CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF LIPIDS

CHAPTER OF CARDIOLOGISTS

DECEMBER 2023

ACADEMY OF MEDICINE
SINGAPORE

CHAPTER OF CARDIOLOGISTS
COLLEGE OF PHYSICIANS
SINGAPORE

MESSAGE

In recent years, there have been many developments which warrant a review of the current literature on lipid targets. The writing of this guideline is led by the Chapter of Cardiologists, College of Physicians, Academy of Medicine Singapore (AMS), and encompasses the professional opinions of professional medical organizations, public healthcare institutions, private healthcare institutions and the cardiology community at large. Other than the AMS, writing committee members include those from the Singapore Cardiac Society, Singapore Heart Foundation, National Heart Centre Singapore, National University Hospital, National Healthcare Group, and physicians in private practice. Members include cardiologists, endocrinologists, and family physicians.

The aim of the guideline is to provide the healthcare community with the necessary information to provide quality care to the patient with the aim of preventing cardiovascular events. While the guideline aims to provide targets for healthcare providers to help achieve the desired therapeutic levels of lipid parameters for the large majority of patients, it does not supplant clinical judgement.

The Academy of Medicine Singapore Clinical Practice Guideline (AMS-CPG) on the Management of Lipids was developed at the same time as the Ministry of Health's Agency for Care Effectiveness (MOH-ACE) Clinical Guidance (ACG) for Lipid Management, and both worked to align specifically on the overarching flowchart for lipid management.

The ACE Clinical Guidance "Lipid Management: Focus on Cardiovascular Risk"[1] is aimed primarily at primary and generalist care. The AMS-CPG further delves into the practice needs of specialists who are involved in the management of lipid disorders. The Clinical Practice Guideline's coverage extends to diagnosis, role of coronary calcium scoring if statin decision is uncertain, and management in specific populations such as pregnant women, elderly, and patients with chronic liver disease. Together, these 2 guidelines will make preventive care an important pillar of Singapore's healthcare.

Dr Michael Lim Chun Leng

Chairman, Chapter of Cardiologists, College of Physicians,

Academy of Medicine, Singapore

CONTENTS

List of Tables

List of Figures

List of Abbreviations

AAA	Abdominal aortic aneurysm
ABI	Ankle-brachial index
ACR	Albumin creatinine ratio
ACS	Acute coronary syndrome
AIDS	Acquired immunodeficiency syndrome
ASCVD	Atherosclerotic cardiovascular disease
ApoB	Apolipoprotein B
BP	Blood pressure
CABG	Coronary artery bypass graft surgery
CV	Cardiovascular
CVD	Cardiovascular disease
CKD	Chronic kidney disease
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
FH	Familial hypercholesterolemia
HDL-C	High density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HPT	Hypertension
IDL	Intermediate density lipoprotein
IHD	Ischaemic heart disease
LDL-C	Low density lipoprotein cholesterol
Lp(a)	Lipoprotein (a)
mAbs	Monoclonal antibodies
MI	Myocardial Infarction
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
RA	Rheumatoid arthritis
SFA	Saturated fatty acid
SG-FRS	Singapore modified Framingham risk score
SLE	Systemic Lupus Erythematous
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischemic attack
VLDL-C	Very low density lipoprotein cholesterol

1. INTRODUCTION

1.1 Background

Cardiovascular (CV) disease is a major cause of morbidity and mortality worldwide.[2-4] Clinical atherosclerotic cardiovascular disease (ASCVD) is the largest component of cardiovascular disease and by convention includes acute coronary syndrome (ACS), previous myocardial infarction (MI), coronary revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD).

Hyperlipidaemia is strongly associated with atherosclerotic cardiovascular disease (ASCVD). There is strong evidence that cardiovascular disease (CVD) can be prevented by aggressive treatment and lifestyle modifications to lower LDL cholesterol. Indeed, statin therapy has been conclusively shown to reduce the risk of cardiovascular events. There are now numerous international guidelines which recommend lipid management based on estimations of ASCVD risk. [5,6] Despite this, there remain misunderstandings among the general public about alleged side effects of statin therapy that are important to address.

The local MOH guidelines for hyperlipidaemia management were published in 2016[7] and these guidelines were based on the best evidence available at the time , which included the ACC/AHA guidelines published in 2013. Since then, there have been major revisions to the lipid treatment targets in international guidelines based on new evidence and the treatment targets for LDL-C have been tightened to better treat and prevent CV disease.

The advent of new classes of cholesterol lowering therapy beyond statins has led to a better understanding of the impact of low cholesterol levels. Trials involving the use of anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs) have resulted in very low post-treatment LDL-C levels of 30 mg/dl or less. These trials imply that the lower the achieved LDL-C values, the lower the risk of future CV events, with no obvious lower limit so far for LDL-C values, and hence no 'J'-curve effect detected yet. However, it should be pointed out that these PCSK9 trials were performed in patients who had acute coronary syndromes (ACS) and so were at very high risk for coronary events, and entry criteria for these trials was an LDL-C of > 1.8 mmol/L.

In contrast to LDL-C lowering, recent studies have indicated that the currently available therapies for elevation of high-density lipoprotein cholesterol (HDL-C) are not correlated with a reduction in cardiovascular events.

