.

2.1 Lipids – TC, HDL-C, LDL-C and TG

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

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

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

LDL-C may also be measured directly although these methods are not well standardized and not routinely performed.

2.2 Lipids – non HDL-C

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

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

*Non HDL-C levels can be calculated from a non-fasting serum. It is a target of therapy in patients with TG > 4.5mmol/l.*
Measurements made from whole blood differs slightly from that obtained from plasma or serum. TC, TG and HDL-C measured using desktop machines are acceptable when performed according to specifications.

Lipid levels especially TG show biological variability. Because of this and laboratory variability more than one measurement is required in borderline cases.

2.3 Apolipoproteins (Appendix I, pg 80)

Apolipoproteins are proteins attached to lipid particles to form lipoproteins. There are several apolipoproteins. Apo B is a better indicator of CVD risk than LDL-C alone.\textsuperscript{11-14} It is found in chylomicrons, VLDL, IDL, LDL and Lp(a) particles. Since each of these particles contains a single Apo B molecule, measurement of Apo B represents the total atherogenic burden. Apo B measurement has been standardized, automated and can be done in the non-fasting state. It is not routinely measured.

Key messages:
- TC and HDL-C can be measured in the fasting and non fasting states. TG is best measured in a fasting sample. LDL-C is calculated using the Friedwald’s equation.
- When TG > 2.3mmol/l, non HDL-C is a better indicator of total atherogenic burden.\textsuperscript{1A}

3. CLASSIFICATION OF DYSLIPIDAEMIAS

Dyslipidaemia is defined as lipid values outside the norm. Based on therapeutic considerations, dyslipidaemias may be classified as follows (Table 4):

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Serum Lipid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia</td>
<td>↑ LDL</td>
</tr>
<tr>
<td>Mixed Hyperlipidemia</td>
<td>↑ LDL + VLDL</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>↑ VLDL</td>
</tr>
<tr>
<td>Low HDL Cholesterol</td>
<td>↓ HDL</td>
</tr>
</tbody>
</table>
### Table 5: Primary Dyslipidaemia

<table>
<thead>
<tr>
<th>Dyslipidaemia Type</th>
<th>Common Risk of CHD</th>
<th>Risk of Pancreatitis</th>
<th>Plasma Cholesterol</th>
<th>Plasma Triglyceride</th>
<th>Serum Physical signs (if present)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common (“polygenic”) Hypercholesterolemia</td>
<td>↑</td>
<td>↔</td>
<td>↑↑</td>
<td>N</td>
<td>Corneal Arcus Xanthelasma</td>
</tr>
<tr>
<td>Familial Combined Hyperlipidemia</td>
<td>↑↑</td>
<td>↔</td>
<td>↑ or ↔</td>
<td>↑ or ↔</td>
<td>Corneal Arcus Xanthelasma</td>
</tr>
<tr>
<td>Familial Hypercholesterolemia</td>
<td>↑↑↑</td>
<td>↔</td>
<td>↑↑↑</td>
<td>↑</td>
<td>Tendon xanthomata, (finger extensor, Achilles’ tendons) Corneal Arcus, Xanthelasma, Aortic stenosis</td>
</tr>
<tr>
<td>Remnant Hypercholesterolemia</td>
<td>↑↑↑</td>
<td>↔</td>
<td>↑↑↑</td>
<td>↑↑</td>
<td>Tuberous xanthomata, (elbows), striae xanthomata, (palm creases) tendon xanthomata</td>
</tr>
<tr>
<td>Chylomicronemia Syndrome</td>
<td>↔ or ↑</td>
<td>↑↑↑</td>
<td>↑</td>
<td>↑↑↑</td>
<td>Eruptive xanthomata, (buttocks, elbows) retinal lipemia, hepatospleno-megaly</td>
</tr>
<tr>
<td>Familial Hypertriglyceridemia</td>
<td>↑</td>
<td>↑↑</td>
<td>↑</td>
<td>↑↑</td>
<td>Eruptive xanthomata, (buttocks, elbows) retinal lipemia, hepatospleno-megaly</td>
</tr>
<tr>
<td>High HDL-C</td>
<td>↓↓</td>
<td>↔</td>
<td>↑</td>
<td>↔</td>
<td>-</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>↑↓</td>
<td>↔</td>
<td>↔ or ↑</td>
<td>↔</td>
<td>-</td>
</tr>
</tbody>
</table>
Dyslipidaemias may be primary or secondary in etiology. (Tables 5 & 6).

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

- When TC exceeds 7.0 mmol/l, exclude conditions such as primary hypothyroidism, nephrosis, obstructive liver disease.
- Cushing’s syndrome (including subclinical disease) can lead to lipid abnormalities in 40-70% of patients. Patients on exogenous steroids may also develop secondary dyslipidemias. Hypothyroidism is another important cause. It is more prevalent in the elderly in whom a high index of suspicion may be necessary for diagnosis.
- 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 (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 past history of thyroid disease.

Table 6: Causes of Secondary Dyslipidaemias

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>CHOLESTEROL</th>
<th>TRIGLYCERIDES</th>
<th>HDL-CHOLESTEROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic / Endocrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>↑↑</td>
<td>⇔</td>
<td>⇔</td>
</tr>
<tr>
<td>T2DM</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>⇔</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Cushing’s Syndrome</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>⇔ or ↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>↑↑</td>
<td>↑↑</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive liver disease</td>
<td>↑↑</td>
<td>⇔</td>
<td>↓</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>↑↑</td>
<td>⇔</td>
<td>↑</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>⇔</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>⇔</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>⇔</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
4. DYSLIPIDAEMIA AS A RISK FACTOR FOR CVD

Dyslipidaemia has been identified as one of the main risk factors for CVD. Our local NCVD – ACS Registry showed that dyslipidaemia was present in 55% of our patients. Specific lipid abnormalities implicated are:

4.1. Elevated LDL-C levels

LDL-C has been shown to be atherogenic in epidemiological studies. There is a direct relationship between levels of LDL-C (or TC) and the rate of new onset CHD in men and women who were initially free from CHD. In people with established CHD, elevated LDL-C correlates with recurrent cardiac events. There is a near absence of clinical CHD in populations with very low levels of serum cholesterol throughout their life (TC<3.9mmol/L or LDL-C< 2.6 mmol/L). The risk for CHD appears to increase progressively above these levels. At levels of LDL-C above 3.4 mmol/L, atherogenesis proceeds at a significant rate particularly in the presence of other major risk factors.

Randomized controlled trials have repeatedly shown that lowering of LDL-C reduces CVD events in both primary and secondary prevention. Studies have also shown that LDL-C particle concentration and size are important predictors of CVD. However measurement of these are not widely available and are not standardized.

Thus LDL-C should be the primary target for cholesterol therapy. Meta- analysis have shown that reducing LDL-C by 1% reduces CHD risk by 1%.
4.2. Low HDL-C levels

There is substantial data linking a low HDL-C level (< 1.0 mmol/L) with increased risk of CHD.18,38,39,40 A 1% decrease in HDL-C, in epidemiological studies, has been associated with 2-3% increase in CHD risk.40 Clinical trials using pharmacotherapy to increase HDL-C levels have, however, showed mixed results. 41,42,43

4.3. Elevated TG levels

Data suggest that a raised TG level indicates a modest but highly significant association with CHD.44,45,46 This suggests that some TG-rich lipoproteins are atherogenic. Weight reduction and drug therapies (fibrates, nicotinic acid and statins) reduce remnant lipoproteins and are accompanied by a reduced risk for CHD.43,47,48

4.4. Elevated Non-HDL-C levels

Non HDL-C reflects the concentration of cholesterol within all lipoprotein particles considered atherogenic. Many 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.49,50,51

4.5. Atherogenic Dyslipidaemia

This consists of low HDL-C, raised TG and small dense LDL particles.52,53 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 CVD risk marker, there have been no outcome studies to support using this as a target of therapy.

4.6 Lipoprotein Lp(a)

Elevated levels of Lp(a) have been shown to be related to cardiovascular risk in some but not all studies.54,55
5. OTHER RISK FACTORS FOR CVD

More than 90% of CVD can be explained by 9 to 10 modifiable risk factors – dyslipidaemia, hypertension, smoking, diabetes, abdominal obesity, psychosocial stress, low intake of fruits and vegetables, alcohol intake and physical inactivity.\(^{56,57}\) (Appendix II, pg 80)

5.1. Age

The incidence of CVD increases with age.\(^{18}\) This is due to the combined effects of age related changes in the vascular system as well the duration of exposure to adverse risk factors.

5.2. Gender

The incidence of CVD is about 3-4 times higher in men than women in the middle decades of life and approximately twice as high in the elderly.\(^{18}\)

5.3. Hypertension

Both elevated systolic and diastolic blood pressures are linked with increased CVD risk.\(^{58,59,60}\) From epidemiological data, elevated systolic blood pressure appears to be more important when compared to diastolic blood pressure as a risk factor especially in middle aged and elderly individuals.\(^{61-64}\) The presence of left ventricular hypertrophy is associated with increased CV risk.

