National Guideline for Management of Dyslipidaemia for Secondary and Tertiary Healthcare Level

Directorate of Non-Communicable Diseases

Ministry of Health

First Edition 2021

Electronic version is available on www.health.gov.lk.

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National Dyslipidaemia management guideline

For Secondary and Tertiary Healthcare Level

Published by the Directorate for Non-Communicable Diseases with the technical support by the Ceylon College of Physicians and financial support by the World Health Organization (WHO)
to serve as a reference to the doctors managing this common condition at secondary and tertiary healthcare level.
This document was reviewed by the Directorate of NCD to be in line with the National policies, strategies and regulations.
Feedback of relevant professional colleges and institution was also incorporated into this guideline

ISBN: 978 – 624- 5719- 55-6

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Table of Contents

List of Tables

List of Figures

List of annexures

Abbreviations

ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AHA	American Heart Association
ALT	Alanine transaminase
Apo	Apo lipoprotein
APOB	Apo lipoprotein B 100 molecule
ASCVD	Atherosclerotic cardiovascular disease
BP	Blood pressure
CA	Coronary angiogram
CCP	Ceylon College of Physicians
CT CA	CT Coronary angiogram
CABG	Coronary artery bypass graft
CAC	Coronary artery calcium score
CAD	Coronary artery disease
CK	Creatinine kinase
CKD	Chronic kidney disease
CRP	C reactive protein
CVD	Cardiovascular disease
CVA	Cerebrovascular accident
CYP	Cytochrome P450
CYP3AS	Cytochrome P450, family 3, subfamily A human gene locus
DM	Diabetes mellitus
DHA	Docosahexaenoic acid
DNA	Deoxyribonucleic acid
DVD	Double vessel disease
ESC	European Society of Cardiology
EAS	European Atherosclerosis Society
EPA	Eicosapentaenoic acid
eGFR	Estimated glomerular filtration rate
FBS	Fasting blood sugar
FH	Familial hypercholesterolemia
FCH	Familial combined hyperlipidemia
GI	Gastro Intestinal
HbA1C	Hemoglobin A 1 C
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HoFH	Homozygous Familial Hypercholesterolemia
HIV	Human Immunodeficiency virus

HMGCR – 3	Hydroxy-3-methylglutaryl-Co A reductase
HMG- Co A	Hydroxymethylglutaryl-coenzyme A
IDL	Intermediate density lipoprotein
IHD	Ischaemic Heart Disease
LCAT	Lecithin cholesterol acyltransferase
LDL	Low density lipoprotein
LDL- C	Low density lipoprotein cholesterol
LDLR	Low density lipoprotein receptor
Lp (a)	Lipoprotein (a)
LPL	Lipoprotein lipase
LVH	Left ventricular hypertrophy
mAbs	Monoclonal antibodies
MET	Metabolic equivalent
MI	Myocardial infarction
MOA	Mode of action
NAFLD	Non-alcoholic fatty liver disease
NICE	National Institute for Health and Care Excellence
OATP1B1	Solute carrier organic action transporter family member 1B1PCI – Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilizing/ kexin type
PPAR-a	Peroxisome proliferator – activated receptor a
PVD	Peripheral vascular disease
SAMS	Statin

Introduction

This national guideline summarizes and evaluates available evidence with the aim of assisting health professionals in implementing the best management strategies for an individual patient with Dyslipidaemia. Guidelines and its recommendations would facilitate the decision making of health professionals in their day-to-day practice. However, the final decision concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A number of guidelines have been issued in recent years by the European Society of Cardiology2019 (ESC), European Atherosclerosis Society (EAS), American college of cardiology/American heart association; Task force on clinical practice guidelines 2018(ACC/AHA), Canadian Cardiovascular society 2016 (CCS), NICE guidelines UK 2020 and Lipid Association of India. We have limited local evidence on Dyslipidaemia and its management strategies. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to the tables 1 and 2.

Dyslipidaemia is an important risk factor for atherosclerotic cardiovascular diseases. Every 38 mg/dL (1.0 mmol/L) reduction in LDL-C reduces all-cause mortality by 10% (Baigent et al., 2009). Statin trial data suggest that the absolute benefits of treatment are related to an individual's risk of atherosclerotic cardiovascular disease (ASCVD) and the absolute reduction in LDL-C that is achieved(Collins et al., 2016).

Sri Lanka is a South Asian country. South Asians have the highest rates of coronary artery disease (Cho et al., Nair and Prabhakaran, 2012). The commonest cause of hospital deaths in Sri Lanka in 2017 was ischemic heart disease (IHD)(Medical Statistics Unit Ministry of Health, 2017). Data on Dyslipidaemia in Sri Lanka is limited. There are very few nationally representative studies carried out on Dyslipidaemia. According to the Non-Communicable Disease Risk Factor Survey Sri Lanka 2015, nearly one fourth of adults (23.7%) were estimated to either have raised total cholesterol (≥ 190mg/dl) or were currently on medication for raised cholesterol(Ministry of Health, 2015). Nearly one third of females (28.4%) and one fifth of males (19.1%) were estimated to be in this category.

Methodology and evidence review

Recommendations in this section are adoptions from the latest guideline of Dyslipidaemia management for ACC/AHA guideline; American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines 2018, ESC 2019 and NICE 2020, considering the resources available in the Sri Lankan setting.

Scope of the guidelines

The purpose of this guideline is to address the practical management of Sri Lankan patients with high blood cholesterol and related disorders at secondary and tertiary care setting. Health professionals are encouraged to adhere to this National Guidelines when planning preventive, diagnostic and

therapeutic approaches at secondary and tertiary care institutions. However, this National Guidelines does not override the individual responsibility of health professionals in appropriate and accurate decision making in management of individual patients with dyslipidaemia

Classes of recommendation

The classes of recommendation indicate the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk.

Classes of recommendation

Classes of recommendations	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is **beneficial, useful, effective.**	Is recommended or is indicated
Class II	**Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.**	
Class II a	Weight of evidence/opinion is in favour **of usefulness/efficacy.**	Should be considered
Class II b	**Usefulness/efficacy is less well** established by evidence/opinion.	Maybe considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Levels of evidence

The level of evidence rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources.

Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analysis
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Chapter 1

LIPIDS AND LIPOPROTEIN

1.1 Biological role of lipids and lipoproteins

Triglyceride (TG) and cholesterol are the two major forms of circulating lipids in the human body but are insoluble in plasma. A lipoprotein is composed of cholesterol, triglycerides, and a single Apo lipoprotein **(Figure 1.1)** (Chiang, 2014).

Lipoproteins have been classified into six major classes **(Table 1.1)** (Feingold, 2000). When secreted into plasma by the liver, they are referred to as a very low-density lipoprotein (VLDL). The triglycerides are rapidly removed by the enzyme lipoprotein lipase and used for energy consumption and storage leaving a VLDL remnant particle. After most of the triglycerides have been removed, the lipoprotein becomes dense and is referred to as a low-density lipoprotein (LDL).

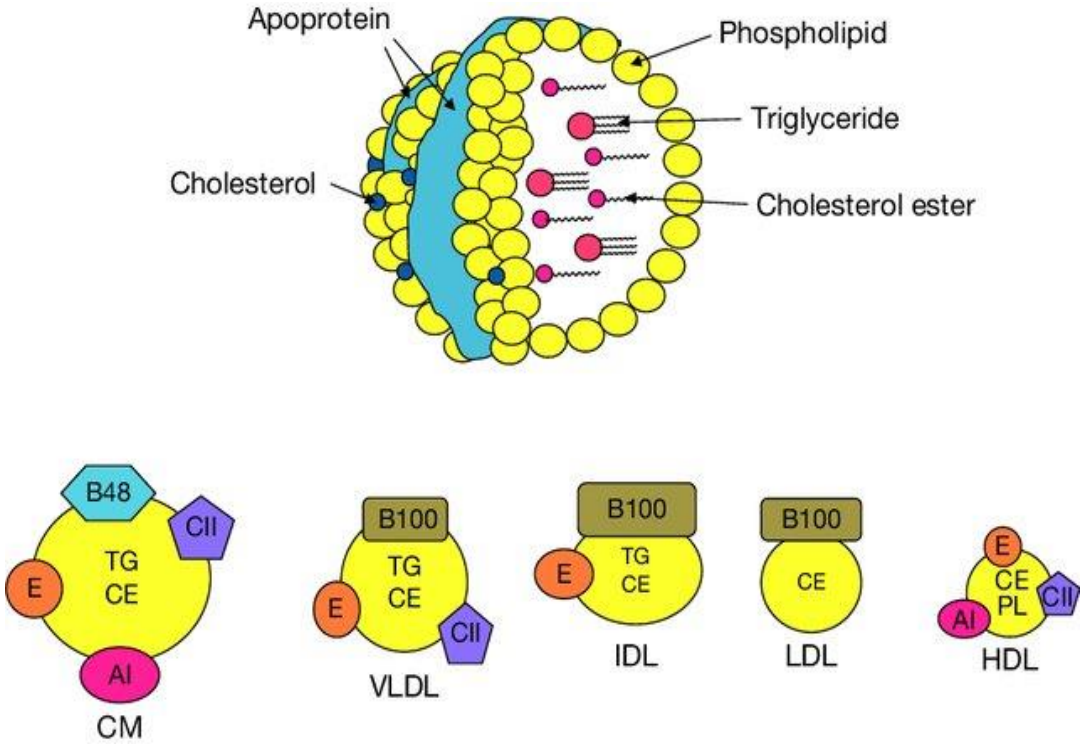

Figure 1.1 Lipoprotien Structures

The major lipoproteins on Chylomicrons are ApoB48, ApoA1, ApoE, and ApoCII, and carries mostly TG. VLDL contains ApoB100, ApoCII, and ApoE, and carries mostly TG. IDL is derived from VLDL

and contains ApoB100 and ApoE, and carries CE and TG. (Figure from ***Pathobiology of Human Disease, pp 1770–1782 (Elsevier, San Diego 2014)***

Trapping of apoB100 containing small diameter lipoproteins (VLDL, IDL, LDL) and Lipoprotein(a) in the arterial wall and subsequent release of its cholesterol content to macrophages provokes a complex process that leads to initiation and progression of an atherosclerotic plaque (Borén and Williams, 2016).

Over time, the atherosclerotic plaque slowly enlarges as more apoB-containing dense lipoprotein particles become trapped in the artery wall. The increase of the atherosclerotic plaque burden as well as the changes occurring in the plaque composition eventually will lead to disruption of a plaque, formation of an overlying thrombus that acutely obstructs blood flow resulting in unstable angina, myocardial infarction or death.