Current evidence confirms that the accumulation of LDL-C and other cholesterol-rich apolipoprotein (Apo) B containing particles within the arterial wall causes atherogenesis. Hence, the role of LDL-C in atherogenesis is not a mere hypothesis or association but a direct causative factor. [8] Data from meta-analyses support the view that greater absolute LDL-C reductions are associated with greater reductions in cardiovascular risk.[9-12] Hence, the lowering of LDL-C is central to the prevention of cardiovascular events.

There is currently no obvious lower limit of LDL-C below which there is no proven benefit or demonstrable harm. However, one consequence of more aggressive statin therapy is a marginally higher risk of diabetes, and risk of potential harm has to be balanced against the benefits. For very high-risk patients, the benefits of prevention markedly outweigh the risks.

Shared decision-making process with the patients is one of the cornerstones in lipid management and this process should take into consideration the risk profile, the options for lifestyle measures, and should be adapted to consider local ethnic and cultural practices and preferences.

For this clinical practice guideline, primary prevention refers to the prevention of cardiovascular disease in individuals without established ASCVD, and secondary prevention refers to the prevention of progression of disease in those with documented ASCVD.

This document also summarizes the latest literature on hyperlipidaemia treatment targets which can serve as a reference document in the local context.

1.2 Writing Process

The committee reviewed high quality research papers spanning a period from January 1990 to October 2022, including studies on hyperlipidaemia, management of lipids, coronary artery disease, primary and secondary cardiovascular prevention and newer therapeutic approaches such as the use of inhibitors of PCSK9 receptor or production. The references quoted are not exhaustive but contain important high-quality trials which support the key conclusions in this guideline.

The writing committee comprised of representatives from the Academy of Medicine, Singapore Cardiac Society, Singapore Heart Foundation, physicians in public sector and physicians in private practice. Members include cardiologists, endocrinologists, and primary care doctors. All writing committee members had to declare any potential conflict of interest and did not have any commercial relationship with any pharmaceutical company which may potentially lead to any biases in the report. The committee worked in parallel with the Ministry of Health Agency for Care Effectiveness Expert Committee on hyperlipidemia to ensure that there was alignment of the Flow Chart for Management of Hyperlipidaemia in Figure 1 from both committees. The document was also circulated to the various specialties in the Academy of Medicine and the final document took into account feedback provided.

1.3 Aim of Clinical Practice Guideline

The aim of this clinical practice guideline is to provide healthcare practitioners with a set of recommendations for management of lipids, including setting targets for patients with or without ASCVD, so as to reduce the risk of potential cardiovascular events.

1.4 Strength of Evidence and Recommendations

The writing committee adopted a system of classifying the strength of recommendations and level of evidence which is consistent with what is commonly used in international cardiology guidelines. Refer to Tables 1 and 2.

Table 1: Strength of Recommendations

Classification of Strength of Recommendations	Definition	Practice Implication
Class I	Current evidence supports that the application of the treatment is beneficial for health	Recommended
Class II	There is no consensus evidence or professional agreement among the medical experts that the treatment is beneficial for health. This is further sub-divided into Class IIa and Class IIb	
• Class II A	Class IIa: Definition Most of the evidence or medical expert opinion is in favour of the use of the treatment	Reasonable and should be considered
• Class II b	Class IIb: Definition There is less evidence or medical expert opinion is in favour of the use of the treatment and its usefulness is unclear	May be considered
Class III	Most of the evidence or medical expert opinion is not in favour of the use of the treatment and it should not be given	Not recommended

Table 2: Quality of Evidence

Classification of Quality of Evidence	Definition
Level A	High quality of evidence including high quality randomised controlled trials (RCTs) or meta-analyses of high quality RCTs
Level B	Moderate quality evidence with data from at least a single RCT or large non-randomized studies
Level C	Consensus of opinion of the experts where there are no RCTs or large randomised studies

2. DIAGNOSIS OF HYPERLIPIDEMIA

2.1 Lipid Fractions

The major fractions of total cholesterol (TC) are distributed among 3 lipoprotein classes, including very low density lipoprotein (VLDL-C), LDL-C, and HDL-C. There are smaller amounts of cholesterol in 2 other minor fractions, namely intermediate density lipoprotein (IDL) and lipoprotein (a) {Lp(a)}.

The atherogenic fraction of the total cholesterol contains a single ApoB molecule and includes VLDL-C, LDL-C and triglycerides (TG) rich remnant particles. Measurement of ApoB allows measurement of the atherogenic particles and fasting samples are not necessary. In most situations, ApoB level is well correlated with LDL-C and non-HDL levels.[13-15]

However, in those with diabetes mellitus, high TG, obesity or low post-treatment LDL-C level, the calculated or directly measured LDL-C level may underestimate the total concentration of cholesterol carried by LDL-C.

2.2 Routine Measurement of Lipids

The most common way of measuring hyperlipidemia is not by measuring lipoprotein levels but by measuring lipid levels, including TC, HDL-C and TG. While direct measurement of plasma LDL-C can be performed, most local laboratories calculate the LDL-C level using the Friedewald formula:

LDL-C (mmol/L) = TC (mmol/L) – HDL-C (mmol)- (TG mmol/L)/2.2)

Or

LDL-C (mg/dl) = TC (mg/dl) – HDL-C (mg/dl) – (TG in mg/dl)/5

Should the TG levels exceed 4.5 mmol/L or 400 mg/dL, this formula is inapplicable.