5.4. Smoking

This is an important CV risk factor and cause of mortality in both men and women.\(^{65,66,67}\) The incidence and mortality of CVD is 2-3 times as high in cigarette smokers compared to non smokers.\(^{68,69}\)

Key messages:
- LDL-C should be the primary target of therapy\(^{1A}\)
- Non HDL-C should be an alternative primary target of therapy in patients with TG > 4.5 mol/L\(^{1A}\)
The risk of developing CVD is directly related to the number of cigarettes smoked.\textsuperscript{70,71} The relative risk of CV events is greater in younger than in older patients although the absolute excess mortality related to smoking increases with age.\textsuperscript{68,70}

Smoking interacts in a multiplicative manner with other risk factors ie the risk is higher than that would have resulted from simply adding together the independent risks.\textsuperscript{72,73}

In individuals who discontinue smoking, the risk decreases within a year or two of stopping and the curve flattens out within 4 years although the relative risk remains slightly higher compared to never-smokers.\textsuperscript{74,75}

5.5. Family History of Premature CVD

Familial and genetic factors may play an important role in the determination of some major risk factors, especially hypertension, lipid abnormalities and glucose intolerance. In addition there appears to be a familial predisposition to CVD.\textsuperscript{76,77,78} The presence of premature CVD in first degree male relatives below the age of 55 years or female relatives below the age of 65 years is a recognized independent risk factor for CVD.\textsuperscript{79} This risk is greater when more family members are affected and the younger their age of onset of CVD.

5.6 Others

Other risk factors include:

5.6.1 Lifestyle Risk Factors

- Abdominal obesity:
  Risk for CVD is increased although a recent analysis seems to indicate that abdominal obesity just helps to identify high risk individuals with metabolic abnormalities. In Asians, a waist circumference of > 90 cm in men and > 80 cm in women has been found to be associated with increased CV risk.\textsuperscript{80-84} (Appendix III, pg 81)
- **Physical Inactivity:**
  Numerous studies have shown that physical inactivity is associated with increased mortality and CVD.\(^{85,86,87}\)

- **Intake of fruits and vegetables:**
  Low intake (less than 5 servings a day) increases CV risk.\(^{88}\)

### 5.6.2.: Risk Markers

The following risk markers maybe helpful in intermediate risk patients to determine the intensity of therapeutic targets.

- **Inflammatory markers (hs-CRP)** –
  Pathological studies strongly support a role for inflammation in the pathogenesis of the early stages of atherosclerosis, plaque progression and rupture. One such acute phase reactant is high sensitivity C-reactive protein (hs-CRP). Data show that an elevated level of hs-CRP identifies healthy individuals who are at an increased risk of an initial and recurrent cardiac events.\(^{89-93}\) Results of a recent trial indicated that healthy persons with LDL-C levels in the normal range but with elevated hs-CRP benefited from statins.\(^{94}\)

- **Hemostatic markers** –
  An elevated level of fibrinogen has been associated with an increased risk for coronary events.\(^{95,96}\)

- **Subclinical atherosclerosis** -
  Individuals with subclinical atherosclerotic disease are at increased risk for major coronary events.\(^{97}\) Subclinical atherosclerosis may be identified by the:
  - presence of abnormalities in the resting and / or stress ECG
  - measurement of the ankle / brachial blood pressure (ABI) (a level of less than 0.9 is significant)
  - measurement of carotid intima-medial thickness (IMT) by ultrasound (more than 75th percentile for age and sex)
  - measurement of coronary calcium score by computed tomography (CT)
  - non invasive imaging of the coronary arteries by CT angiography.
These tests may be used for risk stratification in individuals at intermediate risk. Patients with subclinical atherosclerotic disease may warrant a more aggressive preventive treatment strategy.

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

**6. GLOBAL CARDIOVASCULAR RISK ASSESSMENT**

Based on the Malaysian National Health and Morbidity Survey 2006, the prevalence of dyslipidaemia in Malaysians above the age of 40 years was 28%98. All adults above the age of 40 years should have a complete fasting lipid profile (TC, LDL-C, HDL-C, TG). If the levels are normal, then screening should be done annually.

Individuals who already have evidence of atherosclerosis or are at high risk of developing CVD, should have a complete lipoprotein profile earlier in life. This includes individuals with a family history of premature CVD, genetic dyslipidaemias, metabolic syndrome, T2DM and abdominal obesity.

**6. 1 Risk Stratification**

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

The CHD risk equivalents are:
- Other clinical forms of atherosclerotic disease (atherosclerosis in any vascular bed - aorta including abdominal aortic aneurysm, carotid, cerebral and peripheral vessels)
- T2DM
- Multiple risk factors that confer a 10 year risk for CVD > 20%

These individuals are at high risk of developing CVD. They should be screened for the traditional risk factors and treated appropriately.
In all other patients, their global CVD risk should be determined. There are several risk equations that may be used. All have some limitations and difficulty to extrapolate to our local population. Until local data are available we recommend adopting the latest (2008) Framingham CV risk score. This estimates CVD risk while the earlier version (2002) provides a risk estimate of “hard” CHD events ie cardiac death and nonfatal myocardial infarction.

The intensity of risk reduction therapy is dependent on an individual’s global risk of developing CVD. In determining CV risk the following steps are taken:

- Count the number of major risk factors for CVD (Table 7, pg 28).
- In individuals with more than 2 risk factors, calculate the 10-year CVD risk using the Framingham score sheets (Figures 1A & B, 2A & B, pg 30-31).
- The vascular age can also be determined (Figure 1C and 2C, pg 32).
- In individuals with 0 – 1 risk factors, the CV risk score need not be calculated since the 10-year CVD risk is <10%.

Table 7: Major Risk Factors for CVD (Other than LDL Cholesterol)

<table>
<thead>
<tr>
<th>Positive Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male ≥ 45 years of age</td>
</tr>
<tr>
<td>Female ≥ 55 years of age or premature menopause without hormonal replacement therapy</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
</tr>
<tr>
<td>Family history of myocardial infarction or sudden death prior to age 55 in a male parent or male first degree relative and prior to age 65 in a female parent or other female first degree relative</td>
</tr>
<tr>
<td>HDL-C &lt; 1.0 mmol/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Negative Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL &gt; 1.6 mmol/L</td>
</tr>
</tbody>
</table>

In all other patients, their global CVD risk should be determined. There are several risk equations that may be used. All have some limitations and difficulty to extrapolate to our local population.

Until local data are available we recommend adopting the latest (2008) Framingham CV risk score. This estimates CVD risk while the earlier version (2002) provides a risk estimate of “hard” CHD events ie cardiac death and nonfatal myocardial infarction.
Other risk factors not included in the general risk profile that should be taken into account in evaluating risk include:

- Clinical features of insulin resistance such as abdominal obesity, elevated triglycerides, and dysglycaemia (See Section 6.2)
- ECG evidence of left ventricular hypertrophy
- hs-CRP levels
- Evidence of subclinical atherosclerosis
- Chronic kidney disease (GFR<60ml/min)
- Chronic autoimmune inflammatory disorders such as systemic lupus erythematosis and rheumatoid arthritis
- Chronic HIV infection

These individuals are at high risk of developing CVD. They should be screened for the traditional risk factors and treated appropriately.

Individuals with 0-1 risk factor almost always have a 10 year CVD risk <10%.

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

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

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

Determining an individual’s global CVD risk will guide LDL-C target goal and management strategies. (Table 8, pg 34)

The 10 year risk calculation is to be performed at the outset to help guide the intensity of cholesterol lowering therapy. It cannot be used to track changes in risk over time as risk factors are modified. In calculating the risk scores (Figures 1A & B, 2A & B, pg 30-31), the TC and HDL-C should be the average of at least 2 measurements.

The average baseline blood pressure (BP) must be obtained from an average of several readings. A “smoker” means any cigarette smoking in the past month.
Figure 1A: Estimation of 10 year CVD Points for MEN (Framingham Point Scores)

<table>
<thead>
<tr>
<th>Points</th>
<th>Age,y</th>
<th>HDL-C</th>
<th>TC</th>
<th>SBP (not treated)</th>
<th>SBP (treated)</th>
<th>Smoker</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>1.6+</td>
<td>&lt;120</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>1.3-1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>30-34</td>
<td>1.2-&lt;1.3</td>
<td>&lt;4.2</td>
<td>120-129</td>
<td>&lt;120</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>1</td>
<td>0.9-&lt;1.2</td>
<td>4.2-&lt;5.2</td>
<td>130-139</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>35-39</td>
<td>&lt;0.9</td>
<td>5.2-&lt;6.3</td>
<td>140-159</td>
<td>120-129</td>
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</tr>
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<td>3</td>
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<td>6.3-&lt;7.4</td>
<td>160+</td>
<td>130-139</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&gt;7.4</td>
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<td>140-159</td>
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<tr>
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<td>15</td>
<td>75+</td>
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</tbody>
</table>

**Grand Total : ________________ points**

Figure 1B: CVD Risk for Men

<table>
<thead>
<tr>
<th>Total Points</th>
<th>10 year Risk %</th>
<th>Total Points</th>
<th>10 year Risk %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=3 or less</td>
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<td>8</td>
<td>6.7</td>
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<td>1.1</td>
<td>9</td>
<td>7.9</td>
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<td>9.4</td>
</tr>
<tr>
<td>0</td>
<td>1.6</td>
<td>11</td>
<td>11.2</td>
</tr>
<tr>
<td>1</td>
<td>1.9</td>
<td>12</td>
<td>13.2</td>
</tr>
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<td>2</td>
<td>2.3</td>
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</tr>
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<td>16</td>
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<tr>
<td>6</td>
<td>4.7</td>
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</tr>
<tr>
<td>7</td>
<td>5.6</td>
<td>18+</td>
<td>&gt;30</td>
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</table>
### Figure 2A: Estimation of 10 year CVD Points for WOMEN (Framingham Point Scores)\(^{100}\)