Each apoB-containing lipoprotein has a single apoB molecule. Therefore, plasma apoB concentration is a direct measure of the total number of circulating atherogenic apoB particles that can become trapped in the artery wall (Brunzell et al., 2008).

However, the standard lipid panel does not typically measure apoB levels due to limited availability, high cost and difficulties in measurements. Non-HDL-C levels and apoB levels are highly correlated but and non-HDL-C could be used as a surrogate marker for apo B level (Hermans et al., 2011).

Table 1. 1 Types of lipoproteins

Lipoprotein	Major Lipid Composition	Major Apolipo proteins	Role in Normal Fasting Plasma	Measured Substance
High-density lipoprotein cholesterol (HDL-C)	Cholesterol	ApoA-I	Antiatherogenic (involved in reverse cholesterol transport from the tissues to the liver)	HDL-C
Low-density lipoprotein cholesterol (LDL-C)	Cholesterol	ApoB-100	Major cholesterol carrier	Mostly calculated using the Friedewald equation [LDL-C = Total cholesterol (Lloyd-Jones et al.) - HDL-C - TG/5 in mg/dL] Can also be measured directly (direct LDL-C) in limited situations
Intermediate-density lipoprotein cholesterol (IDL-C)	TG and cholesterol	ApoB-100	Intermediate between very low-density lipoprotein (VLDL) and LDL	Not routinely measured
VLDL	TG	ApoB-100	Major TG carrier	TG/5 is the estimate of the VLDL-C.
Chylomicron	TG	ApoB-48	Absent	Not routinely measured
Lipoprotein (a)	Cholesterol	Apo (a)		Not routinely measured

(*From Introduction to Lipids and Lipoproteins, Endotext 2000*)

1.2 Lipid measurements

A standard serum lipid profile measures the concentration of TC and HDL-C, as well as TG. With these values, the LDL-C concentration is most often calculated using the Friedewald formula :(refer table 3). If the TG value is more than 400 mg/dL (especially in non-fasting samples) this formula cannot be used to calculate LDL level. Although direct measurement of LDL-C is possible, cost, limited availability, systematic bias and inaccuracies in assays limits its use. Fasting serum sample is preferred when assessing the lipid profile due to the lower triglyceride levels in the fasting state which gives more accurate LDL-C estimations though the changes in triglycerides levels in fasting and non-fasting states have shown to be small (Sathiyakumar et al., 2018). If a non-fasting sample is taken, TG and LDL-C levels should be interpreted with caution especially in patients with diabetes, metabolic syndrome and hypertriglyceridemia (CB, 2019).

Table 1. 2 Recommendations for lipid measurement

	Recommendations	Class
1	Fasting serum sample is preferred over non-fasting sample for lipid profile testing at the first contact to ensure more precise lipid assessment	IIb
2	LDL-C analysis is recommended as the primary lipid analysis method for screening, diagnosis, and management.	I
3	LDL-C may be estimated using the Friedewald equation, and becomes increasingly inaccurate and invalid when TG levels are greater than 200mg/dL and 400 mg/dL, respectively (in a non-fasting sample)	IIb
4	The non-HDL-C (total cholesterol – HDLC) should be calculated to assist risk stratification in individuals with moderately elevated TG (200 to 500 mg/dL), diabetes, and/or established ASCVD	I
5	It is recommended that ApoB analysis for further risk assessment, particularly in people with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels.	1

Chapter 2

CARDIOVASCULAR RISK ASSESSMENT

2.1 Cardiovascular risk

Cardiovascular risk means the likelihood of a person developing an atherosclerotic cardiovascular event over a defined period of time.
People of all ages should adopt a healthy lifestyle throughout the life (Cooney et al., 2009).
Patients with established ASCVD and who are at risk of developing ASCVD should improve their lifestyle and reduce risk factor levels.

2.2 Total Cardiovascular Risk

Indicates the combined effect of a number of risk factors on this risk estimate.
This guideline covers lipid-related contribution to total CV risk and clinical management at secondary and tertiary care level.

2.3 Rationale for Estimating Total Cardiovascular Risk

All current guidelines on the prevention of ASCVD in clinical practice recommend estimation of total CV risk. Prevention of ASCVD in a given person relates to total CV risk: the higher the risk, the more intense treatment is needed (Ference et al., 2017).
This guideline uses World Health organization/ International Society of Hypertension (WHO/ISH) risk prediction chart for South East Asia **(Annexure 1)** (WHO, 2019).

WHO/ISH risk prediction chart

- Indicates 10-year risk of a fatal or non-fatal major cardiovascular event (myocardial infarction or stroke),
- Assesses risk according to age, sex, blood pressure, smoking status and total cholesterol.
- It is useful for people who do not have established ASCVD.
- Identifies those at high ASCVD risk
- Helps to educate patients, to change high risk behaviour and to take antihypertensive drugs, lipid-lowering drugs and 75 mg Aspirin.

2.4 Assessing CV Risk

CV risk may be higher in:

- Already on antihypertensive therapy
- Premature menopause
- Obesity
- Sedentary lifestyle
- Family history of premature ASCVD in 1st degree relative (male < 55 years, female < 60 years)

- High TG level >180 mg/dl, CRP, fibrinogen, homocysteine, apo B, low HDL < 40mg/dl
- Psychosocial stress (Foster et al., 2018)
- Chronic inflammatory disease (e.g.; rheumatoid arthritis, asthma, ulcerative colitis)
- Major psychiatric disorders
- Atrial fibrillation
- Treatment for HIV
- Left ventricular hypertrophy
- Albuminuria
- Obstructive sleep apnoea syndrome.
- NAFLD

Risk estimation not indicated in:

- Documented ASCVD
- Blood cholesterol ≥ 309 mg/dL (8 mmol/l)
- DM with renal disease
- CKD (stage 3 and above)
- Heterozygous Familial Hypercholesterolemia (HeFH)
- High Lipoprotein (Lp) (a)
- CAC > 100 HU (Kavousi et al., 2012, Vlachopoulos et al., 2015, Yeboah et al., 2012, Mortensen et al., 2018, Hong et al., 2017, Cho et al., 2018)

2.5 How to use the risk estimation charts

- To estimate a person's 10-year risk of ASCVD death
  - Find the table for gender, smoking status, and age **(Annexure 1).**
  - Within the table, find the cell nearest to the person's BP and TC.

- Risk estimates will need to be adjusted upwards as the person approaches the next age category.

- Risk is initially assessed on the level of TC and systolic BP before treatment, if known.

- The longer and effective the treatment, greater the risk reduction, but in general it will not be more than about one-third of the baseline risk

- Low-risk persons should be offered advice to maintain their low-risk status.

- No threshold is universally applicable, the intensity of advice should increase with increasing risk

- The charts may be used to give some indication of the effects of reducing risk factors, given that there is apparently a time lag before the risk reduces. Smoking cessation halve cumulative risk over a relatively short period of time.

Chapter 3

TREATMENT TARGETS AND GOALS

3.1 Primary prevention goals

Table 3. 1 Primary prevention goals

High risk (WHO risk≥20%)	LDL<70mg/dL (<1.8 mmol/L)
Moderate risk(10- <20%)	LDL<100mg/dL(2.6 mmol/L)
Low risk (<10%)	LDL<116mg/dL (3 mmol/L)

3.2 Secondary prevention goals

Table 3. 2 Secondary prevention goals

Established ASCVD	LDL<55mg/dL(<1.4mol/L)
ASCVD with second event within 2years	LDL<40mg/dL(1mol/L)

The adjustment of lipid-lowering therapy in accordance with these secondary goals may be considered in patients at very high ASCVD risk. The specific goal for non-HDL-C should be 30 mg/dL (0.8 mmol/L) higher than the corresponding LDL-C goal.
When secondary targets are used the recommendations are:
Non- HDL-C Targets (in Very high risk, High risk and Moderate risk):

- Very high risk <85 mg/dL (<2.2 mmol/L),
- High risk <100 mg/dL (<2.6 mmol/L),
- Moderate risk <130 mg/dL (<3.4 mmol/L)

ApoB targets if used in special situations are:

- Very high risk <65mg/dL,
- High risk <80 mg/dL,
- Moderate risk <100 mg/dL

Table 3. 3 Recommendations for Treatment Targets and Goals

	Recommendation	Class
1	In secondary prevention for patients at very-high risk an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <55 mg/dL (<1.4 mmol/L) are recommended.	1
2	In primary prevention for individuals at very-high risk but without FH an LDL-C reduction of ≥ 50% from baseline and an LDL-C goal of <55mg/dL (1.4 mmol/L) are recommended.	1
3	For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of <40 mg/dL (1.0 mmol/L) may be considered	11b
4	In patients at high risk an LDL-C reduction of >50% from baseline and LDL-C goal of <70 mg/dL (1.8 mmol/L) are recommended	1
5	In individuals at moderate risk and LDL-C goal of <100mg/dL (≤ 2.6 mmol/L) should be considered	11b
6	In individual at low risk, an LDL-C goal ≤116mg/dL (<3.0 mmol/L) may be considered	11b

Chapter 4

LIFESTYLE MODIFICATIONS TO IMPROVE THE PLASMA LIPID PROFILE

The pivotal role of lifestyle modifications in combating Dyslipidaemia and subsequent ASCVD has been proved by many landmark trials (Dalen and Devries, 2014, Mente et al., 2009, Chowdhury et al., 2014)
A more detailed explanation of lifestyle measures is provided in **Tables 4.1**.

4.1 Body weight and physical activity

4.1.1 Body weight

Weight reduction improves dyslipidaemia (Shaw et al., 2006, Kelley and Kelley, 2009). To reduce weight, caloric intake should be reduced, and energy expenditure increased. Weight loss should be done to achieve the ideal BMI of <23 kg/m^2. However, body weight reduction, even if modest (5-10% of basal body weight) has been shown to improve lipid abnormalities (Kelley and Kelley, 2009).

It can be achieved by decreasing the consumption of energy-dense foods, inducing a caloric deficit of 300–500 kcal/day.
The intervention should combine diet and exercise.

4.1.2 Physical activity

Physical inactivity should be avoided as far as possible. All adults should undertake regular physical activity as it helps in achieving a favourable lipid profile (Kamani et al., 2015, Wang and Xu, 2017, Kelley et al., 2005, Yu-Poth et al., 1999, Catapano et al., 2016, Mensink et al., 2003).

Adults should do 150 minutes to 300 minutes of moderate-intensity aerobic physical activity throughout the week or do 75 to 150 minutes of vigorous intensity aerobic physical activity throughout the week, or an equivalent combination of moderate and vigorous intensity activity for substantial health benefits. Adults may also do muscle-strengthening activities at moderate or greater intensity that involve all major muscle groups on 2 or more days a week, as these provide additional health benefits.