Given the current evidence that LDL-C has a directive causative role in atherogenesis, many guidelines have focused mainly on the assessment and management of LDL-C. In screening for hyperlipidemia, TC, HDL-C and TG are measured and LDL-C can be calculated or directly measured. Given the importance of LDL-C reduction to the prevention of ASCVD and the concept of "the lower the LDL-C, the better", some guidelines recommend the routine measurement of traditional cardiovascular risk factors commencing in young adults and subsequently at least on the average of once every 5 years.[2,3,6,16-18]

The regular assessment of cardiovascular risk factors of least an average of once in 5 years will guide physician- patient discussions on risk factor assessment and the intensity of risk factor management. The Singapore Ministry of Health clinical practice guidelines on lipids in 2016 and the current committee recommends that for individuals with screening results within the LDL-C target levels and have low TG levels, screening should be repeated at 3 yearly intervals unless they are in the very high or high risk ASCVD group, in which case screening should be repeated annually. Locally, there are some recommendations for screening for other CV risk factors in asymptomatic persons. [19]

If TG levels exceed 4.5 mmol/L or 400 mg/dL, Friedewald formula cannot be used for LDL-C calculation

Screening recommendations for other CV risk factors by Health Promotion Board[19]

Medical condition	Age group to screen	Screening test	Frequency of screening
Obesity	Aged 18 years and above	Body mass index (BMI). Waist circumference.	Once a year
Hypertension	Aged 18 years and above	Blood pressure measurement	Once every two years or more frequently as advised by your doctor
Diabetes mellitus	Age 18 – 39 years only for high-risk individuals identified via the Diabetes Risk Assessment (DRA)* Aged 40 years and above	Fasting blood glucose (FBG)/ Glycated haemoglobin (HbA1c)/ Confirmatory test – Oral Glucose Tolerance Test (OGTT)	Once every three years or more frequently as advised by your doctor
Hyperlipidemia	Aged 40 years and above	Lipid panel	Once every three years or more frequently as advised by your doctor

* Diabetes risk assessment (DRA): To determine the risk for Type II diabetes mellitus, individuals aged 18-39 years old will need to complete an assessment known as the Diabetes Risk Assessment (DRA) available at HealthHub (https://www.healthhub.sg/programmes/screen_for_life/sfl-faqs). Should the individual be assessed to be at higher risk, he/she will be required to log in via Singpass in order to receive the e-screening invitation, and he/she will be eligible for the cardiovascular risk screening subsidies under SFL. It is recommended that to repeat the DRA once every two years, or earlier if there are changes to any of the risk factors such as: weight, high blood pressure, diagnosis of gestational diabetes during pregnancy (for females), diagnosis of Type 2 diabetes in your immediate family.

2.3 Fasting versus non-fasting Lipid Testing

In the past, the emphasis was on obtaining blood testing for lipids after 10 to 12 hours of fasting. However recent studies have shown that the difference between fasting and non-fasting samples is not clinically significant in the large majority of patients. Hence there is a shift towards non-fasting samples which may be more convenient to the general public. [20]

Studies show that non-fasting samples have a higher TG level of 0.3 mmol/L (27 mg/dL) which is of no clinical significance for most patients.[21-24] For patients on a routine diet, there is little change in the LDL-C over time.[25] Currently, some guidelines recommend non-fasting lipid samples.[21,23,24]

Hence, non-fasting lipid samples can be used for general risk assessment, and baseline LDL-C assessment prior to the commencement of lipid lowering therapy in primary and secondary prevention. The main exception to this is for individuals with severe hypertriglyceridemia as the TG level will be significantly higher in a non-fasting state and affect LDL-C assessment. The lipid sample

should be a fasting sample for these individuals. Refer to **Table 3** for recommendations for lipid measurement.

2.4 Lipid Assessment in Special Circumstances

Routine ApoB assessment is not required as there is good correlation of ApoB levels with non-HDL-C and LDL-C levels in most situations. However, in those with hypertriglyceridemia, diabetes mellitus, obesity or post-treatment achieved low LDL-C level, the assessed LDL-C level (measured or calculated) may not reflect the total amount of atherogenic ApoB and thereby may underestimate the cardiovascular risk. As such, in about 20% of patients, there is a discordance between LDL-C level and the ApoB level. [26]

As the assessment of ApoB reflects the total amount of atherogenic cholesterol particles at all times, the measurement of ApoB may be considered for assessment of the effects of lipid lowering therapy in high-risk cohorts. The presence of an elevated lipoprotein (a) or Lp(a) level is associated with a higher ASCVD risk. A Lp(a) level of < 30 mg/dl is considered as normal, and a range of 30 mg/dl to < 50 mg/dl is considered as borderline increase in risk. An elevated Lp(a) level of ≥50 mg/dL or ≥125 nmol/L may be considered as enhancing the risk profile and can be used to adjust risk classification. [27-31]

For those with an extremely elevated level of Lp(a) ≥ 180 mg/dL (≥ 430 nmol/L), the lifetime risk of ASCVD is about similar to that of heterozygous familial hyperlipidemia. Some current guidelines recommend the measurement of Lp(a) at least once to identify those with highly elevated Lp(a) levels or in those with family history of premature cardiovascular disease. Refer to **Table 3** for lipid assessment recommendations. [5,6]