<table>
<thead>
<tr>
<th>Points</th>
<th>Age,y</th>
<th>HDL-C</th>
<th>TC</th>
<th>SBP (not treated)</th>
<th>SBP (treated)</th>
<th>Smoker</th>
<th>Diabetes</th>
</tr>
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<tbody>
<tr>
<td>-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2</td>
<td></td>
<td>1.6+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td></td>
<td>1.3-1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30-34</td>
<td>1.2-&lt;1.3</td>
<td>&lt;=4.2</td>
<td>120-129</td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>1</td>
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<td>0.9-&lt;1.2</td>
<td>4.2-&lt;5.2</td>
<td>130-139</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>35-39</td>
<td>&lt;0.9</td>
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<td>140-149</td>
<td>120-129</td>
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<td>5.2-&lt;6.3</td>
<td>130-139</td>
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<td></td>
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</tr>
<tr>
<td>4</td>
<td>40-44</td>
<td>6.3-&lt;7.4</td>
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<td>150-159</td>
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<td></td>
<td>160+</td>
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<td>9</td>
<td>60-64</td>
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<tr>
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<td>11</td>
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**Grand Total : ____________points**

### Figure 2B: CVD Risk For Women\(^{100}\)

<table>
<thead>
<tr>
<th>Total Points</th>
<th>10 year Risk %</th>
<th>Total Points</th>
<th>10 year Risk %</th>
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<tbody>
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<td>≤-2</td>
<td>&lt; 1</td>
<td>10</td>
<td>6.3</td>
</tr>
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<td>11</td>
<td>7.3</td>
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<td>0</td>
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<td>7</td>
<td>3.9</td>
<td>19</td>
<td>24.8</td>
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<td>8</td>
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<td>20</td>
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<tr>
<td>9</td>
<td>5.3</td>
<td>21+</td>
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</table>
**Figure 1C : Heart Age/ Vascular Age for Men**

<table>
<thead>
<tr>
<th>Points</th>
<th>Heart age, y</th>
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</thead>
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<td>16</td>
<td>76</td>
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<tr>
<td>≥17</td>
<td>&gt;80</td>
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</table>

**Figure 2C : Heart Age/ Vascular Age for Women**

<table>
<thead>
<tr>
<th>Points</th>
<th>Heart age, y</th>
</tr>
</thead>
<tbody>
<tr>
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<td>13</td>
<td>73</td>
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<tr>
<td>14</td>
<td>79</td>
</tr>
<tr>
<td>15+</td>
<td>&gt;80</td>
</tr>
</tbody>
</table>
6.2. Diabetes mellitus and Dysglycaemia as CHD risk equivalents

Patients with type 2 diabetes mellitus (T2DM) and impaired glucose tolerance (IGT) have an increased risk of cardiovascular events.\textsuperscript{101,102} These patients have higher mortality and a higher incidence of recurrent cardiac events.\textsuperscript{103}

The two main types of DM (type 1 and type 2) have different patterns of dyslipidaemia. Type 2 diabetes (T2DM) may be associated with insulin resistance, as in some individuals with the metabolic syndrome.

The current definition of metabolic syndrome (2009) includes any 3 or more of the following (including those on treatment)*:

- Elevated Waist circumference (Asian cut-off):
  - females >80cm
  - males >90cm
- Elevated TG > 1.7 mmol/L
- Reduced HDL-C < 1.3 mmol/L (female) or < 1.0 mmol/L (male)
- Elevated blood pressure (BP):
  - Systolic BP > 130 and / or diastolic BP > 85 mmHg
- Disorders of glycaemia:
  - T2DM, or
  - impaired glucose tolerance (IGT)
    [Fasting plasma sugar < 7.0 mmol/L and 2 hours after 75 gm glucose load: 7.8 – 11.1 mmol/L], or
  - impaired fasting glucose (IFG)
    [Fasting plasma sugar: 6.1 – 7.0 mmol/L]

*Adapted from Joint Interim Statement (Joint Interim Statement of International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart Lung Blood Institute (NHLBI), American Heart Association (AHA), World Heart Federation (WHF), International Atherosclerotic Society (IAS and International Association for Study of Obesity (IASO) Circulation 2009:120:1640-1645

Proatherogenic risk markers like elevated Lp(a), prothrombotic risk markers eg. raised PAI-1, increased fibrinogen and endothelial dysfunction are found in insulin resistance states and contribute to the increased CV risk. These associated abnormalities of insulin resistance can be present for up to 10 years before detection of the glycaemic disorder.
Individuals with type 1 diabetes are more likely to have elevated TC, with rise in LDL-C and increased TG. These lipid abnormalities can be fully corrected with good glycaemic control with insulin. Individuals with T2DM have the atherogenic dyslipidaemia. Improvement of glycaemic control may not fully correct this dyslipidaemia. Some studies show better correlation of non HDL-C than LDL-C to coronary mortality. (see 4.4. & 4.5)

6.3. Target Lipid Levels

**LDL-C is the primary target for therapy.**

The target LDL-C level will depend on the individual’s global risk. (see Table 8)

**Table 8: Target LDL-C levels**

<table>
<thead>
<tr>
<th>Global Risk</th>
<th>LDL-C levels to initiate Drug therapy</th>
<th>Target LDL–C levels (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 risk factor *</td>
<td>≥ 4.9 c</td>
<td>&lt; 4.1</td>
</tr>
<tr>
<td>2 or more risk factors b</td>
<td>3.4 c</td>
<td>≤ 3.4d</td>
</tr>
<tr>
<td>CVD and CVD risk Equivalents</td>
<td>≥ 2.6</td>
<td>&lt; 2.6e</td>
</tr>
<tr>
<td></td>
<td>2.0 to &lt; 2.6</td>
<td>&lt; 2.0f</td>
</tr>
</tbody>
</table>

*a Almost all individuals with 0-1 risk factor have a 10 year risk < 10%, thus 10 year risk assessment in individuals with 0-1 risk factor is not necessary.  
*b These include individuals with multiple risk factors but a 10 year risk of CVD of < 20%.  
*c After 8-12 weeks of TLC.  
*d An optional target of <2.6mmol/L in certain high risk individuals. See flowchart II & III, pg 4  
*e The lower the LDL-C achieved, the greater the CV benefits seen.  
*f Consider LDL-C target goal < 2.0 mmol/L in very high risk individuals eg individuals with ACS, recurrent cardiac events, CHD with T2DM and those with multiple poorly controlled risk factors  

See Flowcharts I-IV, pg 5-8.

**Key messages:**

- Individuals should be risk categorized LC (Table 7, pg 28, Fig 1A & B, 2A & B, pg 30-31).  
- Target lipids levels will depend upon the individual’s global risk.  
- Individuals with CVD and CHD risk equivalents should be treated aggressively with drug therapy LA (Table 8, pg 34; Flowcharts I-IV, pg 5-8).
7. PREVENTION OF CVD

Prevention can be divided into:

- Primary prevention is the prevention of occurrence of CVD events in people without CVD.
- Secondary prevention is the prevention of progression of CVD and its complications in people with established CVD or CVD risk equivalents.

Strategy of primary prevention
The strategy is based on a:

- Population based strategy
  This strategy 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 counseling.

- Individual based strategy
  The aim is to identify individuals at risk of developing CVD and modifying their risk factors. This would include all individuals above the age of 40 years. (See Section 6).

Strategy of secondary prevention

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

8.1. THERAPEUTIC LIFESTYLE CHANGES

Introduction

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

8.1.1. Dietary Modification

This is aimed at optimizing lipid levels while maintaining a balanced diet. It is encouraged to refer an individual to a dietician for medical nutrition therapy. Dietary therapy can lower TC by 10-15% and occasionally >20%. Dietary therapy is continued indefinitely. (Appendix V, pg 83)

The intake of food high in cholesterol content must be reduced. A high intake of saturated fatty acids (SFA) and trans fatty acids (TFA) raise LDL-C levels while a high intake of monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) lower LDL-C and reduce CV risk. Thus both PUFA and MUFA should be encouraged in place of SFA and TFA. SFA should not be replaced with carbohydrates.

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

The use of viscous (soluble) forms of dietary fibre (oats, pectin, guar and psyllium) of at least 5–10 gm per day is encouraged as they have been shown to reduce LDL-C levels.
Plant stanol/sterol esters (2–3 gm/day) also have a LDL-C lowering effect\textsuperscript{117} which is dose related but there is inter-individual variation in their response. Plant sterols and stanols are not routinely recommended for the prevention of CVD since there are no CV outcome data.

High intake of soy protein (25-50 gm/day) can cause small reductions in LDL-C.\textsuperscript{106}

**8.1.2. Weight Reduction**

This is important in overweight and obese individuals particularly those with the metabolic syndrome. Weight reduction helps to lower TG and increase HDL-C levels, in addition to enhancing the cholesterol (TC and LDL-C) lowering effects of dietary modification.\textsuperscript{118}

A weight reduction of 0.5-1.0 kg per week is recommended. According to the Asia Pacific Western Pacific Regional World Health Organization, the recommended BMI in Asians is 18.5 - < 23 kg/m\textsuperscript{2} and a waist circumference < 90 cm for males and < 80 cm for females.\textsuperscript{81}

**8.1.3. Physical Activity**

Physical activity and weight reduction enhance the lipid-lowering effects of dietary therapy. They also improve cardiovascular fitness, lower BP, increase insulin sensitivity, increase HDL-C levels and decrease TG levels.\textsuperscript{119,120} Such activities include aerobic exercises such as brisk walking, jogging, cycling, swimming. Exercise needs to be regular and adequate (30-45 minutes per session at least 5 times a week).