Adults may increase moderate-intensity aerobic physical activity to more than 300 minutes per week or engage in more than 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate and vigorous intensity activity, for additional health benefits. Engaging in at least some physical activity is better than none. If adults are not currently meeting these physical activity recommendations, doing even a minimal level of physical activity will bring benefits to health. They should start with small amounts of physical activity and gradually increase duration, frequency and intensity over time **(Annexure 2).**

4.1.3 Dietary fat

Total fat intake is 30% or less of total energy intake. Avoiding any consumption of trans fat is a key measure of the dietary prevention of ASCVD.

Table 4.2 (Piepoli et al., 2016), **annexures 3,4 and 5** summarizes the currently available evidence on the influences of lifestyle changes and dietary supplements and functional foods on lipoproteins, indicating the magnitudes of the effects and the levels of evidence in relation to the impacts on the specific lipoprotein class.

4.1.4 Dietary carbohydrate and fibre

Total carbohydrate intake is 50-60% of total energy intake and not less than 40% of total energy intake. Dietary carbohydrate has a 'neutral' effect on LDL-C, although excessive consumption is represented by untoward effects on plasma TGs and HDL-C levels (Giner-Galvañ et al., 2016). Dietary fibre (particularly of the soluble type) which is present in legumes, fruits, vegetables, and wholegrain cereals (e.g., oats and barley) has a hypocholesterolaemia effect and represents a good dietary substitute for saturated fat to maximize the effects of the diet on LDL-C levels, and to minimise the untoward effects of a high-carbohydrate diet on other lipoproteins.

4.1.5 General and special dietary advice

Eat a variety of nutritious foods from all the food groups, in appropriate amounts to maintain optimal body weight and to get all the nutrients **(Annexure 3 and 6).** Cardioprotective diet (Hendrani et al., 2016, Lloyd-Jones et al., 2016, Downs and O'Malley, 2015, Jellinger et al., 2017, Rimm et al., 1999, Droste et al., 2013) for high risk or with ASCVD is given in **Annexure 3 and 7**.

"**Heart Healthy diet"** which will reduce LDL cholesterol and increase HDL cholesterol. Heart healthy diet for a sedentary individual with a normal body mass index (BMI 18.5 – 23 kgm^2) to meet the nutrient requirements are given in **Annexure 7**.

4.1.6 Alcohol

Alcohol should be avoided in keeping with the recommendation of the Sri Lankan No alcohol policy.

4.1.7 Smoking

- Smoking cessation should be promoted (Ajay and Prabhakaran, 2010, Law and Rudnicka, 2006, Palmer et al., 2014). At the medical clinic patient should be encouraged to seek help using the Brief Intervention and the 5A strategy is one of the methods being used.
- The 5A's strategy is suggested for achieving this goal in clinical practice:
  - Ask: systematically identify all tobacco users at every visit.
  - Advise: strongly urge all tobacco users to quit.
  - Assess: determine willingness to make a quitting attempt.
  - Assist: aid every willing patient in quitting by behavioural counselling and pharmacotherapy.
  - Arrange: schedule for follow ups. Initiate pharmacotherapy as needed.

Table 4. 1 Recommendations for lifestyle modifications

	Recommendation	Class
1	Diet Healthy diet low in saturated fat with a focus on wholegrain products, vegetables, fruit, and fish	-
2	Weight Reduction improves dyslipidaemia. To reduce weight, caloric intake should be reduced, and energy expenditure increased.	1
3	Physical activity • Physical inactivity should be avoided as far as possible. All adults should undertake regular physical activity as it helps in achieving a favourable lipid profile. • Adults should do 150 minutes to 300 minutes of moderate-intensity aerobic physical activity throughout the week, or do 75 to 150 minutes of vigorous intensity aerobic physical activity throughout the week, or an equivalent combination of moderate and vigorous-intensity activity for substantial health benefits • Adults may also do muscle-strengthening activities at moderate or greater intensity that involve all major muscle groups on 2 or more days a week, as these provide additional health benefits.	1 1 1
4	Smoking cessation should be promoted.	1
5	Alcohol Alcohol should be avoided in keeping with the recommendation of the Sri Lankan No alcohol policy.	1

Table 4. 2 Effects of lifestyle changes on total cholesterol and LDL cholesterol

	Magnitude of the effect	Level of evidence
Lifestyle interventions to reduce TC and LDL-C levels		
M Reduce dietary trans fat	+++	A
Reduce dietary saturated fat	+++	A
Increase dietary fibre	++	A
Use functional foods enriched with phytosterols	++	A
Use red yeast rice supplements	++	A
Reduce excessive body weight	++	A
Reduce dietary cholesterol	+	B
Increase habitual physical activity	+	B
Use soy protein products	+/-	B
Lifestyle interventions to increase HDL-C levels		
Reduce dietary trans fat	+++	A
Increase habitual physical activity	+++	A
Reduce excessive body weight	++	A
Reduce dietary carbohydrates and replace them with unsaturated fat	++	A
Quit Alcohol*	++	B
Quit smoking	+	B
Among carbohydrate-rich foods prefer those with low glycaemic index and high fibre content	+/-	C
Reduce intake of mono-and disaccharides	+/-	C
Lifestyle interventions to reduce TG-rich lipoprotein levels		
Reduce excessive body weight	+++	A
Quit Alcohol*	+++	A
Increase habitual physical activity	++	A
Reduce total amount of dietary carbohydrate	++	A
Use supplements of n-3 polyunsaturated fat	++	A
Reduce intake of mono-and disaccharides	++	B
Replace saturated fat with mono-or polyunsaturated fat	+	B

*Alcohol policy was adjusted according to Sri Lankan No alcohol policy

Source: European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidemia; Although red yeast rice is effective in lipid lowering, due to the variability in potency and possible adulteration of commercially available products, it is not recommended.

4.2 Dietary supplements and functional foods for the treatment of dyslipidaemias

Nutrition evaluation of functional food includes not only the search for clinical evidence of beneficial effects relevant to improved health or the reduction of disease risk, but also the demonstration of good tolerability **(Annexure 5).**

Chapter 5

PHARMACOLOGICAL MANAGEMENT OF DYSLIPIDAEMIA

5.1 Management algorithm

- Evaluate the total CV risk of the individual using WHO/ISH risk charts **(Annexure 1)**
- Exclude secondary causes
- Provide lifestyle advice for primary prevention
- Involve the patient in decisions on CV risk management.
- Choose a statin regimen.
- Where necessary, additional treatments that can meet treatment goals can be used.

*Different drugs used in treatment of dyslipidaemia are shown in **annexure 8**.

Table 5. 1 Recommendations for pharmacological management of dyslipidaemia

	Recommendations	Class
1	It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk	I
2	If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended	I
3	If the goals are not achieved with the maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb
4	If a statin-based regimen is not tolerated at any dosage (even after rechallenging), ezetimibe should be considered	IIa
5	If the goal is not achieved, statin combination with a bile acid sequestrant may be considered	IIIb

Table 5. 2 Recommendations for pharmacological management of hypertriglyceridaemia

	Recommendations	Class
1	Statin treatment is recommended as the first drug of choice to reduce CV risk in high-risk individuals with hypertriglyceridemia. (TG>200mg/dL (2.3 mmol/L)	I
2	In high-risk patients with TG levels between 135-499 mg/dL (1.5-5.6 mmol/L) despite statin treatment, n-3 fatty acid should be considered in combination with a statin.	IIa
3	In patients who are at LDL-C goal with TG levels >200 mg/dL (>2.3 mmol/L) fenofibrate or bezafibrate may be considered in combination with statins.	IIb

5.2 Statin therapy

The decision whether to start statin therapy should be made after an informed discussion between the clinician and the person about the risks and benefits of statin treatment, considering additional factors such as potential benefits from lifestyle modifications, informed patient preferences, comorbidities, polypharmacy, general frailty and life expectancy.

5.2.1 Before starting statin treatment

Perform baseline blood tests and clinical assessment, and treat comorbidities and secondary causes of dyslipidaemia including;

- Tobacco consumption (smoke or smokeless)
- Alcohol consumption
- Blood pressure
- BMI or other measures of obesity
- FBS or HbA1c
- Renal function and estimated glomerular filtration rate
- Alanine aminotransferase (Medical Statistics Unit Ministry of Health)
- Thyroid-stimulating hormone (TSH)

Ask for if they have symptoms related to muscles and if so, measure creatinine kinase (CPK) levels. If CPK levels are more than 5 times the upper limit of normal repeatedly, do not start statin treatment. If creatinine kinase levels are raised but less than 5 times the upper limit of normal, start statin treatment at a lower dose.

Measure baseline ALT before starting a statin. Do not routinely exclude from statin therapy if liver transaminase levels are raised but are less than 3 times the upper limit of normal.

5.2.2 Statin regimens for treatment of dyslipidaemia

- Current available evidence from meta-analyses suggests that the clinical benefit of statin treatment is largely a class effect, driven by the absolute LDL-C reduction; therefore, the type of statin used should reflect the treatment goals for a given patient.
- When a decision is made to prescribe a statin use a statin of high intensity **(Table 5.3)** and low cost (Collins et al., 2016)
- Statins are contraindicated in pregnancy. Therefore, advise;
    - to stop taking statin if pregnancy is a possibility
    - to stop taking statins 3 months before conception If planning pregnancy not to restart statins until breastfeeding is finished.

Table 5. 3 Grouping of statins

	Reduction in low-density lipoprotein cholesterol				
Dose (mg/day)	5	10	20	40	80
Simvastatin	–	27% A	32%B	37% B	42%CD
Atorvastatin	–	37% B	43% C	49% C	55% C
Rosuvastatin	38% B	43% C	48% C	53% C	–

A – 20%-30% reduction (low intensity); B – 31%-40% reduction (medium intensity); C – reduction of more than 40% (high intensity); D – increased risk of myopathy

5.2.3 Adverse effects of statin therapy

Adverse effects on muscle –

Myopathy is the most clinically relevant adverse effect of statins. Risk of myopathy is more due to interaction with concomitant drugs **(Appendix 8).** Rhabdomyolysis is the most severe form of statin-induced muscle damage, characterized by severe muscular pain, muscle necrosis, and myoglobinuria potentially leading to renal failure and death. In rhabdomyolysis CPK levels are elevated by ≥ 10 times, the upper limit of normal (Stroes et al., 2015, Marcum et al., 2012, Golomb and Evans, 2008)

Adverse effects on the liver–

The common definition of clinically relevant ALT elevation is an increase of three times the upper limit of normal on two consecutive occasions. Mild elevation of ALT can occur in 0.5-2.0% of patients but has not been shown to be associated with true hepatotoxicity or changes in liver function. Progression to liver failure is exceedingly rare, therefore routine monitoring of ALT during statin treatment is no longer recommended (Collins et al., 2016, Dongiovanni et al., 2015, Chalasani et al., 2004, Vuppalanchi et al., 2005, Mach et al., 2018).

