BRUNEI DARUSSALAM NATIONAL HYPERLIPIDAEMIA GUIDELINES 2022

Cardiac Society Brunei Darussalam

CONTENTS

It gives me great pleasure to introduce the **2022 Brunei Darussalam National Hyperlipidaemia Guidelines**. The burden of cardiovascular disease in Brunei Darussalam remains high and remains one of the leading causes of death. Cardiovascular disease, and specifically atherosclerotic cardiovascular disease can be thought of as a preventable disease to some extent and is influenced heavily by lifestyle factors which are prevalent in today's modern society.

The Ministry of Health has recently published the **Brunei Darussalam Multisectoral Action Plan for the Prevention and Control of Noncommunicable Diseases (BruMAP-NCD) 2021–2015** building on the work from the previous action plan from 2013-2018. Cardiovascular disease in particular has been targeted as part of the action plan. Key areas include screening for risk factors for cardiovascular disease, strengthening integrated care between primary, secondary and tertiary centres, and the development of clinical practice guidelines to streamline the clinical management of hyperlipidaemia from primary to tertiary health care.

Hyperlipidaemia is a key risk factor for the development of atherosclerotic cardiovascular disease and one of the breakthroughs in modern therapeutics have been the development of statins to lower lipid levels and reduce the morbidity and mortality associated with atherosclerotic cardiovascular disease. The last guideline for the management of hyperlipidaemia in Brunei Darussalam was published in 2003 and there have been many developments since then. I hope the new guideline will help standardise management and offer practical tips to approaching a patient with hyperlipidaemia.

Lastly, I would like to thank the tireless efforts of all those involved in writing the guidelines. Building on the efforts of the Brunei Darussalam National Hypertension Guidelines in 2019, the Brunei Darussalam National Hyperlipidaemia Guidelines were envisaged to follow shortly after, but due to the dramatic effects of the COVID-19 pandemic these guidelines were significantly delayed. I would like to pay tribute to everybody who continued to work on these guidelines during these challenging times. Thank you.

YB Dato Seri Setia Dr Haji Mohammad Isham bin Haji Jaafar

Cardiovascular disease is unfortunately one of the leading causes of death in Brunei Darussalam. We know there are many well established risk factors for cardiovascular disease which include the classical risk factors of hypertension, diabetes, and hyperlipidaemia, all of which are highly prevalent in the Brunei Darussalam population.

It is therefore logical that strenuous efforts should be made to identify and treat these risk factors, to reduce the morbidity and mortality associated with cardiovascular disease. One of the main barriers to this effort is the lack of standardisation of diagnosis and treatment as in the past we have not had up-to-date guidelines using contemporary evidence and data. The multiplicity of guidelines both regionally and internationally also make it difficult to standardise practice as healthcare providers often use guidelines which they are familiar with based on opinion and where they trained. Also, many different risk estimation models for cardiovascular disease exist, used based on preference and different risk thresholds are used to decide on treatment.

Therefore, this guideline is an effort to standardise care of individuals with hyperlipidaemia, in a similar fashion to the Brunei National Hypertension Guideline launched in 2019. We hope this will enable healthcare providers and individuals to improve practice to enable better outcomes and, in the future, reduce the burden of cardiovascular disease

This guideline is a comprehensive document, and the busy clinician is encouraged to read the brief summary, take-home messages, and the key messages at the start of each individual chapter to obtain the important information contained in the guideline overall and in each chapter.

Lastly, the writing of this guideline took place during the backdrop of the COVID-19 pandemic and represents a strenuous effort on everyone's part while simultaneously delivering patient care during this turbulent time.

Thank you.

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Statement of Intent:

This document acts as a guide for clinician on the management of condition based on the available evidence at the time of the development of the document. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every health care provider should consider the patient and management options available in the local setting and administer treatment with the best intent outcome possible guided by the CPG.

Any deviations from the CPG should be documented if possible. In this guideline, no formal grading of levels of evidence or strength of recommendations is included. However, it represents an interpretation of the best available evidence as well as international guidelines.

LIST OF ABBREVIATIONS AND ACRONYMS

A

ABI	Ankle-brachial index
ACC	American College of Cardiology
ACR	Albumin:creatinine ratio
ACS	Acute coronary syndrome
AHA	American Heart Association
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
ApoB	Apolipoprotein B
ASA	American Stroke Association
ASCVD	Atherosclerotic cardiovascular disease
ASO	Antisense oligonucleotides

B

BMI	Body mass index

C

CABG	Coronary Artery Bypass Graft
CAC	Coronary artery calcium
CAD	Coronary artery disease
CK	Creatinine kinase
CKD	Chronic kidney disease
CT	Computed topography
CTT	Cholesterol Treatment Trialists
CyA	Cyclosporine-A

D

DLCNC	Dutch Lipid Clinic Network Criteria
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid

E

eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
ESRD	End stage renal disease

F

FDA	Food and Drug Administration
FH	Familial hypercholesterolaemia

G

GFR	Glomerular filtration rate
GHD	Growth hormone deficiency
GP	General population

H

HbA1c	Glycated haemoglobin
HCM	Hypertrophic cardiomyopathy
HD	Haemodialysis
HDL-C	High density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
HMG CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HRT	Hormone replacement therapy
HTG	Hypertriglyceridemia

I

ICER Institute for Clinical and Economic Review

ICH Intracerebral haemorrhage

IGT Impaired glucose tolerance

ILEP International Lipid Expert Panel

J

JIA Juvenile idiopathic arthritis

K

KDIGO Kidney Disease Improving Global Outcomes

L

LDL Low density lipoprotein

LDL-C Low density lipoprotein cholesterol

LFT Liver function test

Lp(a) Lipoprotein (a) test

M

MetS Metabolic syndrome

MI Myocardial infarction

N

NAFLD Non-alcoholic fatty liver disease

NCD Non-communicable disease

NHANES National health and Nutrition Examination Survey

NHANNS National Health And Nutritional Status Survey

NHSP National Health Screening Programme

NKF-KDOQI National Kidney Foundation-Kidney Disease Outcomes Quality Initiative

P

PAD Peripheral artery disease

PCI Percutaneous Coronary Intervention

PCOS Polycystic ovarian syndrome

PCSK-9 Proprotein convertase subtilisim/kexin type 9

PD Peritoneal disease

PPAR Peroxisome Proliferator Activated Receptor

PUFA Polyunsaturated fatty acid

R

RA Rheumatoid Arthritis

S

SAMS Statin-associated muscle symptoms

SAMSON Self-Assessment Method for Statin Side-effects or Nocebo

SCORE-2 Systemic COronary Risk Evaluation-2

SCORE-OP Systemic COronary Risk Evaluation-Older Persons

siRNA Short interfering RNA

SLE Systemic lupus erhythrometosus

STEPS STEPwise Approach to Surveillance

T

TC Total cholesterol

TG Triglyceride

TGA	Transposition of great arteries
TIA	Transient Ischaemic Attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
TSH	Thyroid stimulating hormone

U

| ULN | Upper limit of normal |

V

| VLDL | Very low density lipoprotein |

W

| WHO | World Health Organisation |

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BRIEF SUMMARY AND TAKE-HOME MESSAGE TO REDUCE ASCVD RISK

Dr Moncy Jacob Oommen & Dr Sofian DP Dr Hj Johar

The "Brunei Darussalam National Hyperlipidaemia Guidelines 2022" by the Cardiac Society Brunei Darussalam and Ministry of Health Brunei Darussalam provide updated recommendations based on the clinical trials and epidemiologic evidence published in this field since the previous "Hyperlipidaemia Management Guidelines, Ministry of Health, Brunei" published in 2004.

The treatment strategy should be based on atherosclerotic cardiovascular disease (ASCVD) risk at all ages and to use the WHO ASCVD risk calculator for primary prevention, for those aged 40 to <75 years of age. For younger individuals, consider an assessment of lifetime risk.

Lipid profile testing can be considered in those <40 years of age for individuals with known traditional ASCVD risk factors including hypertension, family history of premature, ASCVD, diabetes, and smoking. This is in line with The Ministry of Health National Screening Guideline on Non-Communicable Diseases (NCDs) [1]. Repeat screening for individuals not taking lipid-lowering therapy can be undertaken at regular intervals (1-3 years) depending on their overall risk profile and can be repeated sooner if other ASCVD risk factors develop in the interim.

For lipid profile testing, individuals can be either fasted or non-fasted depending on local circumstances. Generally, in Brunei, lipid measurements are taken in a fasting state. However, a non-fasting sample can also be used for risk estimation. A fasting lipid profile should be performed if on a non-fasting lipid profile, the triglyceride (TG) level is >4.5 mmol/L. A shared decision making process should determine the treatment strategy and the personalised treatment plan for each patient [2].

10 TAKE HOME MESSAGES TO REDUCE RISK OF ASCVD THROUGH CHOLESTEROL MANAGEMENT

1. A healthy lifestyle should be advised for all individuals including dietary measures, physical activity and smoking cessation for all individuals being assessed for ASCVD.

2. All individuals being assessed for ASCVD risk should undergo an evaluation consisting of a history and physical examination and measurement of a lipid profile, fasting glucose and/or HbA1c measurements.

3. Individuals aged 40 to <75 years of age without established ASCVD should be assessed for their 10-year ASCVD risk according to the WHO risk chart. Younger individuals <40 years of age can be assessed for lifetime risk. The presence of risk-enhancing factors should be assessed. Coronary artery calcium (CAC) scoring may be considered.

4. Low risk (0-5% 10-year ASCVD risk) and borderline risk (5-10% 10-year ASCVD risk) individuals should be assessed for risk-enhancing factors and consider statin therapy if lifestyle measures are insufficient. CAC scoring may be considered where the risk/benefit is uncertain for those at borderline risk. Target a 30-50% low density lipoprotein cholesterol (LDL-C) reduction or LDL-C <3.0 mmol/L.

5. Moderate risk (10 to <20% 10-year ASCVD risk) groups should be treated with pharmacological therapy, usually a moderate-intensity statin in the first instance. Target a 30-50% risk LDL-C reduction or an LDL-C <2.6 mmol/L. CAC scoring may be considered where the risk/benefit is uncertain.

6. High risk (20 to <30% 10-year ASCVD risk) groups should be treated with a high intensity statin. Aim for an ≥50% reduction in LDL-C level or LDL-C <1.8 mmol/L. Ezetimibe may be needed as add-on therapy to achieve this target.

7. Individuals at very high risk (≥30% ASCVD risk) should be treated with a high intensity statin. Individuals with established ASCVD will fall into this risk category. Aim for an ≥50% reduction in LDL-C level or LDL-C <1.8 mmol/L. A more stringent LDL-C target of 1.4 mmol/L may be considered in selected individuals. Ezetimibe may be needed as add-on therapy to achieve this target. Proprotein convertase subtilisim/kexin type 9 (PCSK-9) inhibitors may be considered as add-on therapy.

8. In individuals with diabetes, ASCVD risk assessment is useful for shared decision-making. Treatment with a statin is recommended in all individuals. For those at borderline/moderate risk, treatment with a moderate intensity statin aiming for a 30-50% LDL-C reduction or target of 2.6 mmol/L can be considered. Those at high or very high risk should be treated with a high intensity statin aiming for a ≥50% reduction or target of 1.8 mmol/L or lower.

9. In individuals <40 years old shared decision making is important and those with elevated lifetime cardiovascular risk with or without the presence of risk-enhancing factors may be considered for statin therapy even if the 10-year ASCVD risk appears low.

10. Adherence to treatment should be emphasised and treatment should be monitored, with dose adjustments or add-on therapy started when required.

01

INTRODUCTION

Dr Sofian DP Dr Hj Johar

Heart disease is one of the leading causes of mortality in Brunei Darussalam [3].

The four leading causes of mortality are non-communicable diseases - cancer, heart diseases, diabetes mellitus and cerebrovascular diseases comprising 52.5% of total deaths. Excluding cancer, much of this burden is related to atherosclerotic cardiovascular disease (ASCVD). Thus, it is important that the burden of ASVCD is reduced in the future to improve cardiovascular morbidity and mortality and reduce the costs to the healthcare system.

According to the Brunei Darussalam Multisectoral Action Plan for the Prevention and Control of Noncommunicable Diseases 2021-2025, there has not been an appreciable reduction in total premature age-related standardized mortality rates [4]. However, these rates appear to have stabilized in recent years.

Classical risk factors for the development of ASCVD are widely prevalent in Brunei Darussalam with 51.3% of the adult population (18-69 years of age) having an elevated cholesterol level (nearly two-thirds (62.8%) are overweight or obese and 28% have hypertension [4]. Another study showed 11% of civil servants have elevated fasting blood glucose and 19.9% of the adult population are current smokers [4]. Physical activity is also an issue with 25.3% being insufficiently active [4].

Hyperlipidaemia is one of the main modifiable risk factors for the development of ASCVD and has been the subject of many efforts over the years both in terms of lifestyle interventions as well as pharmacologic therapy.

It is known that serum cholesterol and its lipoprotein carriers (LDL, very low-density lipoprotein [VLDL], and HDL) are related to ASCVD. The dominant form of atherogenic cholesterol is LDL-C. VLDL is also atherogenic but HDL-C does not appear to play a role in atherogenesis. Non-HDL-C is the combination of LDL-C and VLDL-C. [5]

Several sources such as animal studies, genetic forms of hyperlipidaemia and randomised control trials link serum cholesterol to the development ASCVD [5]. RCTs of cholesterol-lowering drugs in individuals confirm that LDL-C lowering produces marked reductions in ASCVD [6], especially in individuals who have known coronary heart disease.

In general, it is better to consider the idea of 'the lower the better' when it comes to LDL-C levels. A large meta-analysis of randomised trials of statin therapy on lowering the LDL-C reduced all-cause mortality by 10% per 1.0 mmol/L reduction, reflecting reductions in death due to coronary heart disease (20%).

There was also a 22% reduction in major vascular events (first occurrence of any major coronary event, coronary revascularisation or stroke) per 1.0 mmol/L lowering of LDL-C with statin therapy [6].

Thus, treatment of hyperlipidaemia through lifestyle interventions as well as pharmacological interventions is important to lower LDL-C. The main evidence-based therapies for treatment of hyperlipidaemia are statins, ezetimbe and PCSK9 inhibitors. These drugs have all been shown to improve ASVCD outcomes.

The present guideline aims to give clinicians the tools necessary to screen individuals for hyperlipidaemia as well as diagnose and treat hyperlipidaemia after appropriate risk stratification. It is hoped this will help standardise management of hyperlipidaemia and reduce the ASCVD disease burden in Brunei Darussalam.

02

EPIDEMIOLOGY OF HYPERLIPIDAEMIA IN BRUNEI DARUSSALAM

Dr Ong Sok King, Dr Siti Zuhrini binti Hj Kahan, Khairil Azhar bin Hj Si-Ramlee

KEY MESSAGES:

1. The prevalence of hyperlipidaemia is high in Brunei Darussalam with 51.3% among adults aged 18-69 years.

2. Risk factors associated with hyperlipidaemia are common in Brunei Darussalam (about 1 in 5 adults are smokers, 9.7% are diabetics, 25.3% are physically inactive).

BACKGROUND

ASCVD including myocardial infarction and stroke, is one of the leading causes of overall and premature deaths in Brunei Darussalam [7]. Hyperlipidaemia has been identified as a major risk factor in the development of ASCVDs. Factors found to increase risk of hyperlipidaemia include a diet high in saturated or trans-fats, physical inactivity, smoking, obesity and diabetes mellitus [8,9]. Local population-based health surveys including the National Health and Nutritional Status Survey (NHANSS)(2010 – 2011) and STEPwise Approach to Surveillance (STEPS) survey (2015 – 2016) on NCD risk factors were conducted as part of surveillance activities for NCDs and risk factors including hyperlipidaemia.

PREVALENCE OF RAISED TOTAL CHOLESTEROL AND HYPERLIPIDAEMIA

In 2011, the national prevalence of elevated total cholesterol (TC)(>5.2 mmol/L) among adults age 20 – 75 years was 40.5% and was slightly higher in men (41.8%) compared to women (39.5%) (**Table 1**)[10].

In 2016, the STEPS survey reported an overall prevalence of raised TC (≥5.0 mmol/L) at 51.3% among adults aged 18 – 69 years with not much difference between genders (51.6% men, 51.0% women), and the prevalence is higher among older age groups (**Table 2**)[9,11].

In terms of screening for cholesterol levels, 1 in 5 adults (20.6%) aged between 45 – 59 years and 1 in 7 adults (14.8%) aged between 60 – 69 years reported that they have never had their blood cholesterol measured before (**Table 3**)[9,11].

The NHANSS 2010 – 2011 reported 37.2% adults were found to have elevated LDL-C >2.6 mmol/L, 42.1% had high density lipoprotein cholesterol (HDL-C) cholesterol < 1.0 mmol/L for men and <1.3 mmol/L for women and 23.6% had TG measurement >1.7 mmol/L (**Table 1**)[10].

The STEPS survey 2015 – 2016 reported that 31.2% men had HDL-C cholesterol measurement <1.03 mmol/L and 46.0% women had HDL-C cholesterol measurement <1.29 mmol/L. (**Table 4**) 1 in 5 adults or 22.7% had TG ≥1.7 mmol/L, and is higher in men (28.2%) compared to women (17.1%) (**Table 5**)[9,11].

RISK FACTORS FOR HYPERLIPIDAEMIA

91.8% respondents from the NHANSS 2010 – 2011 did not meet the daily national recommendation of servings of fruits and/or vegetables [10].

In 2016, the STEPS survey reported similar findings in which 91.7% reported that they ate less than 5 servings of fruit and/or vegetables on average per day [11].

The NHANSS 2010 – 2011 reported that 35.5% of adults did not meet the recommended duration of moderate physical activity in a week (<150 minutes per week) [10].

In 2016, the STEPS survey found a lower prevalence of physical inactivity at 25.3%, higher in women (33.0%) compared to men (17.5%) [9,11].

The NHANSS found that about 1 in 4 adults (27.1%) were obese (Body Mass Index [BMI] ≥30 kg/m^2) in 2011 [10].

In the STEPS survey 2015 – 2016, 28.2% adults were found to be obese (BMI ≥30 kg/m^2) [11].

The NHANSS 2010 – 2011 found that 18.4% of adults aged between 19 – 75 years were current smokers [10].

The STEPS survey 2015 – 2016 reported smoking prevalence of 19.9% or about 1 in 5 adults aged between 18 – 69 were current smokers [8,9,11].

More men smoke compared to women (35.5% men, 4.0% women for NHANSS 2010 – 2011; 36.3% men, 3.7% women for STEPS survey 2015 – 2016) [8-11].

The prevalence of diabetes (defined as fasting blood glucose ≥7.0 mmol/L and/or 2-hour blood glucose ≥ 11.1 mmol/L following Oral Glucose Tolerance Test or on treatment with oral agents and/or insulin) was 12.4% among adults aged 20 – 75 years as reported by the NHANSS 2010 – 2011 [10].

In 2016, the STEPS survey reported that 9.7% adults were detected to have raised fasting blood glucose (defined as fasting plasma venous value ≥7.0 mmol/L and capillary whole blood value ≥6.1 mmol/L) or currently on medication for raised blood glucose [11].

KEYS:

Unhealthy diet

Physical inactivity

Obesity

Smoking

Diabetes mellitus

NHANSS 2010 – 2011

Age group (years)	Dyslipidaemia			
	% Raised TC	% low HDL -C	% high LDL-C	% high TG
20-29	32.4	36	29	19.7
30 – 39	44.3	46.2	42.1	21.9
40 – 49	44.2	47.8	41.1	26.4
50 – 59	51.1	41.8	42.5	28.9
≥60	38.7	34.9	33	31.1
Overall	40.5	42.1	37.2	23.6

Table 1: Measurement of lipid profile in NHANSS 2010-2011
* TC measurement >5.2 mmol/L
** HDL-C measurement <1.0 mmol/L for men and < 1.3 mmol/L for women
*** LDL–C cholesterol measurement >2.6 mmol/L
**** TG measurement >1.7 mmol/L

STEPS 2015 – 2016

Age group (years)	TC ≥ 5.0 mmol/L or currently on medication for raised cholesterol								
	Men			Women			Both Sexes		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
18-29	64	29.4	23.2, 35.5	100	34.7	28.8, 40.6	164	31.9	27.8, 36.0
30-44	151	70.9	62.4, 79.4	193	54.2	48.4, 60.1	344	62.7	57.3, 68.0
45-59	189	71.3	64.1, 78.5	234	72.8	66.3, 79.3	423	72.1	66.7, 77.5
60-69	103	66.4	57.7, 75.2	102	77.1	67.5, 86.8	205	71.4	64.0, 78.7
18-69	507	51.6	46.5, 56.7	629	51.0	47.0, 55.1	1136	51.3	47.7, 54.9

Table 2: Prevalence of hyperlipidaemia from STEPS 2015-2016

Age group (years)	TC measurement								
	Men			Women			Both Sexes		
	n	% never measured	95% CI	n	% never measured	95% CI	n	% never measured	95% CI
18-29	310	67.4	62.1, 72.8	351	67.5	63.1, 72.0	661	67.5	63.6, 71.4
30-44	161	37.6	32.3, 43.0	256	39.1	34.5, 43.6	417	38.3	34.8, 41.9
45-59	107	23.1	18.6, 27.6	123	18.4	14.2, 22.7	230	20.6	17.4, 23.8
60-69	47	17.0	11.5, 22.5	37	12.5	7.5, 17.4	84	14.8	10.8, 18.7
18-69	625	47.4	44.3, 50.6	767	45.8	43.0, 48.7	1392	46.6	44.4, 48.9

Table 3: Measurement of total cholesterol from STEPS 2015-2016

HDL–C measurement <1.03 mmol/L for men and <1.29 mmol/L for women						
Age group (years)	Men			Women		
	n	%	95% CI	n	%	95% CI
18–29	57	27.9	22.3, 33.5	123	42.3	35.6, 49.1
30–44	73	36.5	28.0, 45.0	203	50.7	44.8, 56.6
45–59	80	31.3	24.8, 37.8	136	45.3	36.6, 54.0
60–69	50	30.6	20.9, 40.3	68	52.7	43.2, 62.2
18–69	**260**	**31.2**	**27.7, 34.6**	**530**	**46.0**	**41.9, 50.1**

Table 4: HDL–C measurement from STEPS 2015-2016

Percentage of respondents with fasting triglycerides ≥1.7 mmol/L									
Age group (years)	Men			Women			Both Sexes		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
18–29	35	16.5	11.1, 21.9	32	10.5	6.1, 14.9	67	13.6	9.9, 17.4
30–44	78	40.9	33.3, 48.6	55	16.8	11.2, 22.4	133	29.0	23.8, 34.2
45–59	88	39.5	32.8, 46.3	75	28.1	22.6, 33.7	163	33.5	28.9, 38.1
60–69	36	26.6	17.4, 35.7	30	32.4	20.6, 44.2	66	29.2	22.7, 35.7
18–69	**237**	**28.2**	**24.1, 32.3**	**192**	**17.1**	**13.8, 20.3**	**429**	**22.7**	**19.8, 25.7**

Table 5: Percentage of respondents with elevated fasting triglycerides

Prevalence of ASCVD risk factors among adults		
Risk factors	NHANSS 2010 - 2011	STEPS Survey 2015 – 2016
Hypercholesterolemia	40.5	51.3
Hypertension	33.8	28
Elevated fasting blood glucose or on diabetes medications	12.4	9.7
Smoking	18.4	19.9
Overweight and Obesity	60.6	62.8

Table 6: Prevalence of ASCVD risk factors among adults in Brunei Darussalam

03

OVERVIEW OF EXISTING INTERNATIONAL GUIDELINES

Dr Mohd Ezam Emran

	Regional Guidelines		**International Guidelines**	
	Singapore [12] (2017)	**Malaysia [13] (2017)**	**AHA/ACC [5] (2018)**	**ESC [14] (2019)**
Risk Stratification Tool	Modified Framingham-based NCEP ATP III 10-year risk score (calibrated for Singapore)	Framingham Risk Score	ASCVD (Atherosclerotic Cardio-Vascular Disease) Score	SCORE (Systematic COronary Risk Evaluation) system
Screening of general population for lipid disorders	**No risk factors for CAD*:** Routine screening recommended in men and women ≥40 years old **Risk factors for CAD present:** Routine screening can be done in younger adults ≥18 years old (both men and women)	**Adult patients (<40 years old) with diabetes:** Lipid profile should be measured at least annually **Adolescents with Type 2 DM*:** • Screening for lipid disorders at time of diagnosis after glycaemic control achieved • If initial screening normal, should be repeated every 2 years		
Fasting vs non-fasting lipid profile?	Fasting lipid profile recommended	Either can be used at physician's discretion	Either can be used at physician's discretion	Either can be used at physician's discretion
Threshold to start treatment	**Low-risk group:** LDL*-C level ≥4.1 mmol/L (160 mg/dL) or ≥3.4 mmol/L (130 mg/dL) at physician's discretion **Intermediate-risk group:** LDL-C level ≥3.4 mmol/L (130 mg/dL) or ≥2.6 mmol/L (100 mg/dL) at physician's discretion **High-risk group:** LDL-C level ≥2.6 mmol/L (100 mg/dL) **Very high-risk group:** LDL-C level ≥2.1 mmol/L (80 mg/dL)	**Low CV* risk:** Clinical judgement **Intermediate CV risk:** LDL-C level >3.4 mmol/L **High CV risk:** LDL-C level >2.6 mmol/L **Very High CV risk:** LDL-C level >1.8 mmol/L	**Primary prevention:** **Low 10-year ASCVD risk (<5%):** Lifestyle modification **Borderline 10-year ASCVD risk (5 – 7.5%):** Statin therapy is reasonable if risk enhancers present **Intermediate 10-year ASCVD risk (7.5 – 20%):** Start statin therapy if risk enhancers favour statin therapy **High 10-year ASCVD risk (>20%):** Initiate statin therapy **Clinical ASCVD:** Start statins regardless LDL-C level	**Primary prevention:** **Low CV risk:** LDL-C level ≥4.9 mmol/L (190 mg/dL) or ≥3.0 mmol/L (116 mg/dL) at physician's discretion **Moderate CV risk:** LDL-C level ≥4.9 mmol/L (190 mg/dL) or ≥2.6 mmol/L (100 mg/dL) at physician's discretion **High CV risk:** LDL-C level ≥2.6 mmol/L (100 mg/dL) or ≥1.8 mmol/L (70 mg/dL) at physician's discretion **Very High CV risk:** LDL-C level ≥1.8 mmol/L (70 mg/dL) or ≥1.4 mmol/L (55 mg/dL) at physician's discretion **Secondary prevention:** LDL-C level ≥1.4mmol/L (55mg/dL) or <1.4mmol/L (55mg/dL) at physician's discretion