**8.1.4. Cigarette Smoking**

Smoking is one of the major risk factors for CVD and must be stopped. Even passive smokers are at high risk of developing CVD. The decline in CVD risk begins within a year or two after smoking cessation.\textsuperscript{74,75}
8.1.5. Alcohol

**I,B** Restriction of alcohol is advised in patients with dyslipidaemia as it increases plasma TG levels.\(^{121,122}\)

**I,A** Moderate alcohol consumption (not more than 14 units for males and 7 units for female per week) increases HDL-C and apo A-I and is associated with a reduction in all cause mortality.\(^ {123-127}\)

Over-consumption is however associated with a higher mortality rate. High intake of alcohol elevates BP and can precipitate acute pancreatitis in individuals with high TG levels. Nondrinkers should therefore not be encouraged to start alcohol consumption to improve their dyslipidaemia.

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

8.1.6. Miscellaneous

**IIa,B** Omega–3 polyunsaturated fatty acids are useful in individuals with high TG and can be considered in addition to fibrates or nicotinic acid. For lowering TG, a dose of 3-9 gm/day of omega-3 fatty acids is required

**IIb,B** In patients with CVD, omega-3 fatty acids (dose of 0.75 gm-1 gm/day) has been shown to reduce sudden cardiac death, CHD mortality and total mortality although a recent trial showed no benefit.\(^ {128,129,130}\)

It is recommended to increase intake of omega-3-fatty acids by eating more fish, walnuts, flaxseed oil and green, leafy vegetables.\(^ {128,131}\)

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

**III,A** The use of anti–oxidants (such as vitamin C, E, beta carotene, bioflavonoids) selenium and Coenzyme Q-10 has not been shown to be effective in preventing or treating CVD. Foods, vitamins and minerals which act as antioxidants include Co-enzyme Q10, ginkgo, green tea, Vitamin A (Beta-carotene), Vitamin C, Vitamin E.\(^ {132,133}\)
None of the formulations of garlic have been shown to produce a statistically significant effect on the cholesterol level.\textsuperscript{134} Guggulipid has not been found to be effective in lowering LDL-C levels and may cause a hypersensitivity rash in some individuals.\textsuperscript{135}

### 8.1.7. Assessing response to TLC

The lipid profile should be measured 6-12 weeks after initiating TLC. Generally, TLC may reduce lipid levels (at best) up to 20%. For individuals who attain target lipid levels, they should continue these lifestyle changes life-long to maintain these effects. They can be assessed every 6 months with a full lipoprotein analysis.

On the other hand, if these levels are not achieved, patient compliance should be re-assessed and TLC intensified. They are then reassessed after 6-12 weeks. There is a genetically determined inter-individual variability in the response to diet. Thus poor response to TLC is not always due to non-compliance.

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

When a decision has been made to start drug therapy, TLC must still be continued indefinitely because it provides substantial additive LDL-C lowering effects.\textsuperscript{136}

**Key messages:**

- A multifactorial lifestyle approach is recommended to reduce the risk of CVD.\textsuperscript{1,8}
- In patients without CVD or CHD risk equivalents, a period of at least 6-12 weeks is given to assess the effectiveness of TLC before considering drug therapy.\textsuperscript{1,6}
8.2. DRUG THERAPY

Therapeutic Lifestyle Change forms an integral component in the management of dyslipidaemia. In secondary dyslipidaemia, efforts should be made to correct the underlying cause.

8.2.1 Lipid Lowering Drugs

In those with established CVD / CHD risk equivalents, drug treatment will need to be initiated in conjunction with TLC (Table 8, pg 33). There are 5 major groups of anti-lipid drugs. (Table 9, pg 41)

8.2.1.1 HMG CoA Reductase Inhibitors (Statins)

Statins are inhibitors of HMG CoA reductase, the rate limiting enzyme in hepatic cholesterol synthesis. They are the most effective drug class and the treatment of choice in reducing LDL-C. They are suitable first-line agents in familial hypercholesterolemia, for primary prevention of CVD, secondary prevention of CVD and CHD equivalents.

They have moderate effect in lowering TG and in elevating HDL-C. Treatment is initiated at the recommended starting dose with the evening meal or at bed time except for long-acting statins that can be taken at any time. The dose is then adjusted accordingly to achieve target levels. Serum lipids and alanine aminotransferase should be measured at 6-8 weeks after starting treatment and thereafter as necessary especially when doses are increased.

Statin therapy is contraindicated in pregnancy and lactation. It should not be prescribed to women of child bearing potential unless adequate contraception is taken.
### Table 9: Major Anti Lipid Drug Classes *(Adapted from ATPIII)*

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

* cyclosporin, macrolide antibiotics, various anti fungal agents and cytochrome P-450 inhibitors (fibrates and nicotinic acid should be used with appropriate caution)
** gemfibrozil and repaglinide
*** 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.
Recent concern about statin and new onset diabetes has not been substantiated. In fact statins have been proven to prevent CV events in diabetics with no overt CVD.\textsuperscript{137,138} There is no evidence that patients on statins have increased risk of cancer, poor memory and renal toxicity.

The routine use of Co enzyme Q 10 to prevent muscle toxicity is unproven and therefore not recommended.

**Recommended Dosages for Statins***

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended initiating dose</th>
<th>Usual dose range</th>
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</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>20 mg</td>
<td>10-80 mg/day in single or divided doses</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>20 mg</td>
<td>10-40 mg daily</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20 mg</td>
<td>5-80 mg once daily</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20 mg</td>
<td>20-80 mg/day single or divided doses</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10 mg</td>
<td>10-80 mg once daily</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10 mg</td>
<td>10-20 mg once daily</td>
</tr>
</tbody>
</table>

* As stated in MIMS,Malaysia

**8.2.1.2. Fibric Acid Derivatives (Fibrates)**

Fibrates are Peroxisome Proliferator Activated Receptor (PPAR)–\(\alpha\) agonist which in turn stimulates synthesis of fatty acid oxidation. Fibrates are particularly useful in individuals with combined (mixed) dyslipidaemia and hypertriglyceridaemia as they reduce serum TG levels and increase HDL-C effectively. Fibrates are alternative treatment in individuals with mild to moderate hypercholesterolemia who are statin intolerant.

* In men with established CHD with low LDL-C and HDL-C, fibrates have been shown to improve CV outcome. In individuals with T2DM, fibrates reduced the composite endpoint of CV death, CV events and the need for coronary and carotid revascularization.\textsuperscript{43,47}
Doses of fibrates need to be adjusted in the presence of CKD. Serum alanine aminotransferase should be monitored when starting therapy or when doses are increased.

**Recommended Dosages for Fibrates***

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bezafibrate</td>
<td>200 mg daily increasing to a maximum dose of 200 mg tds (regular) or 400 mg daily (sustained release)</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>300 mg daily or in divided doses (regular) or 200 mg daily (micronised) or 160 mg daily (supra)</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>600-1500 mg daily in divided doses (regular) or 900 mg daily (sustained release)</td>
</tr>
<tr>
<td>Ciprofibrate</td>
<td>100 mg daily</td>
</tr>
</tbody>
</table>

*As stated in MIMS, Malaysia

8.2.1.3. Bile Acid Sequestrants (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. Monotherapy has a modest effect on CHD in primary prevention. Resins are therefore not suitable as monotherapy in combined hyperlipidaemia. Combination with a statin may be necessary in severe hypercholesterolaemia.

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

This class of drug is currently not available in the Malaysian market.

8.2.1.4. Nicotinic Acid (Niacin) and its derivatives

Nicotinic acid decrease mobilization of free fatty acids from adipose tissues. It is very effective in increasing HDL-C and also effectively lowers both TC and TG levels. It is also the first to show mortality reduction in individuals with CHD.48
However, its side effects (particularly flushing and gastrointestinal side effects) tend to limit compliance. Acipimox is a derivative of nicotinic acid which produces fewer side effects (especially less cutaneous flushing) and does not worsen glucose tolerance. Tredaptive is a combination of modified-release nicotinic acid and laropiprant (a prostaglandin inhibitor) which will reduce the flushing caused by nicotinic acid.

**Recommended Dosages:**

Nicotinic acid (Niacin) is available as capsules of 100 mg or 500 mg, and sustained release form:

- Starting dose: 150-300 mg daily in divided doses, titration of dose up to 2 g/day (Usual dose). It should be taken with meals to reduce gastrointestinal side effects.

Acipimox is currently not available in the Malaysian market.

**8.2.1.5 Cholesterol Absorption Inhibitors**

Cholesterol absorption inhibitors selectively block intestinal absorption of both dietary and biliary cholesterols and other phytosterols. This leads to a reduction in hepatic cholesterol delivery - a mechanism which complements the action of statins. It is indicated as monotherapy for primary hypercholesterolemia in patients who cannot tolerate statin or fibrate. It can also be used in combination with statins to further lower LDL-C. When used with statins, the lipid lowering effects appears to be synergistic.