Table 3: Recommendations for Lipid Measurement

Recommendations for lipid measurement	Strength of Recommendation	Quality of Evidence
Assessment of a lipid profile should include TC, LDL-C (measured or calculated), HDL-C and TG.[2,3,6,16,18,32]	I	C
Routine lipid screening can be performed in young adults (aged 18 years or more) at least once every 5 years.[2,3,6,7,16-18,32]	IIa	B
Cardiovascular risk factor assessment, including, lipid screening should be performed in adults aged 40 years or more. [2,16,33]	I	B
For individuals with screening results within the LDL cholesterol target levels and have low TG levels, screening should be repeated at 3 yearly intervals unless they are in the very high or high risk ASCVD group, in which case screening should be repeated annually.[7]	IIa	C
For patients with acute febrile illness such as an infection, lipid assessment may be deferred for at least 2 weeks until complete recovery from the acute illness.[7]	IIb	C

Non-fasting lipid samples can be used for general risk assessment, and assessment of baseline lipid profile prior to the commencement of lipid lowering therapy in primary prevention and secondary prevention.[21-24]	I	B
ApoB measurement may be considered in those with hypertriglyceridaemia, diabetes mellitus , obesity and post-treatment achieved low LDL-C.[26]	I	C
Lp(a) may be considered at least once to identify those with highly elevated Lp(a) and especially in those with a family history of premature cardiovascular disease.[5,6]	IIb	C

Key Summary points: Lipid measurement
Lipid screening should be performed in adults aged 40 years or more
Non-fasting lipid samples are sufficient for general risk assessment and prior to the commencement of lipid lowering therapy
If the initial screening LDL levels are normal, screening to be repeated annually in very high/high risk ASCVD group, and every 3 years for other risk categories

3. Cardiovascular Risk Assessment [5,6,34]

3.1 Assessment of risk status

The purpose of risk assessment is to assess the likelihood of the development of ASCVD over a period of time. Determining the level of risk will help the physician adjust the intensity of the risk reduction measures according to the future risk of developing ASCVD, a key recommendation of all lipid guidelines. The higher the risk level, the greater the absolute benefit to the patient from lowering LDL-C, and the more this will outweigh any potential risks from long term therapy.

3.2 Risk Groups

The first step towards lipid management is to tailor intensity of treatment to the risk of developing CV events in the individual, and the specific conditions that they may have which influence risk. While risk is a continuum and risk categories are arbitrary, nevertheless, the categorization of individuals into different risk groups provide clinicians with a practical decision-making process on the intensity of the therapy for the individual patient. Broadly speaking, individuals can be assigned into a range of ASCVD risk groups (Table 4).

The Flow Chart for Management of Hyperlipidaemia in Figure 1 is presented in both the MOH ACG and CPG on management of lipids. The main difference between both charts is that the CPG chart has incorporated Coronary Calcium Score (CAC) into the flow chart. Acknowledging that many specialists encounter the application of this test, more details on the selective utilisation of the CAC are available in **section 3.5** and **Table 6.2.** The flow chart (Figure 1) articulates the approach in which the intensity

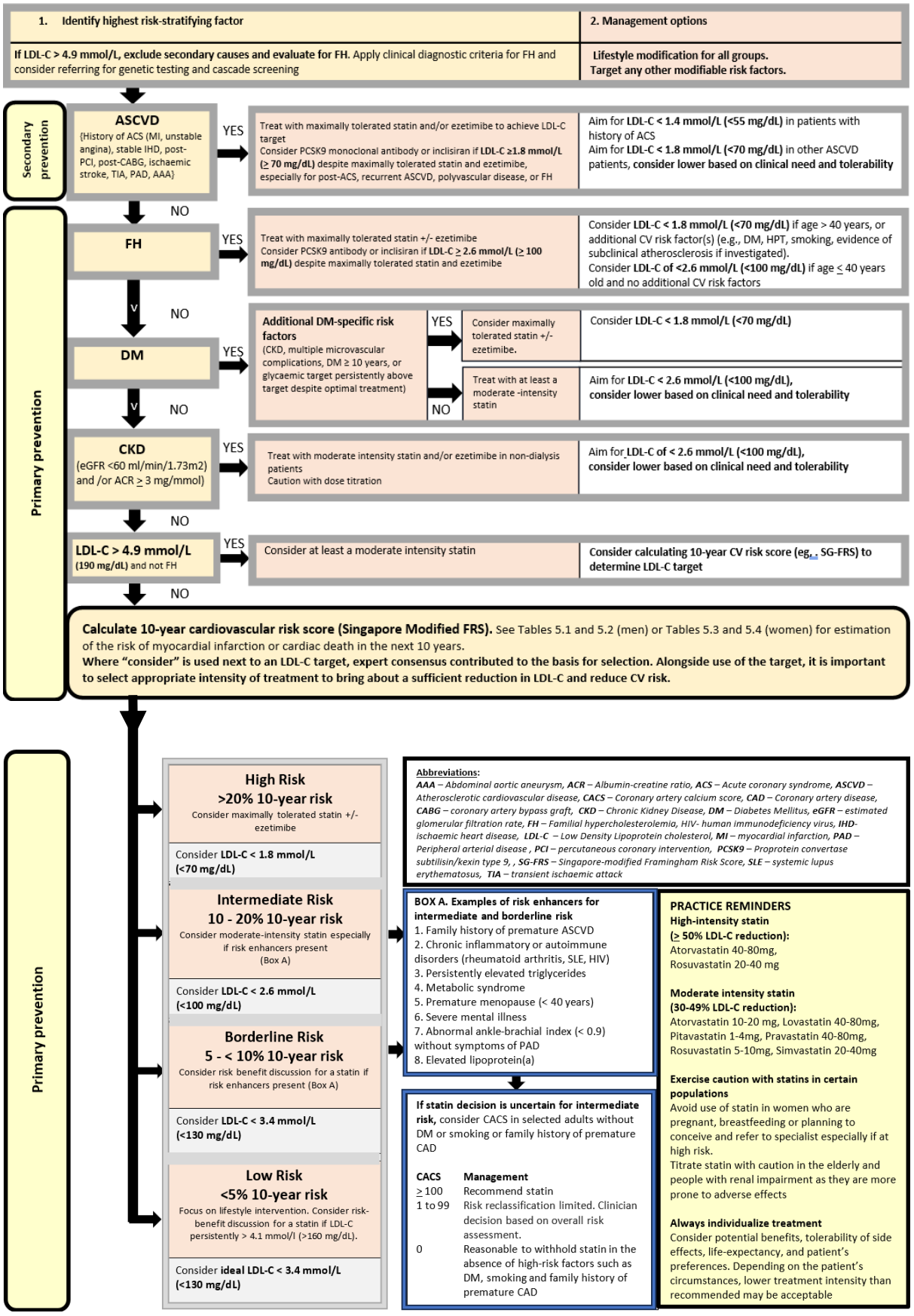
of treatment and the target LDL-C is based on their overall risk profiles, as well as specific conditions such as diabetes, familial hypercholesterolemia and CKD.