	Regional Guidelines		International Guidelines	
	Singapore [12] (2017)	Malaysia [13] (2017)	AHA/ACC [5] (2018)	ESC [14] (2019)
Target LDL level on treatment	**Low-risk group:** <4.1 mmol/L (160 mg/dL)	**Low CV* risk:** <3.0 mmol/L	**Borderline and Intermediate 10-year ASCVD risk:** Reduce LDL-C by 30 – 49%	**Primary prevention:** **Low CV risk:** LDL-C level <3.0 mmol/L (116 mg/dL) **Moderate CV risk:** LDL-C level <2.6 mmol/L (100 mg/dL) **High CV risk:** LDL-C reduction ≥50% from baseline and LDL-C level of <1.8 mmol/L (70 mg/dL) **Very High CV risk with or without FH:** LDL-C reduction ≥50% from baseline and LDL-C level of <1.4 mmol/L (55 mg/dL) **Secondary prevention:** LDL-C reduction ≥50% from baseline and LDL-C level of <1.4 mmol/L (55 mg/dL)
	Intermediate-risk group: <3.4 mmol/L (130 mg/dL)	**Intermediate CV risk:** <3.0 mmol/L		
	High-risk group: <2.6 mmol/L (100 mg/dL)	**High CV risk:** ≤2.6 mmol/L or >50% reduction from baseline	**High 10-year ASCVD risk:** Reduce LDL-C by ≥50%	
	Very high-risk group: <2.1 mmol/L (80 mg/dL)	**Very high CV risk:** <1.8 mmol/L or >50% reduction from baseline		
First line therapy	**Elevated LDL* and mixed hyperlipidaemia:** • High intensity statin therapy for very high-risk patients • Moderate intensity statin therapy for high-risk patients	**Low and Intermediate CV risk:** • Therapeutic lifestyle changes alone • Lipid modifying agents may be added to achieve target lipid levels	**Borderline and Intermediate 10-year ASCVD risk:** Moderate intensity statins	High intensity statin therapy should be prescribed up to the highest tolerated dose to reach goals set for the specific level of risk
	Elevated TG* (>4.5 mmol/L or 400 mg/dL): Fibrates	**High and Very High CV risk:** Drug treatment (statins) to be initiated simultaneously with therapeutic lifestyle changes	**High 10-year ASCVD risk:** High intensity statins	Combination of statin and ezetimibe is recommended if statin alone does not achieve the goals

Table 7: Comparison of the treatment approach in hyperlipidaemia as published in several recent regional and international guidelines

*CAD = Coronary Artery Disease, CV = Cardiovascular, DM = Diabetes Mellitus, LDL = Low Density Lipoproteins, TG = Triglycerides

Specific Groups	Regional Guidelines		International Guidelines	
	Singapore [12] (2017)	Malaysia [13] (2017)	AHA/ACC [5] (2018)	ESC [14] (2019)
Children	Dietary and lifestyle measures the mainstay of treatment	**>8 years old:** Pravastatin can be used as an adjunct to diet	Dietary and lifestyle measures the mainstay of treatment	Dietary and lifestyle measures
	Statins can be considered in children ≥8 years old	**>10 years old:** Any statins can be used as an adjunct to diet	**>10 years old and persistently elevated LDL-C of ≥ 4.9 mmol/L (190 mg/dL) despite lifestyle measures:** Reasonable to start statin therapy	Statin therapy can be initiated from 8 – 10 years of age
	LDL* targets: 8 – 10 years old: <4 mmol/L (<160 mg/dL) ≥10 years old: <3.4 mmol/L (<130 mg/dL)		**>10 years old with evidence of FH* and persistently elevated LDL-C of ≥ 4.1 mmol/L (160 mg/dL):** Reasonable to start statin therapy	LDL targets: LDL-C level of <3.5 mmol/L (135 mg/dL) at >10 years of age
Pregnant patients	Only treat severe hyper triglyceridaemia (TG >10 mmol/L or >900 mg/dL) Statins contraindicated	Statins should not be used in women who are pregnant, intend to become pregnant or who are breastfeeding		Statins should not be used in women who are pregnant, intend to become pregnant or who are breastfeeding
	Only therapy recommended: Omega 3 fish oils and dietary measures	Bile acid sequestrants may be considered		Bile acid sequestrants may be considered
Older patients	Very high risk patients >75 years old: • To consider less intensive targets (e.g. 2.6 mmol/L or 100 mg/dL) • Start with lowest dose of statins and titrate as needed	Lipid lowering medication should be started at a lower dose and titrated with caution to achieve target levels	>75 years old with LDL-C of 1.7 to 4.8 mmol/L (70 to 189 mg/dL): • May be reasonable to start moderate-intensity statin • May be reasonable to stop statin therapy if evidence of functional decline (cognitive or physical)	Treatment with statins recommended for older patients with ASCVD Treatment with statins recommended for primary prevention, according to level of risk, in older patients aged ≤75 years old Initiation of statin treatment for primary prevention in older patients aged >75 years old may be considered, if at high risk or above

Table 7: Comparison of the treatment approach in hyperlipidaemia as published in several recent regional and international guidelines

*CKD = Chronic Kidney Disease, CV = Cardiovascular, CVD = Cardiovascular Disease, DM = Diabetes Mellitus
FH = Familial Hypercholesterolaemia, LDL = Low Density Lipoproteins

Specific Groups	Regional Guidelines		International Guidelines	
	Singapore [12] (2017)	Malaysia [13] (2017)	AHA/ACC [5] (2018)	ESC [14] (2019)
Chronic liver disease	**Transaminases <1.5x upper limit of normal:** **Statins can be given at lower starting dosage** **Transaminases between 1.5-3x upper limit of normal:** **Statins can be given with caution at lower starting dosage** **Transaminases <3x upper limit of normal:** **Fibrates can be given at a lower starting dosage**			
Diabetes mellitus	**Moderate intensity statin recommended**	**All patients with diabetes >40 years old:** **Should be treated with statins regardless of baseline LDL-C levels**	**Adults 40 – 75 years old with diabetes mellitus:** **Start moderate intensity statin therapy regardless of estimated 10-year ASCVD risk**	**Type 2 DM* at very high CV risk:** **LDL–C reduction ≥50% from baseline and LDL–C level of <1.4 mmol/L (55 mg/dL)** **Type 2 DM at high CV* risk:** **LDL–C reduction ≥50% from baseline and LDL–C level of <1.8 mmol/L (70 mg/dL)** **Type 1 DM at very high or high CV risk:** **Statin therapy recommended**
Familial hypercholesterolaemia	**Screening of first-degree relatives is recommended** **LDL-C target of <2.1 mmol/L (<80 mg/dL) is recommended**	**Statins are the drug of choice**	**20 – 75 years old with LDL-C ≥4.9 mmol/L (≥190 mg/dL):** **• Maximally tolerated statin therapy is recommended** **• Ezetimibe may be considered if <50% LDL-C reduction achieved on maximally tolerated statins and/or LDL-C ≥2.6 mmol/L (≥100 mg/dL) on maximally tolerated statins**	**LDL-C reduction ≥50% from baseline and LDL-C level of <1.4 mmol/L (55 mg/dL)**
Chronic kidney disease	**Starting dose of statins should be low** **Fibrates contraindicated when creatinine clearance <30 ml/min (stage 4 or 5 CKD*)**	**Primary and secondary prevention of CVD* in CKD patients:** **Statins or ezetimibe/ simvastatin combination should be initiated** **Statins should not be commenced for primary prevention of CVD in dialysis patients** **Patients with established CVD already on statins at time of initiation of dialysis:** **These drugs should be continued**	**40 – 75 years old with LDL-C 1.7 – 4.8 mmol/L (70 – 189 mg/dL) with 10-year ASCVD risk of ≥7.5%:** **Initiate moderate intensity statins +/- combination with ezetimibe**	**Non-dialysis dependent stage 3 – 5 CKD:** **Statins of statin/ezetimibe combination is recommended** **Statins should not be commenced for primary prevention of CVD in dialysis patients** **Patients with established CVD already on statins at time of initiation of dialysis:** **These drugs should be continued**

04

DIAGNOSIS AND INVESTIGATIONS FOR HYPERLIPIDAEMIA

Dr Ayman Helmi Ibrahim

KEY MESSAGES:

1. A standard lipid profile should be used in the estimation of ASCVD risk.

2. In familial hypercholesterolaemia or if the non-fasting TG level is ≥4.5 mmol/L, a fasting lipid profile should be performed.

3. In people with high TG levels, diabetes mellitus (DM), obesity, or very low LDL-C levels, non-HDL-C or apolipoprotein B (apoB) are recommended for risk assessment.

4. Familial hypercholesterolemia should be suspected if LDL-C is >4.9 mmol/L, there is history of premature coronary artery disease (CAD) or tendon xanthomas in the patient or a family member, or there is history of sudden premature cardiac death of a family member. Genetic testing is suggested when suspecting familial hypercholesterolemia.

A fasting or non-fasting standard lipid profile is used to estimate ASCVD risk and guide therapeutic decision-making [5,15].

A standard lipid profile includes measurement of plasma or serum TC, LDL-C, HDL-C and TG.

TC, HDL-C and TG are measured directly, while LDL-C is usually calculated by Freidewald's equation [5,12,13]. This formula cannot be used if the TG is ≥4.5 mmol/L and direct measurement of LDL-C should be used (if available) in this condition [2].

Friedewald formula:
LDL-C = TC - HDL-C - (0.45 x TG) in mmol/L

Measurement of plasma TC is needed to calculate ASCVD risk. Plasma LDL-C should be measured to estimate the risk of ASCVD that can be modified with LDL-C-lowering therapies. Plasma TG should be assessed to identify people who may have a greater modifiable risk of ASCVD than is reflected by LDL-C, and to identify people in whom calculated and directly measured LDL-C may underestimate the risk of ASCVD, such as those with low levels of LDL-C. This may be especially relevant in individuals with DM or metabolic syndrome.

If familial hypercholesterolaemia is suspected or non-fasting TG is ≥4.5 mmol/L a fasting lipid profile should be performed [15].

Non-fasting lipid testing is acceptable to calculate ASCVD risk. There are only small differences between fasting and non-fasting samples and there is no significant effect on the calculation of ASCVD risk [2,13].

Non-fasting samples have a slightly higher TG level of 0.3 mmol/L. In most individuals, this is of no clinical significance [2].

Practically, non-fasting samples are easier to perform and potentially outweigh the slight imprecision in some individuals. In individuals with metabolic syndrome or DM, calculated LDL-C should be interpreted with caution.

A fasting lipid profile should be considered or preferred if the non-fasting TG is >4.5 mmol/L or in cases of familial hypercholesterolaemia/hypertriglyceridemia.

Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels.

Calculated non-HDL-C is an alternative to calculated LDL-C and can measure TC carried by atherogenic apoB-containing lipoproteins [2,13].

Non-HDL-C is calculated as: Non-HDL-C (mmol/L) = TC (mmol/L) – HDL-C (mmol/L)

It can be used to evaluate ASCVD risk when TG is > 4.5 mmol/L.

Measurement of apoB can be considered for risk evaluation in individuals with DM, elevated TG, obesity, metabolic syndrome or very low LDL-C [15].

Under certain circumstances, including among people with elevated TG levels, DM, obesity, or very low achieved LDL-C levels, the calculated LDL-C level may underestimate both the total concentration of cholesterol carried by LDL-C and, more importantly, underestimate the total concentration of apoB-containing lipoproteins, thus underestimating the risk of ASCVD. In around 20% of individuals there may be discordance between measured LDL-C and apoB levels.

Measurement of apoB (if available) can be performed as part of risk evaluation in selected patients.

Because apoB provides an accurate estimate of the total concentration of atherogenic particles under all circumstances, it can refine the estimate of ASCVD risk that is modifiable by lipid-lowering therapy [2].

Lipoprotein (a) [Lp(a)] should be considered, if available, in certain individuals [12,13,15].

Measurement of Lp(a) has been shown to provide clinically significant improved risk reclassification under certain conditions, and therefore should be considered in individuals who have an estimated 10-year risk of ASCVD that is close to the threshold between moderate and high risk.

Lp(a) measurement also should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >430 nmol/L who may have a lifetime risk of ASCVD   equivalent to the risk associated with heterozygous familial hypercholesterolemia [16].

Familial hypercholesterolaemia (FH) should be suspected if LDL-C is >4.9 mmol/L, there is history of premature CAD or tendon xanthomas in the patient or a family member, or there is history of sudden premature cardiac death of a family member [2].

Currently available definitions rely on a scoring system to increase diagnostic confidence. The Dutch Lipid Clinic Network Criteria (DLCNC) (**Table 8**) is the most used diagnostic criteria for FH. If FH is suspected, it is recommended to use DLCNC scoring.

Genetic testing ideally should be performed as part of a comprehensive service which includes careful counselling and appropriately trained staff [2].

Although it is not necessary for a diagnosis of FH to perform genetic analysis, the presence of a LDL receptor mutation or mutations in other genes involved in the LDL receptor pathway gives a definitive diagnosis of FH. Accordingly, genetic testing for FH should be offered to individuals strongly clinically suspected to have FH, and that cascade genetic screening be offered to first-degree relatives.

On the other hand, if an individual is genetically diagnosed as FH, this constitutes a definite diagnosis of FH in the family.

Criteria	Points
Family History	
(a) First degree relative with known premature (<55 years men; < 60 years women) coronary disease and vascular disease **OR** LDL-C > 95th percentile	1
(b) First degree relative with tendon xanthomata and/or arcus cornealis **OR** childhood (<18 years) with LDL-C >95th percentile	2
Clinical History	
(a) Patient with premature CAD (men <55 years, women <60 years)	2
(b) Patient with premature cerebral or peripheral vascular disease (men <55 years, women <60 years)	1
Physical Examination	
(a) Tendon xanthoma	6
(b) Premature arcus	4
LDL-C	
(a) LDL-C > 8.5 mmol/L	8
(b) LDL-C = 6.5–8.4 mmol/L	5
(c) LDL-C = 5.0–6.4 mmol/L	3
(d) LDL-C = 4.0–4.9 mmol/L	1
Genetic	
DNA* mutations	8
Definite FH: > 8 points, Probable FH: 6–8 points, Possible FH: 3–5	

Table 8: Dutch Lipid Clinic Network Criteria diagnosis of FH[2]
DNA = deoxyribonucleic acid

05

SCREENING FOR HYPERLIPIDAEMIA

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DEFINITION OF HYPERLIPIDAEMIA

Hyperlipidaemia refers to the abnormal elevated levels of cholesterol and/or fats in the blood. The different types of cholesterol:

LDL-C

TG

HDL-C
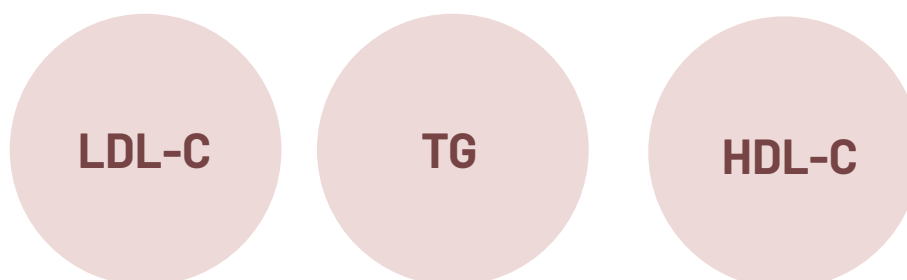
LDL-C is the primary atherogenic cholesterol and is the primary target for cholesterol lowering therapy. It contributes to the formation of atherosclerotic plaques (atherosclerosis). Atherosclerosis is the buildup of plaque in the wall of the blood vessels and this leads to ASCVD. ASCVD can affect the arterial systems in the heart (heart attacks), brain (strokes) and peripheral arteries (intermittent claudication, erectile dysfunction, abdominal aortic aneurysms and carotid artery stenosis). This process of atherosclerotic changes can start in young adults if the lipids are elevated. In a prospective cohort study of 2,824 persons ages 18 to 30 years, non-optimal levels of LDL-C (defined as ≥2.59 mmol/L) is associated with higher risk markers of atherosclerosis two decades later. HDL is inversely related to the risk of CAD [17].

Hyperlipidaemia is asymptomatic in nature.

Therefore, early screening leads to early detection and hence, early intervention can be started. Management strategies would start with healthy lifestyle modifications. If cholesterol levels are still sub-optimally controlled, then one should consider medications to lower elevated cholesterol levels which has been shown to reduce the risk of progression of atherosclerosis and, hence, reduce the morbidity and mortality from cardiovascular disease. Studies have consistently shown that a reduction of each mmol/L of LDL-C leads to a relative risk reduction of 20-22%.

Screening may also detect familial hypercholesterolemia and familial hypertriglyceridemia in our population. Both of these groups are at risk of accelerated atherosclerotic changes which in turn leads to increased risk of morbidity and premature death.

Lp(a), is an apolipoprotein (apo) B-containing lipoprotein particle similar in lipid composition to low-density lipoproteins but characterised by the presence of a carbohydrate rich protein, termed apo(a), covalently linked to apoB. These are determined by the LPA gene locus encoding apo(a). Epidemiological and Mendelian randomization studies have provided strong support for a causal role of elevated Lp(a) in the development of ASCVD. It is the most prevalent form of inherited dyslipidemia. Lp(a) is measured by immunoassays using antibodies specific to apo(a). Studies suggest Lp(a) concentration levels are reasonably stable, regardless of statin use, suggesting that serial measurements are not required for ASCVD assessment in the context of primary prevention. International professional society guidelines recommend measuring Lp(a) in either select population or at least once in a lifetime in the general population. This allows patients and clinicians to determine if Lp(a)-related risk is present.

Cholesterol Reference range (RIPAS Hospital lab)	
Total Cholesterol	<5.18 mmol/L
HDL-C	>1.04 mmol/L (Desirable >1.55 mmol/L)
LDL-C	<3.36 mmol/L
Triglycerides	<1.7 mmol/L

Table 9: Cholesterol reference range (RIPAS Hospital lab)

	LDL-C level (mmol/L)	<1.8	1.8 to <2.6	2.6 to <4.9	>4.9
Primary prevention	Risk Category	Intervention Strategy			
	Low	Lifestyle intervention		Lifestyle intervention. Consider adding drug if not controlled	Lifestyle intervention and concomitant drug intervention
	Borderline	Lifestyle intervention. Consider adding drug if not controlled		Lifestyle intervention and concomitant drug intervention	
	Moderate	Lifestyle intervention. Consider adding drug if not controlled	Lifestyle intervention and concomitant drug intervention		
	High	Lifestyle intervention and concomitant drug intervention			
Primary or secondary prevention	Very High	Lifestyle intervention and concomitant drug intervention			

Table 10: Intervention strategies for the different risk categories and LDL-C level. Adapted from the 2019 ESC/EAS Guidelines for the management of dyslipidaemias [2]. See **Chapter 6**, **Table 13** for ASCVD risk category definition.

CLASSIFICATION OF SCREENING FOR HYPERLIPIDAEMIA

PRIMARY PREVENTION

refers to screening for an individual who had not had any ASCVD event yet. Essentially, they are healthy individuals or individuals with some risk factors. In this chapter, we are focusing on screening for primary prevention.

SECONDARY PREVENTION

refers to screening done after the patient has already had an event (e.g. heart attack or stroke). These groups of patients should be screened for risk factors that had led to the event and should already have been started on optimal medical therapy. By controlling the risk factors, we aim to reduce the chance of recurrent cardiovascular events such as myocardial infarction or stroke or death.

HOW IS SCREENING PERFORMED?

Screening starts with full history and physical examination. Assess the individual's cardiovascular risk assessment using WHO risk chart for High Income Asia Pacific, which includes Brunei. (See **Figures 1 & 2** in **Chapter 6**)

Blood tests to check for the lipid panel which includes the TC, LDL-C, TG, HDL-C. These can be fasting samples (which is routinely practiced and the preferred option) or non-fasting samples. Other tests to consider include fasting plasma glucose (or HbA1c), eGFR, lipoprotein(a), ApoB and urine albumin: creatinine ratio (ACR) (if eGFR <60ml/min/1.73m^2, hypertension or diabetes).

Serum blood tests to check for the lipid panel which includes the TC (Total cholesterol), LDL, TG, HDL. These can be fasting samples (which is routinely practiced and the preferred option) or non-fasting samples.

Fasting lipids panels are obtained after 12-14 hours of fasting. The exception is that water and medications are allowed. Fasting lipids panels are required especially if the patient has high non-fasting TG > 4.5mmol/L or after recovering from hypertriglyceridemic pancreatitis. Fasting samples are recommended for assessment of cardiovascular risk if based on the individual components: Total cholesterol, LDL or non-HDL cholesterol.

Non-fasting lipids panels can be obtained without the need to fast for a period of time. The total cholesterol and the HDL components are not altered much between fasting or non-fasting samples. Situations where non-fasting lipid panels may be used: (1) initial lipid profile panel, (2) to assess cardiovascular risk, (3) during admission for an ASCVD event, (4) young or elderly patients, (5) those already on drug therapy and (6) patient preference. Non-fasting lipid panels may be sufficient in most cases except for patients with high triglyceride level, then fasting lipid panels should be obtained.

Other screening tests to consider include fasting plasma glucose (or HbA1c), eGFR and hypertension.

ApoB and Lipoprotein(a) are not routinely performed. However, for individuals with strong family history of premature cardiovascular disease or recurrent coronary events despite optimal medical therapy or low LDL, ApoB and Lipoprotein(a) [Lp(a)] can be done (once in a lifetime) to help further risk stratify the individual. Currently there is no specific intervention to lower Lp(a). If elevated, one can consider initiating early preventive management strategies starting with emphasis on healthy lifestyles and for those who are already on medical therapy, to consider optimising or escalating medical therapies. Studies are ongoing regardings more standardised measurements of Lp(a) and whether new treatment strategies to lower Lp(a) affect ASCVD outcomes [2,18-20].

WHO TO SCREEN?

The National Health Screening Programme (NHSP) was launched in February 2019 to offer all adults aged 40 and above to have cardiovascular risks (including hyperlipidaemia) screening at any of the primary healthcare clinics [21]. The screening programme is based on the National NCD Screening Guideline (November 2019) which was developed by the technical workgroup which comprised of experts and specialists from various departments in the RIPAS Hospital, Primary Health Care and Public Health [1].

With this updated Brunei National Lipids Guideline, we recommend screening in all adults above age 18 years, with or without risk factors, in order to identify individuals early so that early interventions to reduce lipids levels can be done to prevent or delay the onset of ASCVD [22]. Re-evaluate once every 5 years in those without risk factors. For those with additional risk factors or sub-optimally controlled, re-evaluate every 1 to 5 years as necessary. Emphasis on healthy lifestyle changes, healthy diet and physical activity are crucial at every opportunity [23].

At risk population groups as listed in **Table 11** should be screened and treatment optimised.

Men and Female 40 years old or older (earlier if higher risk based on ethnicity)
All patients with one or more of the following conditions regardless of age: • Clinical evidence of atherosclerosis (e.g. abdominal aortic aneurysm, peripheral vascular disease, carotid artery disease, CAD) • Diabetes Mellitus • Arterial hypertension • Smoker • Chronic Obstructive Pulmonary Disease • Signs of hyperlipidaemia (corneal arcus, xanthelasma, xanthema) • Family history of hyperlipidaemia • Family history of premature ASCVD (first degree relatives: Male <55 years old; Female <65 years old) • Chronic kidney disease (eGFR ≤60 ml/min/1.73m2 or ACR ≥ 3mg/mmol) • Inflammatory disease (e.g. Rheumatoid Arthritis, Systemic Lupus Erythematosus, Psoariatic arthritis, Ankylosing Spondylosis, Inflammatory bowel disease) • Obesity (BMI ≥30) • Infections (e.g. human immunodeficiency virus (HIV)) • Erectile dysfunction • Hypertension during pregnancy

Table 11: At risk population groups to screen [16]

Those confirmed to have familial hypercholesterolemia or familial hypertriglyceridemia will need to be followed up and their risk factors managed aggressively. Family screening will need to be done to identify other individuals in the family who may have the same conditions. Counselling and early management strategies can be initiated and their progress monitored.

For patients who are reluctant to start therapy or those where additional information is required to help patients and/or physicians in decision making; additional tests such as measuring ApoB or Lp(a), CAC score may be may be considered to help reclassify the risk of the individual and help encourage compliance with treatment or decision to escalate therapies.

06

OVERVIEW OF RISK STRATIFICATION OF ASCVD

Dr Sofian DP Dr Hj Johar

KEY MESSAGES:

1. ASCVD Risk calculation should be performed in patient without known ASCVD (i.e. primary prevention).

2. WHO chart should be used for risk estimation.

3. Calculation of lifetime risk is useful in individuals <40 years of age to decide on treatment.

4. The use of risk-enhancing factors and coronary artery calcium scoring can help refine decision making.

The decision to recommend pharmacological treatment for elevated lipid levels in individuals with no known ASCVD (i.e. primary prevention) depends on the overall risk of ASCVD in a given patient. The assessment of an individual at risk begins with a detailed history and examination, looking for risk factors such as hypertension, presence or absence of diabetes and smoking history. Baseline investigations usually include a lipid profile (fasting or non-fasting) and estimation of blood sugar levels (fasting plasma glucose or glycated haemoglobin (HbA1c) measurements) in order to help calculate overall ASCVD risk [2,5].

Overall ASCVD risk is normally calculated over a 10-year period and is performed in individuals without established ASCVD, as individuals with established ASCVD are already considered high risk and therefore should already be given pharmacological treatment. Most risk calculators restrict the calculation to a specific age group for estimation of 10-year ASCVD risk. There are many different risk stratification schemes such as the WHO cardiovascular disease risk chart [24], the pooled cohort equation from the ACC/AHA and the Systemic Coronary Risk Evaluation-2 / Systemic Coronary Risk Evaluation-Older Persons (SCORE-2/SCORE-OP) from the ESC [5,25].

The WHO cardiovascular risk chart is in widespread use in Brunei Darussalam and with the 2019 revision has been calibrated to estimate cardiovascular disease risk in 21 Global Burden of Disease regions [24]. Brunei Darussalam is in the High Income Asia Pacific category along with Japan, South Korea and Singapore (**Figure 1** and **2**). The risk chart uses sex, age, systolic blood pressure, smoking status, total cholesterol levels and presence or absence of diabetes (**Table 12**) to provide a 10-year estimate of cardiovascular disease (fatal and non-fatal myocardial infarction or stroke).