**Recommended Dose:**

- Ezetimibe 10 mg daily

**8.2.2. Recommended Drug Treatment for Dyslipidaemia**

The choice of drugs will depend on the type of dyslipidaemia. (Table 10, pg 45)
### Table 10: Suggested Drug Therapy for Dyslipidaemia

<table>
<thead>
<tr>
<th>Lipid Values</th>
<th>Initial Drug</th>
<th>Suggested Addition (in order of preference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C &gt; 3.4 mmol/l</td>
<td>Statins</td>
<td>Resin</td>
</tr>
<tr>
<td>TG &lt; 2.3 mmol/l</td>
<td></td>
<td>Ezetimibe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nicotinic Acid</td>
</tr>
<tr>
<td>LDL-C ≥ 3.4 mmol/l</td>
<td>Statins</td>
<td>Fibrates</td>
</tr>
<tr>
<td>TG : 2.3-5.7 mmol/l</td>
<td></td>
<td>Nicotinic Acid</td>
</tr>
<tr>
<td>HDL-C &lt; 1.0 mmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG &lt; 5.7 mmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C &lt; 2.6 mmol/l</td>
<td>Statins</td>
<td>Fibrates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nicotinic Acid</td>
</tr>
<tr>
<td>If:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C &gt; 2.6 mmol/l</td>
<td>Statins</td>
<td>Fibrates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nicotinic Acid</td>
</tr>
<tr>
<td>TG &gt; 5.7 mmol/L</td>
<td>Fibrates</td>
<td>Nicotinic Acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Omega 3 FA</td>
</tr>
</tbody>
</table>

LDL-C reduction with statin treatment remains the cornerstone of lipid lowering therapy to reduce risk of CVD. If target lipid goals have not been achieved after 8-12 weeks of optimal monotherapy, combination therapy is suggested (Table 10, pg 45). Combination of statin and cholesterol absorption inhibitors have been shown to reduce CV events and renal outcomes in patients with CKD.\(^{141}\)

Some combination therapies carry a potential for adverse effects, especially myositis (particularly combination of fibrates plus statins) although the incidence is still low (0.5 - 2.5%). For monotherapy, the incidence of myopathy is 0.1 - 0.5%.\(^{142,143}\) The combination of gemfibrozil and statin is discouraged. If used, caution and close monitoring should be stressed.

#### 8.2.3. Monitoring and Duration of Therapy

It should be stressed that these individuals will be on lifelong therapy. It is therefore important to assess them on a regular basis,
ie. in terms of response to treatment and to look out for possible side-effects related to the drugs. After starting drug therapy, LDL-C level should be measured at 6-8 weeks and drug doses titrated if necessary. Once target lipid levels are achieved, a 4-6 monthly follow up is recommended.

Monitoring of ALT is necessary if statins and fibrates are used for treatment. Liver function tests should be carried out before and within 1-3 months of starting treatment. Statins should be discontinued if transaminase levels rise to at 3 times the upper limit of normal. If the levels are elevated between 2 to 3 times upper limit of normal, the trend should be monitored at monthly intervals. If the levels are stable, they only need be checked periodically or if the dose of statin or fibrate is increased. If myositis is suspected, then creatine kinase levels should be measured. If the level is more than 10 times the upper limit of normal, then the drug should be discontinued.

### 8.2.4 Pharmacoeconomics of Lipid Lowering Therapy

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. Local data is lacking at this present time.

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 favorable even for patented statins.\(^{144}\)

A substantial proportion of statin acquisition cost was offset by reduction in health care resource use as a consequence of lesser CV events. Even taking into consideration the cost of patented statin and measurement of hs- CRP, statin use is cost effective even in primary prevention of medium risk individuals.\(^{145}\) This is also true for fibrate treatment in T2DM.\(^{146}\)

Cost effective analysis showed that prescribing generic statins may not necessarily translate into the most cost effective option for treating dyslipidemia.\(^{147}\)
8.3 LDL-C APERESIS

LDL-C apheresis is indicated in patients with homozygous familial hypercholesterolemia (FH) who do not respond satisfactorily to maximum multiple drug therapy.148-153 This form of treatment may also be considered in individuals with severe heterozygous FH and progressive coronary artery disease who do not achieve target lipid levels with maximal drug therapy (high intensity statin at maximal dose with ezetimibe).148-153

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.154,155

9. MANAGEMENT IN SPECIAL CONDITIONS

9.1. Specific Lipid Disorders

9.1.1. Elevated TG
There is evidence of a strong association between TG levels and CVD.44,45,46 This may in part be due to its association with the other CV risk factors found in the metabolic syndrome. Very high serum TG (> 5.7 mmol/L) can give rise to acute pancreatitis and needs urgent and definitive treatment. High (2.3-5.7 mmol/L) and borderline high levels (1.7-2.3 mmol/L) of TG are a common association with low HDL cholesterol, small dense LDL particles and insulin resistance.
9.1.1.1. Targets of therapy

In individuals with elevated TG, the primary target of therapy remains achieving LDL-C goal depending upon the individual’s global risk. (Table 8, pg 34)

In individuals where the TG > 2.3 mmol/L, non HDL-C is more representative of all atherogenic lipoproteins than LDL-C. (see also section 2 and 4.4) In these individuals, the secondary target of therapy is non HDL-C as listed in Table 11, pg 48.

Another secondary target of therapy is TG < 1.7 mmol/L.

Table 11: Targets of LDL-C and non HDL-C

<table>
<thead>
<tr>
<th>Global Risk</th>
<th>Target LDL–C levels (mmol/L)</th>
<th>non HDL-C levels corresponding to LDL-C goals (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 risk factor</td>
<td>&lt; 4.1</td>
<td>&lt; 4.9</td>
</tr>
<tr>
<td>2 or more risk factors*</td>
<td>&lt; 3.4**</td>
<td>&lt; 4.1</td>
</tr>
<tr>
<td>CHD and CHD risk Equivalents</td>
<td>2.0 to &lt; 2.6</td>
<td>&lt; 3.4</td>
</tr>
<tr>
<td></td>
<td>&lt; 2.0</td>
<td>&lt; 2.6</td>
</tr>
</tbody>
</table>

* These include individuals with multiple risk factors but a 10 year risk of CVD of < 20%
** Optional target <2.6mmol/L in certain high risk individuals. See Flowchart II & III

9.1.1.2. Classification of TG (see Table 12, pg 48)

With reference to Table 12, pg 50:

- Factors contributing to elevated TG include: obesity and overweight, physical inactivity, cigarette smoking, excessive alcohol intake, high carbohydrate intake (>60% of energy intake), T2DM, chronic kidney disease, nephrotic syndrome, Cushing’s disease, lipodystrophy, pregnancy and various drugs {corticosteroids, beta-blockers, retinoids, oral estrogens (not transcutaneous estrogen), tamoxifen, protease inhibitors for AIDS}. 
• Genetic disorders associated with high TG (familial combined hyperlipidaemia, familial hypertriglyceridaemia and familial dysbetalipoproteinaemia)

9.1.1.3. Management of elevated TG (see Appendix VI, pg 78)

In individuals with mixed hyperlipidaemia, the primary target of therapy is to achieve LDL-C goal.

In those individuals with:
• TG between 2.3 and 4.5mmol/l the secondary target of therapy is non HDL-C
• TG > 4.5mmol/L, the primary target of therapy is non HDL-C.

Once LDL-C target has been achieved, the next step is to target TG < 1.7 mmol/L.

a) **Borderline high TG (1.7–2.3 mmol/L)**

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

• Lifestyle changes of weight reduction, low carbohydrate diet, control of diabetes or insulin resistance, exercise, reduction of alcohol intake and cessation of smoking.\[106,109,112,113,118-121\]
• Medications are rarely required.

b) **High TG (2.3–5.7 mmol/L)**

Treatment should include:

• Lifestyle changes as outlined above.
• Ensure diabetes if present is controlled.
• Drug therapy should be considered in high risk individuals.

There are two options to achieve targets:\[139:\]

- intensifying statin therapy if LDL-C target not achieved\[156\
- adding fibrates or niacin as a combination therapy to statin\[157,158,159\
- caution should be exercised when gemfibrozil is used in combination with statins because of the significant risk of rhabdomyolysis.\[141,142\]
<table>
<thead>
<tr>
<th>Classification of serum TG</th>
<th>Causes of elevated TG</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal TG (&lt; 1.7 mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borderline High TG (1.7-2.3 mmol/L)</td>
<td>• Acquired causes - Overweight and obesity - Physical inactivity - cigarette smoking - excess alcohol intake - high carbohydrate intake (&gt; 60% of total energy) • Secondary causes • Genetic causes various genetic polymorphism</td>
<td>• Marker for atherogenic dyslipidemia - elevated small LDL particles - Low HDL-C • Marker for the metabolic syndrome - elevated BP - insulin resistance and glucose intolerance - prothrombotic state - proinflammatory state</td>
</tr>
<tr>
<td>High TG (2.3-5.7 mmol/L)</td>
<td>• Acquired causes - same as for borderline high TG (usually combined with foregoing causes) • Secondary causes • Genetic causes - familial combined hyperlipidemia -familial hypertriglyceridemia -polygeneic hypertriglyceridemia - familial dysbetalipoproteinemia</td>
<td>• Elevated atherogenic-remnant lipoproteins • Marker for other components of atherogenic dyslipidemia (see above) • Marker for the metabolic syndrome (see above)</td>
</tr>
<tr>
<td>Very high TG (≥ 5.7mmol/L)</td>
<td>• Usually combined causes - same as for high TG •Familial lipoprotein lipase deficiency •Familial apolipoprotein C-11 deficiency</td>
<td>• Metabolic syndrome,- T2DM and increased risk for CHD • Increased risk for acute pancreatitis • Chylomicronemia syndrome - eruptive skin xanthomas - hepatic steatosis - lipemia retinalis - mental changes - high risk for pancreatitis</td>
</tr>
</tbody>
</table>
There are no clinical trial evidence that show a reduction in CVD events with drug therapy in individuals with only elevated TG both in primary and secondary prevention. (Appendix VI, pg 84)

c) Very high TG > 5.7 mmol/L:

When TG is extremely high (>10mmol/L) treatment goal is to prevent acute pancreatitis.