Table 4: ASCVD Risk Groups

Patient Groups by highest risk-stratifying factor	
Cardiovascular risk by medical condition	
Very high risk (secondary prevention)	ASCVD
Very high risk to high risk (primary prevention)	FH +/- additional risk factors
	DM +/- additional risk factors
	CKD
Otherwise healthy patients without the above conditions*: CV risk by 10-year risk scoring	
High risk	SG-FRS>20%
Intermediate risk	SG-FRS 10-20%
Borderline risk	SG-FRS 5-<10%
Low risk	SG-FRS<5%
*For patients with LDL-C>4.9 mmol/L but not FH, consider calculating 10-year CV risk to determine risk level	

Key Summary points: Cardiovascular risk assessment
Patients are stratified into different risk groups based on established ASCVD or the SG-FRS-2023 risk scoring as: *Very high risk, high risk, intermediate risk, borderline risk, low risk*
For primary prevention, in patients with intermediate or borderline risk, use of additional risk enhancers can be helpful in guiding physicians make decisions on cholesterol lowering therapy

Figure 1: Flow Chart for Management of Hyperlipidaemia



"Polyvascular" in the context of Figure 1 refers to atherosclerosis within 2 or more arterial beds

3.3 Approach to Cardiovascular Risk Assessment

All current guidelines recommend the assessment of total cardiovascular risk using risk scoring for primary prevention in apparently healthy individuals. Apparently healthy people are those without established ASCVD, DM or severe comorbidities.

3.3.1 Singapore Modified Framingham Risk Score (SG-FRS)

The Framingham risk score has been adapted to Singapore's cardiovascular epidemiology as part of a collaboration between investigators at the Singapore Ministry of Health, Singapore General Hospital, National University of Singapore and Prof Ralph B D'Agostino from the Framingham Heart Study, USA. This Singapore modified Framingham risk score (SG-FRS) provides an essential estimate of CVD risk, being adapted for Singaporeans of different ethnicity. However, it was developed based on data from more than a decade ago. Thus it is fortunate that a recalibration of the SG-FRS has been conducted as a collaboration between National University of Singapore, Saw Swee Hock School of Public Health, and the Ministry of Health Singapore.[35] The 2023 recalibrated SG-FRS score reflects the improved 10-year survival from coronary events across all sex and ethnic groups in more recent years, based on the Multi-Ethnic Cohort 1 dataset. This practice guideline provides the latest updated 2023 SG-FRS. Refer to flow chart in **Figure 1** for the cardiovascular risk assessment algorithm. The flow chart is a practical guide to CV risk stratification and management for patient groups with ASCVD (secondary prevention) and without ASCVD (primary prevention). Details can be found under each recommendation in the CPG. The sequence is ordered from highest to lowest risk categories. For patients with multiple comorbidities, refer to the comorbidity that confers the highest risk to guide management (e.g., for a patient with ASCVD and diabetes, refer to the box for ASCVD). In the absence of ASCVD, DM, CKD, or FH, a 10-year risk score can be calculated to classify patient as high, intermediate, borderline, or low risk.

Step 1

For individuals in the very high risk or high-risk groups, including those with documented ASCVD, diabetes mellitus, chronic kidney disease or uncontrolled individual risk factors, the 10-year CAD risk score assessment is not required as all those in these categories have specific clinical management needs. Individuals in the very high risk and high-risk groups will largely be patients with established coronary artery disease or conditions such as diabetes or familial hypercholesterolemia. For the family physician community, many patients will fall into the low, borderline or intermediate risk groups where management of lipids will follow primary prevention targets.

Step 2

For all other individuals who do not fall into the very high risk or high-risk groups, 10-year CAD risk should be estimated by the available CAD risk scoring systems.

The SG-FRS 10-year CAD risk score provides scoring for the different ethnic subsets – Chinese, Malay and Indian males and females in Singapore. Ethnic minorities were excluded in this risk scoring, as there was insufficient data. These risk scores were derived from the Framingham-based NCEP ATP III 10-Year Risk Score Tables. While the NCEP ATP III is no longer used in the American Heart

Association/American College of Cardiology guidelines on the treatment of blood cholesterol, the risk scores derived from them are presented in these guidelines because the SG-FRS risk functions have been re-calibrated based on our own local epidemiological data, with representation of the three ethnic groups in Singapore, unlike the risk scores currently available in other international guidelines which were derived from other populations. The updated 2023 SG-FRS 10-year CAD risk score which estimates the risk of having **myocardial infarction** or **cardiac death** in the next 10 years. Estimation of **10-Year CAD Risk Score** using the updated SG-FRS-2023 is shown in **Tables 5.1, 5.2 (for men) and Tables 5.3, 5.4 (for women)**.