Increased risk of new-onset diabetes mellitus –

This is a consistent, dose-related effect. The number needed to cause one case of diabetes has been estimated as 255 over 4 years of statin treatment. The risk is higher with the more potent statins at high doses, and is also higher in the elderly, and in the presence of other risk factors for diabetes such as overweight or insulin resistance. However, absolute reduction in the risk of CVD in high-risk patient clearly outweighs the possible adverse effects (Baigent et al., 2009, Preiss et al., 2011, Waters et al., 2013, Sattar et al., 2010, McKinney and Kostis, 2012).

Increased risk of haemorrhagic stroke –

Total cholesterol is negatively associated with haemorrhagic stroke in observational studies, but this need to be further studied due to conflicting findings in different studies (Hackam et al., 2011, Davidson, 2004, Franssen et al., 2009)

Adverse effects on kidney function –

There is no clear evidence that statins have a clinically significant beneficial or adverse effect on renal function (Jellinger et al., 2017). An increased frequency of proteinuria has been reported for all statins, but in most cases, is not higher than for placebo (Ajay and Prabhakaran, 2010). This has been analysed in more detail for rosuvastatin and with a dose of 80 mg, a frequency of 12% was reported but with the approved doses of <40 mg, the frequency is much lower and in line with the frequency for other statins. The proteinuria induced by statins is of tubular origin, usually transitory, and is believed to be due to reduced tubular reabsorption and not to glomerular dysfunction (Holoshitz et al., 2008).

Drug interactions –

Occurs due to CYP system involvement in metabolism. All currently available statins except, rosuvastatin, and pitavastatin undergo major hepatic metabolism via the CYPs. Combination of statins with gemfibrozil enhances the risk of myopathy but there is very little increased risk for myopathy when combining statins with other fibrates, such as fenofibrate, bezafibrate, or cipro fibrate (Mach, 2019, Ueda, 2005). List of common drug interactions are given in **Table 5.4**.

Table 5. 4 Drugs potentially interacting with statins metabolized by cytochrome P450 leading to drug interactions (Holoshitz et al., 2008)

Anti-infective agents	Calcium antagonists	Other
Itraconazole	Verapamil	Ciclosporin
Ketoconazole	Diltiazem	Danazol
Posaconazole	Amlodipine	Amiodarone
Erythromycin		Ranolazine
Clarithromycin		Grapefruit juice
Telithromycin		Nefazodone
HIV protease inhibitors		Gemfibrozil

5.3 Prescription of statins

5.3.1 Primary Prevention

Start atorvastatin 20 mg/ rosuvastatin 10 mg (high intensity statins) to the following people (**Figure5.*1***)

- People with an estimated WHO/ISH CV risk ≥ 20%
- Adults with diabetes mellitus with an estimated WHO/ISH CV risk ≥ 20%

- Start either Atorvastatin 20 mg OD or Rosuvastatin 10 mg OD for patients with CKD stage 3 - 5
- Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])
- It is reasonable to prescribe moderate intensity statins to diabetics
- Aged 40–75 years, without past history of ASCVD
- Who are younger than 40 years of age and/or have type 1 diabetes with other ASCVD risk factors

** For people 85 years or older, consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate

- Ezetimibe monotherapy is recommended as an option for treating primary dyslipidaemia in adults in whom initial statin therapy is contraindicated.

5.3.2 Secondary prevention

- Start atorvastatin 40mg/ rosuvastatin 20mg nocte in Sri Lankans with past history of ASCVD and without CKD. However, the recommendation is 80mg in Western guidelines (Zomer et al., 2016)***(Figure 5.1)***
- Start atorvastatin 20 mg or rosuvastatin 10mg nocte in patients with past history of ASCVD and CKD.
    - Increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and estimated glomerular filtration rate(eGFR) is 30 ml/min/1.73m^2 or more.
    - Discuss the use of higher doses of statins with a renal specialist if eGFR is less than 30ml/min/1.73m^2
    - Recommendation on lipid lowering therapy in patients on renal replacement therapy is outside the scope of this guideline.
- Ezetimibe monotherapy is recommended if initial statin therapy is contraindicated.

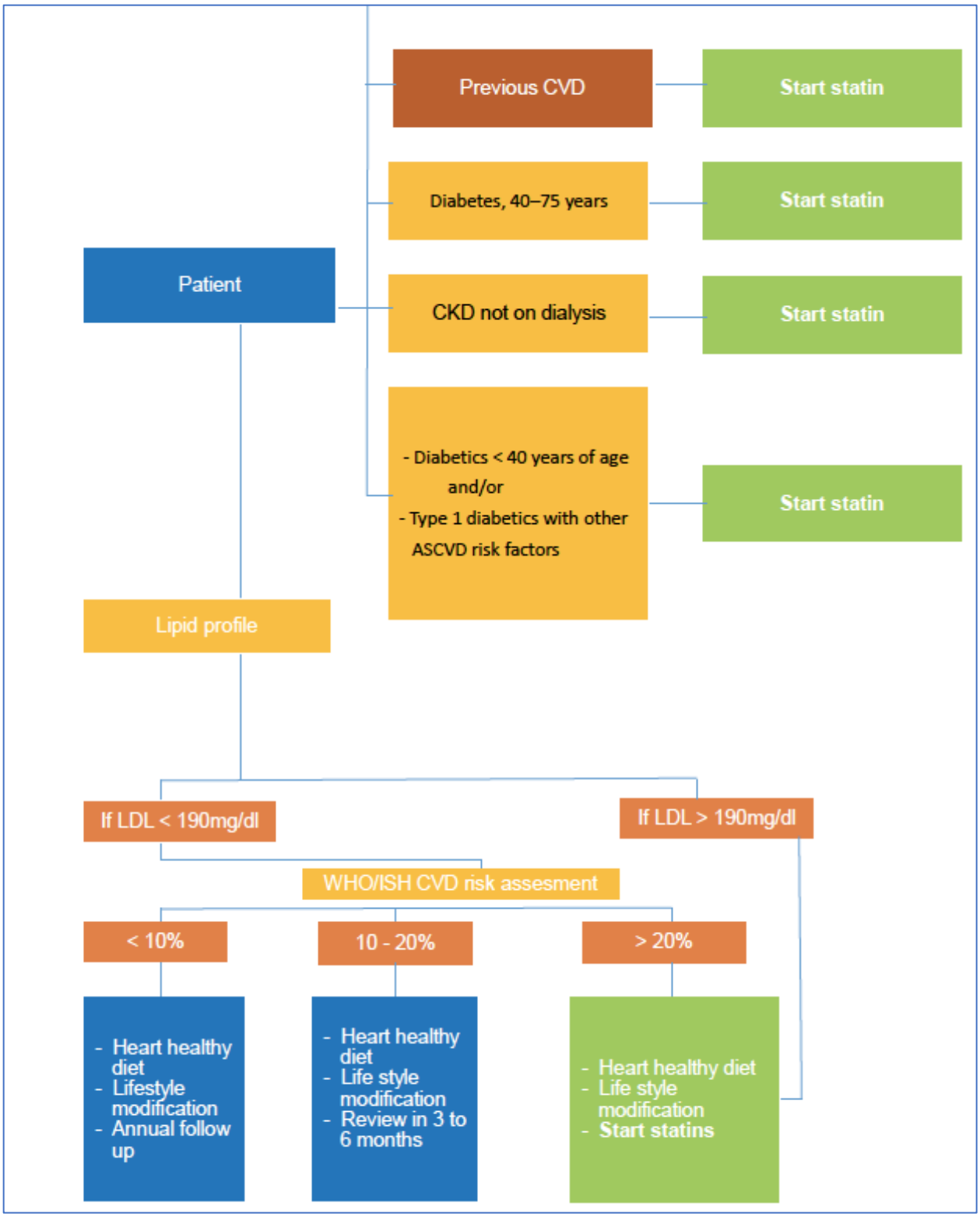

Figure 5. 1 Algorithm of management of dyslipidaemia (WHO risk levels will be changed accordingly Low risk <10%, Moderate risk 10 - <20%, High risk ≥20%)

5.4 Statin intolerance

If a person is not able to tolerate a high-intensity statin, aim to treat with the maximum tolerated dose as statins at any dose reduce cardiovascular disease risk.
Discuss the following possible strategies with them:

- Stopping the statin and trying again when the symptoms have resolved
- Reducing the dose within the same intensity group
- Changing the statin to a lower intensity group

5.5 Follow-up and monitoring (Zomer et al., 2016)

- Do not routinely measure creatinine kinase levels in asymptomatic patients on statins.
- Measure liver transaminase enzymes at baseline, within 3 months of starting treatment and at 12 months, but not again unless clinically indicated.
- Do not stop statins if an increase in blood glucose level is noted while on treatment.
- Repeat lipid profile 3 months after initiation of statins or after dose adjustment.
- Arrange annual reviews for people taking statins long term;
    - To discuss medicines adherence, lifestyle modification and other ASCVD risk factors.
    - To assess control with a fasting/ non-fasting blood test for non-HDL cholesterol.
    - If a greater than 40% reduction in non-HDL cholesterol is not achieved.
    - Discuss adherence and timing of dose.
    - Optimise adherence to diet and lifestyle measures.
    - Consider increasing the dose if on atorvastatin less than 80 mg and the person is judged to be at higher risk.

5.6 Intolerance or insufficient response to lipid-lowering therapy

Can try the following options:

1. Ezetimibe monotherapy - in adults who cannot tolerate statin therapy
2. Ezetimibe co-administered with initial statin therapy, when:
   Serum total or LDL cholesterol concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy **or**
   Because dose titration is limited by intolerance to the initial statin therapy **or**
   A change from initial statin therapy to an alternative statin is being considered.

Chapter 6

MANAGEMENT OF DYSLIPIDAEMIAS IN DIFFERENT CLINICAL SETTINGS

6.1 Familial dyslipidaemias

Plasma lipid levels are determined by genetic factors to a large extend and in the extreme forms are presented as familial dyslipidaemias (FD). Indifferent types of FD it is common to find high LDL-C, high TG, or low HDL-C levels affecting several family members **(Table 6.1)** (Sibley and Stone, 2006)

Out of these genetic disorders of lipid metabolism, Familial hypercholesterolemia (FH) is the most common form and it is strongly related to ASCVD at a younger age. FH is an autosomal-dominant disorder associated with mutations in the LDL receptor gene resulting in markedly elevated plasma low-density lipoprotein cholesterol levels (Ward et al., 2007).