Treatment include:

- Start with a fibrate or nicotinic acid
  - Gemfibrozil and Fenofibrate lower TG by about 70%.\textsuperscript{43,47,160,161}  
  - Nicotinic acid is effective at doses of above 2gm per day.\textsuperscript{139,162}  
- Very low fat diets (< 15% of calorie intake) and lifestyle changes (See Section 8.1)\textsuperscript{106,111,139}  
- Severe hypertriglyceridaemia associated with uncontrolled diabetes warrants initiation of insulin therapy. The TG level will improve but may not normalize.\textsuperscript{IIa,B}  
- Fish oils which contain long chain omega-3 polyunsaturated fatty acids can also lower TG. Doses of 3 to 9 gm per day can lower TG by up to 50%.\textsuperscript{139,163} They can be considered as an addition to fibrate or nicotinic acid.  
- Statins are not useful as a first line therapy in this situation.

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

9.1.2. Low HDL-C and High TG:

Low HDL-C and high TG are seen in insulin resistance states and very high carbohydrate intakes.\textsuperscript{I,A}  

Treatment of this dyslipidaemia in individuals with CVD or CHD risk equivalents is aimed at lowering LDL-C to target.\textsuperscript{164} The choice of anti lipid drug will depend upon the level of LDL-C (Table 10, pg 45). If the HDL-C is still low despite adequate TLC then consider,

- fibrates or niacin if LDL-C is < 2.6mmol/L.\textsuperscript{43,47,160,161,162}  
- statin if LDL-C is > 2.6mmol/L\textsuperscript{165,166}
9.1.3. Isolated Low HDL-C

Individuals with isolated low HDL-C have HDL-C < 1.0 mmol/L and TG < 1.7 mmol/L. Low HDL-C is an independent major risk factor for CVD. The major causes are obesity, physical inactivity, cigarette smoking and genetic factors. There are however no large outcome studies to date showing that increasing HDL-C improves CVD outcomes.

Treatment for isolated low HDL-C is mainly aimed at those individuals with CVD or CHD risk equivalent.

Statin is still the mainstay of treatment even in patients with low LDL-C (<2.6 mmol/L). Statin trials have showed that lowering LDL-C in persons with isolated low HDL-C, significantly reduces CVD risk.

Fibrates have also been shown to reduce major CVD events in persons with isolated low HDL-C. This benefit has been attributed in part to the HDL-C raising effects of fibrates.

Key messages:

- In patients with isolated hypertriglyceridemia, isolated low HDL-C or its combination, the primary goal of treatment is lowering LDL-C to target.
- The other targets of therapy are lowering non HDL-C (if TG > 2.3mmol/L) to target, maintaining TG < 1.7 mmol/L and HDL-C > 1.0 mmol/L.

9.2. Diabetes Mellitus (T2DM)

Diabetes (T2DM) is a CHD risk equivalent. Recent long-term follow up studies showed that the benefits of intensive glucose control was not apparent early on but a legacy effect of a significant reduction in CV events was realized only 9-10 years after good glycaemic control. Despite this, the CV risk still remains high when compared to non-diabetics. Thus efforts must also be directed to control hypertension, lipids and other abnormalities.
Optimal Lipid values in individuals with diabetes are:

- **Primary target:**
  - LDL-C < 2.6 mmol/L (<1.8 mmol/L for DM with established CVD)

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

These targets are usually not achievable by TLC or glucose control. Improvement of glycaemic control alone will not fully correct the atherogenic dyslipidaemia. (See Table 13, pg 53)

**Table 13: Lipid Lowering Drug Therapy In Diabetics**

<table>
<thead>
<tr>
<th>Lipid Goal</th>
<th>Initial Drug</th>
<th>Suggested Addition In order of preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower LDL–C</td>
<td>Statins</td>
<td>Fibrates</td>
</tr>
<tr>
<td>Increase HDL-C</td>
<td>Fibrates* or,</td>
<td>Statins***</td>
</tr>
<tr>
<td></td>
<td>Nicotinic Acid**</td>
<td></td>
</tr>
<tr>
<td>Lower TG</td>
<td>Fibrates</td>
<td></td>
</tr>
<tr>
<td>Treat Combined Hyperlipidemia</td>
<td>Statins***</td>
<td>Fibrates Nicotinic Acid</td>
</tr>
</tbody>
</table>

* statins should be the initial drug if LDL-C goal is not achieved.
** with careful monitoring and keeping the dose < 1.5 gm / day.
*** high doses may be required.

Statins should be initiated for all individuals above the age of 40 years with T2DM regardless of baseline LDL-C.\(^{170}\)

Target should be to LDL-C <2.6 or 30-40% below baseline LDL-C.\(^{169,170}\) For those with T2DM and with established CVD, LDL-C should be <1.8 mmol/L.\(^{169}\)
Key messages:

- Control of glycaemia alone is inadequate in preventing CV events. Concomitant treatment of dyslipidaemia, hypertension and other metabolic abnormalities are also important. [IA]
- Target LDL-C goal in individuals with diabetes is <2.6 mmol/L. [IA] In the presence of established CVD, LDL-C should be <1.8 mmol/L. [IA]

9.3 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 depending on the acuteness and severity of the coronary occlusion.

9.3.1. Acute Coronary Syndromes (ACS)

Early initiation of statin therapy soon after admission for ACS is safe and improves outcome regardless of baseline LDL-C levels in patient with ACS. [IA,171-175] These benefits are independent of the lipid lowering effects of statins.

Patient with ACS should be treated with a higher intensity statins. More aggressive lipid lowering further lowers cardiovascular event rates. [IA,171,172,176-179]
Lipid management includes:

**I**

Assessment of a fasting lipid profile for all patients, within 24 hours of hospitalization.

**IIa**

Statins, in the absence of contra-indications, regardless of baseline LDL-C and diet modifications, should be initiated soon after admission and continued indefinitely to provide life long benefits.\(^{180-182}\) Statin treatment should not be delayed until lipid levels are available or management of other modifiable risk factors.

Lipids should be re-tested about 2-3 months after the start of statin therapy.

**IIa**

LDL-C level should be targeted <2.0mmol/L for most patients.

**IIa, B**

Patients with low HDL-C may benefit from fibrates or nicotinic acid.\(^{43,162}\)

### 9.3.2. Coronary Revascularizations

**IIa, B**

Pre-treatment with statins 7 days prior to elective PCI has been shown to reduce post-procedure MI.\(^{183}\)

**IIa, B**

A loading dose of statins pre-procedure has also been shown to reduce post-procedure MI in individuals who are statin-naïve and those already on regular statins.\(^{184,185}\)

**IIa, A**

All cardiac patients post-revascularization (CABG, PCI) should be on long term statin therapy, the dose being adjusted to achieve target lipid levels.\(^{186,187}\)

### 9.3.3 Stable CAD

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

In individuals with stable CAD, PCI did not confer additional CV benefits when added to optimal medical therapy as an initial management strategy.\(^{188}\). Those individuals who had undergone
PCI however, had improvement in their quality of life during follow up.\textsuperscript{189}

Irrespective of the baseline LDL-C level, statin therapy reduces the risk of major CV events by 24%.\textsuperscript{29}

Individuals with stable CAD should be treated with optimal medical therapy using a combination of antiplatelet agents, statins, β-blockers and angiotensin converting enzymes inhibitors.\textsuperscript{190}

Statin therapy should always be considered for individuals with stable coronary artery disease.

Therapy should aim at statin dosages documented to reduce morbidity and mortality in clinical trials.

### Key messages:
- Statins should be started early in individuals with ACS, and on all post revascularisation individuals irrespective of their baseline cholesterol levels.\textsuperscript{IA}
- In high risk individuals, high intensity statin treatment confers more benefit.\textsuperscript{IA}
- Statins are an integral component of optimal medical therapy in CAD individuals.\textsuperscript{IA}

### 9.4. Hypertension

CV risk depends not only on blood pressure but also on associated risk factors, clinical conditions and target organ damage.\textsuperscript{191}

Hypertensive individuals without established CVD but with moderate to high CV risk (≥ 10% risk of events in 10 years) should also be considered for statin therapy irrespective of baseline LDL-C levels.\textsuperscript{192}

The choice of antihypertensive agent should be individualized. Certain antihypertensive agents may have an adverse effect on lipid levels eg high dose thiazides increases TC, LDL-C and TG levels, β-blockers with no intrinsic sympathetic activity reduce HDL-C and increase serum TG. These effects are modest and should not affect the selection of an antihypertensive agent.\textsuperscript{139}
Key messages:

- Hypertension and elevated cholesterol levels often coexist and synergistically increase the risk of developing CVD and treatment of both conditions reduces CVD events.
- Statins should be considered in high risk hypertensive individuals. I,A

9.5 Stroke

Recent studies have shown an association between raised serum lipids and risk of ischaemic stroke.¹⁹³

Statins have been shown to prevent ischaemic stroke in high risk individuals.²⁹,¹⁹⁴

Individuals with ischaemic stroke or transient ischaemic attacks benefit from lipid modifying therapy.¹⁸¹,¹⁹⁴,¹⁹⁵ High intensity statins has been found to prevent recurrent stroke⁷.