Based on the updated SG-FRS-2023, the risk of the individual is classified as low, borderline, intermediate or high risk for CVD corresponding respectively to a < 5%, 5 - <10%, 10%–20% and > 20% risk of CV events over a ten-year period, including non-fatal myocardial infarction or cardiac death. Refer to **Figure 1 for** the cardiovascular risk assessment algorithm.

The use of 10-year risk was retained in these guidelines as opposed to lifetime risk because most randomized controlled trials addressed the short term impact of statin therapy, and the impact of long term treatment in individuals with low risk in the short term, but elevated lifetime risk, is unclear.[36]

It should be noted that ischaemic stroke is not a measured endpoint in the updated SG-FRS-2023 and hence, the SG-FRS does not measure total ASCVD.

Table 5.1: Updated SG-FRS-2023 - Risk score calculation (Men): Estimation of 10-year CAD risk

Allocate points based on person's age, total and HDL cholesterol levels, smoking status and systolic blood pressure. Check the total points against **table 5.2** for an estimate of that person's 10-year CAD risk.

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-59	13

Total Cholesterol mmol/L (mg/dL)	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<4.1 (160)	0	0	0	0	0
4.1-5.1 (160-199)	4	3	2	1	0
5.2-6.1 (200-239)	7	5	3	1	0
6.2-7.2 (240-279)	9	6	4	2	1
≥7.3 (280)	11	8	5	3	1

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

HDL Cholesterol mmol/L (mg/dL)	Points
≥1.6 (60)	-1
1.3-1.5 (50-59)	0
1.0-1.2 (40-49)	1
<1.0 (40)	2

Systolic BP* (mmHg)	Points	
	If untreated	If treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Table 5.2: Updated SG-FRS-2023 - Estimation of 10-Year Coronary Artery Disease Risk for Men

Total Points	10-Year Risk (%) from the recalibrated SG-FRS-2023		
	Chinese	Malay	Indian
-5	<1%	<1%	<1%
-4	<1%	<1%	<1%
-3	<1%	<1%	<1%
-2	<1%	<1%	<1%
-1	<1%	<1%	<1%
0	<1%	<1%	<1%
1	<1%	<1%	1%
2	<1%	1%	1%
3	<1%	1%	1%
4	1%	1%	1%
5	1%	1%	2%
6	1%	2%	2%
7	1%	2%	3%
8	2%	3%	4%
9	2%	3%	5%
10	3%	4%	6%
11	3%	5%	7%
12	4%	7%	10%
13	5%	9%	12%
14	7%	11%	15%
15	9%	14%	19%
16	11%	18%	24%
17	14%	22%	30%
18	18%	28%	37%
19	23%	34%	45%
20	28%	42%	54%

These risk scores are derived from the Framingham-based NCEP ATP III 10-Year Risk Score Tables which have been recalibrated using data from the Singapore Population Health Studies – Multi-ethnic Cohort Phase 1 (MEC1) and National Registry of Diseases Office. This recalibration (SG-FRS-2023) was carried out as part of a collaboration between investigators at the Singapore Ministry of Health and Saw Swee Hock School of Public Health, National University of Singapore and National University Health System.

Lim, C.G.Y. et al. (2023). Recalibrated Singapore-Modified Framingham Risk Score 2023 (SG-FRS-2023). blog.nus.edu.sg/sphs/files/2023/10/2023_Recalibrated_Singapore-Modified_Framingham_Risk_Score_SG-FRS-2023_report.pdf

Table 5.3: Updated SG-FRS-2023 - Risk score calculation (Women): Estimation of 10-year CAD risk

Allocate points based on person's age, total and HDL cholesterol levels, smoking status and systolic blood pressure. Check the total points against Table 5.4 for estimate of that person's 10-year CAD risk.

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-59	16

Total Cholesterol mmol/L (mg/dL)	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<4.1 (160)	0	0	0	0	0
4.1-5.1 (160-199)	4	3	2	1	1
5.2-6.1 (200-239)	8	6	4	2	1
6.2-7.2 (240-279)	11	8	5	3	2
≥7.3 (280)	13	10	7	4	2

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

HDL Cholesterol mmol/L (mg/dL)	Points
≥1.6 (60)	-1
1.3-1.5 (50-59)	0
1.0-1.2 (40-49)	1
<1.0 (40)	2

Systolic BP* (mmHg)	Points	
	If untreated	If treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
>160	4	6

Table 5.4: Updated SG-FRS-2023 - Estimation of 10-Year Coronary Artery Disease Risk for Women