Factors
Age (40-74)
Gender
Smoking status
Systolic blood pressure
Total cholesterol
Diabetes status

Table 12: Factors required for risk calculation

The chart uses several risk levels as per **Table 13**

Colour code	Risk category	Predicted 10-year ASCVD event rate
Green	Low risk	<5%
Yellow	Borderline risk	5% to <10%
Orange	Moderate risk	10% to <20%
Red	High risk	20% to <30%
Dark red	Very high risk	≥30%

Table 13: ASCVD risk categories and predicted 10-year ASCVD event rate. See **Figures 1** & **2** for WHO Cardiovascular Risk Chart.

Treatment will generally be directed at those with moderate risk and above. Shared decision-making for those at low risk and below and treatment may be recommended in the presence of high lifetime risk and other risk factors associated with higher cardiovascular risk

Risk enhancing factors for developing ASCVD should also be taken into consideration such as presence of chronic kidney disease (CKD) and presence of metabolic syndrome (see **Table 14**). CAC scoring may be helpful in the further risk stratification of individuals at moderate risk and below. In cases where the risk/benefit is uncertain, they can be offered CAC scoring in order to further define their risk. A CAC score of 0 indicates a low risk and individuals may not require pharmacologic treatment.

ASCVD Risk Enhancing Factors
Family history of premature ASCVD (males, age <55 years; females, age <65 years)
Primary hypercholesterolaemia
Metabolic syndrome
Chronic kidney disease
Chronic inflammatory conditions, such as psoriasis, RA, lupus, or HIV/AIDS
History of premature menopause (before age 40 years) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia
High-risk race / ethnicity (e.g. South Asian ancestry)
Persistently elevated* primary hypertriglyceridemia

Table 14: ASCVD Risk Enhancing Factors (Adapted from 2019 ACC/AHA guideline on primary prevention of cardiovascular disease)[26]

RA = rheumatoid arthritis, AIDS = Acquired Immunodeficiency Syndrome

For younger individuals aged 20-39 years, a different approach is required as the WHO risk scoring system does not give an estimate of 10-year risk. If an estimate is required for individual discussion, then age 40 can be entered into the risk scoring system for purposes of discussion. In this age group, 10-year ASCVD risk is usually low and lifetime risk of ASCVD can be calculated using a different calculator such as the ACC/AHA risk calculator [27]. There is no universally accepted standard for what constitutes a high lifetime risk, however ≥39% is thought to be a reasonable threshold [28,29]. In individuals at high lifetime risk, pharmacological therapy could be considered. This may be important in the Brunei population due to a high prevalence of risk factors of ASCVD and premature ASCVD.

In the older population >75 years old, the utility of risk estimation of ASCVD events to target pharmacologic therapy is more debatable. For certain at-risk individuals, treatment with pharmacologic therapy may be considered in this age group after counselling. Individuals who reach this age who are already on treatment should be continued on treatment unless there are other reasons for discontinuation.

In summary, risk estimation of ASCVD is a useful tool to help decide which individuals need pharmacologic therapy and is also a useful indicator to individuals to help them understand their ASCVD risk.

High-income Asia Pacific

Risk Level | <5% | 5% to <10% | 10% to <20% | 20% to <30% | ≥30%

People without Diabetes

Age (years): columns are **Men** (Non-smoker, Smoker) and **Women** (Non-smoker, Smoker). Each block of 5 columns corresponds to Total cholesterol (mmol/l): <4, 4-4.9, 5-5.9, 6-6.9, ≥7. Rows are SBP (mmHg): ≥180, 160-179, 140-159, 120-139, <120.

Age 70-74

SBP (mmHg)	Men Non-smoker					Men Smoker					Women Non-smoker					Women Smoker				
≥180	21	22	24	26	28	25	27	29	32	34	16	17	18	19	21	24	25	27	28	30
160-179	18	19	21	22	24	21	23	25	27	30	13	14	15	16	17	20	21	22	24	25
140-159	15	16	17	19	21	18	20	21	23	25	11	12	12	13	14	16	17	18	20	21
120-139	13	14	15	16	18	15	17	18	20	22	9	10	10	11	11	14	14	15	16	17
<120	11	12	13	14	15	13	14	15	17	18	8	8	8	9	9	11	12	12	13	14

Age 65-69

SBP (mmHg)	Men Non-smoker					Men Smoker					Women Non-smoker					Women Smoker				
≥180	17	18	20	22	24	21	23	25	28	30	12	13	14	15	16	19	21	22	24	26
160-179	14	15	17	18	20	18	20	21	23	26	10	10	11	12	13	16	17	18	19	21
140-159	12	13	14	15	17	15	16	18	20	22	8	8	9	10	10	13	14	15	16	17
120-139	10	11	12	13	14	13	14	15	17	18	6	7	7	8	8	10	11	12	13	14
<120	8	9	10	11	12	10	11	13	14	15	5	5	6	6	7	8	9	9	10	11

Age 60-64

SBP (mmHg)	Men Non-smoker					Men Smoker					Women Non-smoker					Women Smoker				
≥180	14	15	16	18	20	18	20	22	24	27	9	10	10	11	12	15	17	18	20	22
160-179	11	12	13	15	16	15	17	18	20	22	7	8	8	9	10	12	13	14	16	17
140-159	9	10	11	12	13	12	14	15	17	19	6	6	6	7	8	10	11	11	13	14
120-139	7	8	9	10	11	10	11	12	14	15	4	5	5	5	6	8	8	9	10	11
<120	6	7	7	8	9	8	9	10	11	13	3	4	4	4	5	6	7	7	8	9

Age 55-59

SBP (mmHg)	Men Non-smoker					Men Smoker					Women Non-smoker					Women Smoker				
≥180	11	12	13	15	16	16	17	19	21	24	7	7	8	8	9	12	14	15	17	18
160-179	9	10	11	12	13	13	14	15	17	19	5	6	6	7	7	10	11	12	13	14
140-159	7	8	9	10	11	10	11	13	14	16	4	4	5	5	6	8	8	9	10	11
120-139	6	6	7	8	9	8	9	10	11	13	3	3	4	4	4	6	6	7	8	9
<120	5	5	6	6	7	7	7	8	9	10	2	3	3	3	3	4	5	5	6	7

Age 50-54

SBP (mmHg)	Men Non-smoker					Men Smoker					Women Non-smoker					Women Smoker				
≥180	9	10	11	12	14	13	15	16	18	21	5	5	6	6	7	10	11	12	14	16
160-179	7	8	9	10	11	11	12	13	15	17	4	4	4	5	5	8	8	9	11	12
140-159	6	6	7	8	9	8	9	10	12	13	3	3	3	4	4	6	6	7	8	9
120-139	4	5	5	6	7	7	7	8	9	11	2	2	3	3	3	4	5	5	6	7
<120	3	4	4	5	5	5	6	7	7	8	2	2	2	2	2	3	4	4	5	5

Age 45-49

SBP (mmHg)	Men Non-smoker					Men Smoker					Women Non-smoker					Women Smoker				
≥180	7	8	9	10	11	11	13	14	16	18	4	4	4	5	5	8	9	10	11	13
160-179	6	6	7	8	9	9	10	11	13	14	3	3	3	4	4	6	7	8	9	10
140-159	4	5	5	6	7	7	8	9	10	11	2	2	2	3	3	4	5	6	6	7
120-139	3	4	4	5	5	5	6	7	8	9	2	2	2	2	2	3	4	4	5	5
<120	3	3	3	4	4	4	5	5	6	7	1	1	1	1	2	2	3	3	3	4

Age 40-44

SBP (mmHg)	Men Non-smoker					Men Smoker					Women Non-smoker					Women Smoker				
≥180	6	7	7	8	9	10	11	12	14	16	3	3	3	4	4	7	7	8	10	11
160-179	5	5	6	6	7	7	8	9	11	12	2	2	2	3	3	5	5	6	7	8
140-159	3	4	4	5	5	6	6	7	8	10	1	2	2	2	2	3	4	4	5	6
120-139	3	3	3	4	4	4	5	5	6	7	1	1	1	1	2	2	3	3	4	4
<120	2	2	2	3	3	3	4	4	5	6	1	1	1	1	1	2	2	2	3	3

Total cholesterol (mmol/l): <4, 4-4.9, 5-5.9, 6-6.9, ≥7

Figure 1: WHO Cardiovascular Risk Chart for People without Diabetes [30]

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High-income Asia Pacific

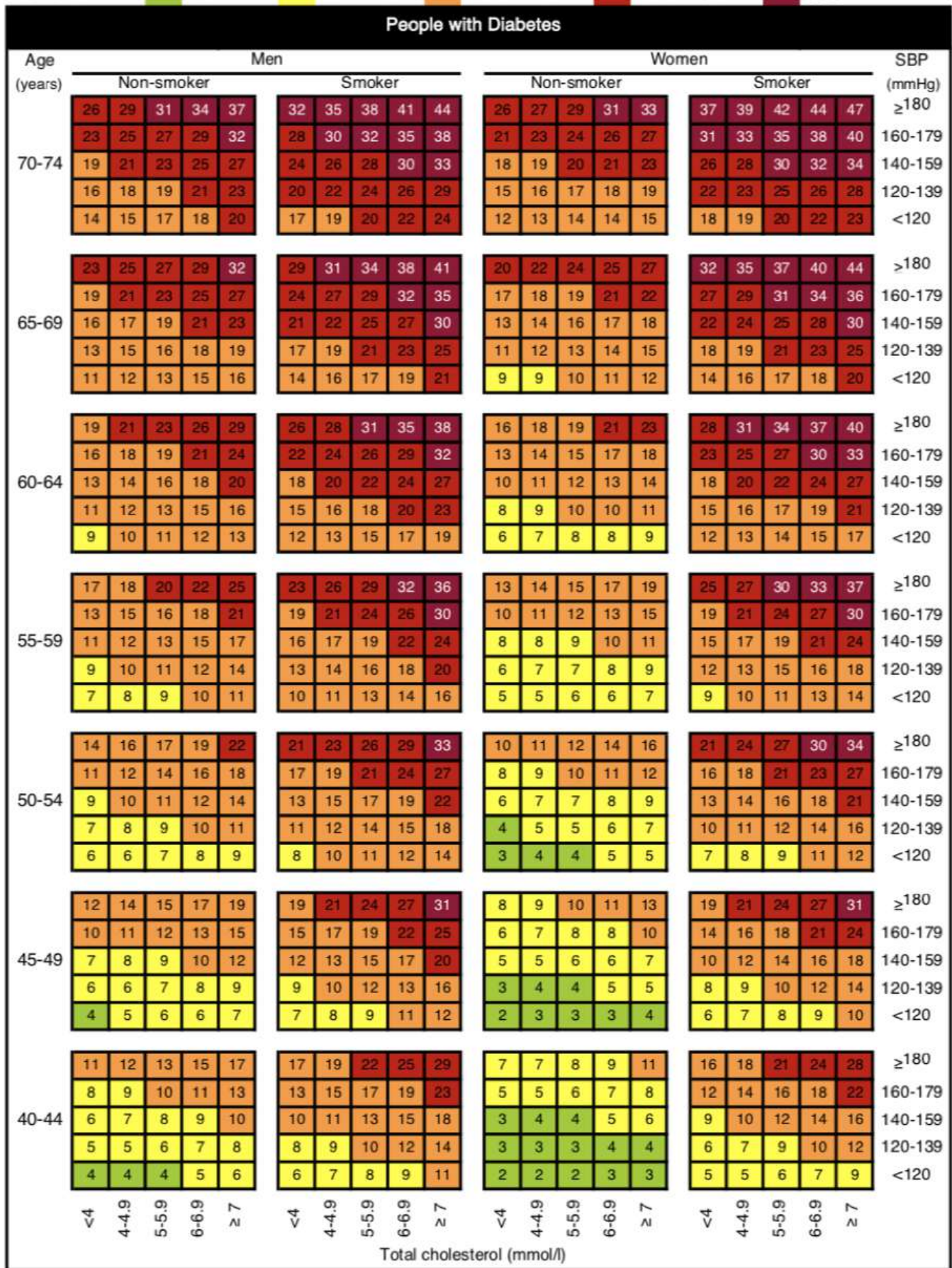**Risk Level** ■ <5% ■ 5% to <10% ■ 10% to <20% ■ 20% to <30% ■ ≥30%

People with Diabetes

Age (years)	Men Non-smoker					Men Smoker					Women Non-smoker					Women Smoker					SBP (mmHg)
70-74	26	29	31	34	37	32	35	38	41	44	26	27	29	31	33	37	39	42	44	47	≥180
	23	25	27	29	32	28	30	32	35	38	21	23	24	26	27	31	33	35	38	40	160-179
	19	21	23	25	27	24	26	28	30	33	18	19	20	21	23	26	28	30	32	34	140-159
	16	18	19	21	23	20	22	24	26	29	15	16	17	18	19	22	23	25	26	28	120-139
	14	15	17	18	20	17	19	20	22	24	12	13	14	14	15	18	19	20	22	23	<120
65-69	23	25	27	29	32	29	31	34	38	41	20	22	24	25	27	32	35	37	40	44	≥180
	19	21	23	25	27	24	27	29	32	35	17	18	19	21	22	27	29	31	34	36	160-179
	16	17	19	21	23	21	22	25	27	30	13	14	16	17	18	22	24	25	28	30	140-159
	13	15	16	18	19	17	19	21	23	25	11	12	13	14	15	18	19	21	23	25	120-139
	11	12	13	15	16	14	16	17	19	21	9	9	10	11	12	14	16	17	18	20	<120
60-64	19	21	23	26	29	26	28	31	35	38	16	18	19	21	23	28	31	34	37	40	≥180
	16	18	19	21	24	22	24	26	29	32	13	14	15	17	18	23	25	27	30	33	160-179
	13	14	16	18	20	18	20	22	24	27	10	11	12	13	14	18	20	22	24	27	140-159
	11	12	13	15	16	15	16	18	20	23	8	9	10	10	11	15	16	17	19	21	120-139
	9	10	11	12	13	12	13	15	17	19	6	7	8	8	9	12	13	14	15	17	<120
55-59	17	18	20	22	25	23	26	29	32	36	13	14	15	17	19	25	27	30	33	37	≥180
	13	15	16	18	21	19	21	24	26	30	10	11	12	13	15	19	21	24	27	30	160-179
	11	12	13	15	17	16	17	19	22	24	8	8	9	10	11	15	17	19	21	24	140-159
	9	10	11	12	14	13	14	16	18	20	6	7	7	8	9	12	13	15	16	18	120-139
	7	8	9	10	11	10	11	13	14	16	5	5	6	6	7	9	10	11	13	14	<120
50-54	14	16	17	19	22	21	23	26	29	33	10	11	12	14	16	21	24	27	30	34	≥180
	11	12	14	16	18	17	19	21	24	27	8	9	10	11	12	16	18	21	23	27	160-179
	9	10	11	12	14	13	15	17	19	22	6	7	7	8	9	13	14	16	18	21	140-159
	7	8	9	10	11	11	12	14	15	18	4	5	5	6	7	10	11	12	14	16	120-139
	6	6	7	8	9	8	10	11	12	14	3	4	4	5	5	7	8	9	11	12	<120
45-49	12	14	15	17	19	19	21	24	27	31	8	9	10	11	13	19	21	24	27	31	≥180
	10	11	12	13	15	15	17	19	22	25	6	7	8	8	10	14	16	18	21	24	160-179
	7	8	9	10	12	12	13	15	17	20	5	5	6	6	7	10	12	14	16	18	140-159
	6	6	7	8	9	9	10	12	13	16	3	4	4	5	5	8	9	10	12	14	120-139
	4	5	6	6	7	7	8	9	11	12	2	3	3	3	4	6	7	8	9	10	<120
40-44	11	12	13	15	17	17	19	22	25	29	7	7	8	9	11	16	18	21	24	28	≥180
	8	9	10	11	13	13	15	17	19	23	5	5	6	7	8	12	14	16	18	22	160-179
	6	7	8	9	10	10	11	13	15	18	3	4	4	5	6	9	10	12	14	16	140-159
	5	5	6	7	8	8	9	10	12	14	3	3	3	4	4	6	7	9	10	12	120-139
	4	4	4	5	6	6	7	8	9	11	2	2	2	3	3	5	5	6	7	9	<120

Total cholesterol (mmol/l): <4, 4-4.9, 5-5.9, 6-6.9, ≥7

Figure 2: WHO Cardiovascular Risk Chart for People with Diabetes [30]

Low Risk	10-year ASCVD risk <5%
Borderline Risk	10-year ASCVD risk 5 to <10%
Moderate Risk	• Young diabetics (Type 1 diabetes <35 years; Type 2 diabetes <50 years) diagnosed <10 years, without other risk factors • 10-year ASCVD risk 10 to <20%
High Risk	People with: • Markedly elevated single risk factors including TC >8mmol/L, LDL-C >4.9 mmol/L, blood pressure ≥180/110 mmHg • Family history without other major risk factors • Diabetes (diagnosed ≥10 years) without target organ damage or another additional risk factor • Moderate CKD (eGFR 30-59 ml/min/1.73m^2) • 10-year ASCVD risk 20 to <30%
Very High Risk	People with any of the following: • Documented ASCVD, either clinical or on investigations (Previous ACS*, stable angina, coronary revascularization (PCI*/CABG*), stroke and TIA*, PAD* • Diabetes with target organ damage, or at least 3 major risk factors • Severe CKD (eGFR <30 ml/min/1.73m^2) • Family history with ASCVD or with another major risk factor • 10-year ASCVD risk ≥30%

Table 15: Definitions of ASCVD Risk Categories [2]

ACS = acute coronary syndrome, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft,
TIA = transient ischaemic attack, PAD = peripheral artery disease

SECONDARY PREVENTION

Individuals who have had a history of documented ASCVD are at very high risk of future ASCVD event. Treatment targets should follow very high risk category.

Risk Category	Target LDL-C % reduction	Target LDL-C Level (mmol/L)
Low	<30 – 50%	<3.0
Borderline	<30 – 50%	<3.0
Moderate	<30 – 50%	<2.6
High	≤50%	<1.8
Very High	≤50%	<1.8 (consider 1.4)

Table 16: Target LDL-C according to risk categories for primary prevention

07

MANAGEMENT OF HYPERLIPIDAEMIA

07

7.1 THERAPEUTIC LIFESTYLE CHANGES

Dr Norhayati binti Hj Md Kassim

KEY MESSAGES:

1. Discourage smoking and give smoking cessation advice to smokers.

2. Encourage a healthy diet low in saturated fat, prioritising vegetables, wholegrain products, fruit and fish.

3. Encourage physical activity and reduce sedentary behaviour.

4. Weight reduction is recommended to aim within healthy range.

SMOKING

Smoking should be discouraged and individuals who smoke should be advised to stop smoking. Smoking cessation improves HDL-C, total HDL-C and large HDL-C particles. Increases in HDL-C may mediate part of the reduced cardiovascular disease risk observed after smoking cessation [31].

Physicians should give brief advice on smoking cessation as in **Figure 3**.

Please refer to **Appendix A**: The 5A's brief tobacco intervention and **Appendix B**: List of Smoking Cessation Clinics in Brunei Darussalam.

ASK — Do you use tobacco?

Current smoker → Ex-smoker/Non–smoker

ADVISE — to quit

ASSESS — Are you willing to quit?

Ready to quit → Not ready to quit

ASSIST — in quiting

Provide information and leaflets on smoking

ARRANGE — appointment with smoking cessation clinic
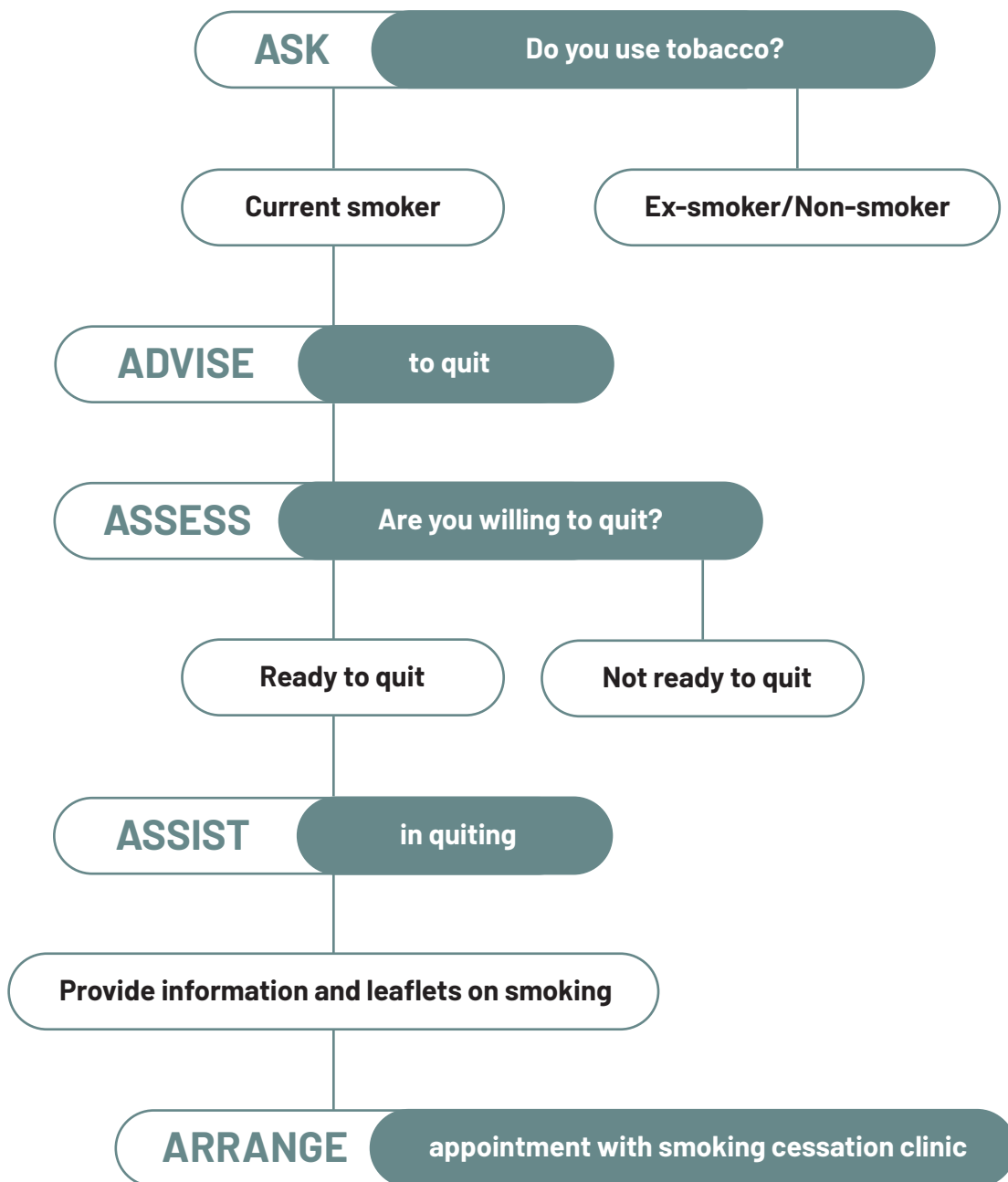
Figure 3: Flowchart for Smoking Cessation Advice

DIET

Physicians are encouraged to advise their individuals on the following recommended dietary guidelines to lower their lipid levels:

1. Enjoy a wide variety of nutritious food daily within the recommended amount [32]

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2. Consume a diet rich in wholegrain foods, vegetables, fruits, legumes, nuts, fish and unsaturated oils and low in saturated and trans fats, refined grains and cholesterol [12]

a) Saturated fat should be replaced with mono and polyunsaturated fats to lower cholesterol and LDL-C [12,33]

b) Trans fat intake should be limited to <1% of total energy or <2 g per day [12]

c) Cholesterol intake should be reduced to less than 300 mg per day [12,32]

d) Saturated fat intake should be reduced to <7% of total calories and polyunsaturated fat intake should be around 10% of total calories. A total fat intake of 25-35% total calories will be most compatible with the targets [12]

e) Dietary fibre intake should be at least 25-30 g per day by increasing consumption of whole-grains, fruits and vegetables and reducing consumption of processed grains and sugar [12]

f) For individuals with high triglyceride levels, simple sugars (mono and disaccharides) should be limited to <10% of total calories [12,34]

---

3. Only consume fried food twice per week [34,35]

A brief guide on ways to achieve the dietary recommendations above is presented in **Appendix C**; this can be given to individuals in the form of a leaflet at the end of the clinical consultation. In addition, a sample of a one-week fat reduction menu plan can also be given to individuals as a guide for their daily meals (**Appendix D**).

Referral to clinical dietitians in the primary care or hospital setting for individualised dietary assessment and dietary counselling with appropriate follow-up should be considered, depending on the patient's clinical condition.

PHYSICAL ACTIVITY

Health professionals are encouraged to advise their individuals on the following recommended physical activity guidelines to reduce their lipid levels and to promote healthier lifestyles.

> **Any amount of physical activity is better than none, and more is better.**

For health and wellbeing, at least 150 to 300 minutes of moderate aerobic activity per week (or the equivalent vigorous activity) is recommended for all adults and older adults [36].

An average of 60 minutes of moderate aerobic physical activity per day is recommended for children and adolescents [36].

1. Physical activity is good for heart, body and mind [36].

Regular physical activity can prevent and help manage heart disease, type 2 diabetes and cancer. Physical activity can also reduce symptoms of depression and anxiety, and enhance thinking, learning and overall well-being.

2. All physical activity counts [36].

Physical activity can be done as part of work, sport and leisure or transport (walking, wheeling and cycling), as well as every day and household tasks.

3. Muscle strengthening benefits everyone [36].

Older adults (aged 65 years and older) should add physical activities which emphasize balance and coordination, as well as muscle strengthening, to help prevent falls and improve health.

4. Too much sedentary behaviour can be unhealthy [36].

It can increase the risk of heart disease, cancer and type 2 diabetes. Limiting sedentary time and being physically active is good for health.

Everyone can benefit from increasing physical activity and reducing sedentary behaviour, including people living with chronic conditions or disability [36].

A brief guide on a description of the different levels of intensity and also corresponding examples of physical activity is presented in **Appendix E**. This advice can be given to individuals in the form of a leaflet at the end of the consultation.