The diagnosis of both homozygous and heterozygous FH is based primarily on the finding of severe LDLc elevations in the absence of secondary causes of hypercholesterolemia. Xanthomas are noted commonly on the Achilles tendons and metacarpophalangeal extensor tendons of the hands of untreated patients. Several different criteria are available for the clinical diagnosis of FH and the commonly used Dutch Lipid Clinic Network criteria for diagnosis of FH is shown in (**Table 6.2)** (Sibley and Stone, 2006).

Diagnosis of FH can be verified by showing causative mutations in genetic testing. If left untreated the risk of ASCVD is greatly increased and early diagnosis and appropriate treatment can significantly reduce the risk for ASCAD in these patients (Cannon et al., 2006).

Table 6. 1 Genetic disorders of lipoprotein metabolism (from ESC/EAS guidelines for the management of dyslipidaemia 2019)

Disorder	Prevalence	Gene(s)	Effect on Lipoproteins
HeFH	1 in 200—250	LDLR APO B PCSK 9	↑LDL-C
HoFH	1 in 160 000 - 320 000	LDLR APO B PCSK 9	↑↑ LDL-C
FCH	1 in 100/200	USF1 + modifying genes	↑ LDL-C ↑VLDL-C ApoB↑
Familial dysbetalipoproteinaemia	1 in 5000	APO E	↑↑ IDL and chylomicron remnants (β VLDL)
Familial lipoprotein lipase deficiency (familial chylomicron syndrome)	2 in 10^6	LPL, APO C2 LMF1 ApoAV, GPIHBP1	↑↑ Chylomicrons and VLDL-C
Tangier disease (analphalipoproteinaemia)	1 in 10^6	ABCA1	↓↓ HDL-C
Familial LCAT deficiency	1 in 10^6	LCAT	↓ HDL-C

Apo = apolipoprotein; FCH = familial combined hyperlipidaemia; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolaemia; HoFH = homozygous familial hypercholesterolaemia; IDL = intermediate-density lipoprotein; LCAT = lecithin cholesterol acyltransferase; LDL-C = low-density lipoprotein cholesterol; VLDL = very low-density lipoprotein cholesterol.

Table 6. 2 Dutch Lipid Network Criteria for FH (from ESC/EAS guidelines for the management of dyslipidaemia 2019)

Criteria	Points
1) Family history	
First-degree relative with known premature (men aged <55 years; women <60 years) coronary or vascular disease, or first-degree relative with known LDL-C above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or corneal arcus, or children aged <18 years with LDL-C above the 95th percentile	2
2) Clinical history	
Patient with premature (men aged <55 years; women <60 years) CAD	2
Patient with premature (men aged <55 years; women <60 years) cerebral or peripheral vascular disease	1
3) Physical examination *	
Tendinous xanthomata	6
Corneal Arcus before age 45 years	4
4) LDL-C levels (without treatment)	
LDL-C ≥325 mg/dL (≥8.5 mmol/L)	8
LDL-C 251—325 mg/dL (6.5—8.4 mmol/L)	5
LDL-C 191—250 mg/dL (5.0—6.4 mmol/L)	3
LDL-C 155—190 mg/dL (4.0—4.9 mmol/L)	1
5) DNA analysis	
Functional mutation in the LDLR, apoB, or PCSK9 genes	8
Choose only one score per group, the highest applicable; diagnosis is based on the total number of points obtained	
A 'definite' FH diagnosis requires >8 points	
A 'probable' FH diagnosis requires 6—8 points	
A 'possible' FH diagnosis requires 3—5 points	

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2 CAD = coronary artery disease; FH = familial hypercholesterolemia; LDL-C = low- density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.

* Exclusive of each other (i.e., maximum 6 points if both are present).

Table 6. 3 Recommendations for familial dyslipidaemia

	Recommendations	Class
1	Diagnosis of FH should be considered in patients with CHD aged <55 years for men and <60 years for women, in people with relatives with premature fatal or non-fatal ASCVD, severely elevated LDL-C [in adults (>190 mg/dL), in children (>150 mg/dL)], and in first-degree relatives of FH patients.	I
2	FH should be diagnosed using clinical criteria and when possible confirmed with genetic tests.	I
3	Screening should be offered to the family members of a confirmed patient with FH.	I
4	FH patients with ASCVD or who have another major risk factor should be treated as other very-high-risk patients and FH patients with no prior ASCVD or other risk factors should be treated as high-risk patients.	I
5	FH patients in the very-high risk category should be treated with a single(statin) or combination lipid lowering therapy (statin plus ezetimibe) to achieve more than 50% reduction of LDL-C from baseline and an LDL-C goal of <55 mg/dL.	IIa
6	Treatment with a PCSK9 inhibitor is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe.	I
7	In children, testing for FH is recommended from the age of 5 years, or earlier if Homozygous FH is suspected.	I

6.2 Diabetes and metabolic syndrome

Hyperlipidaemia in association with insulin resistance is common in patients with type 2 diabetes mellitus. Hyperinsulinemia secondary to insulin resistance is associated with hypertriglyceridemia, increased small dense low-density lipoprotein (LDL), and low serum high-density lipoprotein (HDL) cholesterol concentrations. These atherogenic dyslipidaemia is one of the major risk factors for ASCVD in patients with type 2 diabetes. Lipid lowering therapy with statins have consistently demonstrated significant benefits on reducing ASCVD events in people with T2DM (Zomer et al., 2016, Sibley and Stone, 2006, Pearce, 2004, Amarenco et al., 2006)

Table 6. 4 Recommendations for dyslipidaemia in diabetes and metabolic syndrome

	Recommendations	Level
Primary prevention		
1	Lifestyle intervention (diet, weight loss, increased physical activity) is recommended in all patients with diabetes to improve lipid levels	A
2	Moderate-intensity statin therapy is recommended in patients with diabetes aged 40–75 years without ASCVD	A
3	It is reasonable to use high-intensity statin therapy in patients with diabetes at higher CV risk (WHO/ISH risk ≥ 20%), especially those with multiple ASCVD risk factors or aged 50–70 years	B
4	It is reasonable to use moderate intensity statins in patients who are younger than 40 years of age and/or have type 1 diabetes with other ASCVD risk factors,	B
Secondary prevention		
5	high-intensity statin therapy should be added to lifestyle therapy in patients with diabetes of all ages with atherosclerotic cardiovascular disease	A
6	Consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor) if LDL cholesterol is ≥70 mg/dL on maximally tolerated statin dose in patients with diabetes and ASCVD considered to be at very high risk.	A
7	It is reasonable to continue statin treatment in adults with diabetes aged >75 years who are already on statin therapy	B
6	Statin therapy is contraindicated in pregnancy.	B

6.3 Hypothyroidism

Many patients with hypothyroidism have high serum concentrations of total cholesterol and low-density lipoprotein (LDL) cholesterol and some patient may even have high triglyceride levels. The primary mechanism for hypercholesterolemia in hypothyroidism is accumulation of LDL cholesterol due to a reduction in the number of cell-surface receptors for LDL, resulting in decreased catabolism of LDL. Variable changes in plasma lipoprotein concentration has been observed in hypothyroid patients treated with levothyroxine (Kjekshus et al., 1997).

Table 6. 5 Recommendations for dyslipidaemia in hypothyroidism

	Recommendations	Class
1	All patients with Hyperlipidaemia should be screened for hypothyroidism before being given specific lipid-lowering drug therapy	I
2	If hypothyroidism is present, the patient should be first treated for three to four months with levothyroxine therapy and if the serum lipid levels are still abnormal, then lipid-lowering therapy may be indicated	IIa

6.4 TIA and strokes

Association between dyslipidaemia, ischemic stroke and transient ischemic attacks (TIA) is well known. Patients with ischemic stroke or TIA are at high risk of recurrent events as well as other cardiovascular events like myocardial infarctions. Secondary prevention with statins reduces the risk of recurrent stroke, myocardial infractions, and vascular death (Milin et al., 2014).

Table 6. 6 Recommendations for dyslipidaemia in TIA and stroke

	Recommendation	Class
1	Patients with ischemic strokes and TIA are at increased risk of recurrent events, ASCVD and intense lipid lowering therapy with statins is recommended (Pearce, 2004).	I

6.5 Heart failure and valvular heart disease

Cholesterol lowering therapy with statins have clearly shown to reduces the incidence of heart failure in patients with prior CAD (stable CAD or a history of ACS) (Franczyk-Skóra et al., 2013). There is no evidence that statins can prevent heart failure of non-ischemic origin. There is insufficient evidence to suggest that statins would slow the progression of aortic valve stenosis (Loncar et al., 2015).

Table 6. 7 Recommendations for dyslipidaemia in heart failure and valvular heart disease

	Recommendation	Class
1	Routine administration of statins in patients with HF without other indications for their use (e.g., CAD) is not recommended.	III
2	Initiation of lipid-lowering treatment in patients with aortic valvar stenosis without CAD to slow progression of aortic valve stenosis in the absence of other indications for their use is not recommended (Loncar et al., 2015).	III

6.6 chronic kidney diseases (CKD)

Lipid abnormalities are common in patients with all stages of chronic kidney disease. Primary lipid abnormality seen in CKD patients is elevated TG levels. Low HDL-C levels and excess of small dense LDL particles are also seen in these patients. Patients with CKD have a much higher risk of ASCVD and CV mortality rate compared with patients with normal renal functions (Franczyk-Skóra et al., 2013, Loncar et al., 2015)

Table 6. 8 Recommendations for dyslipidaemia in CKD

	Recommendations	Class
1	Patients with CKD stage 3-5 are considered to be at high or very-high risk of ASCVD (Franczyk-Skóra et al., 2013, Loncar et al., 2015).	I

2	Patients with CKD who have established ASCVD should receive maximally tolerated statin therapy, similar to patients with established ASCVD disease who do not have CKD.	I
3	The use of statins therapy may benefit patients with non-dialysis-dependent stage 3-5 CKD even in the absence of other ASCVD.	I
4	In patients with dialysis-dependent CKD who are free of ASCVD and who are not already on statin therapy, newly commencement of statin therapy is not recommended (Wanner et al., 2005).	III
5	Statins should be considered as first-line agents in renal transplant patients (Davidson, 2004).	IIa

6.7 Pregnancy and lactation or planning pregnancy

- Routine screening should not be done.
- If a female belongs to above category detected to have dyslipidaemia always needs to screen for secondary causes, e.g., hypothyroidism
- Routine treatment with statins should not be commenced unless risk over weigh the benefit. In these circumstances patient should be referred to a physician / endocrinologist / cardiologist for expert opinion to decide on statin therapy.
- Females with fertility wishes who are on statin therapy needs to carefully assess by a physician /endocrinologist / cardiologist for discontinuation of statins. In a situation where statin therapy is indicated, they should be offered temporary contraceptive methods after proper counselling.
- Females who are having a risk of dyslipidaemia must be referred for lifestyle modification.
- If diabetic individuals aged ≤30 years have no evidence of vascular damage and, in particular, microalbuminuria, it seems reasonable to delay statin therapy in asymptomatic patients until the age of 30. Below this age, statin therapy should be managed on a case-by-case basis, considering the presence of microalbuminuria, end organ damage, and ambient LDL-C levels.
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Chapter 7

SCREENING AND REFERRAL PATHWAYS FOR MANAGING HYPERLIPIDEMIA

7.1 National NCD screening programme

The national NCD screening programme provides a comprehensive package for NCD screening through the Healthy Lifestyle Centres (HLC) established at the Primary Health Care (PHC) level hospitals. The package includes a comprehensive history and examination and measurements of

waist circumference, waist to height ratio, BMI, BP, FBS/RBS, Total Cholesterol and CV risk assessment for clients. Two categories of people have been identified as eligible to be screened by the national NCD screening programme as described below.