Total Points	10-Year Risk (%) from the recalibrated SG-FRS-2023		
	Chinese	Malay	Indian
0	<1%	<1%	<1%
1	<1%	<1%	<1%
2	<1%	<1%	<1%
3	<1%	<1%	<1%
4	<1%	<1%	<1%
5	<1%	<1%	<1%
6	<1%	<1%	<1%
7	<1%	<1%	<1%
8	<1%	<1%	<1%
9	<1%	<1%	1%
10	<1%	1%	1%
11	<1%	1%	1%
12	<1%	1%	1%
13	1%	1%	2%
14	1%	1%	2%
15	1%	2%	3%
16	1%	2%	3%
17	2%	3%	4%
18	2%	4%	6%
19	3%	5%	7%
20	4%	7%	10%
21	5%	9%	12%
22	7%	11%	16%
23	8%	14%	20%
24	11%	18%	25%
25	14%	23%	31%
26	18%	29%	39%
27	22%	36%	47%

3.4 Limitations in risk estimation

There are certain practice points which clinicians need to be aware of when using risk assessment tools for local patients. All risk estimation tools are approximations and hence the risk profile obtained must be interpreted in the context of the patient and the clinician's assessment of the likelihood of CVD in the patient. The risk estimation tools use gender, smoking status, age, and TC as risk parameters, though other risk modifiers may have to be factored in when considering the risk profile.

There is recognition that the risk estimation tools may underestimate or overestimate individual risk. Hence, the 2018 AHA/ACC cholesterol guideline advocate that a clinician–patient risk discussion should be incorporated as part of decision making process instead of only relying on risk estimation tools, such as the Framingham risk score or pooled cohort equation to make decisions on commencement of lipid lowering medication. [6]

While there is no specific risk threshold that is universally applicable across different population cohorts in different countries, in principle, the intensity of treatment should increase with increasing CVD risk.

When assessing the risk of an individual, there is no lower threshold of total CVD risk that precludes management of risk factors. In primary prevention, the categorisation of an individual into a risk category does not automatically mandate the commencement of drug therapy.

The decision to commence drug therapy is a shared decision-making process taking into consideration patient's preference, other pre-existing medical conditions, and the risk profile. The risk discussion goes beyond the initial management and includes monitoring therapy and adherence to medication as cholesterol lowering therapy may require a lifelong commitment.

In all age groups, consideration of risk enhancers, lifetime CVD risk, treatment benefit, comorbidities, frailty, and patient preferences may further guide treatment decisions.

Where there is uncertainty as to whether to initiate statin therapy, the guideline offers a third step, which is the incorporation of risk enhancers as well as tests such as coronary artery calcium score (CACS) as part of the decision-making process. Refer to **Table 6.1** for recommendations on risk enhancers.

3.5 Risk enhancers

In addition to the risk factors which are used in the risk score estimation, the presence of other factors has to be considered which can lower or increase the risk.

I. **Risk reduction**
   - high HDL-C up to 2.3 mmol/L (90mg/dL) or [37],
   - family history of longevity (The term **longevity** describes the ability to live a long life beyond the average age at death)

II. **Risk elevation**: The following factors may be associated with risk elevation as mentioned in **table 6.1**

Table 6.1 : Primary Prevention: Recommendations for Risk Enhancers [18]

Risk Enhancing Factors
History and Examination
Family history of premature ASCVD (males, age <55 y; females, age <65 y)[38]
Metabolic syndrome (as defined by 3 out of the following factors - increased waist circumference , elevated triglycerides [>150 mg/dL, non fasting], elevated blood pressure, elevated glucose, and low HDL-C [<1.0 mmol/L or < 40 mg/dL in men; < 1.3 mmol/L or < 50 mg/dL in women])
Chronic inflammatory conditions, such as psoriasis, rheumatoid arthritis, lupus,[39,40] or HIV [41]
History of premature menopause (before age 40 y) [42-44]
Ankle brachial index (ABI) (<0.9)
Severe mental Illness[45,46]
Lipids/biomarkers associated with increased ASCVD risk if previously measured
Persistently elevated primary hypertriglyceridemia (≥175 mg/dL or ≥2.0 mmol/L , non-fasting) for at least 3 determinations
Elevated Lp(a) ≥50 mg/dL or ≥125 nmol/L
Imaging evidence of atherosclerosis.
Incidental imaging evidence of atherosclerotic plaque in the carotid or femoral arteries

The presence or absence of risk enhancers can be useful in guiding the physician on the decision to commence cholesterol lowering drug therapy, especially for patients in the intermediate risk category. Refer to **Table 6.1**. When the decision to commence cholesterol lowering drug therapy remains uncertain, the use of imaging modalities such as the coronary artery calcium (CAC) score in the intermediate risk and in selected individuals in the borderline risk categories may also be useful.

An individual's risk is increased in the presence of markers such as CAC score >100 Agatston units, abnormal ankle brachial index (ABI) <0.9 or >1.40, or the presence of atherosclerotic plaques. The use of ultrasound to measure the carotid or femoral plaque burden has been predictive of CV events and is comparable to CAC. [47-50] The use of carotid intima media thickness is fraught with limitations such as consistent reproducibility and operator variation. It is inferior to CAC score and carotid plaque measurement.[51-53] Currently, among the markers being considered, CAC score is considered the best biomarker for risk discrimination and reclassification of risk .[51,54] CAC score provides an estimate of the atherosclerotic burden and is strongly associated with CV events.[55]

There is a risk calculator from the Multi-Ethnic Study of Atherosclerosis (MESA) study which is available as a free app or online. This calculator includes a Chinese population variable for risk calculation and can further refine risk for patients into low, intermediate and high-risk categories.[56,57] The MESA score was developed in a different population and does not include all ethnic groups in Singapore. Hence though it may be useful to indicate the impact of calcium scores on the ten-year risk of individuals, these limitations must be considered when the MESA score is used.