> For individuals with hypertension and/or type 2 diabetes,
>
> • When not able to meet the above recommendations, adults with these chronic conditions should aim to engage in physical activity according to their abilities.
>
> • Adults with these chronic conditions should start by doing small amounts of physical activity and gradually increase the frequency, intensity and duration over time.
>
> • Adults with these chronic conditions may wish to consult with relevant healthcare professionals for advice on the types and amounts of activity appropriate for their individual needs, abilities, functional limitations/complications, medications and overall treatment plan.

Pre-exercise medical clearance is generally unnecessary for individuals without contraindications prior to beginning light- or moderate-intensity physical activity not exceeding the demands of brisk walking or everyday living [36].

WEIGHT MANAGEMENT

01 Individuals should maintain calorie intake balanced with regular physical activity to keep body weight within a healthy range [12,34].

02 Weight reduction reduces fasting triglyceride and increase HDL-C with some effect on lowering total cholesterol and LDL-C [12,34].

03 Physicians should give brief advice to individuals on reducing their weight, where applicable, as presented in **Appendix F**. This can be further reinforced in the form of appropriate health education materials at the end of the consultation.

04 Obese adult individuals who are motivated to lose weight may be referred to the Obesity Clinic, Endocrine Centre, RIPAS Hospital.

	Magnitude of the effect
Lifestyle interventions to reduce TC and LDL-C levels	
Avoid dietary trans fats	5-10%
Reduce dietary saturated fats	5-10%
Increase dietary fibre	5-10%
Use functional foods enriched with phytosterols	5-10%
Use red yeast rice nutraceuticals	5-10%
Reduce excessive body weight	5-10%
Reduce dietary cholesterol	≤5%
Increase habitual physical activity	≤5%
Lifestyle interventions to reduce TG-rich lipoprotein levels	
Reduce excessive body weight	≤5%
Reduce alcohol intake	≥10%
Increase habitual physical activity	5-10%
Reduce total amount of dietary carbohydrates	5-10%
Use supplements of n-3 polyunsaturated fats	5-10%
Reduce intake of mono- and disaccharides	5-10%
Replace saturated fats with mono- or polyunsaturated fats	≤5%
Lifestyle interventions to increase HDL-C levels	
Avoid dietary trans fats	5-10%
Increase habitual physical activity	≥10%
Reduce excessive body weight	5-10%
Reduce dietary carbohydrates and replace them with unsaturated fats	5-10%
Modest consumption in those who take alcohol may be continued	5-10%
Quit smoking	≤5%

Table 17: Impact of specific lifestyle interventions on lipid levels. Adapted from 2019 ESC/EAS Guideline for the management of dyslipidaemias [2].

07

7.2 LIPID LOWERING DRUGS

Dr V Jacob Jose, Dr Norzaidi bin Hj Md Saini

KEY MESSAGES:

1. LDL-C is a causative factor for the development of ASCVD. There are currently 3 potent drugs namely, statins, ezetimibe and PCSK9 inhibitors to reduce LDL-C to very low levels.

2. A step-wise approach is suggested to achieve the target level of LDL-C, starting with a statin, and then adding ezetimibe as a second-line drug. PCSK9 inhibitors are used as a third-line drug in select cases.

3. The target for LDL-C reduction is based on the risk characteristics of the individual. For secondary prevention in very-high-risk individuals, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L are recommended and an LDL-C goal of <1.4 mmol/L may be considered for selected cases. For high-risk individuals, the target is <1.8 mmol/L and for moderate-risk group the target is <2.6 mmol/L.

4. Coronary artery calcium scoring can be an additional tool to help in decision making in individuals in the moderate risk group and selected cases in borderline or low-risk individuals.

5. Hypertriglyceridemia is also a target for treatment.

INTRODUCTION

—

A number of drugs are now available for hyperlipidaemia treatment in Brunei Darussalam and they include statins, ezetimibe, PCSK9 inhibitors, fibrates and bile acid resins. Other drugs not yet available in Brunei Darussalam are n-3 fatty acids, bempedoic acid, mipomersen, lomitapide and niacin. In the pipe line are RNA based drugs that target the apolipoprotein (a), PCSK9, apo CIII, ANGPTL3 using antisense oligonucleotides (ASO) or short interfering RNA (siRNA). In addition, there is gene therapy for LDL receptors [37].

The initial dose of statin is decided based on the statin benefit group. (See **Figure 4** and **5**). Response to statin treatment is variable, therefore up titration of the statin dose may be required before additional LDL-C lowering treatments are started. One of the major issues in primary prevention is not achieving the target levels. Not achieving the target level, itself is a risk factor for future events [38].

In individuals with diabetes, ASCVD risk assessment is useful for shared decision-making. Treatment with a statin is recommended in all individuals. For those at borderline/ moderate risk, treatment with a moderate intensity statin aiming for a 30-50% LDL-C reduction or target of 2.6 mmol/L can be considered. Those at high or very high risk should be treated with a high intensity statin aiming for a ≥50% reduction or target of 1.8 mmol/L or lower.

PRIMARY PREVENTION

Measure TC for risk calculator
Use LDL-C measurements for target

LDL >4.9 mmol/L
Maximally tolerated statin

AGE <40 YEARS

Calculate Lifetime risk*
Consider statin if FH or LDL-C >4.9 mmol/L

AGE 40-74 YEARS

Calculate ASCVD Risk

Diabetics aged 40-74 years
Moderate intensity statin**

Aged >74 years
Clinical decision

Lifestyle Measures: Smoking cessation, dietary advice, increase physical activity

Risk <5%
Low Risk

Risk 5-10%
Borderline Risk

Risk 10-20%
Moderate Risk

Risk 20-30%
High Risk

Risk >30%
Very High Risk

Moderate intensity statin

High intensity statin

If a risk decision uncertain,
Consider risk enhancing factors
Consider CAC Scoring:
CAC Score = 0: No statin
CAC Score = 100: Initiate statin
CAC Score = 1-99: Favours statin

ASCVD Risk Enhancing Factors:

• Family history of premature ASCVD
• Primary hypercholesterolaemia
• Metabolic syndrome
• CKD
• Chronic inflammatory conditions
• History of premature menopause and history of pregnancy-associated conditions
• High-risk race / ethnicity
• Persistently elevated hypertriglyceridaemia

Figure 4: Decision pathway for individuals without known ASCVD being assessed for therapy (primary prevention).

*In individuals aged <40 years, use age = 40 years in WHO Cardiovascular risk chart to calculate ASCVD risk to help a decision on starting statin therapy
**All diabetics regardless of age should be considered for moderate intensity statin depending on diabetes enhancing factors. If ASCVD risk >20%, consider high intensity statin