In-hospital lipid testing should be performed in individuals with ischaemic stroke and TIA.¹⁹⁶,¹⁹⁷

Statin therapy should be considered in individuals with LDL-C ≥2.6 mmol/L ¹⁹⁸,¹⁹⁹.

Key messages:

- Statins have been shown to reduce the incidence of ischaemic strokes when used in high risk individuals. I,B
- Lipid lowering therapy with statins should be considered in all individuals with previous ischaemic stroke or transient ischaemic attack. I,B
9.6. Renal disease
Chronic Kidney Disease (CKD) is associated with significant CV morbidity and mortality.\(^{200,201}\) Mortality increases progressively with worsening renal function. The risk of death from CVD is higher than the risk of eventually requiring renal replacement therapy.\(^{202,203}\) Currently, there are differing views about recognizing CKD as a CHD Risk Equivalent although all stages of CKD including individuals with asymptomatic microalbuminuria are at increased CVD risk.\(^{139,200,204-209}\) They should be screened for traditional risk factors and treated according to their determined risk.

Dyslipidaemia occurs in all stages of CKD, on dialysis, after renal transplantation and in individuals with the nephrotic syndrome.

In individuals with CKD and in those on dialysis, the main lipid abnormalities are elevated levels of TG, low levels of HDL-C and elevated levels of Lp (a). The TC is usually normal or low. A number of studies have shown that in these individuals, lower levels of TC are associated with increased mortality most likely due to the adverse effects of malnutrition and chronic inflammation.\(^{210-217}\)

In the nephrotic syndrome both TC and LDL-C are elevated. The lipid abnormalities may improve or resolve following resolution of the nephrosis. If the dyslipidaemia still persists, drug therapy should be considered.

Caution must be exercised when starting anti lipid drug therapy in individuals with renal insufficiency.

The use of fibrates in these individuals carries a higher risk of rhabdomyolysis and there is no proven long term CV benefits.\(^{218}\)

\[\text{IIb,B}\] In individuals with very high TG levels (more than 5.7 mmol/L), low dose fibrates may be initiated cautiously to prevent pancreatitis.\(^{43,47,160,161}\)

\[\text{IIa,B}\] Omega 3 Fish oils (at a dose of 4 gm/day) may also be used.\(^{219}\)

\[\text{IIa,B}\] Statins have been shown to have differential effects on the kidney. Some statins reduce proteinuria and slow the rate of progression of renal disease while others have been neutral.\(^{220,221}\)
In individuals with CHD and mild to moderate CKD, statins have been shown to be beneficial.\textsuperscript{29,218}

A recently presented large prospective trial in patients with stages 3-5 CKD without CHD, showed that the use of a statin and ezetimibe combination resulted in a significant reduction in atherosclerotic events.\textsuperscript{131,222,223}

A third of these patients were on dialysis and they did not show any benefit, a finding consistent with that of previous studies.\textsuperscript{141,222,223}

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

The initiating dose of anti lipid drugs in patients with CKD should be lower. (Table 14, pg 60).

**Key messages:**
- Individuals with CKD have high CV Risk.
- Statins have been found to be beneficial in individuals with CHD and mild to moderate CKD.\textsuperscript{1,8}
- In individuals on dialysis, the benefits of lipid lowering therapy are doubtful.\textsuperscript{11b,B}
- Statins are safe in CKD.\textsuperscript{1,8}
- Fibrates should be used cautiously in individuals with CKD and very high TG.\textsuperscript{11b,B}
### Table 14. Dosing Modifications for Lipid-Lowering Drugs in CKD

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mild GFR 60–90 ml/min/1.73 m²</th>
<th>Moderate GFR 15–59 ml/min/1.73 m²</th>
<th>Severe GFR &lt;15 ml/min/1.73 m²</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STATINS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>No</td>
<td>Not defined</td>
<td>Not defined</td>
<td>↓dose to one-half at GFR &lt;30 ml/min/1.73 m²</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>No</td>
<td>↓to 50%</td>
<td>↓to 50%</td>
<td>↓dose to one-half at GFR &lt;30 ml/min/1.73 m²</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Start at 10 mg/day for GFR &lt;60 ml/min/1.73 m²</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>No</td>
<td>5–10 mg</td>
<td>Avoid</td>
<td>Contraindicated for GFR &lt;30 ml/min/1.73 m², max dose 10 mg/day</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>No</td>
<td>No</td>
<td>↓to 50%</td>
<td>Start at 5 mg if GFR &lt;10 ml/min/1.73 m²</td>
</tr>
<tr>
<td><strong>NONSTATINS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>No</td>
<td>No</td>
<td>↓to 50%</td>
<td>34% kidney excretion</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Not absorbed</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Not absorbed</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>↓to 50%</td>
<td>↓to 25%</td>
<td>Avoid</td>
<td>May ↑serum creatinine</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NLA recommends a dose of 600 mg/day for GFR 15–59 ml/min/1.73 m² and avoiding use for GFR &lt;15 ml/min/1.73 m²</td>
</tr>
</tbody>
</table>
10. MANAGEMENT IN SPECIAL GROUPS

10.1. Women

Women develop heart disease about 10 to 15 years later than men. 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. In premenopausal women, CVD tends to occur in those with T2DM and multiple risk factors.

In secondary prevention, women have similar benefits on CVD outcomes as men. Statins should be the drug of first choice.

Statins should not be used in women who are pregnant, intend to become pregnant or who are breast feeding.

In women who have normal LDL-C but low HDL-C and high TG, fibrates may be used.

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

Women at high risk who do not achieve their target levels should be considered for pharmacological intervention although there is little data on the effect of lipid lowering therapy on CVD events for primary prevention in women. Current practice is to treat these women in the same manner as men based on extrapolation of benefit in men at similar risk.

Women with genetic dyslipidaemias such as familial hypercholesterolemia with very high levels of TC or LDL-C may be considered for lipid lowering therapy from the outset.

10.2. Children & Adolescents

Atherosclerosis begins in childhood, the rate of progression depending on the presence and number of risk factors and their severity. Risk factors for atherosclerosis in children include:

61
• obesity and the metabolic syndrome\textsuperscript{238}
• T2DM
• post organ transplantation
• systemic lupus erythematosis
• nephrotic syndrome
• HIV infections

These risk factors have been shown to persist into adult life and lead to premature CVD.

Screening begins with an assessment of family history for CVD or genetic dyslipidaemia.\textsuperscript{239} In addition, obese and overweight children and those with the risk factors mentioned above should also have a full lipoprotein profile, BP measurement and a fasting glucose assessment.

Children whose lipid levels are significantly elevated should be referred to specialists interested in this field.

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

In children with elevated cholesterol levels, statins are the drug of choice.\textsuperscript{240}

There has been limited data on the use of niacin, fibric acid derivatives and ezetimibe in children.

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 counseled prior to initiation of drug therapy.

10.3. Elderly (> 65 years)

 Increasing age is a major risk factor for CVD and death. For secondary prevention, the elderly derive a greater absolute benefit from lipid lowering therapy.\textsuperscript{241,242}
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.

Renal function should be assessed and drug dosages adjusted accordingly.

The benefits of lipid lowering therapy for primary prevention in elderly individuals with no other risk factors besides dyslipidaemia are less well established. Global risk assessment using standard risk factors as mentioned earlier is generally less reliable in older persons. Clinical judgement and consideration of co-morbid factors, co-existing disease and functional age become essential in deciding the need for drug therapy in this situation. (see Table 8, pg 34)

Key messages:
- Women and the elderly with CHD and CHD risk equivalent should be treated in the same manner as man. $^{1A}$
- Children with very high cholesterol levels benefit from statin therapy. $^{1A}$

11. ADHERENCE, COMPLIANCE AND QUALITY ASSURANCE

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

Lack of adherence threatens the success of the guideline recommendation and implementation. Clinical trials have shown that the amount of risk reduction achieved is related to the level of adherence to treatment.$^{243,244,245}$ 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.
To improve adherence and compliance the following are recommended:

- **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

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

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

- Measurement of lipid values
- Risk categorization of patients
- Appropriate usage of drug therapy
- Achieving primary lipid target goal: LDL-C to target
- Achieving secondary lipid target goals: HDL-C and TG to target
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### APPENDIX I: APOLIPOPROTEINS : MAJOR CATEGORIES

<table>
<thead>
<tr>
<th>MAJOR CLASSES</th>
<th>SUBCLASSES/ISOFORMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo A</td>
<td>apo A-I, apo-II, apo A-IV, apo A-V</td>
</tr>
<tr>
<td>Apo B</td>
<td>apo B-48, apo B-100</td>
</tr>
<tr>
<td>Apo C</td>
<td>apo C-I, apo C-II, apo C-III, apo C-IV</td>
</tr>
<tr>
<td>Apo D</td>
<td>apo C-IV</td>
</tr>
<tr>
<td>Apo E</td>
<td>apo E-2, apo E-3, apo E-4</td>
</tr>
<tr>
<td>Apo H</td>
<td>apo H</td>
</tr>
</tbody>
</table>