Category A: All apparently healthy persons aged 35 years and above.

Category B: Persons aged between 20-34 years having the following risk factors.

1. Smoking tobacco during the past one year
2. Overweight & obesity (BMI ≥ 25kg/m^2)
3. Abdominal Obesity (waist circumference – male > 90cm, female >80cm)
4. Persistently Raised BP (≥140/90mmHg)
5. Symptoms suggestive of Diabetes Mellitus
6. History of premature cardiovascular disease in first degree relatives (male relative < 55 years, female relative <65 years)
7. History of Diabetes Mellitus in first degree relatives
8. History of Familial Dyslipidaemia in first degree relatives

*Those with established ASCVD, Renal dysfunction and Diabetic nephropathy are excluded from screening (refer section 2.4)

7.2 Investigations for dyslipidaemia at primary care level

1. At HLC – screening

1. **Total cholesterol levels**

   - Can be performed on a random capillary blood sample using cholesterol strips.
   - Some centres collect blood samples and send to the closest hospital laboratory.

   If total cholesterol level is equal to 240 mg/dl (approx. 6 mmol/l) or more, a lipid profile needs to be carried out and clients should be referred to the medical clinic at primary care level.

All HLC attendees receive individualized lifestyle modification guidance based on their NCD risk factors and total CV risk

2. Medical clinic (Primary Care)- diagnosis

- Lipid Profile
  a. Require 12-14 hours fasting and a venous blood sample

Refer **Chapter 4** for details on lifestyle modification guidance for dyslipidaemia management.

Figure below illustrates the referral pathways for screening, diagnosis and management of NCDs including hyperlipidaemia across all levels of care

Lifestyle modification guidance should be provided to all the patients diagnosed with hyperlipidemia at all levels of care.

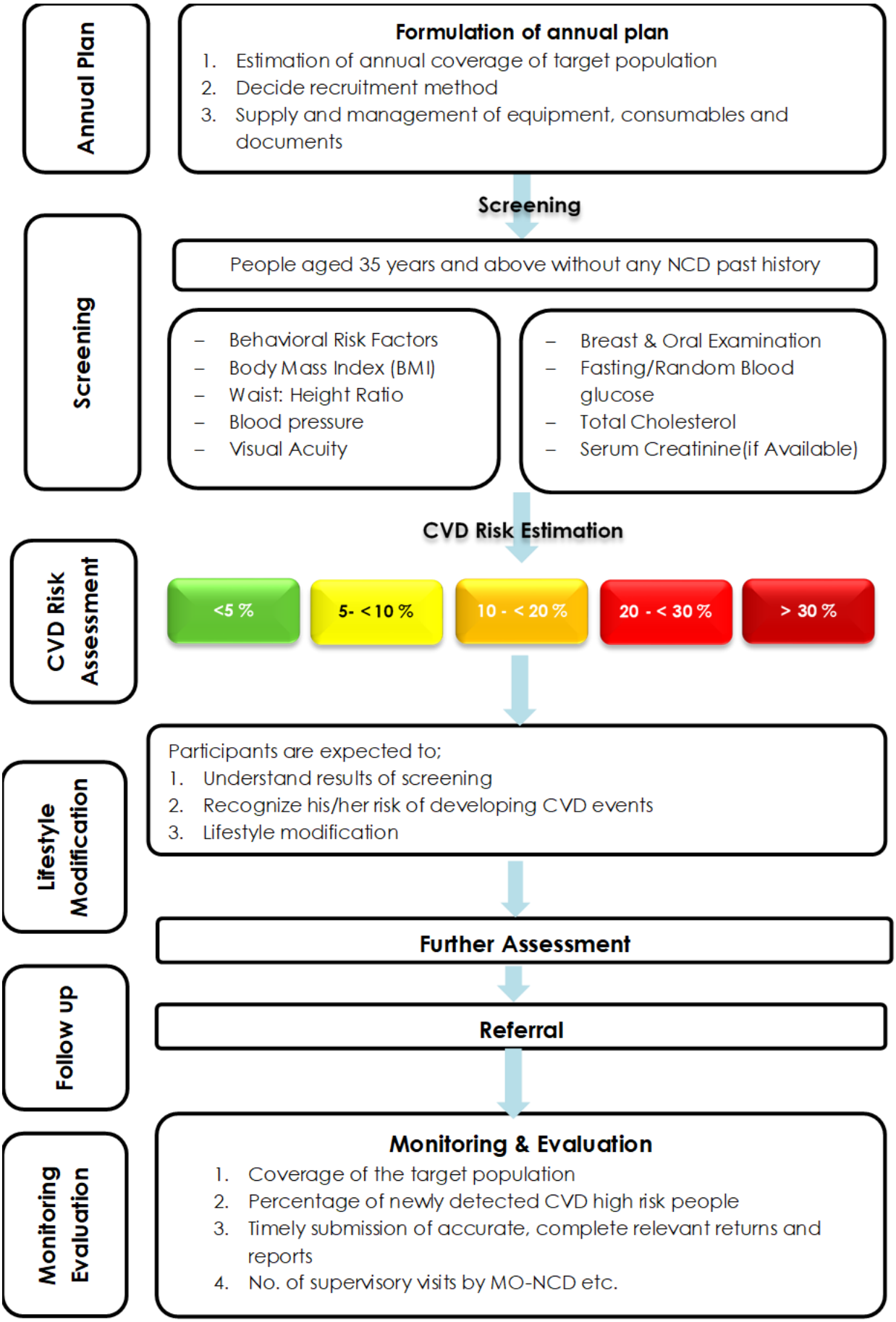
Annual Plan
Formulation of annual plan
1. Estimation of annual coverage of target population
2. Decide recruitment method
3. Supply and management of equipment, consumables and documents
Screening
Screening
People aged 35 years and above without any NCD past history
– Behavioral Risk Factors
– Body Mass Index (BMI)
– Waist: Height Ratio
– Blood pressure
– Visual Acuity
– Breast & Oral Examination
– Fasting/Random Blood glucose
– Total Cholesterol
– Serum Creatinine(if Available)
CVD Risk Assessment
CVD Risk Estimation
<5 %
5- <10 %
10 - < 20 %
20 - < 30 %
> 30 %
Lifestyle Modification
Participants are expected to;
1. Understand results of screening
2. Recognize his/her risk of developing CVD events
3. Lifestyle modification
Further Assessment
Follow up
Referral
Monitoring Evaluation
Monitoring & Evaluation
1. Coverage of the target population
2. Percentage of newly detected CVD high risk people
3. Timely submission of accurate, complete relevant returns and reports
4. No. of supervisory visits by MO-NCD etc.

Figure 7. 1 Referral pathways for screening, diagnosis and management of NCDs Outline of standards Screening Programme

GAPS IN EVIDENCE

- A model to risk stratifies Sri Lankan Population needs to be developed.
- Prospective studies are required to determine the incremental value of reclassifying total CV risk and also to define eligibility for lipid lowering in consideration of CAC score at moderate or high risk.
- Outcome based comparison of CAC scores vs. assessment of arterial plaque burden by ultrasonography for CV risk reclassification in those with moderate or high risk are needed.
- TC is used for WHO/ISH system and treatment goals for statins. However, LDL-C is the primary lipid analysis for screening, diagnosis and management.
- The maximum dose of statin to be used in Sri Lankan population need to be studied.
- Absence of outcome-based comparison of LDL-C in comparison to ApoB as primary measurement methods.
- Clinical impact therapy on altering the function of HDL is unknown in the background where raising HDL does not show effects on CVD events.
- Studies using outcomes with Lp(a) lowering therapies are needed.

KEY MESSAGES

- Emphasize a heart-healthy lifestyle across the life course for all individuals.
- Treatment of dyslipidaemia is guided by total cardiovascular risk.
- Statins are the drugs of choice to reduce cardiovascular disease risk in any type of dyslipidaemia.
- Dyslipidaemia treatment targets are based on control of low-density lipoprotein cholesterol (LDL-C).
- In patients with clinical atherosclerotic cardiovascular disease (ASCVD), reduce low-density lipoprotein cholesterol (LDL-C) with high intensity or maximally tolerated statin therapy.
- Do not stop or reduce statin dosage after achieving the lipid targets.
- Assess lipid measurement 4 to 12 weeks after statin initiation or dose adjustment. Repeat lipid measurements every 3 to 12 months based on individual risk.