(Adapted from 2018 AHA/ACC Guideline on the Management of Blood Cholestrol)[5]

```
┌─────────────────────────────────────────────┐
│  ASCVD – Hyperlipidaemia drug treatment     │
└─────────────────────────────────────────────┘
        └───┐
    ┌──────────────────────────────────────────────┐
    │   Moderate risk gets moderate intensity statin│
    │   High intensity statin for very high risk /   │
    │   Tolerable dose to reach goal                 │
    └──────────────────────────────────────────────┘
            └────┐
        ┌───────────────────────────────────────────┐
        │   If LDL-C is not on target, add ezetimibe │
        └───────────────────────────────────────────┘
                └─────┐
            ┌────────────────────────────────────────┐
            │  If LDL-C not on target with maximum    │
            │  statin + ezetimibe, consider adding    │
            │  PCSK9 inhibitor for high to very high  │
            │  risk individuals                       │
            └────────────────────────────────────────┘
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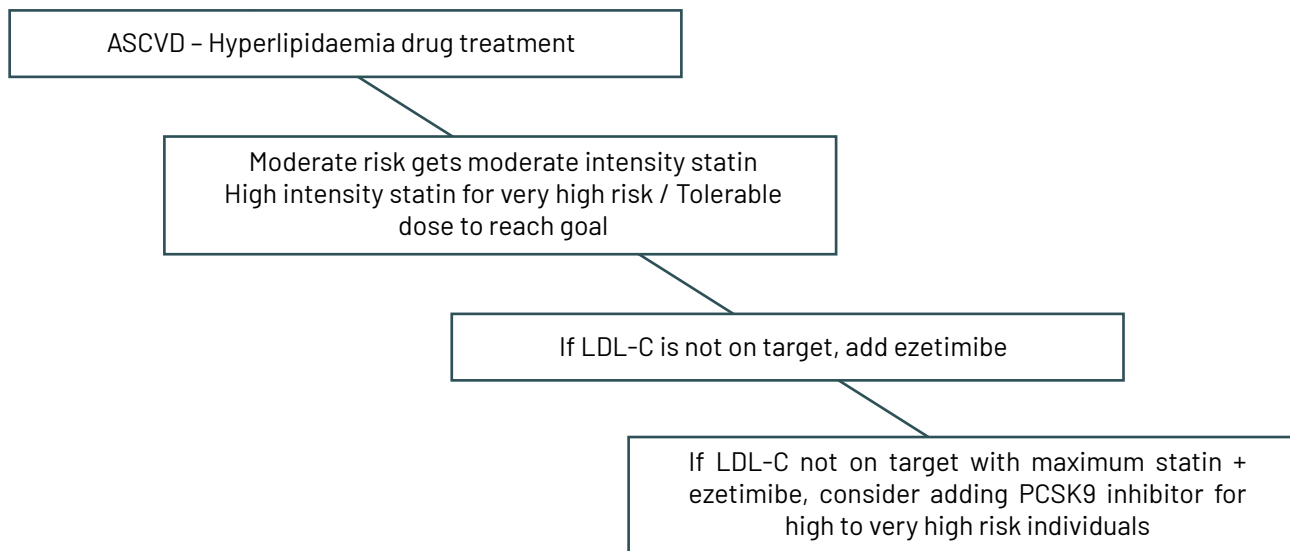
Figure 5: Decision pathway for individuals with known ASCVD being assessed for therapy (secondary prevention)

LIPID LOWERING TREATMENT IN SECONDARY PREVENTION

In individuals who are 75 years of age or younger with clinical ASCVD*, high intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels [5].

In individuals with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels [5].

In individuals with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at very high risk and have an LDL-C level ≥1.8 mmol/L, it is reasonable to add ezetimibe therapy [5].

Consider ezetimibe monotherapy if recommended statin therapy is contraindicated or not tolerated in secondary prevention [39].

In individuals with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe [5].

Figure 6 illustrates secondary prevention treatment algorithm for Diabetes and Endocrine conditions.

Clinical ASCVD includes ACS, those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, TIA, or PAD including aortic aneurysm, all of atherosclerotic origin.
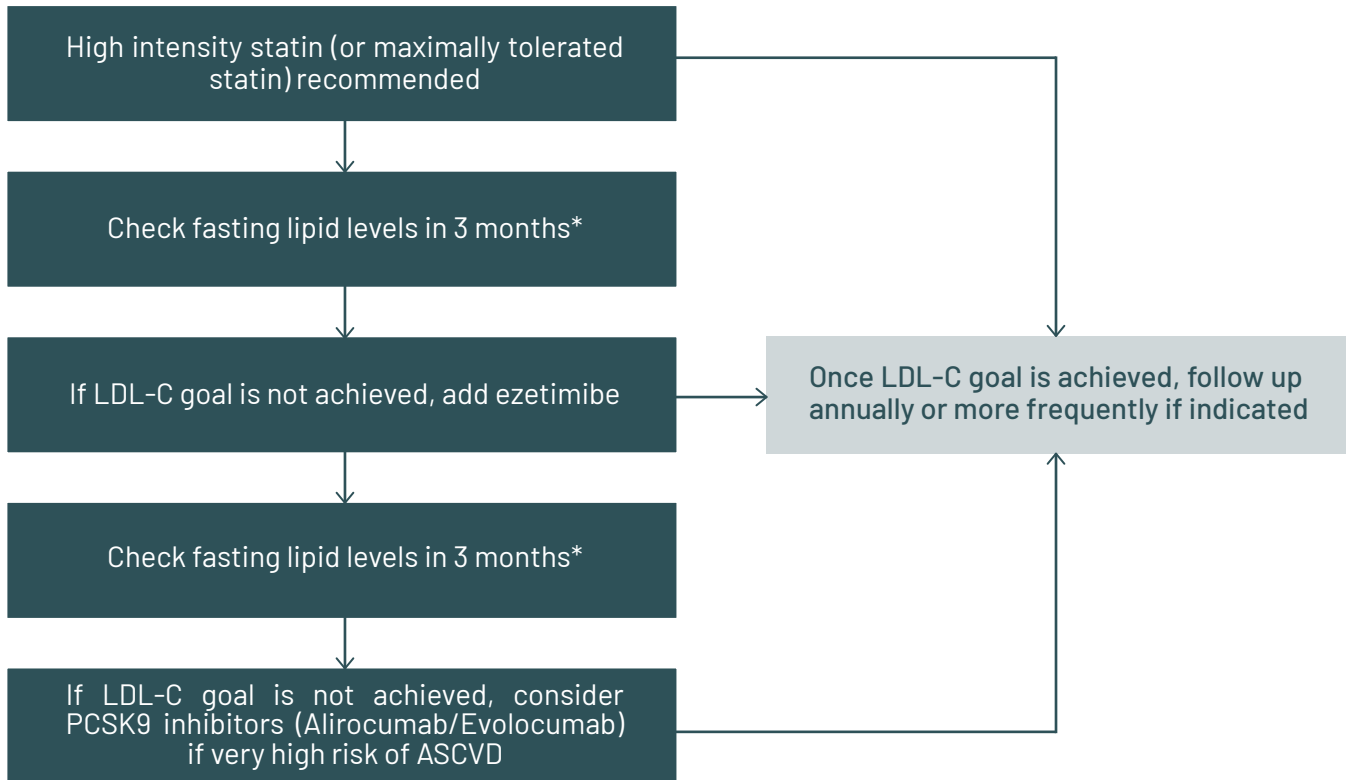
Figure 6: Secondary Prevention treatment algorithm

Notes

*Lipid profile at least once every 1-3 months to assess response to treatment (recommended on practical grounds).
Adapted from 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary [5].

STATINS

Of the several class of drugs we have for the treatment of hyperlipidaemia, statin forms the cornerstone of treatment. Statins are inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) reductase, the rate limiting enzyme in hepatic cholesterol synthesis. In the Cholesterol Treatment Trialists (CTT) meta-analysis, a 1 mmol/L reduction in LDL-C was associated with a 21% reduction in ASCVD events, regardless of baseline LDL-C [40].

Doses of commonly used statins and the LDL-C expected reduction is given in **Table 18**. It should be noted that doubling the dose does not double the reduction of LDL-C. The intensity of statin treatment is divided into 3 groups and given in **Table 19**.

Expected % Reduction of LDL-C reduction based on Dose					
Dose mg/day	**5**	**10**	**20**	**40**	**80**
Simvastatin		27	32	37	42
Atorvastatin		37	43	49	55
Rosuvastatin	38	43	48	53	

Table 18: Expected LDL-C reduction and Statin dose

• Simvastatin dose of 80 mg is not recommended due to high incidence of myopathy with this dose
• Doubling of the dose of statin does not double the reduction of LDL-C.

Treatment	Expected LDL–C reduction
Low intensity statin Simvastatin 10mg	<30%
Moderate intensity statin Atorvastatin 10 to 20 mg Rosuvastatin 5 to 10 mg Simvastatin 20 to 40 mg	30% – 50%
High Intensity statin Atorvastatin 40 to 80 mg Rosuvastatin 20 to 40 mg	>50%
High intensity statin + ezetimibe	65%
PCSK9 inhibitor	60%
PCSK9 inhibitor plus high intensity statin	75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	85%

Table 19: Intensity of LDL–C reduction and Statin Dose needed [2,5]

The beneficial effects of statins are a class effect and statins can be selected based on the ASCVD risk category and their target LDL-C level. The following 4 groups are suggested for consideration of statin therapy.

Individuals with known ASCVD (i.e. secondary prevention)

Individuals with elevated LDL–C of ≥4.9 mmol/L

Individuals with Diabetes

Primary prevention for LDL–C level <4.9 mmol/L after ASCVD risk assessment

No specific screening measurements for creatinine kinase (CK) levels or liver function test (LFT) are necessary prior to initiation of statin therapy (see **Chapter 7.3** for more details).

| CAC scoring is useful in decision making

CAC scoring provides direct evidence of atherosclerotic burden. CAC scoring can be used to reclassify to decide on starting statins in the moderate risk group and selected individuals in borderline and low risk. It helps in the discussion to make an informed decision about the need for statin [41].

A CAC measurement >100 AU is associated with a high risk (>2% annual risk) of an ASCVD event within 2-5 years and a score more than >300 AU is associated with a 10-year risk of MI / cardiovascular death of approximately 28%. On the other hand, a CAC measurement of 0 AU, has a very high negative predictive value of 95 to 99% for ASCVD events in asymptomatic, low-risk adults within the next 2-5 years [42]. Although a CAC of 0 AU is indicative of a low event rate (1.5%/10 years)) it is not indicative of a zero-event rate. This is likely due to the fact that non-calcified soft plaques may be present and these lesions may progress with time.

Recommendations: CAC score may be considered for asymptomatic adults ≥40 years for whom treatment decisions are uncertain. If the calcium score is zero in the moderate risk group, we can withhold statin unless high risk conditions such as smoking, family history of premature ASCVD or diabetes is present.

STATIN DOSE RECOMMENDATIONS

(see **Figures 4** and **5**)

• For primary prevention the first step is to calculate the risk using ASCVD risk calculator. Based on the risk score level we choose the intensity of statin.

• If the score is 10% or more, choose a moderate intensity statin e.g. atorvastatin 20 mg.

• If the 10-year ASCVD risk is <10% i.e. borderline or low risk individuals, then lifestyle modifications should take priority initially. If further LDL-C reduction is required, then treatment can be initiated with a moderate-intensity statin.

• Statins are given for persons on low calculated ASCVD risk, if the LDL-C >4.9 mmol/L as this is consistent with the diagnosis of FH.

• For secondary prevention of ASCVD, a high intensity statin dose should be used and that can reduce LDL-C levels by ≥50%.

• The dose of statin may need to be up-titrated to reach maximum dose of a given statin to achieve the desired LDL-C target. If the desired LDL-C levels are not attained, add on therapy with a second-line drug – ezetimibe and third-line drug such as PCSK9 inhibitors can be considered in selected individuals (**Figure 5**).

• The target level for various categories are summarized in **Figure 7**.
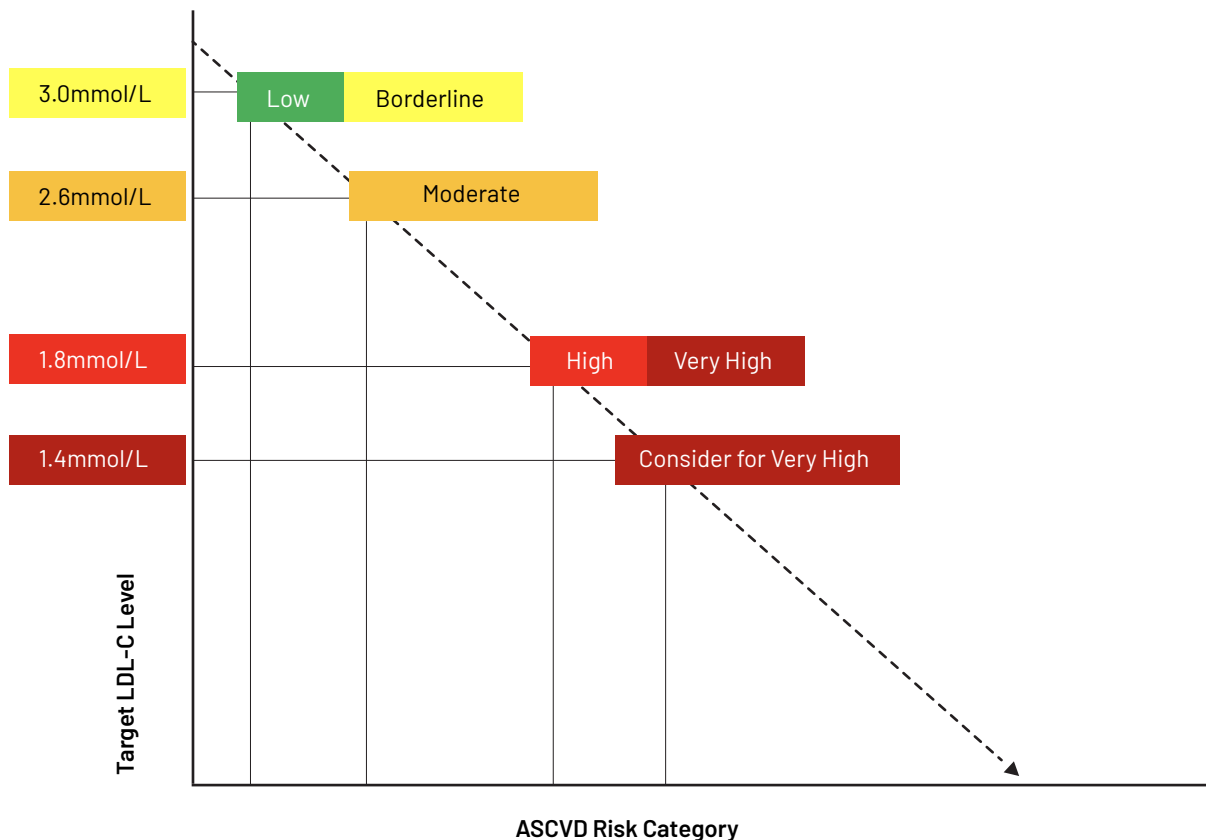
Figure 7: Treatment target LDL-C level according to patient ASCVD Risk Category. *Adapted from 2019 ESC/EAS Guideline for the management of dyslipidaemia* [2]

Risk assessment as low, borderline, moderate, high and very high risk as per ASCVD risk assessment
In moderate risk group, risk enhancing factors will help in the decision making to start statin therapy. This is also useful in the low to borderline risk group
In the moderate risk group, use of CAC score to help in the decision making to start statin therapy **CAC score is 0**: Consider withholding statin therapy as long as high-risk factors such as diabetes, smoking or family history of ischaemic heart disease are not present **CAC score 1 to 99**: reasonable to start statin therapy **CAC score is 100 or more**: reasonable to start statin therapy
In the moderate risk group, if statin therapy is not tolerated or if add on drug is required, it is reasonable to add ezetimibe

Table 20: Recommendations for primary prevention: LDL-C ≤4.8 mmol/L

In individuals aged 20 to 75 years of age with LDL-C > 4.9 mmol/L – maximum tolerated statin dose.
In individuals aged 20 to 75 years, if the achieved LDL-C is >2.6 mmol/L with maximum tolerated statin add on ezetimibe.
In individuals aged 40 to 75 years, baseline LDL-C of ≥5.7 mmol/L and they achieve only 3.4 mmol/L or higher on maximum statin + ezetimibe, add on a third drug – PCSK9 inhibitors.

Table 21: Primary Prevention: LDL-C > 4.9 mmol/L (Familial Hypercholesterolaemia)

Individuals with clinical ASCVD are considered at very high risk.
In individuals with clinical ASCVD, high-intensity statin therapy should be initiated or continued with the aim of achieving a ≥50% reduction in LDL-C levels.
In individuals with clinical ASCVD who are on maximally tolerated statin therapy and have an LDL-C level of <1.8 mmol/L or higher it is reasonable to use ezetimibe as add on therapy. A target of <1.4 mmol/L can be considered for selected individuals.
In individuals with clinical ASCVD who are judged to be very high risk with maximally tolerated LDL-C lowering therapy of statin + ezetimibe can be considered for PCSK9 inhibitor therapy, following a discussion about the net benefit, safety, and cost. The LDL-C target should be <1.8 mmol/L or <1.4 mmol/L in selected individuals.

Table 22: Recommendations for individuals with clinical ASCVD

TIMING OF THE DRUG

They are usually given at night since cholesterol synthesis usually takes place in the body in the night – early morning hours. Hence statins with short half-lives such as simvastatin should be given at night. For drugs such as atorvastatin or rosuvastatin, they can be given during the day, as their half-lives are 14 hours and 19 hours respectively.

RESPONSE TO THERAPY

A lipid profile should be measured 1 to 3 months of starting statins to see the drop in LDL-C levels. If the target is achieved, then repeat lipid profile measurements can be done at 6 to 12 months intervals. If the target LDL-C level is not achieved, up-titration of statins is done first if tolerated; if not, ezetimibe can be added next. PCSK9 Inhibitors are added as a third step in selected individuals.

EZETIMIBE

Ezetimibe inhibits intestinal uptake of dietary and biliary cholesterol at the level of the brush border of the intestine without affecting the absorption of fat-soluble nutrients and reduces the amount of cholesterol delivered to the liver. In response to reduced cholesterol delivery, the liver reacts by upregulating LDL-receptor expression, which in turn leads to increased clearance of LDL from the blood.

Ezetimibe monotherapy at 10 mg/day reduces LDL-C in hypercholesterolaemic individuals by 15% to 22% with relatively high interindividual variation. It also significantly increases HDL-C by 3%, significantly reduces TGs by 8% and reduces TC by 13% compared with placebo [2]. Ezetimibe, when added to ongoing statin therapy, reduces LDL-C levels by an additional 21% to 27% compared with placebo in individuals with hypercholesterolaemia with or without established CAD [2].

The combination of ezetimibe with bile sequestrants reduces LDL-C levels by an additional 10% to 20% when compared to bile acid sequestrant regimen alone. Combination of ezetimibe with PCSK9 inhibitors also results in an additional effect [2].

Consider treatment with ezetimibe for individuals who have clinically significant adverse effects with statin treatment [39]. Consider co-administration with statin therapy when maximum tolerated statin therapy fails to achieve LDL-C target [2,5,39].

According to the National Standard Drug List in Brunei Darussalam, ezetimibe is currently restricted to Cardiologists, Endocrinologists and Specialist Physicians and will require referral when considering initiation [43].

• The recommended dose is 10 mg per day.
• This drug can be given as monotherapy if statin is contraindicated or add on if LDL-C targets are not attained with statins.

PCKS9 INHIBITORS

This group of drugs inhibits the binding of PCSK9 to the LDL-receptors. This interaction decreases the degradation of the LDL-receptors, resulting in higher LDL-receptors density at the cell surface. The higher expression of LDL-receptors at the cell surface leads to increased clearance with resulting decrease in LDL-C levels. These drugs can reduce LDL-C level by 60%. Unlike statins, these drugs can lower the Lp(a) by 30% [44].

Consider co-administration of PCSK9 inhibitors with maximum tolerated statin and ezetimibe when LDL-C target is not reached [2,5]. Prescriptions of PCSK9 inhibitors in Ministry of Health institutions require approval on Named Patient Basis and will require referral when considering initiation.

DOSE OF DRUGS

• Evolocumab: 140 mg SC every two weeks or 420 mg SC monthly.
• Alirocumab: 75 mg once every 2 weeks SC, or 300 mg once a month.

The main barrier to widespread use of PCSK9 inhibitors is their cost. The Institute for Clinical and Economic Review (ICER) has suggested a reduction by 85% to an annual cost of $2177 will be a correct price to avoid excessive cost burdens to the health care system [45].

FIBRATES

Fibrates are Peroxisome Proliferator Activated Receptor (PPAR) – α agonist which have an important role in fatty acid oxidation. Gemfibrozil, fenofibrate and bezafibrate are the commonly used ones. Gemfibrozil can retard the elimination of statin and so a combination of this drug with statin can increase the risk of myopathy by 15 times and so this combination is not recommended. In comparison, fenofibrate is well tolerated with statins [46]. The use of gemfibrozil should be avoided in combination with simvastatin [47].

The clinical impact on lipid profiles varies among members of the fibrate class, but are estimated to reach a 50% reduction of the triglyceride level, a ≤20% reduction of the LDL-C level and an increase of the HDL-C level of ≤20%.

Recommended Dose:
Fenofibrate 100 mg thrice daily or 160 mg once daily (micronized)
Gemfibrozil: 600 mg in divided doses to 1.5 g max; should be taken 30 min before meal
Bezafibrate: 200 mg once daily to 200 mg thrice daily or 400 mg of sustained release.

Indications:
Fibrates are recommended for severe hypertriglyceridemia of 11 mmol/L to prevent pancreatitis. In High-risk individuals whose LDL C is at goal but with TG >2.3 mmol/L or higher, fenofibrate or bezafibrate may be considered.

BILE ACID SEQUESTRANTS

Bile acid sequestrants (cholestyramine, colesevelam, colestimide and colestipol) bind the bile acids and prevent the reabsorption of both the drug and cholesterol into the blood thereby removing a large portion of the bile acids from the enterohepatic circulation. The liver, depleted of bile, synthesizes more from hepatic cholesterol, therefore increasing the hepatic demand for cholesterol and increasing LDL-receptor expression, which results in a decrease of circulating LDL-C [48].

The LDL-C is reduced between 15 to 25% and HDL-C may increase by 5%. Its use is discouraged in individuals with TG ≥3.4 mmol/L. Other medications should be taken 1 hour before and/or 4 hours after resins.

Recommended Dose:
Cholestyramine: 4 g/day increased by 4 g at weekly intervals to 12-24 g/day in 1-4 divided doses. The maximum dose for cholestyramine is 24 g/day, for colestipol is 20 g and for colesevelam 4.5 g per day.

Indication:
These drugs are used as add on to statin if LDL-C targets are not reached or statin are not tolerated. However, they are infrequently used due to side effects.

TREATMENT FOR HYPERTRIGLYCERIDEMIA

The goal of drug treatment is to reduce the risk of pancreatitis in individuals with severe hypertriglyceridemia (HTG) and cardiovascular disease in those with moderate hypertriglyceridemia. HTG is commonly defined as fasting serum TG of 1.7 mmol/L or above, although the "optimal" fasting triglyceride concentration, which confers the lowest risk of incident and recurrent ASCVD, may be below 1.13 mmol/L [49]. The ESC considers 1.7 to 9.9 as HTG and severe if it is more than 10 mmol/L [14]. Many studies do suggest that non fasting TG may better predict the risk of ASCVD and pancreatitis than fasting level of TG because postprandial TG rich remnant particles are more [50].

The available pharmacological interventions include statins, fibrates, PCSK9 inhibitors, and n-3 polyunsaturated fatty acids [51]. Statins can reduce TG by 15 to 30% [52]. Statin combination with fibrate can increase the problem of myositis especially with gemfibrozil.

Recommendations for the treatment of Hypertriglyceridemia [53,54] (see **Table 23**)

• When the TG level is more than 5.7 mmol/L, confirm elevated levels with a repeat test after 4 weeks. In adults aged 40 to 75 years with ASCVD or Diabetes or ASCVD risk of ≥5%, increase the intensity of statin first. Consider fibrate (fenofibrate) or prescription omega 3 fatty acids [55].

• If the TG level is between 1.7 to 5.6 mmol/L, it should be confirmed with a repeat test after 3 months. If the TG level is more than 2.3 mmol/L and the individual qualifies for statin treatment due to ASCVD risk, start on a statin first. Add fibrates on follow up if needed especially in individuals with low HDL–C levels as seen in the Asian population.

Recommendations
Statin therapy is the first choice for TG level of >2.3 mmol/L in high or very high–risk groups
For primary prevention: If TG level >2.3 mmol/L, fenofibrate or bezafibrate may be considered in addition to statin
In high risk individuals whose LDL C is at goal but with TG level >2.3 mmol/L, fenofibrate or bezafibrate may be considered in addition to statin [56,57]

Table 23: Drug treatment for Hypertriglyceridemia

07

7.3 SAFETY AND MONITORING ASPECTS OF LIPID LOWERING DRUGS

Dr Amir Chughtai, Dr Norzaidi bin Hj Md Saini

KEY MESSAGES:

1. Side effects from statin use is uncommon and any reported side effects should be thoroughly evaluated before stopping therapy completely.

2. Other lipid lowering drugs are generally well tolerated.

STATINS

Statin therapy is usually well tolerated. The incidence of true side effects is low but unfortunately in clinical practice the reported incidence of complaint such as myalgia may be as high as 20%. The assessment and management of statin associated side effects can sometimes be challenging. Majority of self-reported symptoms on starting or stopping statins has been proved to be nocebo as seen in the SAMSON (Self-Assessment Method for Statin Side-effects Or Nocebo) trial [58].

No specific screening measurements for CK levels or LFT are necessary prior to initiation of statin therapy. However, if the individual has symptoms or is at high risk of potential safety issues, this can be considered either prior to initiation of therapy or during therapy and treatment adjusted accordingly.

DEFINITION OF STATIN ASSOCIATED INTOLERANCE – INTERNATIONAL LIPID EXPERT PANEL (ILEP) UNIFIED DEFINITION, 2015 [59]

1. The inability to tolerate at least two different statins – one statin at the lowest starting average daily dose and the other statin at any dose

2. Intolerance associated with confirmed, intolerable statin-related adverse effect(s) or significant biomarker abnormalities

3. Symptom or biomarker changes resolution or significant improvement upon dose decrease or discontinuation

4. Symptoms or biomarker changes not attributable to established predispositions such as drug-drug interactions and recognized conditions increasing the risk of statin intolerance

• Most individuals who experience statin intolerance have partial intolerance, and so, this is an important group to consider

• Only a relatively small number of individuals (3%–5%) have complete statin intolerance, whereby they cannot take any statin at all without severe adverse effects

1. STATIN-ASSOCIATED MUSCLE SYMPTOMS (SAMS): -

Definition   An assessment by the Statin Muscle Safety Task Force: 2014 update [60]

Myalgia – A symptom of muscle-discomfort, including muscle aches, soreness, stiffness, tenderness, or cramps with or soon after exercise, with a normal CK level.

Myopathy – Muscle weakness (not due to pain), with or without an elevation in CK level.

Myositis – Muscle inflammation.

Myonecrosis – Elevation in muscle enzymes compared with either baseline CK levels (while not on statin therapy) or the upper limit of normal that has been adjusted for age, race, and sex:

• Mild – 3- to 10-fold elevation in CK
• Moderate – 10- to 50-fold elevation in CK
• Severe – 50-fold or greater elevation in CK

Clinical rhabdomyolysis – Defined by the Task Force as myonecrosis with myoglobinuria or acute renal failure (an increase in serum creatinine of at least 44 μmol/)

RISK FACTORS

Statin characteristics	Substantially increased when taking statins extensively metabolized by CYP3A4 such as simvastatin and atorvastatin
Pre-existing neuromuscular disorders	Amyotrophic lateral sclerosis, etc.
Hypothyroidism, hypovitaminosis D, renal failure	Enhanced susceptibility to statin-associated myopathy
Patient characteristics	Genetic factors • SLCO1B1 variant (SLCO1B1*5)
Concurrent drug therapy	CYP3A4 inhibitors • Calcium channel blockers • HIV and HCV protease inhibitors • Grapefruit juice • Colchicine • Niacin • Fibrates esp. gemfibrozil • Fusidic acid • Amiodarone
Exercise	Often subclinical
Metabolic syndrome	Insulin resistance increases the incidence of SAMS

Table 24: Risk factors to develop statin-associated muscle symptoms

Statin use, especially at high doses, is associated with an increased incidence of diabetes. However, the benefit from ASCVD reduction outweighs this potential risk [5].

INCIDENCE

Statin-associated muscle symptoms	Frequency
Myalgias (CK Normal)	Infrequent (1% to 5%)
Myositis/myopathy (CK > ULN) with concerning symptoms or objective weakness	Rare
Rhabdomyolysis (CK >10 x ULN + renal injury)	Rare
Memory/Cognition	Infrequent
Cancer	No definite association
Renal function	Unfounded
Cataracts	Unfounded
Tendon rupture	Unfounded
Haemorrhagic stroke	Unfounded
Interstitial lung disease	Unfounded
Low testosterone	Unfounded

Table 25: Incidence of statin-associated muscle symptoms
Adapted from 2018 ACC/AHA Guideline on management of blood cholesterol [5] (ULN = upper limit of normal)

RECOMMENDATIONS

• Aim: Achieve LDL-C goal with maximally tolerated dose of statin

• Severe statin-associated muscle symptoms or recurrent statin associated muscle symptoms despite appropriate statin re-challenge, it is reasonable to use RCT proven non-statin therapy

• Coenzyme Q10 is not recommended for routine use in individuals treated with statins or for the treatment of SAMS

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┌─────────────────────────────────────────────────────────────────┐
│       Consider if statin-induced attributed muscle symptoms       │
└─────────────────────────────────────────────────────────────────┘
         │                                          │
         ▼                                          ▼
┌──────────────────────┐              ┌──────────────────────────┐
│ Symptomatic & CK     │              │ CK ≥5 X ULN              │
│ <5 x ULN             │              │ Men >1600 IU/L,          │
│                      │              │ Women >1000 IU/L         │
└──────────────────────┘              └──────────────────────────┘
         │                                          │
         ▼                                          ▼
┌──────────────────────┐              ┌──────────────────────────┐
│ 2–4 weeks washout    │              │ Monitor CK & Renal       │
│                      │              │ function                 │
└──────────────────────┘              └──────────────────────────┘
         │                                          │
         ▼                                          ▼
┌──────────────────────┐              ┌──────────────────────────┐
│ Symptoms persist:    │              │ Improves:                │
│ 1. Statin            │              │ Add different statin at  │
│    re-challenge      │              │ usual or starting dose   │
│ 2. Check for other   │              │ - Monitor monthly at     │
│    causes of         │              │   first                  │
│    muscular symptoms │              │                          │
└──────────────────────┘              └──────────────────────────┘
         │                                          │
         ▼                                          ▼
┌─────────────────────────────────────────────────────────────────┐
│ Symptoms re-occur:                                                │
│ 1. Low-dose third efficacious (potent) statin                     │
│ 2. Efficacious statin with alternate day or once / twice weekly   │
│    dosing                                                          │
└─────────────────────────────────────────────────────────────────┘
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Figure 8: Algorithm for the treatment of muscular symptoms during statin treatment

2. STATIN INDUCED HEPATOTOXICITY [5]

Statin-associated side effects	Frequency
ALT (alanine aminotransferase) 3x ULN	Infrequent
Hepatic failure	Rare

Table 26: Incidence of statin induced hepatotoxicity

Baseline ALT and Liver function is advised

Left branch	Right branch
ALT < 3 x ULN	ALT > 3 x ULN
Statin therapy started	Repeat to assess the trend
Monitoring	Investigate the aetiology
LFTs in 3 to 12 months	Fatty liver
ALT < 3 x ULN	ALT > 3 x ULN
No routine monitoring	Withhold Statin & trend ALT
ALT > 3 x ULN	ALT > 3 x ULN
Dose Reduction Alternate Statin	Investigate alternate aetiology
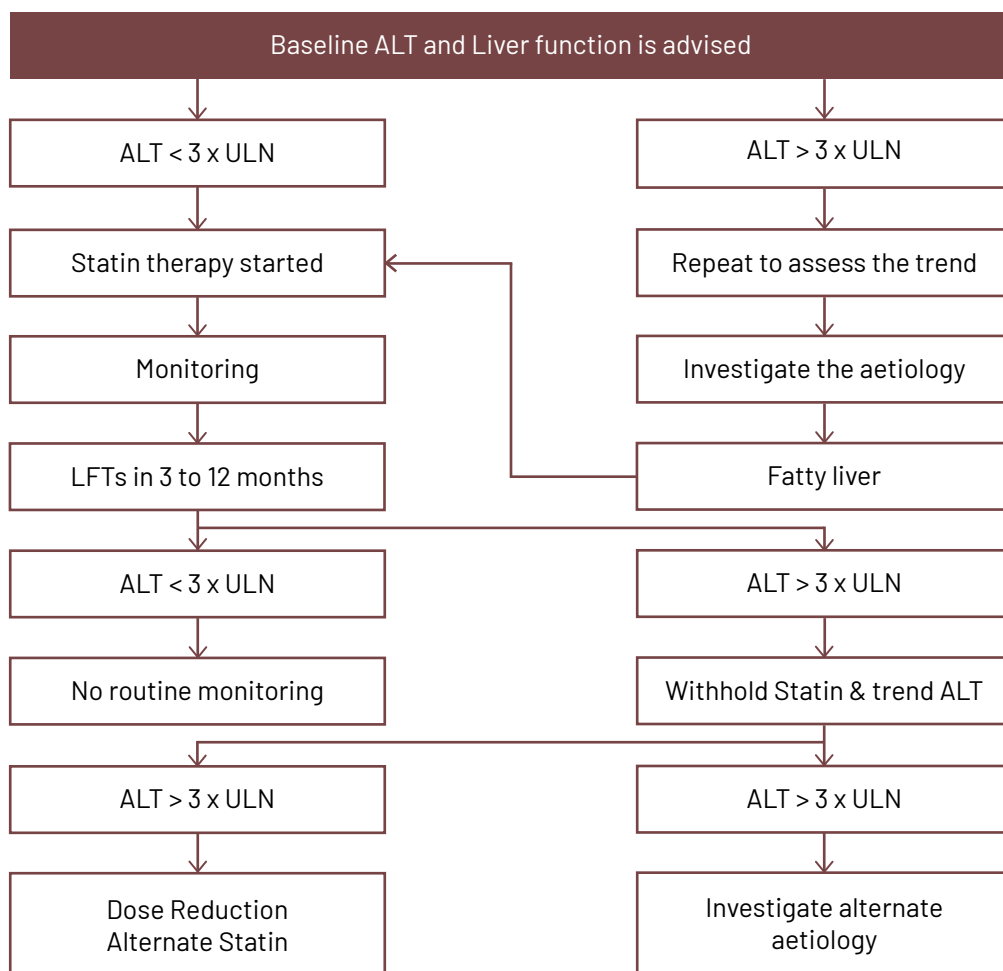
Figure 9: Algorithm for the treatment of muscular symptoms during statin treatment

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Ezetimibe

There are no clinically significant effects of age, sex, or race on ezetimibe pharmacokinetics, and no dosage adjustment is necessary in individuals with mild hepatic impairment or mild-to-severe renal insufficiency. The addition of ezetimibe to statin therapy does not appear to increase the incidence of elevated CK levels beyond what is noted with statin treatment alone.

PCSK-9 inhibitors

The main side effects of these drugs are nasopharyngitis, upper respiratory tract infection, back pain and nausea. Of note, the most common adverse events leading to drug discontinuation include myalgia and dizziness [61].

Fibrates

In general, myopathy, liver enzyme elevations and cholelithiasis represent the most well-known adverse effects associated with fibrate therapy. The risk of myopathy has been reported to be 5.5- fold greater with fibrate monotherapy (mainly with gemfibrozil) compared with a statin, and it varies with different fibrates and statins used in combination. Gemfibrozil inhibits the metabolism of statins via the glucuronidation pathway, which leads to marked increases in plasma concentrations of statins. As fenofibrate does not share the same pharmacokinetic pathways as gemfibrozil, the risk of myopathy is much less with this combination therapy [2].

Bile Acid Sequestrants

Gastrointestinal adverse effects most commonly flatulence, constipation, dyspepsia, and nausea are often present with these drugs, even at low doses, which limits their practical use. These adverse effects can be attenuated by beginning treatment at low doses and ingesting ample fluid with the drug. The dose should be increased gradually. Reduced absorption of fat-soluble vitamins has been reported. Furthermore, these drugs may increase circulating TG levels in certain individuals.

08

MANAGEMENT OF HYPERLIPIDAEMIA IN SPECIFIC CONDITIONS

8.1
ACUTE CORONARY SYNDROME

Dr Sofian DP Dr Hj Johar,
Dr Dk Nur Izyan Nadhirah

High-dose statin therapy is recommended to be initiated or continued as early as possible in all individuals with ACS unless there are contraindications or a definite history of intolerance [2].

The target LDL-C level at 4-6 weeks after ACS is a reduction of ≥50% from baseline and a target LDL-C <1.8 mmol/L [2,5]. A stricter target of <1.4 mmol/L can be considered in selected individuals [2].

If the target is not achieved by that time period with a maximally tolerated statin dose, it is recommended to add ezetimibe [2,5].

If the target still not achieved with maximally tolerated statin dose and ezetimibe, then PCSK9 inhibitors can be considered as add-on therapy [2,5].

If individuals are found to have statin intolerance or have contraindication to statin use, then ezetimibe should be considered as first-line therapy [2].

08

8.2 RENAL DISEASE

Dr Jayakrishnan K Pisharam

KEY MESSAGES:

1. In adults aged >50 years with CKD and eGFR >60ml/min/1.73m^2 (GFR categories G1-G2) treatment with a statin is recommended.

2. In adults aged >50 years with eGFR <60ml/min/1.73m^2 but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5), treatment with a statin or statin and ezetimibe combination is recommended.

3. In adults with dialysis-dependent CKD, statins or statin and ezetimibe combination can be considered on an individual basis depending on overall risk.

4. In individuals already receiving statins or statin and ezetimibe combination at the time of dialysis initiation, these agents can be continued.

5. In individuals who have a functional kidney transplant benefit from statin therapy.

INTRODUCTION

Renal disease worldwide is an important, non-communicable disease and raises important public health concerns.

The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI), classify CKD based on the eGFR and the level of proteinuria and helps to risk stratify individuals (**Figure 10**).

Renal dysfunction changes the level, composition and quality of the lipids in favour of a more atherogenic profile.

CARDIOVASCULAR DISEASE IN CHRONIC KIDNEY DISEASE

A graded inverse relationship exists between eGFR and cardiovascular disease, which is independent of age, gender, and other conventional cardiovascular risk factors. This relationship is present even in the setting of minor renal impairment. Individuals with CKD, particularly in end stage renal disease (ESRD) treated with haemodialysis (HD), peritoneal dialysis (PD) and those individuals who had undergone kidney transplantation are known to have high risk of ASCVD.

Although some individuals with CKD will ultimately develop renal failure, most individuals with CKD will die of cardiovascular disease before dialysis becomes necessary [62].

Individuals with ESRD requiring dialysis have an extremely high risk of cardiovascular events. Cardiovascular mortality accounts for approximately 50% of all deaths in kidney transplant Individuals.

The risk associated with CKD is age-dependent. For example, the rate of coronary death or incident MI among CKD individuals aged more than 50 years (both men and women) is consistently greater than 10 per 1000 patient-years, even in those without diabetes or prior MI [63].

GFR and ACR categories and risk of adverse outcomes		ACR categories (mg/mmol), description and range		
		<3 Normal to mildly increased	3-30 Moderately increased	>30 Severely increased
		A1	A2	A3
≥ 90 Normal and high	G1	No CKD in the absence of markers of kidney damage	(yellow)	(orange)
60-89 Mild reduction related to normal range for a young adult	G2	No CKD in the absence of markers of kidney damage	(yellow)	(orange)
45-59 Mild –moderate reduction	G3a	(yellow)	(orange)	(red)
30-44 Moderate – severe reduction	G3b	(orange)	(red)	(red)
15-29 Severe reduction	G4	(red)	(red)	(red)
<15 Kidney failure	G5	(red)	(red)	(red)

GFR categories (ml/min/1.73m²) description and range

Increasing risk

Increasing risk

Figure 10: NKF-KDOQI classification of CKD
(GFR: glomerular filtration rate)

EPIDEMIOLOGICAL ASSOCIATION BETWEEN DYSLIPIDAEMIA & CARDIOVASCULAR OUTCOMES IN SEVERE CKD

In the general population every 1 mmol/L rise in LDL-C is associated with a coronary risk increase by 40%. Lowering LDL-C with statin therapy has been shown to reduce the incidence of atherosclerotic events in many types of individual, but it remains uncertain whether it is of net benefit among individuals with severe CKD.

Atorvastatin had no statistically significant effect on the composite primary end point of cardiovascular death, non-fatal MI, and stroke in individuals with diabetes receiving HD.

In individuals undergoing HD, the initiation of treatment with rosuvastatin lowered the LDL-C level but had no significant effect on the composite primary end point of death from cardiovascular causes, non-fatal MI, or non-fatal stroke.

LIPID LOWERING DRUGS IN INDIVIDUALS ON DIALYSIS

The pathophysiology and spectrum of ASCVD in this group of individuals is markedly different compared to that of general population or even to earlier stages of CKD.

Arterial stiffness, vascular calcification, left ventricular hypertrophy, left ventricular diastolic dysfunction, congestive cardiomyopathy and sudden death from arrhythmias are all accounting for cardiovascular mortality and morbidity in individuals with renal failure, besides atherosclerosis.

In addition to conventional risk factors like age, gender and diabetes, individuals on dialysis also suffer from other pathologies that also play a role in developing cardiovascular complication. They include uremic milieu, anaemia, mineral bone disease, hyperparathyroidism and chronic inflammation.

LDL-C may not be elevated in CKD individuals, a higher prevalence of small, dense LDL-C has been found. These particles are more easily oxidized and penetrate more easily into the endothelial wall; for this reason, they are more atherogenic [64].

In individuals on dialysis, LDL-C has a negative association with all-cause mortality at a below average level. It may be representing malnutrition or inflammation.

KDIGO (Kidney Disease Improving Global Outcomes) guidelines on hyperlipidaemia for individuals with CKD and on dialysis are as follows

In adults aged >50 years with eGFR < 60ml/min/1.73m^2 but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5), treatment with a statin or statin and ezetimibe combination is recommended.

In adults aged >50 years with CKD and eGFR >60ml/min/1.73m^2 (GFR categories G1-G2) treatment with a statin is recommended.

Given less concern about drug toxicity in the setting of better kidney function, individuals with eGFR >60ml/min/1.73m^2 (and no history of kidney transplantation) may be treated with any statin regimen that is approved for use in the general population.

Safety data from large clinical trials suggest that the excess risk of adverse events associated with these regimens is similar among people with and without CKD.

In adults aged 18-49 years with CKD but not treated with chronic dialysis or kidney transplantation, statin treatment in people with one or more of the following is suggested:

1. Known coronary disease (MI or coronary revascularization)
2. Diabetes mellitus
3. Prior ischemic stroke
4. Estimated 10-year incidence of coronary death or non-fatal MI >10%

The 10-year incidence of ASCVD estimated using WHO cardiovascular risk chart.

In adults with dialysis-dependent CKD, statins or statin and ezetimibe combination may be considered on an individual basis depending on risk profile.

In individuals already receiving statins or statin and ezetimibe combination at the time of dialysis initiation, these agents can be continued.

• Discontinuation of statin or statin and ezetimibe may be warranted in individuals who place a relatively low value on a small potential relative reduction in cardiovascular events, and a relatively high value on the risks of polypharmacy and drug toxicity.

Follow-up measurement of lipid levels should be reserved for instances where the results would alter management. Potential reasons to measure LDL-C (or the lipid profile) in people with CKD after their initial presentation might include:

1. Assessment of adherence to statin treatment;
2. Change in renal replacement therapy modality
3. Concern about the presence of new secondary causes of hyperlipidaemia

HYPERLIPIDAEMIA IN INDIVIDUALS WHO HAVE UNDERGONE KIDNEY TRANSPLANTATION

The major reasons for pathogenesis of lipid abnormalities in post kidney transplant includes traditional and non-traditional risk factors. One of the major risk factors are immuno-suppressive agents like steroids, calcineurin Inhibitors, especially cyclosporine and mTOR receptor inhibitors like Sirolimus. Other risk factors include proteinuria, diuretics and beta blockers.

• Cyclosporine-A (CyA) interferes with binding of LDL-C to LDL-receptors leading to LDL clearance leading to increase in LDL level
• CyA by virtue of being lipophilic, is transported within the core of LDL-C particles thereby changing the molecular configuration of LDL-C.
• Sirolimus – may inhibit lipoprotein lipase leading to overproduction of lipoproteins in general

RECOMMENDATIONS

In adult kidney transplant recipients, treatment with a statin is suggested.

The age at which statin treatment should begin in kidney transplant recipients is uncertain.

In younger individuals (for example, those aged <30 years and without traditional cardiovascular risk factors) without established ASCVD or DM, the decision to treat with statin therapy should be individualized, considering individual's preferences and relatively small expected ASCVD reduction over 10 years vs risks of polypharmacy and drug toxicity.

TRIGLYCERIDE-LOWERING TREATMENT IN ADULTS WITH CKD

• In adults with CKD (including those treated with chronic dialysis or kidney transplantation) and HTG, therapeutic lifestyle changes are advised.

• Therapeutic lifestyle changes include dietary modification, weight reduction, increased physical activity, reducing alcohol intake, and treatment of hyperglycaemia (if present).

• Fibric acid derivatives are not recommended to prevent pancreatitis or reduce cardiovascular risk in adults with CKD and hypertriglyceridemia.

MANAGEMENT OF HYPERLIPIDAEMIA IN NEPHROTIC SYNDROME

• Associated with HTG and hypercholesterolemia.

• According to current evidence, presence of albuminuria does not decrease beneficial effect of the statin treatment.

• Existing data suggest that the relative benefit of statin treatment is not influenced by the presence of albuminuria.

• Considering the high ASCVD risk in CKD stages 1 and 2 individuals and evidence of demonstrating statins to be equally effective in the presence or absence of proteinuria, individuals aged above 50 years with CKD and GFR >60 should be treated with a statin.

LIPID LOWERING DRUG PROFILES IN RENAL IMPAIRMENT

Statin	eGFR G1–G2	eGFR G3a–G5, including individuals on dialysis or with a kidney transplant
Atorvastatin	GP	20 [65]
Rosuvastatin	GP	10 [66]
Simvastatin / Ezetimibe	GP	20/10 [67]
Simvastatin	GP	40

Table 27: Recommended doses (mg/day) of statins in adults with CKD

All statins may not be available in all countries. Lower doses than those used in major trials of statins in CKD populations may be appropriate in Asian countries. Note that rosuvastatin 40mg daily is not recommended for use in CKD 1-2 non-transplant individuals, as it may increase the risk of adverse renal events. Cyclosporine inhibits the metabolism of certain statins resulting in higher blood levels. Data based on ALERT [65], 4D [66], AURORA [67]. (GP = general populations)

RECOMMENDATIONS

• Rosuvastatin may be used in individuals who received a kidney transplant

• United States Food and Drug Administration (FDA) warning label 2011 that concomitant use of Simvastatin with CyA is contraindicated

Clinicians need to be aware that tacrolimus and cyclosporine are not the same with regard to causing drug interactions with statins. Tacrolimus can be used with statins without the need for dose adjustments because of lack of an interaction [68]

Statin	Dose (mg/d)	Intensity	LDL Reduction (%)	Clearance	Dose adjustment in CKD (mg/d)	Use with Cyclosporine
Simvastatin	5-10 20-40	Low Moderate	18-68	Liver	CKD 4-5, start dose: 5	Avoid use
Atorvastatin	10-20 40-80	Moderate High	15-61	Liver	None	Avoid use
Rosuvastatin	5-10 20-40	Moderate High	47-63	Liver / Kidney	CKD 3-4, max dose: 5-10	Max dose: 5mg/day

Table 28: Statin doses with intensity in various CKD subgroups

Ezetimibe

Ezetimibe has good evidence in individuals with CKD as evident from SHARP study [69].

Bile acid sequestrants

• They are used in combination with statins.

• The interaction is most notable with individuals on mycophenolic acid products.

• There is decreased absorption of cyclosporine and oral corticosteroids when co-administered with bile acid sequestrants.

Fibric acid derivatives

The combination with statins markedly increased the myopathy risk associated with fibric acid derivatives, especially in CKD.

PCSK9 inhibitors

• There are limited data on PCSK9 inhibitors in CKD.

• Furthermore, their benefits are dependent of the degree of cholesterol lowering and it seems that their efficacy decreases as CKD turns into more severe stages [70].

08

8.3 DIABETES AND OTHER ENDOCRINE DISORDERS

Dr Lina Chong Pui Lin, Dr Umer Malik

KEY MESSAGES:

1. Recommend moderate intensity statin therapy in adults with diabetes aged 40 years and above irrespective of 10-year ASCVD risk estimate.

2. For individuals aged 20 to 39 years, estimated lifetime ASCVD risk and presence of diabetes-specific risk factors may guide the need to initiate statin therapy.

3. In adults with endocrine conditions, use the 10-year ASCVD risk calculator to determine the need to initiate statin therapy.

4. In adults with diabetes having multiple ASCVD risk factors or adults with LDL-C ≥4.9 mmol/L, recommend high-intensity statin therapy.

5. Suggest correction of hypothyroidism prior to initiation of statin therapy in the presence of hyperlipidaemia.

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Chronic hyperglycaemia in diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Diabetes is characterized as at least moderate risk of ASCVD [2]. Individuals with diabetes have 2 to 4 times increased risk of cardiovascular morbidity and mortality than individuals without diabetes [71]. According to the National Health and Nutrition Examination Survey (NHANES), the prevalence of diabetes in Brunei Darussalam is 12.4% [72]. Diabetes remains the third leading cause of death and the mortality rate from diabetes was 9.8% in 2019 [7].

The benefit of lipid lowering drugs, particularly statins, in reducing MI or coronary death, coronary revascularization and stroke in individuals with diabetes has been supported by numerous trials [2,5,25,73]. Meta-analyses of randomized controlled trials on statin therapy indicate that major vascular events decrease by 22% and total mortality by 10% for every 1.0 mmol/L reduction in LDL-C in individuals with diabetes [2].

Traditional risk factors of ASCVD include age, gender, ethnicity, diabetes, hypertension, hyperlipidaemia and smoking. ASCVD risk-enhancing factors include family history of premature ASCVD; persistently elevated LDL-C ≥4.1 mmol/L; metabolic syndrome (MetS); CKD; chronic inflammatory conditions (such as RA, psoriasis); history of early menopause or preeclampsia; and ethnicity such as South Asian [5]. The Endocrine Society considers persistent Cushing's syndrome and Cushing's disease, high-dose chronic glucocorticoid therapy, adult growth hormone deficiency (GHD), acromegaly and hypothyroidism as risk enhancing factors of ASCVD [74]. The effect of diabetes and endocrine conditions on lipid profile is shown in **Table 29**.

Disease	LDL-C	HDL-C	TG
Type 2 diabetes	No change or ↑	↑ Normal or ↓	↑
Type 1 diabetes	No change or ↑	↑ Normal or ↓	↑
Obesity	No change or ↑	↓	↑
Hypothyroidism	No change or ↑	Normal or ↑	Normal or ↑
Subclinical hypothyroidism	No change or ↑	Normal or ↓	Normal
Hyperthyroidism	↓	Normal or ↓	Normal or ↑
Cushing's syndrome or Cushing's disease	No change or ↑	Normal or ↓	↑
Chronic glucocorticoid therapy	No change or ↑	Normal or ↑	Normal or ↑
Adult growth hormone deficiency	↑	Normal or ↓	Normal or ↑
Acromegaly	No change or ↑	Normal or ↓	↑
Polycystic ovary syndrome	No change or ↑	↓	↑
Menopause vs pre-menopause	↑	Normal or ↓	Normal
Oral HRT for menopause	↓	↑	↑
Male hypogonadism	↑	Normal or ↓	↑
Testosterone replacement for male hypogonadism	No change or ↓	Normal or ↓	Normal or ↓
Anabolic steroid abuse	↑	↓	Normal or ↑

Table 29: Effect of Diabetes and Endocrine Conditions on Lipid Profile

↓, decreased; ↑, increased; Normal, indicates within the normal range.
Adapted from Endocrine Society Clinical Practice Guideline: Lipid Management in Patients with Endocrine Disorders [74].

CARDIOVASCULAR RISK ASSESSMENT

1. Use 10-year WHO cardiovascular risk chart to estimate risk of a ASCVD event in individuals for primary prevention[5].

Individuals with diabetes aged 40 years and above are considered at high risk of ASCVD and it is recommended to initiate statin therapy irrespective of estimated 10-year ASCVD risk. However, risk assessment can be undertaken to determine the intensity of statin therapy to initiate.

The WHO cardiovascular risk chart only provides estimated risk for individuals aged 40-74 years. For individuals aged 20 to 39 years, lifetime ASCVD risk can be calculated.

Consider diabetes-specific risk enhancers:
• long duration (≥10 years for type 2 diabetes or ≥20 years for type 1 diabetes)
• albuminuria ≥30 mcg albumin/mg creatinine
• eGFR <60 ml/min/1.73m2
• retinopathy
• neuropathy
• ABI <0.9.

• **In adults with endocrine conditions**, use the WHO cardiovascular risk chart in such individuals to determine their risk and the need to initiate treatment (**Table 30**)[2].However, if diabetes co-exists with any of these endocrine conditions, then risk assessment should be based on recommendations for diabetes.

• Consider use of CAC score if the decision to initiate statin therapy remains uncertain[5,74].

• **Figure 11** illustrates ASCVD assessment for primary prevention.

2. The WHO cardiovascular risk chart is not required for secondary prevention as adults with established ASCVD are considered very high risk of ASCVD events[5].

Conditions	Recommendations
• Obesity • Hyperthyroidism^ • Cushing syndrome: cured • Chronic glucocorticoid therapy above replacement levels • Growth hormone deficiency • Acromegaly • Male hypogonadism • Polycystic ovarian syndrome • Women with premature menopause (<40 to 45 years old)	Assess 10-year risk for ASCVD to guide the use of lipid-lowering therapy
Overt hypothyroidism	Treat with thyroxine to achieve euthyroid state before re-assessing lipid profile and ASCVD risk score
Subclinical hypothyroidism (TSH >10 mIU/L) with associated hyperlipidaemia	Consider thyroxine treatment as a means of reducing LDL-C levels; reassess lipid profile and ASCVD risk score once euthyroid
Active Cushing's Syndrome	Suggest statin therapy irrespective of cardiovascular risk score
Postmenopausal women on hormone therapy and with other risk factors for ASCVD	Recommend statin therapy to reduce cardiovascular risk

Table 30: Recommendation on Cardiovascular Risk Assessment in Specific Endocrine Conditions[74].
^For hyperthyroidism, reassess lipid profile once euthyroid
(TSH = thyroid stimulating hormone)

PRIMARY PREVENTION

Measure TC for risk calculator
Use LDL-C measurements for target

LDL >4.9 mmol/L
Maximally tolerated statin

Diabetics aged 40-74 years
Moderate intensity statin**

Aged >74 years
Clinical decision

AGE <40 YEARS

Calculate Lifetime risk*
Consider statin if FH or LDL-C >4.9 mmol/L

AGE 40-74 YEARS

Calculate ASCVD Risk

Lifestyle Measures: Smoking cessation, dietary advice, increase physical activity

Risk <5%
Low Risk

Risk 5-10%
Borderline Risk

Risk 10-20%
Moderate Risk

Risk 20-30%
High Risk

Risk >30%
Very High Risk

Moderate intensity statin

High intensity statin

If a risk decision uncertain,
Consider risk enhancing factors
Consider CAC Scoring:
CAC Score = 0: No statin
CAC Score = 100: Initiate statin
CAC Score = 1-99: Favours statin

ASCVD Risk Enhancing Factors:

• Family history of premature ASCVD
• Primary hypercholesterolaemia
• Metabolic syndrome
• CKD
• Chronic inflammatory conditions
• History of premature menopause and history of pregnancy-associated conditions
• High-risk race / ethnicity
• Persistently elevated hypertriglyceridaemia

Endocrine-specific Risk Enhancers:

• Persistent Cushing's syndrome and Cushing's disease
• High-dose chronic glucocorticoid therapy
• Adult growth hormone deficiency (GHD)
• Acromegaly
• Hypothyroidism

Figure 11: Decision pathway for individuals without known ASCVD being assessed for therapy (primary prevention) for adults with Endocrine disorders.

*In individuals age <40 years, use age = 40 years in WHO Cardiovascular risk chart to calculate ASCVD risk to help a decision on starting statin therapy
**All diabetics regardless of age should be considered for moderate intensity statin depending on diabetes enhancing factors. If ASCVD risk >20%, consider high intensity statin

(Adapted from 2018 AHA/ACC Guideline on the Management of Blood Cholestrol) [5]

LIPID LOWERING TREATMENT IN PRIMARY PREVENTION IN ADULTS WITH DIABETES

In adults with diabetes aged 40 years and above, a moderate intensity statin (e.g. atorvastatin 20mg ON) is indicated [5].

In adults with diabetes who have multiple ASCVD traditional risk factors, consider high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more [5].

In adults with diabetes and a 10-year ASCVD risk of 20% or higher, consider adding ezetimibe to maximally tolerated statin therapy to reduce LDL-C levels by 50% or more [5].

If maximum tolerated dose of statin does not achieve target LDL-C reduction after 3 months consider adding ezetimibe 10mg OD [2].

In adults with diabetes aged 20 to 39 years, consider initiation of statin therapy if any diabetes-specific risk enhancers are present.

Special considerations

• In adults with confirmed statin intolerance/ contraindication, ezetimibe should be considered [5].

• Statin is not recommended in women of child-bearing potential who are planning to conceive or not using adequate contraception [2].

• Statins are contraindicated during pregnancy [2].

• In adults with type 2 diabetes and diabetic retinopathy, consider fibrates in addition to statin therapy to reduce retinopathy progression [74].

LIPID LOWERING TREATMENT IN PRIMARY PREVENTION IN ADULTS WITH ENDOCRINE CONDITIONS

In adults with hyperlipidaemia, perform a thyroid function test to rule out hypothyroidism before initiating lipid lowering treatment [5].

In adults with a 10-year ASCVD risk of 10%, a moderate intensity statin (e.g. atorvastatin 20mg ON) is indicated [5].

• LDL-C levels should be reduced by ≥30%, and for optimal ASCVD risk reduction, especially in high-risk individuals (ASCVD risk ≥20%), LDL-C levels should be reduced by ≥50% [5].

For adults who require more aggressive LDL-C lowering, high-intensity statins are advisable but if not acceptable or tolerated, it may be reasonable to add a non-statin drug (ezetimibe or bile acid sequestrant) to a moderate-intensity statin [5].

Figure 12 illustrates the primary prevention treatment algorithm for the adults with diabetes and endocrine conditions.

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┌─────────────────────────────────────┐
│ Assess cardiovascular risk with 10-year ASCVD │
│ risk score and consider risk enhancing factors* │
└─────────────────────────────────────┘
              ↓
┌─────────────────────────────────────┐
│ Assess if statin therapy is indicated** │
└─────────────────────────────────────┘
              ↓
┌─────────────────────────────────────┐
│ Start moderate intensity statins │
└─────────────────────────────────────┘
              ↓
┌─────────────────────────────────────┐
│ Review in 1-3 months with fasting lipid │
│ profile^ and LFT │
└─────────────────────────────────────┘
              ↓
┌─────────────────────────────────────┐
│ If LDL-C goal is not achieved, intensify │
│ statin therapy; review every 1-3 months with │
│ fasting lipid profile^ and titrate statin │
│ therapy to maximum treated dose │
└─────────────────────────────────────┘
              ↓
┌─────────────────────────────────────┐
│ If LDL-C goal in not achieved, add ezetimibe │
└─────────────────────────────────────┘
              ↓
┌─────────────────────────────────────┐
│ If LDL-C goal in not achieved, consider use │
│ of PCSK9 inhibitor │
└─────────────────────────────────────┘

┌─────────────────────────────────────┐
│ Once LDL-C goal is achieved, follow up │
│ 6-12 months or more frequently if │
│ indicated │
└─────────────────────────────────────┘
```