### APPENDIX II: RISK FACTORS FOR MI AND STROKE IN THE INTERHEART AND INTERSTROKE STUDIES*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>INTERSTROKE (all stroke; 3000 cases, 3000 controls)*</th>
<th>INTERHEART (acute myocardial infarction; 15152 cases, 14820 controls)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>34.6% (30.4-39.1)</td>
<td>17.9% (15.7-20.4)</td>
</tr>
<tr>
<td>Smoking</td>
<td>18.95 (15.3-23.1)</td>
<td>35.7% (32.5-39.1)</td>
</tr>
<tr>
<td>Waist-to-hip ratio (abdominal obesity)</td>
<td>26.5% (18.8-36.0)</td>
<td>20.1% (15.3-26.0)</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet risk score</td>
<td>18.8% (11.2-29.7)</td>
<td>13.7% (9.9-18.6)</td>
</tr>
<tr>
<td>Fruits and vegetables daily</td>
<td>..</td>
<td></td>
</tr>
<tr>
<td>Regular physical activity</td>
<td>28.5% (14.5-48.5)</td>
<td>12.2% (5.5-25.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.0% (2.6-9.5)</td>
<td>9.9% (8.5-11.5)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>3.8% (0.9-14.4)</td>
<td>6.7% (2.0-20.2)</td>
</tr>
<tr>
<td>Psychosocial factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All psychosocial factor</td>
<td>4.6% (2.1-9.6)</td>
<td>32.5% (25.1-40.8)</td>
</tr>
<tr>
<td>Psychosocial stress</td>
<td>5.2% (2.7-9.8)</td>
<td>..</td>
</tr>
<tr>
<td>Depression</td>
<td>4.6% (2.1-9.6)</td>
<td>..</td>
</tr>
<tr>
<td>Cardiac causes</td>
<td>6.7% (4.8-9.2)</td>
<td>..</td>
</tr>
<tr>
<td>Ratio of apolipoproteins B to A1</td>
<td>24.9% (15.7-37.1)</td>
<td>49.2% (43.8-54.5)</td>
</tr>
</tbody>
</table>


APPENDIX III: BODY MASS INDEX

Calculation of body mass index (BMI) is one way of determining the ideal weight for an individual. BMI is the relationship of body weight to height. Increased BMI is associated with increased mortality and morbidity. The predictive value of BMI is enhanced by taking the waist circumference into consideration as well.

Body Mass Index = \( \frac{\text{Weight in kg}}{(\text{Height in m})^2} \)

### CLASSIFICATION OF WEIGHT BY BMI

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>BMI (Kg / m²)</th>
<th>Risk of co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>Low (but increased risk of other clinical problems)</td>
</tr>
<tr>
<td>Normal range</td>
<td>18.5-22.9</td>
<td>Average</td>
</tr>
<tr>
<td>Overweight</td>
<td>&gt; 23.0</td>
<td></td>
</tr>
<tr>
<td>Pre-Obese</td>
<td>23.0-27.4</td>
<td>Increased</td>
</tr>
<tr>
<td>Obese I</td>
<td>27.5-34.9</td>
<td>Moderate</td>
</tr>
<tr>
<td>Obese II</td>
<td>35.0-39.9</td>
<td>Severe</td>
</tr>
<tr>
<td>Obese III</td>
<td>&gt; 40.0</td>
<td>Very Severe</td>
</tr>
</tbody>
</table>

### APPENDIX IV: COMPARISON OF GLOBAL CORONARY AND CARDIOVASCULAR RISK SCORES

<table>
<thead>
<tr>
<th>Risk factors considered</th>
<th>Framingham</th>
<th>SCORE</th>
<th>PROCAM (Men)</th>
<th>Reynolds (Women)</th>
<th>Reynolds (Men)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>5,345</td>
<td>205,178</td>
<td>5,389</td>
<td>24,558</td>
<td>10,724</td>
</tr>
<tr>
<td>Age (y)</td>
<td>30 to 74;</td>
<td>19 to 80;</td>
<td>35 to 65;</td>
<td>&gt;45;</td>
<td>&gt;50;</td>
</tr>
<tr>
<td>Mean: 49</td>
<td>Mean: 46</td>
<td>Mean: 47</td>
<td>Mean: 52</td>
<td></td>
<td>Mean: 63</td>
</tr>
<tr>
<td>Mean follow-up, y</td>
<td>12</td>
<td>13</td>
<td>10</td>
<td>10.2</td>
<td>10.8</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Age, sex, total cholesterol, HDL cholesterol, smoking, systolic blood pressure, antihypertensive medications</td>
<td>Age, sex, total-HDL cholesterol ratio, smoking, systolic blood pressure</td>
<td>Age, LDL cholesterol, HDL cholesterol, smoking, systolic blood pressure, family history, diabetes, triglycerides</td>
<td>Age, HbA1C (with diabetes), smoking, systolic blood pressure, total cholesterol, HDL cholesterol, hsCRP, parental history of MI at &lt;60 y of age</td>
<td>Age, systolic blood pressure, total cholesterol, HDL cholesterol, smoking, hsCRP, parental history of MI at &lt;60 y of age</td>
</tr>
<tr>
<td>Endpoints</td>
<td>CHD (MI and CHD death)</td>
<td>Fatal CHD</td>
<td>Fatal/nonfatal MI or sudden cardiac death (CHD and CVD combined)</td>
<td>MI, ischemic stroke, coronary revascularization, cardiovascular death (CHD and CVD combined)</td>
<td>MI, stroke, coronary revascularization, cardiovascular death (CHD and CVD combined)</td>
</tr>
</tbody>
</table>
## APPENDIX V: LIPID LOWERING DIET

<table>
<thead>
<tr>
<th>PRINCIPLE</th>
<th>AMOUNT</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease dietary cholesterol</td>
<td>&lt; 200 mg / day</td>
<td>Reduce intake of organ meat (offal) eg liver, heart, brains, kidney. Limit to 3 oz once fortnightly. A small amount of prawn / crab / oysters / cockles may be taken once or twice a week if desired.</td>
</tr>
<tr>
<td>Decrease total fat/oil</td>
<td>&lt; 30% of total energy</td>
<td>Modify cooking methods – grill /steam / boil / bake / microwave to reduce use of oils and fats. Avoid oily / fatty food eg deep fat fried foods.</td>
</tr>
<tr>
<td>Types:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) saturated fat</td>
<td>7-10% (not more than 10% of total calorie intake)</td>
<td>Minimize the use of following – butter, hard margarine, full cream milk (including condensed milk) cream, high fat cheese, fatty meats, bacon and sausages, coconut oil, santan, products containing hydrogenated oil and some non dairy creamers. Choices may include the following: olive oil, sunflower oil, corn oil, palm oil, soybean oil, peanut oil and polyunsaturated margarine.</td>
</tr>
<tr>
<td>b) monounsaturated and polyunsaturated oils/margarine</td>
<td>Not more than 6 teaspoonsfuls per day to be used in cooking or as a spread</td>
<td></td>
</tr>
<tr>
<td>Increase intake of complex carbohydrate / grains and fiber</td>
<td>20-25 gm fiber / day. Include 2-3 servings of fruit and 3-4 servings of vegetables and 5-7 servings per day of grains</td>
<td>Sources of complex carbohydrates/grains: rice, bread, pasta, noodles and tuber Sources of fiber: fruits, vegetables, pulses, legumes and unrefined cereals.</td>
</tr>
<tr>
<td>Choose food high in protein but low in saturated fat</td>
<td>2-3 servings per day</td>
<td>Choices may include: chicken without skin, fish, Legumes and pulse (tofu, dhal, green peas and beans), egg whites, lean meat, skim milk and milk products (low fat milk may be used but some low fat milk may contain up to 50% of its original fat).</td>
</tr>
</tbody>
</table>

Consuming an egg a day does not substantially increase CVD risk.\(^{246,247}\) The method of cooking the egg is important.

APPENDIX VI: CONVERSION TABLE

Screen With Nonfasting Triglycerides

<table>
<thead>
<tr>
<th>&lt;200</th>
<th>≥200</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Follow-up as required</td>
<td>Fasting lipoprotein panel</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Optimal</th>
<th>Normal</th>
<th>Borderline</th>
<th>High</th>
<th>Very High</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 (&lt;1.14 mmol/L)</td>
<td>&lt;160 (&lt;1.7 mmol/L)</td>
<td>150–199 (1.7–2.3 mmol/L)</td>
<td>200–499 (2.3–5.7 mmol/L)</td>
<td>≥500* (≥5.7 mmol/L)</td>
</tr>
</tbody>
</table>

**Recommendations**

- **Weight loss**: Up to 5% → 5%–10% → 5%–10%
- **Carbohydrates**: 50%–60% → 50%–55% → 45%–50%
- **Added sugars**: <10% → 5%–10% → <5%
- **Fructose**: <100 g → 50–100 g → <50 g
- **Protein**: 15% → 15%–20% → 20%
- **Fat**: 25%–35% → 30%–35% → 30%–35%
- **TFA**: Avoid
- **SFA**: <7% → <5% → <5%
- **MUFA**: 10%–20% → 10%–20% → 10%–20%
- **PUFA**: 10%–20% → 10%–20% → 10%–20%
- **EPA/DHA**: 0.5–1 g → 1–2 g → ≥2 g
- **Aerobic activity**: at least 2x weekly → Pharmacologic therapy

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