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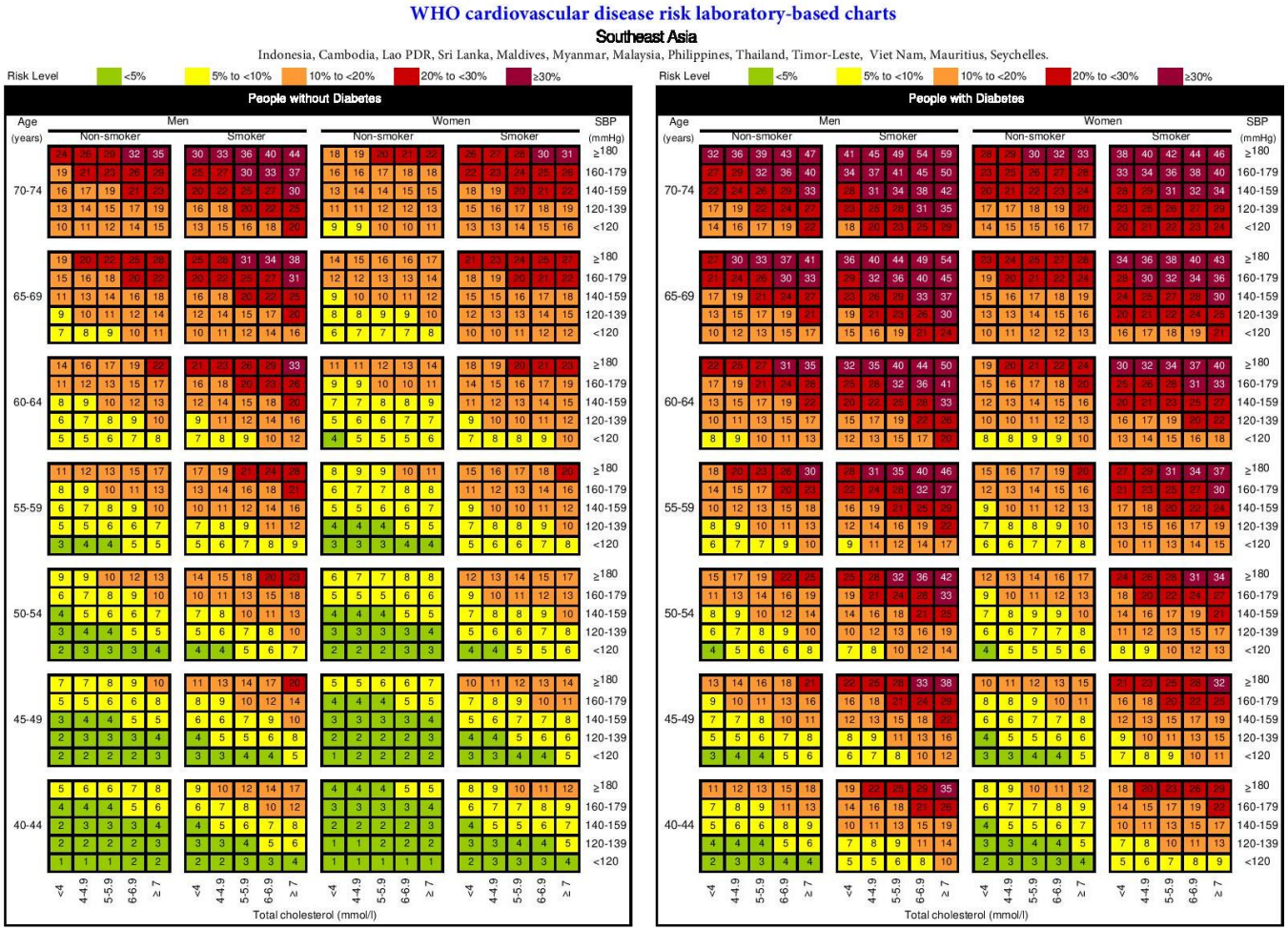
10. ANNEXURES

Annexure 1

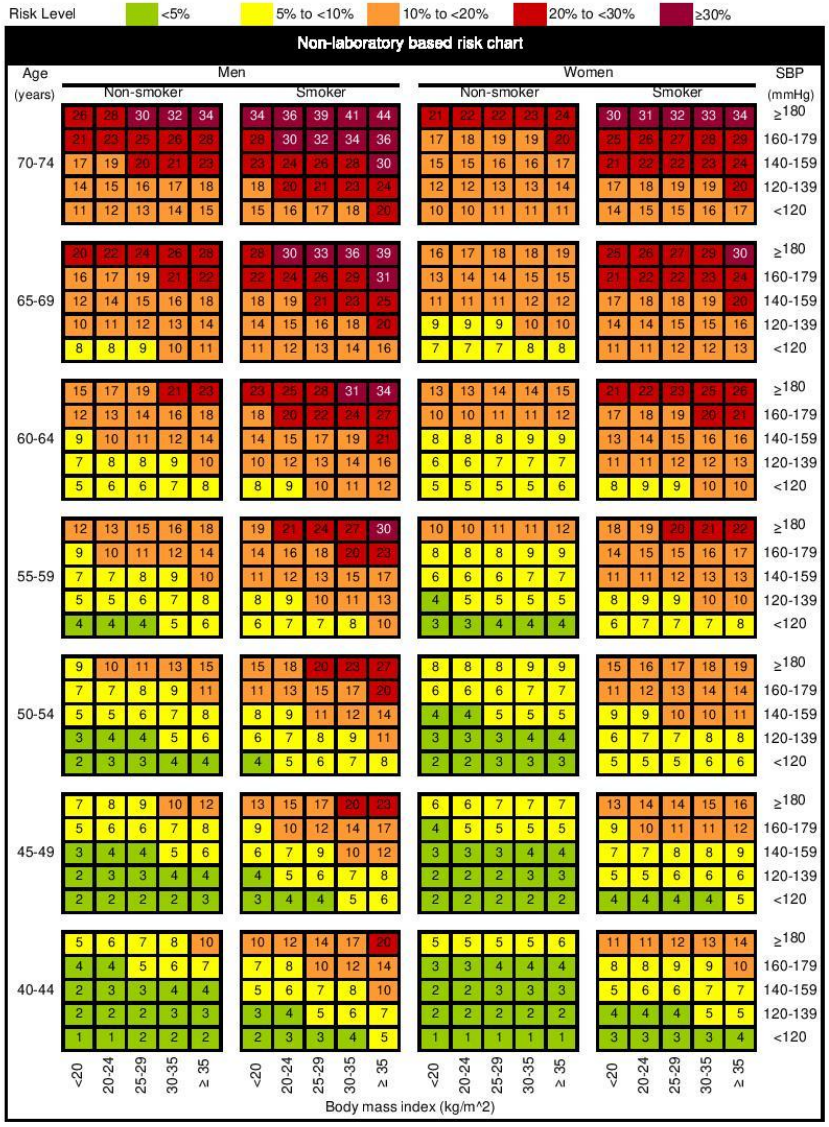
WHO/ISH (SEAR B) risk charts



WHO cardiovascular disease risk non-laboratory-based charts

Southeast Asia

Indonesia, Cambodia, Lao PDR, Sri Lanka, Maldives, Myanmar, Malaysia, Philippines, Thailand, Timor-Leste, Viet Nam, Mauritius, Seychelles.



- **Estimate the 10 year cardiovascular risk as follows using laboratory based charts;**

  Step 1 Select the appropriate chart depending on the presence or absence of diabetes

  Step 2 – Select male or female tables

  Step 3 – Select smoker or non-smoker boxes

  Step 4 – Select age group box (if age is 54; select 50-54, if age is 55; select 55-59)

  Step 5 – Within this box find the nearest cell where the individual's systolic blood pressure (mmHg) and the total blood cholesterol level (mmol/l) cross. The colour and the number of this cell determines the 10 year cardiovascular risk.

- **Estimate the 10 year cardiovascular risk as follows using non laboratory based charts;**

  Step 1 – Select male or female tables

  Step 2 – Select smoker or non-smoker boxes

  Step 3 – Select age group box

  Step 4 – Within this box find the nearest cell where the individual's systolic blood pressure (mmHg) and the Body Mass Index (kg/m^2) value cross. The colour and the number of this cell determines the 10 year cardiovascular risk.

< 5% **5 % - < 10 %** **10 % - < 20 %** **20 % - < 30 %** **≥ 30 %**

Annexure 2

Physical activity

How to measure the intensity of an activity	The easiest method of subjective assessment of the intensity of an activity is by the **talk test**. It is important to explain the patient on how to measure the intensity of an activity utilizing the talk test. 1. If he/she is able to talk and sing while doing a certain activity, that indicates that the particular activity is of light intensity. 2. If he/she is able to talk but, finds it difficult to sing while doing a certain activity, that indicates that the activity is of moderate intensity. 3. If he/she finds difficulty in talking while doing a certain activity, it indicates that the activity is of vigorous intensity.
Vigorous-intensity activity	Examples include jogging, running, carrying heavy groceries or other loads upstairs, or participating in a strenuous fitness class
Major muscle groups	Major muscle groups include the legs, back, abdomen, chest, shoulders and arms
Muscle-strengthening activity	Physical activity and exercise that increase skeletal muscle strength, power, endurance, and mass (e.g., strength training, resistance training, or muscular strength and endurance exercises).

Annexure 3

Dietary recommendations to lower low-density lipoprotein cholesterol

	To be preferred	To be used with moderation	To be chosen occasionally in Limited amounts
Cereals	Unpolished rice, Wholegrain wheat,	Refined bread, rice and pasta, biscuits, corn flakes	Pastries, muffins, pies, croissants
Vegetables	Raw and cooked vegetables	Potatoes	Vegetables prepared in butter or margarine
Legumes	Dhal, cowpea, green gram, chickpeas, soybean		
Fruit	Fresh or frozen fruit	Dried fruit, jelly, jam, canned fruit, sorbets, popsicles, fruit juice	
Sweets and sweeteners	Non-caloric sweeteners	Sucrose, honey, chocolate, candies	Cakes, ice creams, fructose, soft drinks
Meat and fish	Lean and oily fish, poultry without skin	Lean cuts of beef, lamb, pork or seafood, shellfish	Sausages, salami, bacon, spare ribs, hot dogs, organ meats
Dairy food and eggs	Non-fat milk and yogurt	Low fat milk, low fat cheese and other milk products, eggs	Regular cheese, curd, whole milk and yogurt
Cooking fat and dressings	Vinegar, mustard, fat-free dressings	Olive oil, coconut oil, soft margarines, salad dressing, mayonnaise, ketchup	Trans fats and hard margarines (better to avoid them), palm and other vegetable oils, butter, lard, bacon fat
Nuts/seeds	All, unsalted (except coconut)	Coconut scrapings	Nuts/seeds
Cooking procedures	Grilling, boiling, steaming	Stir-frying, roasting	Frying

(Source: European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS) Guidelines for the management of Dyslipidaemias)

Annexure 4

Cardio protective diet for high risk or with ASCVD

1. Total carbohydrate intake is 50/60% of total energy intake and not less than 40% of total energy intake,
2. Total protein intake is 15-20% of total energy intake
3. Total fat intake is 30% or less of total energy intake
4. Saturated fats are 7% or less of total energy intake
5. Intake of dietary cholesterol is less than 300mg/day
6. Increase their mono-unsaturated fat intake with olive oil, avocado, small fish
7. Choose wholegrain varieties of starchy food such as parboiled unpolished rice
8. Reduce their intake of sugar to less than 6 teaspoons and food products containing refined sugars including fructose
9. eat at least 5 portions of fruit and vegetables per day, 1 portion is equivalent to 3 tablespoons of cooked vegetables
10. Eat at least 2 portions of fish per week, including a portion of oily fish such as herrings, 1 portion is equivalent 2 matchbox size piece.
11. Eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week, 1 portion is equivalent to 1 tablespoon.