*Consider risk enhancers in individuals with endocrine disorders, and assess diabetes-specific risk enhancers in individuals with diabetes. Individuals who do not require estimation of 10-year ASCVD risks include adults with diabetes ≥40 years and adults with very high LDL-C levels (≥4.9 mmol/L). For adults aged 20-39 years, estimate lifetime ASCVD risk. Concurrent or prior lifestyle modification before initiation of statin should be provided.

**Individuals with diabetes aged ≥40 years, or aged <40 years with diabetes-specific risk enhancers. In individuals with diabetes having multiple ASCVD traditional risk factors (IIa) or those with LDL-c ≥ 4.9 mmol/l, start high-intensity statin therapy. Individuals with Endocrine disorders, statin therapy is based on 10-year ASCVD risk calculation. Consider initiating statins if there is a family history of premature cardiovascular disease and LDL-C ≥4.1 mmol/L.

^Lipid profile at least once every 1-3 months to assess response to treatment (recommended on practical grounds).

Figure 12: Primary prevention treatment algorithm for the adults with Diabetes and Endocrine conditions

Adapted from 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary (5), Endocrine Society Clinical Practice Guideline: Lipid Management in Patients with Endocrine Disorders (74), and 2019 ESC/EAS guidelines for the management of dyslipidaemia (2).

TREATMENT

1. Lifestyle modification

• Lifestyle modification is vital and is recommended [2].
• **Table 31** shows recommendations on lifestyle modification in diabetes and pre-diabetes [73].
• Lipid lowering therapy will follow recommendations in **Chapter 7.1**

2. Correction of hypothyroidism if present [74].

Recommendations
Smoking cessation guided by structured advice is recommended in all individuals with DM and pre-DM
Lifestyle intervention is recommended to delay or prevent the conversion of pre-DM states, such as IGT, to type 2 diabetes
Reduced calorie intake is recommended for lowering excessive body weight in individuals with pre-DM and DM.ᵃ
Moderate-to-vigorous physical activity, notably a combination of aerobic and resistance exercise, for ≥150 min/week is recommended for the prevention and control of DM, unless contraindicated, such as when there are severe comorbidities or a limited life expectancy.ᵇ
A Mediterranean diet, rich in polyunsaturated and monounsaturated fats, should be considered to reduce cardiovascular events

Table 31: Lifestyle modification in diabetes and pre-diabetes

IGT = impaired glucose tolerance
ᵃA commonly stated goal for obese pindividuals with DM is to lose ≥5% of baseline weight.
ᵇRecommended that all individuals reduce the amount of sedentary time by breaking up periods of sedentary activity with moderate-to-vigorous physical activity in bouts of ≥10 min (broadly equivalent to 1000 steps).
Adapted from 2019 ESC guidelines on diabetes, pre-diabetes and cardiovascular diseases [73].

MEASURING AND MONITORING LIPID PROFILE

Following initiation of statin therapy, check fasting lipid profile every 1-3 months then every 6-12 months depending on need to assess adherence or safety [5,39].

Discuss treatment adherence, side effects and timing of dose.

If adults on a high intensity statin have side effects, offer a lower dose or an alternative statin.

Monitor LFT for statin-related transaminitis (Please see **Chapter 7.3**).

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8.4 STROKE

Dr Jessie Colacion, Dr Yong Chee Shin

KEY MESSAGES:

1. All individuals who have had a stroke should have their cardiovascular risk assessed.

2. The intensity of lipid lowering regimen will depend on stroke aetiology hence the need for delineation to improve risk stratification.

3. Individuals who have had a stroke should be empowered about the cause of their stroke, the rationale behind set targets for secondary prevention and educated on both the non-pharmacological and pharmacological ways to achieve said targets.

4. Lipid lowering therapy with statins should be considered in everyone with previous non-cardio-embolic ischaemic stroke or transient ischaemic attack to a recommended target LDL-C of 50% reduction from baseline and <1.8 mmol/L for secondary prevention of atherosclerotic cardiovascular disease.

5. During the acute phase of haemorrhagic strokes, statins should be continued in those individuals who are on pre-existing statin therapy. For statin-naïve individuals, statins are not recommended to be started acutely phase for the purpose of improving clinical outcome, or during the chronic phase unless there is a high and/or previously unrecognized thromboembolic or atherosclerotic vascular risk.

INTRODUCTION

Stroke is defined as neurological deficits attributed to an acute neurovascular event and is broadly divided into ischaemic stroke (infarcts can be further subtyped according to aetiology as per the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification) or haemorrhagic stroke. More recently there is a paradigm shift towards defining stroke according to aetiology. This is reflected in the revised guidelines by the AHA and American Stroke Association (ASA) for Prevention of stroke and Transient Ischaemic Attacks that was released in May 2021[75].

The significance of blood lipids as a risk factor for stroke is not as well established as that in cardiac diseases due to the heterogeneity in stroke aetiology. The benefit of lipid-lowering therapy varies among individuals with different stroke aetiologies [76-78]. The Asia Pacific Cohort Studies Collaboration showed that there is a stronger positive association with cholesterol in ischaemic strokes and a weaker negative association in haemorrhagic strokes[79]. High intensity lipid lowering has been shown to be most beneficial in large vessel atherosclerotic disease. It is still unclear if non-atherosclerotic ischaemic strokes (Small Vessel Disease, Vasculitis, Moya-Moya Disease) should be considered at the same high levels of atherosclerotic cardiovascular risk.

High intensity lipid lowering regimens are not without side effects and the longer-term complications are still unclear. Evaluating the aetiology of all strokes is therefore paramount as it has implications on the intensity of lipid lowering and targets when making decisions in risk-benefit analysis and cost-effectiveness. Bearing in mind also, co-existence and overlap of aetiologies can occur in the same individual.

ISCHAEMIC STROKES

Ischaemic strokes and transient ischaemic attacks have previously been classed as high cardiovascular risk in many international guidelines on par with coronary syndromes, angina and peripheral artery disease requiring arterial revascularisation. This is unsurprising as large vessel atherosclerotic ischaemic strokes share the same pathophysiology with coronary artery disease. Many previous studies have shown that individuals with ischaemic stroke are at high risk of MI or sudden death (>20% absolute risk over 10 years)[16,80-84].

A strong association between hyperlipidaemia and risk of large vessel atherosclerotic strokes in particular the role of LDL-C, has been shown by several trials (SPARCL[85], J-STARS[86], SiGN [87] and TST [88]). The CTT Collaboration had performed a meta-analysis of 26 randomised trials of statin therapy and reported 21% relative risk reduction of recurrent ischaemic stroke per mmol/L of LDL-C [6]. Statins has so far remained the main cornerstone of lipid pharmacotherapy [89-93].

RECOMMENDATIONS FOR LIPID MANAGEMENT IN ISCHAEMIC STROKES

1. All individuals should be fully evaluated for their baseline cardiovascular risks and initiated on statins after 48 hours from onset of ischemic stroke.

2. In individuals who are already on statin before their acute ischaemic stroke, they should be continued on statin therapy.

3. All individuals should be educated about lifestyle, dietary modifications and importance of adherence to medical therapy.

4. With regards to lipid pharmacotherapy and following the latest revised latest AHA/ASA guidelines, 2021 [75]:

a) Atorvastatin 80mg ON is indicated in individuals with ischaemic stroke with no known coronary heart disease, major cardiac sources of embolism, and LDL-C is above 2.6 mmol/L.

b) Individuals with ischaemic stroke or TIA with atherosclerotic disease (intracranial, carotid, aortic or coronary) should have lipid lowering with statin and ezetimibe if needed to a goal of <1.8 mmol/L.

c) Once initiated on lipid lowering treatment, adherence to lifestyle modifications and medications should be monitored with fasting lipid profile 1 to 3 months with appropriate safety indicators (LFT and CK if develops myalgia) then repeated every 6 to 12 monthly once stable for dose adjustments.

d) In individuals with ischaemic stroke who are very high risk, already taking maximally tolerated statin and ezetimibe but still not achieving the goal of <1.8 mmol/L it is reasonable to consider escalation of therapy to PCSK-9 inhibitors on a case-by-case basis.

e) Identify the reason and address the cause of severe HTG in stroke with fasting TG >5.7 mmol/L. Lowering may be by dietary means and introduction of fibrate therapy may be considered to reduce the risk of pancreatitis.

HAEMORRHAGIC STROKES

Cholesterol, an essential cell membrane component, helps maintain the integrity of small cerebral vessels, such that low levels of cholesterol may potentially increase the risk for intracerebral haemorrhage (ICH). This haemorrhagic risk in individuals with low blood cholesterol levels was augmented among those individuals with concomitant hypertension [94].

This protective mechanism was thought to be due to the pleiotropic effects of statins, such as anti-inflammatory and antithrombotic properties that may protect the cerebral vessels [95]. Though low blood cholesterol levels afford a potential risk for ICH, particularly in those with hypertension, statin use does not appear to increase the ICH risk in the normal population and may mitigate ICH severity.

Unfortunately, there have been no randomized controlled trials examining the efficacy or hazards of lipid-lowering therapy in individuals with ICH. Statin use after ICH may not increase the risk of further ICH and may even improve the functional outcome and mortality in individuals with ICH. However, excessive lowering of cholesterol levels by statins may have to be avoided. Prospective, controlled trials are still needed to elucidate whether statin therapy is necessary in individuals with ICH, and if so, when to and with what dosage to initiate.

RECOMMENDATIONS FOR LIPID MANAGEMENT IN HAEMORRHAGIC STROKES

1. During the acute phase of ICH admission of individuals on pre-existing statin therapy, statins should not be discontinued.

2. Statins are not recommended for statin-naïve individuals with ICH in the acute phase for the purpose of improving clinical outcome, or during the chronic phase unless there is a high and/or previously unrecognized thromboembolic or atherosclerotic vascular risk.

09

MANAGEMENT IN SPECIFIC GROUPS

9.1 PREGNANT AND BREASTFEEDING WOMEN

Dr V Jacob Jose

- Statin treatment is recommended for primary prevention of ASCVD in high-risk women as well as secondary prevention in women (similar to men) [2].

- However, lipid-lowering treatment is contraindicated when pregnancy is planned, during pregnancy, or during the breastfeeding period.

- Hence it is preferable to avoid statins in women of child bearing potential unless contraception methods are being followed [96,97].

- The only medications currently acceptable during pregnancy are bile acid sequestrants, since they are not systemically absorbed and therefore not felt to pose foetal risk.

09

9.2 OLDER PEOPLE

Dr Teo Shyh Poh, Dr Sanny Choo Zi Lung

KEY MESSAGES:

1. The use of statin as therapy is recommended but with careful consideration of its overall benefits versus risks.

2. There is no consensus on treatment target of hyperlipidaemia in older people [98].

3. Intolerance to statins are more common in older people. Close monitoring for tolerance and safety is advocated especially in the weeks after initiation, increase in dose or switching to another statin.

4. Drug interaction is common especially in older people with polypharmacy which may result in drug induced toxicity or reduced drug efficacy.

5. As the intended benefit of hyperlipidaemia treatment is long term, the role of treatment older people with short life expectancy of under 12 months is limited.

CONSIDERATION OF OVERALL BENEFITS VERSUS RISKS WITH HYPERLIPIDAEMIA TREATMENT IN OLDER PEOPLE

In the majority of older people, the 10-year CVD risk is >10%. Based solely on this, most if not all older people should be started on treatment for hyperlipidaemia. However, due to the heterogeneity of older people (in terms of comorbidities, polypharmacy, frailty, cognitive impairment and variable life expectancy), initiation or continuation of hyperlipidaemia treatment should be carefully considered [98].

Treatment target: As there are very limited studies on the effects of hyperlipidaemia treatment on morbidity and mortality in older people, there is no general consensus on the target lipid levels.

TREATMENT OF HYPERLIPIDAEMIA IN OLDER PEOPLE

1. Non-pharmacological Therapy
Older people should be advised to reduce fat intake. However, this should not be done at the expense of malnutrition. Healthy lifestyle including regular exercise (if physically able) of at least 30 minutes for 5 times a week is also encouraged.

2. Pharmacological Therapy
Statins are widely accepted as the first-line therapy. There is no preference of one statin over another as long as it is tolerated.

CONSIDERATIONS WITH PHARMACOLOGICAL THERAPY

1. Intolerance to statins
Muscular disorders are the most recognised adverse effects associated with the use of statins. This ranges from non-specific myalgia to more serious myopathy (associated with rise in CK) and rhabdomyolysis [99]. The incidence rate is dose related and is more commonly reported with the use of statins in older people and female individuals.

2. Drug to drug interactions
Polypharmacy is a well-known but under-recognised problem amongst older people [100]. Older people on statin should be monitored for interactions with other drugs as it may lead to drug induced toxicity and/or reduced drug efficacy.

3. Treatment in older people with vascular dementia
Optimal management of all cardiovascular risk factors including hyperlipidaemia in older people with vascular dementia is recommended to reduce the rate of disease progression [101].

4. Life expectancy
The benefit of pharmacological therapy is long-term. Its benefit is in question for older people with life expectancy of under 12 months.

STATINS IN ELDERLY

Data taken from 2 primary prevention trails – JUPITER and HOPE – 3, in subjects above the age of 70 years and free of ASCVD, showed that the composite outcome of nonfatal MI, nonfatal stroke, or cardiovascular death were reduced by 26%, compared with placebo [98].

RECOMMENDATIONS

• Statin may be stopped if life expectancy is limited or frail or multimorbidity.

• The decision to start treatment should consider the potential risk reduction associated with treatment, risk of adverse effects, drug-drug interactions and patient preferences.

For persons aged more than 75 years with LDL-C of 1.7 to 4.8 mmol/L, moderate intensity of statin is reasonable.
In adults above the aged more than 75 years, statin may be stopped if life expectancy is limited or frail or multimorbidity.

Table 32: Statin recommendations in older people

09

9.3 CHILDREN AND ADOLESCENTS

Dr Hjh Rohayati Hj Md Taib, Dr Sukhendu Shekhar Sen

KEY MESSAGES:

1. Individualize lipid screening by identifying children at risk and targeting screening to those with a positive family history, high-risk factors, or comorbid medical conditions such as diabetes mellitus, nephrotic syndrome, obesity, and hepatitis.

2. Lifestyle modification of diet and exercise are first-line therapies for hyperlipidaemia; however, individuals with homozygous familial hypercholesterolemia will need statin therapy as additional management.

3. Statin therapy in children may be associated with increased costs and harmful effects and should not be used in the general paediatric population because the risk of ASCVD in children is almost zero.

4. The long-term effects of statins on children are unknown, and more research is needed.

1. Cholesterol in youth (age <18 years)

• Cholesterol levels, including LDL-C and non-HDL-C are low at birth and increase in the first two years of life
• Levels peak between 9-11 years and decrease during adolescence (age <18 years)

2. Definition of hyperlipidaemia in children and adolescents

• Definitions are consistent with the National Heart, Lung, and Blood Institute, the American Academy of Pediatrics, and the American Heart Association/American College of Cardiology
• These cut-off points have not been validated as accurate predictors for accelerated atherosclerosis or ASCVD events [102]

Category	Acceptable, mmol/L	Borderline, mmol/L	High, mmol/L
TC	4.4	4.4 to 5.2	≥5.2
LDL-C	2.8	2.8 to 3.3	≥3.4
Non-HDL-C	<3.1	3.1 to 3.7	≥3.8
ApoB	<2.3	2.3 to 2.8	≥2.8
TG 0 to 9 years	<0.8	0.8 to 1.1	≥1.1
TG 10 to 19 years	<1	1 to 1.5	≥1.5
HDL-C	>1.2	1 to 1.2	<1
ApoA-1	>3.1	3 to 3.1	<3

Table 33: Lipid profile in children and adolescents

3. Risk factors for atherosclerosis in this age group include [103]:

• Genetic dyslipidaemia such as familial hypercholesterolemia
• Overweight or obese
• Kawasaki disease
• Nephrotic syndrome
• CKD
• Type 1 and 2 diabetes mellitus
• Chronic inflammatory diseases such as systemic lupus erythematous
• HIV
• Cigarette smoking

4. Lipid Screening in children and adolescents

• For children with underlying risk factors for premature ASCVD, lipid screening begins at the time the risk factor is first identified (generally not earlier than age 2 years)
• Subsequent testing every 1 to 3 years depending on the nature of the risk factor(s)

5. Screening Samples

There is only a small difference between non-fasting and fasting lipid measurements (that are likely clinically insignificant - Data from the National Health and Nutrition Examination Surveys (1999 to 2008))

• Non-fasting panels are used for initial screening
• If the non-fasting panel is abnormal or borderline, a fasting lipid panel should be done
• At least two fasting profiles should be measured over 3 months to confirm the diagnosis

6. 4 general classes of paediatric hyperlipidaemias

• Medication related hyperlipidaemia
• Dyslipidaemia related to lifestyle factors
• Genetic Dyslipidaemia
• Hyperlipidaemia related to a medical condition

7. 3 main genetic hyperlipidaemias

Dyslipidaemia	Abnormal Lipid Fraction	Prevalence Estimate	Mechanism of defect
Familial Hypercholesterolaemia	High LDL-C	Heterozygous 1 in 300 Homozygous 1 in 1,000,000	Decreased LDL-C clearance
Familial Combined Hyperlipidaemia	High LDL-C and High TG / VLDL	1 in 100	Increased ApoB production
Familial Severe Hypertriglyceridaemia	High TG / VLDL	1 in 100,000	Decreased TG / VLDL degradation

Table 34: Three main genetic hyperlipidaemia
(VLDL = very low density lipoprotein)

8. Increased risk of Familial Hyperlcholesterolaemia (FH)

• Consider assessment for FH if two fasting or non-fasting non-HDL-C >5.5 mmol/L or LDL-C >4.9 mmol/L
• It is suggested to use the DLCNC criteria (see **Chapter 4**) to diagnose FH

9. Management of hyperlipidaemia

Refer all children and adolescents with LDL-C >3.4 mmol/L for Specialist assessment

LDL-C = 3.4-5.0 mmol/L	Assess risk factors and family history	Diet and lifestyle changes + specialist assessment
LDL-C >5.0 mmol/L	Assess risk factors, family history and consider assessment for FH	Diet lifestyle and specialist review regarding pharmacotherapy

Table 35: Management of hyperlipidaemia in children and adolescents

• **Elevated TG** - Children with TG levels >5.6 mmol/L are at increased risk of pancreatitis. Diet and lifestyle changes together and/or medications could be considered.

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10. Risk stratification for early cardiovascular disease

No current scoring system has been validated for establishing ASCVD risk in Paediatric Population (<18 years).

High-risk conditions and risk factors

• Homozygous FH
• Diabetes mellitus (type 1 or 2)
• End-stage kidney disease
• Kawasaki disease and persistent coronary aneurysms
• Solid-organ transplant vasculopathy
• Childhood cancer survivor following stem cell transplantation
• Multiple comorbidities – Any **moderate-risk** condition plus ≥ additional **moderate-** or **at-risk** factors

Moderate-risk conditions and risk factors

• Severe obesity (BMI ≥99th percentile or ≥35 kg/m^2)
• Confirmed hypertension (BP >95th percentile or ≥130/80 mmHg on 3 separate occasions)
• Heterozygous FH
• Pre-dialysis CKD
• Aortic stenosis or coarctation
• Childhood cancer survivor with exposure to chest irradiation
• Multiple risk factors - ≥3 **at-risk** conditions or risk factors

At-risk conditions and risk factors

• Obesity that is not severe (BMI ≥95th to <99th percentile)
• Insulin resistance with comorbidities (e.g. NAFLD, PCOS)
• Family history of premature ASCVD
• Parent with known hyperlipidaemia (e.g. FH) or TC >6.2 mmol/L
• Current smoker or significant exposure to second-hand smoke
• White-coat hypertension (elevated BP measurements in the office with normal values outside the office setting)
• Chronic inflammatory disease (e.g., SLE, systemic JIA)
• HIV infection
• Kawasaki disease with regressed coronary aneurysms
• Cardiomyopathy (e.g. HCM)
• Surgically repaired congenital heart disease involving coronary artery translocation (e.g. TGA repair)
• Childhood cancer survivor with cardiotoxic chemotherapy only
• Adolescent depressive and bipolar disorders

NAFLD = non-alcoholic fatty liver disease
PCOS = polycystic ovarian syndrome
SLE = systemic lupus erythematosus
JIA = juvenile idiopathic arthritis
HCM = hypertrophic cardiomyopathy
TGA = transposition of great arteries

Table 36: Disease Stratification of children and adolescents with hyperlipidaemia by risk [104]

11. Risk based management approach

• Non-pharmacologic measures for all individuals with hypercholesterolemia

• The main approach is a healthy lifestyle with appropriate diet, maintenance of "desirable weight" and regular exercise (i.e. heart-healthy lifestyle changes, including dietary modification, physical activity, weight loss, and avoidance of nicotine)

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12. Pharmacological therapy

This is reserved for high-risk individuals and those who do not achieve adequate response to lifestyle changes

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

• In individuals with FH, statins are the drug of choice. All statins can be used as an adjunct to diet, in children >10 years of age.

• 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. Individuals should be extensively counselled prior to initiation of drug therapy.

• There has been increasing risk for type 2 diabetes in adolescents. Thus, the risk of new onset diabetes should also be considered when prescribing statins in children with risk factors for diabetes.

LIST OF MEDICATIONS FOR HYPERLIPIDAEMIA MANAGEMENT IN BRUNEI DARUSSALAM

The following list and related information gathered from List of Registered Medicinal Products (updated September 2018)[105], National Standard Drug List (NSDL) 7th Edition (Updated March 2019)[43], British National Formulary (BNF).

The doses here are for guidance only, the user is advised to refer to the local formulary.

Statins

Preparation Name	Dose	Starting Dose	Recommended maximum daily dose
Simvastatin	10mg	10-20mg od	80mg od
	40mg		
Atorvastatin	10mg	10mg od	80mg od
	20mg		
	40mg		
Rosuvastatin	5mg	5mg od	20mg od
	10mg		
	20mg		

Ezetimibe

Preparation Name	Dose	Starting Dose	Recommended maximum daily dose
Ezetimibe	10mg	10mg od	10mg od

Statin + Ezetimibe combination

(for dose recommendations, please consult individual product literature)

Preparation Name
Simvastatin (10mg) + Ezetimibe (10mg)
Simvastatin (20mg) + Ezetimibe (10mg)

Fibrates

Preparation Name	Dose	Starting Dose	Recommended maximum daily dose
Bezafibrates	200mg	200mg tds	200mg tds
	400mg (SR)	400mg od	400mg od
Fenofibrate (NPB)	145mg	160mg od	160mg od
	160mg		
Gemfibrozil	600mg	600mg bd	600mg bd

Bile Acid Sequestrants

Preparation Name	Dose	Starting Dose	Recommended maximum daily dose
Cholestyramine	4g/sachet	4g od	36g per day (1–4 divided doses)

PCSK-9i

Preparation Name	Dose	Starting Dose	Recommended maximum daily dose
Evolocumab (NPB)	140mg/ml injection	140mg every 2 weeks	420mg every 2 weeks

APPENDIX

APPENDIX A: THE 5A'S BRIEF TOBACCO INTERVENTION

The 5As (**Ask**, **Advise**, **Assess**, **Assist**, **Arrange**) summarise all the activities that a primary care provider can do to help a tobacco user within 3–5 minutes. Please find below action and strategies for implementing each of the 5As.

ASK	**Systematically identify all tobacco users at every visit**

• Ask ALL of your patients at every encounter if they use tobacco and document it.
• Keep it simple, some sample questions may include:

"Do you smoke cigarettes?"
"Do you use any tobacco products?"

• Make it part of your routine.
• Tobacco use status should be included in all medical notes. Health facilities should consider expanding the vital signs to include tobacco use or using tobacco use status stickers on all patient charts.

ADVISE	**Persuade all tobacco users that they need to quit**

Urge every tobacco user to quit in a clear, strong and personalised manner.

Advice should be:

• **Clear** – "It is important that you quit smoking now, and I can help you." "Cutting down while you are ill is not enough." "Occasional or light smoking is still dangerous."
• **Strong** – "As your doctor, I need you to know that quitting smoking is the most important thing you can do to protect your health now and in the future. We are here to help you."

ASSESS	**Determine readiness to make a quit attempt**

Ask two questions in relation to "importance" and "self-efficacy":

1. **"Would you like to be a non-tobacco user?"**
2. **"Do you think you have a chance of quitting successfully?"**

Any answer in the shaded area indicates that the tobacco user is NOT ready to quit. In these cases, you can discuss benefit of quitting and explore barriers such as fear of failure, coping with stress, etc. Then review at future visits.

Question 1	**Yes**	**Unsure**	**No**
Question 2	**Yes**	**Unsure**	**No**

If the patient is ready to go ahead with a quit attempt you can move on to Assist and Arrange steps.

ASSIST	**Help the patient with a quit plan**

• Help the patient develop a quit plan.
• Use the STAR method to facilitate and help your patient to develop a quit plan:

o Set a quit date ideally within two weeks.
o Tell family, friends, and coworkers about quitting, and ask for support.
o Anticipate challenges to the upcoming quit attempt.
o Remove tobacco products from the patient's environment and make the home smoke free.

• Provide supplementary materials, including information on smoking cessation clinic and other referral resources.
• Recommend the use of approved medication if needed.

ARRANGE	**Schedule follow-up contacts or a referral to specialist support**

• Arrange a follow-up contact with your patient either in person or by telephone.
• Refer the patient to a Smoking Cessation Clinic (refer Appendix B)

APPENDIX B: LIST OF SMOKING CESSATION CLINICS IN BRUNEI DARUSSALAM

BERAKAS
📞 2333991 / 2340228 / 2340238

PENGIRAN ANAK PUTERI HAJAH RASHIDAH SA'ADATUL BOLKIAH, SG. ASAM
📞 2201593 / 2201594 / 2201597

JUBLI EMAS, BUNUT
📞 2655074 / 2655073 / 2650450

JUBLI PERAK, SENGKURONG
📞 2661068 / 2661069

LAMUNIN
📞 4237397

TELISAI
📞 4244456

SUNGAI KELUGOS
📞 4240134

SUNGAI LIANG
📞 3230428

PENGIRAN ANAK PUTERI HAJAH MUTA'WAKKILAH HAYATUL BOLKIAH, GADONG
📞 2424991

PEKAN TUTONG
📞 4260805

SERIA
📞 3222564 / 3222651

KUALA BELAIT
📞 3335331 / ext 3282

PENGKALAN BATU
📞 2683403 / 2683404 2683405 / 2683406

MUARA
📞 2772991

HOSPITAL PIHM
📞 5221526

APPENDIX C: BRIEF DIETARY ADVICE FOR INDIVIDUALS WITH HYPERLIPIDAEMIA

1

Choose a wide variety of nutritious foods from five groups every day [12,33]
(refer to **Figure D1**: National Dietary Guidelines)

• Vary your food choices from within each food group
• Foods should be eaten in the right amount and combination
• Choose complex carbohydrates such as whole grain food instead of refined carbohydrates
• Consume less high-fat dense food groups
• Choose unsaturated oils and spreads, eaten in small amounts
• Eat at least 2 servings of fruits and 3 servings of vegetables everyday

2

Limit intake of fatty foods [32]
(refer to **Figure D2**: Limiting Your Intake of Fatty Food)

• Trim off any visible fat and/or skin on meat and poultry
• Avoid or limit intake of processed foods such as nuggets, corned beef and sausages
• Avoid or limit intake of foods with high content of trans fat such as crisps, cakes, pastries, biscuits, margarine, ghee, butter-blend and ice-cream

3

Replace saturated and trans fats with food containing polyunsaturated and monounsaturated fats [12,33]

• Replace food high in saturated fats such as palm oil, butter, ghee, coconut oil with foods which contain predominantly polyunsaturated and monounsaturated fats such as canola oil, olive oil, sunflower oil, soybean oil and other cooking oil
• Avoid using used cooking oil repeatedly
• Choose low fat dairy products such as skimmed or low fat milk to replace non-dairy creamer, evaporated milk and sweetened condensed milk
• Use reduced fat milk to replace coconut milk in dishes
• Consume at least two servings of fish per week, preferably oily fish such as duai kuning, kembura, balanak, tamban (sardines), tenggiri and salmon
• Choose trans fat free food products

4

Only consume fried food twice per week [34,35]
(refer to **Figure D2**: Limiting Your Intake of Fatty Food)

• Avoid or limit intake of deep fried and battered food to no more than twice per week
• Pick healthier cooking method such as air fried or stir fried with minimal oil usage
• Replace deep frying with alternative low fat cooking methods such as grilling, steaming, baking and boiling [34,35]

APPENDIX D: SAMPLE OF A ONE-WEEK FAT REDUCTION MENU PLAN

MONDAY

Breakfast (255 kcal)	kcal
1 cup tea/coffee (250 ml) + low-fat milk (60 ml), no added sugar	35
2 slices wholemeal/wholegrain bread	160
2 teaspoon peanut butter spread	60

Morning Snack (104 kcal)	kcal
1 apple	104

Lunch (435 kcal)	kcal
1 cup rice, cooked	200
1 portion (palm size) baked chicken breast, no skin	130
2 scoops stir-fried chye sim (*sawi*)	105

Afternoon Snack (80 kcal)	kcal
1 cup tea/coffee, no sugar (250ml)	5
2 pieces low sodium plain crackers	75

Dinner (405 kcal)	kcal
1 cup rice, cooked	200
1 portion (palm size) lemongrass steamed fish	100
2 scoops stir-fried cabbage	61
2 scoops stir-fried cabbage	44

TOTAL CALORIES (kcal)	1279

TUESDAY

Breakfast (257 kcal)	kcal
4 tablespoons or 1/3 cup (dry) oats	119
2/3 cup (180 ml) low fat milk	88
1 small banana (sliced)	50

Morning Snack (60 kcal)	kcal
¾ cup low fat plain yoghurt	60

Lunch (430 kcal)	kcal
1 cup spaghetti aglio olio with prawn (remove head and vein)	390
1 cup green leafy salad + 1 tablespoon (15 g) balsamic vinegar dressing	40

Afternoon Snack (70 kcal)	kcal
Unsweetened soya milk (200 ml)	70

Dinner (486 kcal)	kcal
1 cup rice, cooked	200
1 piece grilled chicken with garlic and herbs	160
2 scoops grilled eggplant	92
10 grapes (50 g)	34

TOTAL CALORIES (kcal)	1303

WEDNESDAY

Breakfast (198 kcal)	kcal
1 cup tea/coffee (250 ml) + low-fat milk (60 ml), no added sugar	35
1 egg, hard or soft boiled	83
1 slice wholemeal/wholegrain bread	80

Morning Snack (118 kcal)	kcal
20g (one small handful) unsalted almonds	118

Lunch (375 kcal)	kcal
1 bowl sliced fish bee hoon soup	375

Afternoon Snack (55 kcal)	kcal
1 cup tea/coffee, no sugar (250ml)	5
1 small banana	50

Dinner (495 kcal)	kcal
1 cup rice, cooked	200
1 piece curry chicken (no skin), replace coconut milk with low fat milk	149
2 scoops stir-fried long beans	70
1 wedge papaya (225 g)	76

TOTAL CALORIES (kcal)	1241

THURSDAY

Breakfast (250 kcal)	kcal
1 cup tea/coffee (250 ml) + low-fat milk (60 ml), no added sugar	35
1 steamed chicken pau	215

Morning Snack (50 kcal)	kcal
1 small banana	50

Lunch (418 kcal)	kcal
1 cup rice, cooked	200
7 mediumsized (120 g) black pepper prawns (remove head and veins)	161
2 scoops stir fried broccoli	57

Afternoon Snack (95 kcal)	kcal
1 cup tea/coffee, no sugar (250ml)	5
1/3 cup steamed chickpeas, unsweetened	90

Dinner (453 kcal)	kcal
1 cup rice, cooked	200
1 scoop lean beef slices with ginger and spring onion	129
2 scoops *bayam masak tumis*	80
1 cup watermelon, no skin (120 g)	44

TOTAL CALORIES (kcal)	1266

APPENDIX D: SAMPLE OF A ONE-WEEK FAT REDUCTION MENU PLAN

FRIDAY

Breakfast (261 kcal)	kcal
1 cup tea/coffee (250 ml) + low-fat milk (60 ml), no added sugar	35
1 cup fried bee hoon	226

Morning Snack (104 kcal)	kcal
1 apple	104

Lunch (348 kcal)	kcal
1 wholemeal wrap	130
3 slices roasted chicken breast	140
1 cup lettuce	8
2 tablespoon dressing (low-fat Greek yoghurt, olive oil, lemon juice, salt and pepper)	70

Afternoon Snack (109 kcal)	kcal
1 cup tea/coffee, no sugar (250ml)	5
2 pieces steamed *kuih apam*	104

Dinner (480 kcal)	kcal
1 cup rice, cooked	200
1 portion (palm size) fish stew (*ikan rebus/ampap*)	144
2 scoops stir fried mixed vegetables	61
1 wedge papaya (225 g)	44

TOTAL CALORIES (kcal)	1302

SATURDAY

Breakfast (223 kcal)	kcal
1 cup tea/coffee (250 ml) + low-fat milk (60 ml), no added sugar	35
1 vegetables spring roll, non-fried	188

Morning Snack (80 kcal)	kcal
1 cup tea/coffee, no sugar (250ml)	5
2 pieces low sodium plain crackers	75

Lunch (400 kcal)	kcal
1 cup garlic rice, cooked (white rice, garlic, chicken stock)	250
1 portion steamed chicken, no skin	142
½ cup chopped cucumber	8

Afternoon Snack (50 kcal)	kcal
1 small banana	50

Dinner (502 kcal)	kcal
1 cup rice, cooked	200
½ cup (120 g) steamed tofu with minced chicken	188
2 scoops stir-fried kailan	80
10 grapes (50 g)	34

TOTAL CALORIES (kcal)	1255

SUNDAY

Breakfast (245 kcal)	kcal
1 cup tea/coffee (250 ml) + low-fat milk (60 ml), no added sugar	35
2 slices wholemeal/wholegrain bread	160
1 tablespoon tuna in water (add ground black pepper to taste)	45
4 slices cucumber	5

Morning Snack (63 kcal)	kcal
1 orange	63

Lunch (484 kcal)	kcal
1 whole wheat roti/chapati	144
1 cup vegetables and lentil stew without coconut milk (Dhal)	133
1 portion chicken tikka (no skin)	207

Afternoon Snack (70 kcal)	kcal
Unsweetened soya milk (200 ml)	70

Dinner (410 kcal)	kcal
1 cup rice, cooked	200
1 scoop lean teriyaki beef slices	110
2 scoops stir-fried *labu air*	60
½ cup pineapple (80 g)	40

TOTAL CALORIES (kcal)	1272

Portion guide (per serving) in the menu:

Chicken / beef = 85g (3 oz)
Fish = 90g (3.2 oz)

Frequency (per week) in the menu:

Chicken (no skin) – everyday
Fish - thrice
Prawn - twice
Beef (lean meat) - twice

FIGURE D1: NATIONAL DIETARY GUIDELINES FOR BRUNEI DARUSSALAM [34]

1. Enjoy a wide variety of nutritous food daily within the recommended amount

- Eat two servings of fruits and three servings of vegetable everyday
- Base meals on grains with at least half of the grains whole grains
- Eat fish, poultry, lean meat, legumes, nuts and other proteins in moderation
- Consume milk, yoghurt, cheese and alternative, preferably reduced fat
- Use recommended cooking oil sparingly

2. Drink plenty of water

3. Reduce intake of energy-dense food, sugary drinks and salty food

FIGURE D2: LIMITING YOUR INTAKE OF FATTY FOOD [34]

INSTEAD OF THIS		PICK THIS
Deep Fried Chicken	→	**Grilled or Air fried chicken**
Fried Spring Rolls	→	**Plain Spring Rolls**
Prawn fritter (*cucur udang*)	→	**Grilled prawn skewer**
Corned Beef	→	**Lean minced beef**
Fried chicken nuggets or sausages	→	**Baked chicken bites**
Cookies and cakes	→	**Crackers, fruits or nuts**
Ice cream	→	**Low-fat yoghurt**
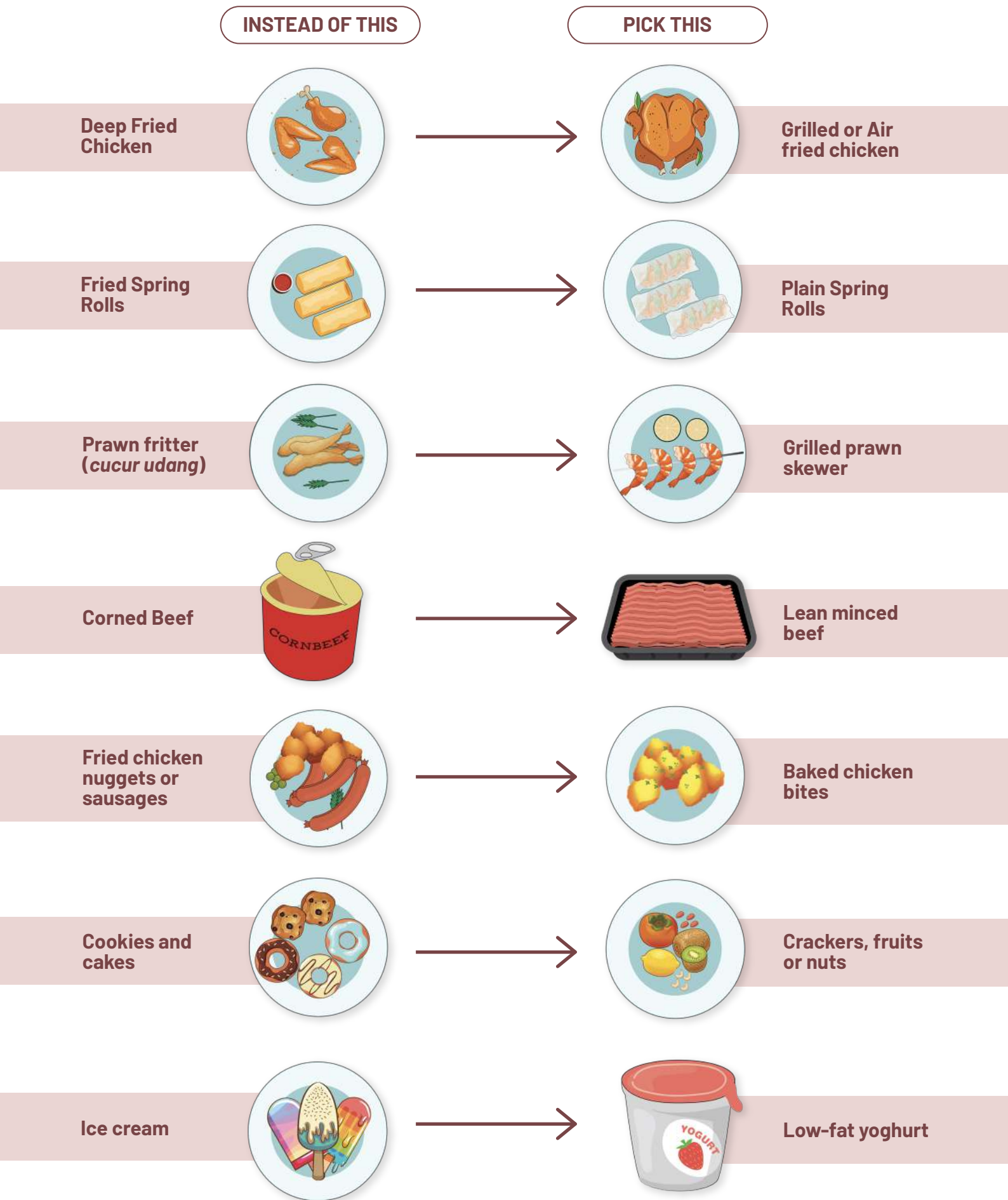
APPENDIX E: BRIEF DESCRIPTION OF THE DIFFERENT INTENSITIES OF PHYSICAL ACTIVITIES [36,107]

FIGURE E1: DIFFERENT INTENSITIES OF PHYSICAL ACTIVITY

Intensity	Light	Moderate	Vigorous
Relative	No noticeable changes in heart rate and breathing rate. At a pace where able to easily talk and sing.	Mild increase in heart rate and breathing rate. At a pace where able to comfortably talk but not sing. Develop a light sweat after about 10 minutes of activity. *A general rule of thumb is that 2 minutes of moderate-intensity activity counts the same as 1 minute of vigorous-intensity activity.*	Large increase in a heart rate and breathing rate. At a pace where cannot say more than a few words without pausing for a breath. Develop a sweat after only a few minutes of activity.
Target heart rate zone		40 to about 60% of your maximum heart rate*	60 to about 85% of your maximum heart rate*
Examples	Walking at a slow or leisurely pace, cooking activities, or light household chores.	Walking briskly or with purpose, using an elliptical machine, cycling, mopping or vacuuming	Walking very fast, running, carrying heavy groceries or other loads upstairs, or participating in a strenuous fitness class

220 - age = maximum heart rate*(for age ≥19 years)

FIGURE E2: EXAMPLES OF PHYSICAL ACTIVITY AND LEVEL OF INTENSITY

Type of Physical Activity	Examples of Physical Activity	
Light Intensity	Social dancing Light training Gardening + raking Playing darts Leisure cycling	
Moderate Intensity	Brisk walking Golf with cart Lawn mowing Rowing machine Slow cycling Gardening (carrying, loading and digging) Jumping on a trampoline	Washing + waxing car (45-60 minutes) Shooting in basketball (30 minutes) Jumping rope (15 minutes) Running 1.5 miles in 10 minutes Boxing – punching Slow walking
Vigorous Intensity	Running Vigorous swimming Badminton, tennis / squash (single event) Power walking Star walking in 15 minutes	Hiking vigorously Fartlek / speed play Step aerobics Jumping ropes Martial arts
Muscle Strengthening	Weight lifting Sit-up and push-ups	
Bone Strengthening	Hopping, skipping and jumping Sports such as gymnastic, basketball, tennis	

01.