Annexure 5

Recommendations for dietary supplements and functional foods

Dietary supplements / functional foods	Action	Recommendation
1.Phytosterols	Plant sterols or stenos (rich in Green leafy vegetables) lower cholesterol.	Supplements are not recommended due to absent of conclusive evidence on Phytosterol help to prevent CVD
2.Red yeast rice	red yeast rice is effective in lipid lowering	It is not recommended due to the variability in potency and possible adulteration of commercially available products
3. Dietary fibre	The consumption of certain types of soluble fibres slower gastric emptying, enhanced satiety, inhibition of hepatic cholesterol synthesis, and/or enhanced faecal excretion of cholesterol and bile salts, including psyllium, pectin (Banana, Guava, Belie fruit, passion fruit, grapefruit, apple, oranges etc.), certain pulses (e.g., Cowpea, Green gram, Chickpea etc.), dhal, nuts (Cotton, almond, walnut etc.) can produce a reduction in both total cholesterol and LDL cholesterol. The gel-forming attributes of soluble fibre may be the basis for improved lipid profiles and glucose homeostasis. The molecular weight and amount of beta-glucan in food products such as oats and oats products may contribute to LDL cholesterol lowering	Fibre is effective whether added to the diet as a supplement or used as a component of a dietary modification plan.
4. Soy and soy products (Soya	Contains isoflavones, which are phytoestrogens. Isoflavones have some	

meat, Tofu, Tempeh etc.)	properties similar to oestrogen and may have a small effect on cholesterol levels and inhibition on LDL oxidation. The efficacy of soy on improving serum lipids is modest; it may produce a meaningful reduction on total cholesterol and LDL cholesterol when combined in the diet with other cholesterol-lowering foods.	
5. Isoflavone	Isoflavone supplements do not appear to be of benefit and should not be taken with a goal of improving lipids and cardiovascular risk	Not recommended
6. Berbine	Although the berberine supplements (between 900 to 1500 mg/day) improved total cholesterol, LDL cholesterol, and triglycerides, considering alkolid content and few available studies,	not recommended
7. Policosanol	no improvement in any measurement of serum lipids	not recommended
8. n-3 unsaturated FA	It raises HDL and lower LDL. No evidence that omega-3 FA supplements help to prevent ASCVD	Recommend consuming 90-180 g of fish (Hurulla, Sprates, Tuna, Kumbalawaetc.) per week. omega-3 FA supplements not recommended
9. Garlic, Resveratrol	No evidence	not recommended
10. Selenium and calcium	No beneficial effect on serum lipid	not recommended

Annexure 6

General advice

- Eat a variety of nutritious foods from all the food groups, in appropriate amounts as given above to maintain optimal body weight and to get all the nutrients.
- Encourage to choose fibre rich whole grains / less polished grains for most of the grain servings.
- Main aim is to change the fat composition by increasing healthy fats in the diet. Therefore;
    - Encourage to include the fish containing omega 3 fatty acids such as Sardines, Salaya, Hurulla, Kumbalawa, Salmon, Mackerel and Tuna
    - Restrict foods containing saturated fat such as red-meat, cheese and full fat dairy.
    - Include foods containing unsaturated fats such as fish, nuts, seeds, avocado and olive oil.
- Use healthy cooking methods
    - Prepare more fresh salads with vegetables to minimize the loss of nutrients and reduce the amount of coconut milk used for cooking
    - Use alternative cooking methods such as steaming, mirisata, ambulata etc.
    - Restrict deep frying / heating oil to very high temperatures
    - Minimize deep frying of foods. If deep frying is needed, can use other options such as use of air frying
- Avoid re-using oil.

Annexure 7

Daily recommendation for heart healthy diet for a person with sedentary life style

Food group	Number of servings per day	1 serving size	1 serving size equal to:
Cereal / Yam/ Starchy food	6	½ cup	½ cup rice ½ cup of cooked noodles 1 slice of bread 2 - 3 string hoppers 1 hopper ½ rotti (about 10cm diameter and 0.5cm thick) 1 dosai (about 10cm in diameter) 3 cm height pittu ½ cup of boiled sweet potato/ Manioc/ Raja ala/ other yams ½ cup jack/ bread fruit ¾ cup of boiled corn
Pulses	3	1/2 cup / 3 tbs	3 tbs dhal 3 tbs kadala parippu 3 tbs mung parippu ½ cup chickpeas ½ cup cowpea ½ cup green gram 2 tbs soya meat
Fish / Poultry /meat / Egg	2	30 g (Size of Two match boxes)	2 match box size fish 2 match box size chicken 1 match box size dry fish 10 - 20 sprats 1 egg
Milk	1	1/2 cup	1/2 cup non-fat fresh milk Full 1 tbs non-fat milk powder
Nuts and seeds	1	1 full tbs	1 full tbs Peanut 5 full Cashew 1 full tbs pumpkin / sun flower seeds 1 Thala guli 10 Kottang
Root vegetables	1	3 tbs	3 tbs Ash plantain / Pumpkin/ Bread fruit/ Jack fruit/ Potato/ Sweet potato/ Manioc/ other yams/ Carrot/ Beet/ Radish/ Knol khol/ Kohila/ Lotus roots
Green Vegetables	1 ½	3 tbs	3 tbs Beans/ Murunga/ Wetakolu/ Pathola/ Dambala/ Bitter gourd(Karavila)/ Thibbatu / Elabatu/ Lunu mal/

Leafy vegetables	3	3 tbs	3 tbs Gotukola/ Kathurumurunga/ Mukunuwenna/ Spinach/ Kungkun/ Anguna/ Thembu/ Sarana/ Thampala/ Murunga leaves/ Pumpkin leaves/ Carrot leaves/ Beet leaves/ Radish leaves/ Knol khol leaves/ Cabbage leaves/ Passion leaves/ Manioc leaves/ Tender kohila leaves/ Onion leaves
Other vegetables	1	3 tbs	3 tbs Brinjal/ Cucumber/ Capsicum/ Tomato/ Keselmuwa/ Cauliflower/ Ambaralla/ Green mangoes
Fruits	2	1small (100g) or ½ cup of fresh cut fruit or canned fruit ½ cup unsweetened fruit juice 1 ½ tbs of dried fruit	1 cup cubed Papaya 1 small Banana ½ large Guava 1 medium Pomegranate 1 medium Mango ½ small Jambola (grapefruit) ½ cup fresh Pineapple 5 large / 10 small Grapes 1 cup cubed Water melon 5-6 jack fruit 1 medium Wood apple 1 small Belli fruit 2 medium Ambarella 10 – 15 Jambu 7-9 Rambuttan ½ cup Anoda 2 pieces of Durian 2 medium Passion fruits 10 fruits of Nelli / Lovi / Veralu 2 small Mandarin 1 small Orange (6 cm across) 1 small Apple (5 cm across) 5 Strawberries ½ cup Mulberry ½ medium Avocado
Coconut	½	2 tbs Grated coconut or ½ cup Coconut milk	½ cup of coconut milk 2 tbs coconut 3 tbs gravy
Oil*	1	1 tbs (15 ml)	1 tbs Coconut oil/ Olive oil/ sesame oil/ Soya oil/ Sun flower oil/ Rice bran oil
Sugar	3	1 tsp	1 tsp Honey

			1 tsp Trickle Thumb size piece of Jiggery
Salt	1	1 level tsp	
Water	6 – 8	1 cup	
Other Beverages	2 -3	1 cup	1 cup Light plain tea/ Coffee/ Herbal drinks (Belimal, Ranawara) /Coriander water/ king coconut / Coconut water

1 cup – 200 ml cup, tbs = table spoon, tsp = tea spoon

All given food are edible portions, otherwise specified

**When choosing oil, take only 5 ml from coconut oil and use 10 ml from other oil to improve the fat composition*

Annexure 8 Features of Different Medications Used in the Treatment of Dyslipidaemia

Different drugs	LDL-C reduction	Triglyceride reduction	HDL-C increase	ADR
Statins **MOA - inhibit HMG-CoA reductase enzyme, the rate-limiting step in cholesterol biosynthesis.**	dose-dependent and varies between the different statins o low intensity statins - 20%-30% reduction is o medium intensity statins - 31%-40% reduction is o high intensity statin - >40% is	10-20%	1-10% increase	Mentioned above in 6.2.4
Ezetimibe **MOA - inhibit the absorption of cholesterol by the small intestine**	15-22%	8%	3%	Rare (No need of dose reduction in mild hepatic impairment and mild to severe renal impairment)

Bile acid sequestrants ***E.g., Cholestyramine, colesevelam*** **MOA - remove a large portion of the bile acids from the enterohepatic circulation.**	18-25	May increase TG	-	o Gastrointestinal (GI) adverse effects (most commonly flatulence, constipation, dyspepsia, and nausea) o Reduced absorption of fat-soluble vitamins o drug interactions with several o commonly prescribed drugs
PCSK9 inhibitors ***e.g. Alirocumab*** **(MOA – increase expression of LDL receptors at cell surfaces**	60	26	9	itching at the site of injection and flu-like symptoms increase of patient-reported neurocognitive effects hypersensitivity
Fibrates **MOA - Fibrates are agonists of peroxisome proliferator-activated receptor a (PPAR-a), acting on, various steps in lipid and lipoprotein metabolism.**	20%	50%	20%	myopathy, liver enzyme elevations, and cholelithiasis
Omega-3 fatty acids **eicosapentaenoic acid (Lloyd-Jones et al.) and docosahexaenoic acid (DHA)** **Has no overall effect of omega-3 PUFAs on total mortality**	-	45%	-	o GI disturbance. o Increase bleeding with the antithrombotic effects o ??risk of prostate cancer

Proprotein convertase subtilizing/kexin type 9 inhibitors (PCSK9 inhibitors) ***e.g.; alirocumab evolocumab*** **Inhibit PCSK9 protein and thereby increase LDLR expression.**	46-73%	26%	4	○ Limited data on long-term safety ○ Possible new onset diabetes mellitus and patient-reported neurocognitive effects has been described