All calories consumed should meet all energy needs.

Remember to maintain a healthy energy balance.

• Eat according to estimated calorie needs based on age, sex and physical activity level
• Be habitually physically active
• Take note of unusual weight gain/loss
• Maintain BMI in a healthy range

02.

Watch your calorie intake wherever you are.

Be aware of the energy content of foods and beverages at home, at work, while shopping and during events.

• Be more aware of foods & beverages high in sugar & fats
• Learn to use Nutritional Information Labels
• Compare similar products and choose one with lower calories
• Choose lower calorie snack options (such as fresh fruits, salads)
• Choose smaller portions.
• Encourage and advocate the use of calorie content labels (catering, workplace, etc)

03.

Be active wherever you are.

• Walk or cycle instead of using a car
• Take the stairs instead of a lift
• Park further away from your destination and walk the rest of the way
• Do your own household chores
• Play with your children
• Invite family, friends and colleagues to be active with you
• Spend more time on outdoor activities
• Limit sedentary behaviour such as watching TV and using electronic media
• Break up long periods of sitting as much as possible

REFERENCES

1. Ministry of Health Brunei Darussalam. National Health Screening Guideline on Noncommunicable Diseases (NCDs). 2019;(November):1–36. Available from: http://www.moh.gov.bn/Shared Documents/MOH_National Health Screening Guideline on NCDs_23 Jul 2020.pdf

2. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–88.

3. Department of Policy and Planning Ministry of Health Brunei Darussalam. Health Information Booklet 2017. 2017; Available from: http://www.moh.gov.bn/SitePages/Health Information Booklet.aspx%0A

4. Ministry of Health Brunei Darussalam. Brunei Darussalam Multisectoral Action Plan for the Prevention and Control of Noncommunicable Diseases (BruMAP-NCD) 2021-2025. 2021.

5. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Vol. 139, Circulation. 2019. 1046–1081 p.

6. Cholesterol Treatment Trialists' (CTT) Colaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet [Internet]. 2010;376(9753):1670–81. Available from: http://dx.doi.org/10.1016/S0140-6736(10)61350-5

7. World Health Organization, Ministry of Health Brunei Darussalam. Brunei Darussalam National Multisectorial Action Plan for the Prevention and Control of Noncommunicable Diseases (BruMAP-NCD) 2013-2018 Joint Evaluation. 2021.

8. Pg Suhaimi AMA, Abdul Rahman H, Ong SK, Koh D. Predictors of non-communicable diseases screening behaviours among adult population in Brunei Darussalam: a retrospective study. J Public Heal. 2021;29(6):1303–12.

9. Ong SK, Lai DTC, Wong JYY, Si-Ramlee KA, Razak LA, Kassim N, et al. Cross-sectional STEPwise Approach to Surveillance (STEPS) Population Survey of Noncommunicable Diseases (NCDs) and Risk Factors in Brunei Darussalam 2016. Asia-Pacific J Public Heal. 2017;29(8):635–48.

10. Ministry of Health Brunei Darussalam. The 2nd National Health and Nutritional Status Survey (NHANSS) Report. 2015.

11. Ministry of Health Brunei Darussalam. Brunei STEPS Survey 2015 / 16 [Fact sheet]. 2016;(August 2015):2.

12. Ministry of Health Singapore. MOH Clinical Practice Guidelines for Lipids 2016. 2016. 30–84 p.

13. Ministry of Health Malaysia. Clinical Practice Guidelines: Management of Dyslipidaemia 2017 (5th Edition). Minist Heal Malaysia [Internet]. 2017;17(July):1–107. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1768388&tool=pmcentrez&rendertype=abstract

14. Catapano AL, Graham I, De Backer G, Wiklund O, John Chapman M, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J. 2016;37(39):2999-3058I.

15. Salah H, Din Taha E, Mahfouz Badran H, Kandil H, Farag N, Oraby A, et al. Egyptian practical guidance in lipid management 2020. Available from: https://doi.org/10.1186/s43044-021-00140-1

16. Pearson GJ, Thanassoulis G, Anderson TJ, Barry AR, Couture P, Dayan N, et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. Can J Cardiol. 2021;37(8):1129–50.

17. Pletcher MJ, Bibbins-Domingo K, Liu K, Sidney S, Lin F, Vittinghoff E, et al. Non-Optimal Lipids Commonly Present in Young Adults and Coronary Calcium Later in Life: The Coronary Artery Risk Development In young Adults (CARDIA) Study. Ann Intern Med. 2010;153(3):137–46.

18. Wilson DP, Jacobson TA, Jones PH, Koschinsky ML, Mcneal CJ, Nordestgaard BG, et al. Use of Lipoprotein (a) in clinical practice : A biomarker whose time has come . A scientific statement from the National Lipid Association. J Clin Lipidol [Internet]. 2019;13(3):374–92. Available from: https://-doi.org/10.1016/j.jacl.2019.04.010

19. Cegla J, Neely RDG, France M, Ferns G, Byrne CD, Halcox J, et al. Review article HEART UK consensus statement on Lipoprotein (a): A call to action. Atherosclerosis [Internet]. 2019;291(February):62–70. Available from: https://doi.org/10.1016/j.atherosclerosis.2019.10.011

20. Marconiva SM, Shapiro MD. Measurement of Lipoprotein(a). A Once in a Lifetime Opportunity. 2022;79(7):4–5.

21. Home - PPKK [Internet]. [cited 2022 Apr 23]. Available from: http://ppkk.gov.bn/SitePages/Cardiovascular-Disease.aspx

22. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, Agostino Sr RBD, Gibbons R, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Endorsed. J or Am Coll Cardiol. 2014;63(25).

23. National Institutes of Health. Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. NIH Publ. 02–5215.

24. Kaptoge S, Pennells L, De Bacquer D, Cooney MT, Kavousi M, Stevens G, et al. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. Lancet Glob Heal. 2019;7(10):e1332–45.

25. Visseren FLJ, MacH F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227–337.

26. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Vol. 140, Circulation. 2019. 563–595 p.

27. ASCVD Risk Estimator [Internet]. [cited 2022 Apr 16]. Available from: https://tools.acc.org/ldl/ascvd_risk_estimator/index.html#!/calulate/estimator/patient

28. Berry JD, Liu K, Folsom AR, Lewis CE, Carr JJ, Polak JF, et al. Prevalence and Progression of Subclinical Atherosclerosis in Younger Adults With Low Short-Term but High Lifetime Estimated Risk For Cardiovascular Disease. Circulation. 2009;119(3):382–9.

29. Miedema MD, Nauffal VD, Singh A, Blankstein R. Statin therapy for young adults: A long-term investment worth considering. Trends Cardiovasc Med [Internet]. 2020;30(1):48–53. Available from: https://doi.org/10.1016/j.tcm.2019.02.004

30. World Health Organization. HEARTS Technical package for cardiovascular disease management in primary health care: risk based CVD management. 2020.

31. Gepner AD, Piper ME, Johnson HM, Fiore MC, Baker TB, Stein JH. Effects of Smoking and Smoking Cessation on Lipids and Lipoproteins: Outcomes from a Randomized Clinical Trial.

32. Krauss RM, Daniels SR, Deckelbaum RJ, Erdman JW, Kris-Etherton P, Goldberg IJ, et al. AHA Dietary Guidelines Revision 2000: A Statement for Healthcare Professionals From the Nutrition Committee of the American Heart Association A Healthy Eating Pattern Including Foods From All Major Food Groups AHA Scientific Statement [Internet]. 2000. Available from: http://www.circulationaha.org

33. De Jesus JM, Nancy ;, Miller H, Hubbard VS, Lee ; I-Min, Lichtenstein AH, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk. S76 (Circulation [Internet]. 2014;129:76–99. Available from: http://circ.ahajournals.org/lookup/suppl/doi:10.1161/01.cir.0000437740.48606.d1/-/DC1.

34. Technical Working Group of the National Dietary Guidelines Ministry of Health Brunei Darussalam. National Dietary Guidelines for Healthy Eating Brunei Darussalam [Internet]. 2020. Available from: http://moh.gov.bn/Shared Documents/National Dietary Guideline 2020/NDG finalised 2020.pdf

35. HealthHub Ministry of Health Singapore. Healthy Eating for Lowering Cholesterol [Internet]. [cited 2021 Aug 5]. Available from: https://www.healthhub.sg/live-healthy/836/healthy-eating-for-lowering-cholesterol

36. World Health Organization. WHO Guidelines on physical activity and sedentary behaviour. World Heal Organ [Internet]. 2020;535. Available from: http://apps.who.int/bookorders.%0Ahttps://apps.who.int/iris/bitstream/handle/10665/325147/WHO-NMH-PND-2019.4-eng.pdf?sequence=1&isAllowed=y%0Ahttp://www.who.int/iris/handle/10665/311664%0Ahttps://apps.who.int/iris/handle/10665/325147%0Ahttp://apps.who.int

37. Landmesser U, Poller W, Tsimikas S, Most P, Paneni F, Luscher TF. From traditional pharmacological towards nucleic acid-based therapies for cardiovascular diseases. Eur Heart J. 2020;41(40):3884-3899G.

38. Akyea RK, Kai J, Qureshi N, Iyen B, Weng SF. Sub-optimal cholesterol response to initiation of statins and future risk of cardiovascular disease. Heart. 2019;105(13):975–81.

39. Khatib R, Neely D. Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD. Accel Access Collab [Internet]. 2020;1–2. Available from: www.nice.org.ukguidance 385

40. Cholesterol Treatment Trialists' (CTT) Colaboration. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267–78.

41. Cheong BYC, Wilson JM, Spann SJ, Pettigrew RI, Preventza OA, Muthupillai R. Coronary artery calcium scoring: an evidence-based guide for primary care physicians. J Intern Med. 2021;289(3):309–24.

42. Sarwar A, Shaw LJ, Shapiro MD, Blankstein R, Hoffman U, Cury RC, et al. Diagnostic and Prognostic Value of Absence of Coronary Artery Calcification. JACC Cardiovasc Imaging. 2009;2(6):675–88.

43. Ministry of Health Brunei Darussalam. National Standard Drug List.

44. Gaudet D, Kereiakes DJ, McKenney JM, Roth EM, Hanotin C, Gipe D, et al. Effect of alirocumab, a monoclonal proprotein convertase subtilisin/kexin 9 antibody, on lipoprotein(a) concentrations (a pooled analysis of 150 mg every two weeks dosing from phase 2 trials). Am J Cardiol [Internet]. 2014;114(5):711–5. Available from: http://dx.doi.org/10.1016/j.amjcard.2014.05.060

45. Institute for Clinical and Economic Review. PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value Based Price Benchmarks. New Engl Comp Eff Public Advis Counc. 2015;1–116.

46. Guo J, Meng F, Ma N, Li C, Ding Z, Wang H, et al. Meta-analysis of safety of the coadministration of statin with fenofibrate in patients with combined hyperlipidemia. Am J Cardiol. 2012;110(9):1296–301.

47. Wiggins BS, Saseen JJ, Page RL, Reed BN, Sneed K, Kostis JB, et al. Recommendations for Management of Clinically Significant Drug-Drug Interactions with Statins and Select Agents Used in Patients with Cardiovascular Disease: A Scientific Statement from the American Heart Association. Circulation. 2016;134(21):e468–95.

48. Sonne DP, Hansen M, Knop FK. Mechanisms in endocrinology. Bile acid sequestrants in type 2 diabetes: Potential effects on GLP1 secretion. Eur J Endocrinol. 2014;171(2).

49. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, et al. Triglycerides and cardiovascular disease: A scientific statement from the American Heart Association. Circulation. 2011;123(20):2292–333.

50. Pedersen SB, Langsted A, Nordestgaard BG. Nonfasting mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis. JAMA Intern Med. 2016;176(12):1834–42.

51. Chapman MJ, Redfern JS, McGovern ME, Giral P. Niacin and fibrates in atherogenic dyslipidemia: Pharmacotherapy to reduce cardiovascular risk. Pharmacol Ther [Internet]. 2010;126(3):314–45. Available from: http://dx.doi.org/10.1016/j.pharmthera.2010.01.008

52. Karlson BW, Palmer MK, Nicholls SJ, Lundman P, Barter PJ. A VOYAGER Meta-Analysis of the Impact of Statin Therapy on Low-Density Lipoprotein Cholesterol and Triglyceride Levels in Patients with Hypertriglyceridemia. Am J Cardiol [Internet]. 2016;117(9):1444–8. Available from: http://dx.doi.org/10.1016/j.amjcard.2016.02.011

53. Oh RC, Trivette ET, Westerfield KL. Management of Hypertriglyceridemia: Common Questions and Answers. Am Fam Physician. 2020;102(6):347–54.

54. Simha V. Management of hypertriglyceridemia. BMJ. 2020;371.

55. Virani SS, Morris PB, Agarwala A, Ballantyne CM, Birtcher KK, Kris-Etherton PM, et al. 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;78(9):960–93.

56. The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. Lancet. 2005;366:1849–61.

57. Catapano AL, Farnier M, Foody JAM, Toth PP, Tomassini JE, Brudi P, et al. Combination therapy in dyslipidemia: Where are we now? Atherosclerosis [Internet]. 2014;237(1):319–35. Available from: http://dx.doi.org/10.1016/j.atherosclerosis.2014.09.026

58. Howard JP, Wood FA, Finegold JA, Nowbar AN, Thompson DM, Arnold AD, et al. Side Effect Patterns in a Crossover Trial of Statin, Placebo, and No Treatment. J Am Coll Cardiol. 2021;78(12):1210–22.

59. Banach M, Rizzo M, Toth PP, Farnier M, Davidson MH, Al-Rasadi K, et al. Statin intolerance - An attempt at a unified definition. Position paper from an International Lipid Expert Panel. Arch Med Sci. 2015;11(1):1–23.

60. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA. An assessment by the statin muscle safety task force: 2014 update. J Clin Lipidol [Internet]. 2014;8(3 SUPPL):S58–71. Available from: http://dx.doi.org/10.1016/j.jacl.2014.03.004

61. Chaudhary R, Garg J, Shah N, Sumner A. PCSK9 inhibitors: A new era of lipid lowering therapy. World J Cardiol. 2017;9(2):76.

62. Harper CR, Jacobson TA. Managing Dyslipidemia in Chronic Kidney Disease. J Am Coll Cardiol. 2008;51(25):2375–84.

63. Tonelli MA, Wanner C, Cass A, Garg AX, Holdaas H, Jardine AG, et al. KDIGO clinical practice guideline for lipid management in chronic kidney disease. Kidney Int Suppl. 2013;3(3):1–315.

64. Kwan BCH, Kronenberg F, Beddhu S, Cheung AK. Lipoprotein metabolism and lipid management in chronic kidney disease. J Am Soc Nephrol. 2007;18(4):1246–61.

65. Holdaas H, Fellström B, Cole E, Nyberg G, Olsson AG, Pedersen TR, et al. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: The ALERT extension study. Am J Transplant. 2005;5(12):2929–36.

66. Mikolasevic I, Zutelija M, Mavrinac V, Orlic L. Dyslipidemia in patients with chronic kidney disease: Etiology and management. Int J Nephrol Renovasc Dis. 2017;10:35–45.

67. Weiner DE, Sarnak MJ. Managing dyslipidemias in chronic kidney disease. J Gen Intern Med. 2004;19:1045–52.

68. Migliozzi DR, Asal NJ. Clinical Controversy in Transplantation: Tacrolimus Versus Cyclosporine in Statin Drug Interactions. Ann Pharmacother. 2020;54(2):171–7.

69. SHARP Collaborative Group. Study of Heart and Renal Protection (SHARP): Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. Am Heart J [Internet]. 2010;160(5):785–94. Available from: http://dx.-doi.org/10.1016/j.ahj.2010.08.012

70. Barbagallo CM, Cefalù AB, Giammanco A, Noto D, Caldarella R, Ciaccio M, et al. Lipoprotein abnormalities in chronic kidney disease and renal transplantation. Life. 2021;11(4):1–14.

71. Bertoluci MC, Rocha VZ. Cardiovascular risk assessment in patients with diabetes. Diabetol Metab Syndr. 2017;9(1):1–13.

72. World Health Organization, Ministry of Health Brunei Darussalam. Country Fact Sheet: Public Health Data at a Glance Brunei Darussalam. 2020;12–5. Available from: https://www.who.int/docs/default-source/wpro—-documents/countries/brunei-darussalam/fact-sheet-brunei-darussalam.pdf?sfvrsn=b91eddf4_5

73. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255–323.

74. Newman CB, Blaha MJ, Boord JB, Cariou B, Chait A, Fein HG, et al. Lipid management in patients with endocrine disorders: An endocrine society clinical practice guideline. Vol. 105, Journal of Clinical Endocrinology and Metabolism. 2020. 3613–3682 p.

75. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack; A guideline from the American Heart Association/American Stroke Association. Stroke. 2021. 364–467 p.

76. Kim JS. Role of blood lipid levels and lipid-lowering therapy in stroke patients with different levels of cerebral artery diseases: Reconsidering recent stroke guidelines. J Stroke. 2021;23(2):149–61.

77. Seo W-K, Hosseini MB, Bang OY, Liebeskind DS. Recent updates in dyslipidemia management: perspectives in stroke-specific situation. Precis Futur Med. 2020;4(1):9–20.

78. Yaghi S, Elkind MS V. Lipids and Cerebrovascular Disease: Research and Practice. Stroke. 2015;46(11):3322–8.

79. Woodward M, Martiniuk A, Lee CMY, Lam TH, Vanderhoorn S, Ueshima H, et al. Elevated total cholesterol: Its prevalence and population attributable fraction for mortality from coronary heart disease and ischaemic stroke in the Asia-Pacific region. Eur J Prev Cardiol. 2008;15(4):397–401.

80. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. Circulation. 2002;106(3):388–91.

81. Stead LG, Vaidyanathan L, Kumar G, Bellolio MF, Brown RD, Suravaram S, et al. Statins in Ischemic Stroke: Just Low-Density Lipoprotein Lowering or More? J Stroke Cerebrovasc Dis [Internet]. 2009;18(2):124–7. Available from: http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2008.09.016

82. Hackam DG, Hegele RA. Cholesterol Lowering and Prevention of Stroke: An Overview. Stroke. 2019;50(2):537–41.

83. Flint AC, Kamel H, Navi BB, Rao VA, Faigeles BS, Conell C, et al. Statin use during ischemic stroke hospitalization is strongly associated with improved poststroke survival. Stroke. 2012;43(1):147–54.

84. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol [Internet]. 2009;8(5):453–63. Available from: http://dx.doi.org/10.1016/S1474-4422(09)70058-4

85. The Stroke Prevention by Aggressive Reduction in Cholestrol Levels (SPARCL) Investigators. High-Dose Atorvastatin after Stroke or Transient Ischaemic Attack. N Engl J Med. 2006;355(6):549–59.

86. Hosomi N, Nagai Y, Kohriyama T, Ohtsuki T, Aoki S, Nezu T, et al. The Japan Statin Treatment Against Recurrent Stroke (J-STARS): A Multicenter, Randomized, Open-label, Parallel-group Study. EBioMedicine [Internet]. 2015;2(9):1071–8. Available from: http://dx.doi.org/10.1016/j.ebiom.2015.08.006

87. Hindy G, Engström G, Larsson SC, Traylor M, Markus HS, Melander O, et al. Role of blood lipids in the development of ischemic stroke and its subtypes: A mendelian randomization study. Stroke. 2018;49(4):820–7.

88. Amarenco P, Kim JS, Labreuche J, Charles H, Abtan J, Béjot Y, et al. A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke. N Engl J Med. 2020;382(1):9–19.

89. Ruscica M, Ferri N, Santos RD, Sirtori CR, Corsini A. Lipid Lowering Drugs: Present Status and Future Developments. Curr Atheroscler Rep. 2021;23(5).

90. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015;372(25):2387–97.

91. Bohula EA, Wiviott SD, Giugliano RP, Blazing MA, Park JG, Murphy SA, et al. Prevention of Stroke with the Addition of Ezetimibe to Statin Therapy in Patients with Acute Coronary Syndrome in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). Circulation. 2017;136(25):2440–50.

92. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376(18):1713–22.

93. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med. 2018;379(22):2097–107.

94. Ebrahim S, Sung J, Song YM, Ferrer R, Lawlor DA, Smith GD. Serum cholesterol, haemorrhagic stroke, ischaemic stroke, and myocardial infarction: Korean national health system prospective cohort study. Br Med J. 2006;333(7557):22–5.

95. Devaraj S, Rogers J, Jialal I. Statins and biomarkers of inflammation. Curr Atheroscler Rep. 2007;9(1):33–41.

96. Zarek J, Koren G. The Fetal Safety of Statins: A Systematic Review Meta-Analysis. J Obstet Gynaecol Canada [Internet]. 2014;36(6):506–9. Available from: http://dx.doi.org/10.1016/S1701-2163(15)30565-X

97. Edison RJ, Muenke M. Central Nervous System and Limb Anomalies in Case Reports of First-Trimester Statin Exposure. N Engl J Med. 2004;350(15):1579–82.

98. Ridker PM, Lonn E, Paynter NP, Glynn R, Yusuf S. Primary prevention with statin therapy in the elderly new meta-analyses from the contemporary jupiter and hope-3 randomized trials. Circulation. 2017;135(20):1979–81.

99. Hilmer S, Gnjidic D. Statins in older adults. Aust Prescr. 2013;36(5):79–82.

100. Dagli RJ, Sharma A. Polypharmacy: a global risk factor for elderly people. J Int oral Heal JIOH [Internet]. 2014;6(6):i–ii. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25628499%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4295469

101. McVeigh C, Passmore P. Vascular dementia: prevention and treatment. Clin Interv Aging. 2006;1(3):229–35.

102. Expert Panel on Integrated Guidelines For Cardiovascular Health and Risk Reduction in Children and Adolescents. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics. 2011;128(SUPP.5):S213–56.

103. Elkins C, Fruh S, Jones L, Bydalek K. Clinical Practice Recommendations for Pediatric Dyslipidemia. J Pediatr Heal Care [Internet]. 2019;33(4):494–504. Available from: https://doi.org/10.1016/j.pedhc.2019.02.009

104. De Ferranti SD, Steinberger J, Ameduri R, Baker A, Gooding H, Kelly AS, et al. Cardiovascular Risk Reduction in High-Risk Pediatric Patients: A Scientific Statement From the American Heart Association. Vol. 139, Circulation. 2019. 603–634 p.

105. Brunei Darussalam Medicine Control Authority Ministry of Health Brunei Darussalam. Registered Medicinal Products. 2019;(February 2019):1–13.

106. World Health Organization. Toolkit for delivering the 5A's and 5R's brief tobacco interventions in primary care. 2014;17.

107. Kassim N, HA Hamid HN-E, Magpusao MSJ, Keasberry B, Bakri KF, Arrif US, et al. National Physical Activity Guidelines for Brunei Darussalam [Internet]. Ministry of Health Brunei Darussalam. 2011. Available from: http://onlinelibrary.wiley.com/doi/10.1002/cbdv.200490137/abstract