In general, there is no need to use a CAC score when the decision to initiate statin therapy is clear. However, where there is uncertainty about initiation of statin therapy in asymptomatic individuals at intermediate risk (primary prevention), the CAC score may be useful in selected individuals as a risk modifier in making a decision on commencing or withholding statin therapy. The CAC score has no

value in patients with established ASCVD such as patients with prior MI, stent or bypass surgery. [6,51,52,54,56,58-60]

Those with CAC scores of zero have low 10-year event rates and the value of statin therapy is limited, provided they do not have other high risk factors such as diabetes, family history of premature CAD or cigarette smoking.[61,62]

Hence, if the CAC score is zero, it is reasonable to withhold statin therapy and reassess in 5 years, in the absence of high-risk factors such as diabetes mellitus, family history of premature CAD, and cigarette smoking. A MESA risk score can be used to integrate the CAC result with other risk factors to estimate the overall 10-year risk in these individuals, into low, intermediate and high-risk categories.[6,63-66]

If the CAC score is 1 to 99, the incremental value for risk reclassification is modest, and there is variation in international recommendations on how this should influence the decision to start a statin. In general, the decision to start a statin should not be based on a single test or risk factor, but on the individual's global ten-year risk.

In asymptomatic individuals at intermediate risk (or selected individuals at borderline risk), where the decision to start a statin is uncertain, if the CAC score is 100 or more, the commencement of statin therapy can be considered. [6,59,61,67] **Refer to Table 6.2.**

Table 6.2: Primary Prevention: Coronary Artery Calcium score

Recommendation for cardiovascular imaging for risk assessment	Strength of Recommendation	Quality of Evidence
In the CV risk assessment of asymptomatic individuals at intermediate risk where the decision about the use of statin is uncertain, it is reasonable to consider the use of CAC score as a risk modifier in making a decision on commencing or withholding statin therapy.[6,51,52,54,56,58-60]	**IIb**	**B**
In the CV risk assessment of asymptomatic individuals at intermediate risk where the CAC score is measured for the purpose of making a decision on the use of statin, ▪ If the CAC score is zero, it is reasonable to withhold statin therapy and reassess in 5 years in the absence of high risk factors such as diabetes mellitus, family history of premature CAD, and cigarette smoking.[6,63-66] ▪ If CAC score is 1 to 99, the incremental value for risk reclassification is modest, and there is variation in international recommendations on how this should influence the decision to start a statin. In general, the decision to start a statin should not be based on a single test or risk factor, but on the individual's global ten-year risk.[6,67] ▪ If CAC score is 100 or higher, it is reasonable to commence statin therapy.[6,59,61,67]	**IIa**	**B**

The routine collection of other potential modifiers such as genetic risk scores, circulating or urinary biomarkers or vascular tests or imaging methods (other than CAC scoring or carotid ultrasound for plaque determination) is not recommended.[34]	**III**	**B**

4. LIPID THERAPEUTIC TARGETS

4.1 LDL Cholesterol Therapeutic Targets

Lifestyle modifications are part of the management process, and these have to be discussed prior to initiation of therapy. Therapeutic goals of treatment for hyperlipidaemia can be achieved by statins with or without addition of ezetimibe. In the very high risk or high risk groups, the use of anti-PCSK9 therapy may be required to achieve desired therapeutic targets.

In deciding on the therapeutic LDL-C targets, a few key facts are taken into consideration:

1) LDL-C is a direct causative factor for ASCVD,
2) Data from more recent cholesterol lowering studies have demonstrated that reduction of LDL-C beyond previous EAS/ESC Guidelines was associated with fewer ASCVD events, [68-70]and
3) Current clinical data supports the principle of the lower the LDL-C, the lower the risk of ASCVD[9-12]

Consistent with these general guiding principles, for the very high-risk group and the high-risk group, in line with current evidence, the CPG and the latest ACG on lipid management have recommended lower LDL-C targets for the very high risk and high-risk groups as compared to the 2016 Ministry of Health Clinical Practice Guidelines: Lipids.

Based on data from anti-PCSK-9 therapy trials involving patients who have sustained ACS and had entry criteria of LDL-C > 1.8 mmol/L, benefits have correlated with the substantially reduced LDL-C levels. For this very high-risk group with a history of ACS, an LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended. For other patients in the very high-risk cohort with ASCVD, a target LDL-C of < 1.8 mmol/l is recommended, while recognizing that lower is generally better. Refer to the ASCVD Risk Groups in **Table 4** and the Flow Chart for Management of Hyperlipidaemia in **Figure 1**.

As the risk profile decreases, the absolute benefit is lower, and the therapeutic LDL-C targets are adjusted correspondingly. For those in the high-risk group, it is recommended that the LDL target be considered at <1.8 mmol/L (<70 mg/dL). For those patients who are in the intermediate cardiovascular risk group, a LDL-C goal <2.6 mmol/L (<100 mg/dL) should be considered.[68]

For those individuals at low or borderline risk, an LDL-C < 3.4 mmol/L (< 130 mg/dl) is an ideal goal and can be considered. However, for the low-risk group, lifestyle modification is the mainstay of management and statins should only be considered if the LDL-C is persistently > 4.1 mmol/L (>160 mg/dl) despite lifestyle modifications, and if the physician assesses that the benefits of more intensive lipid lowering therapy far outweighs the risks. [10,71-73] Familial hypercholesterolemia should be

considered when the LDL-C is > 4.9 mmol/L. Refer to Management of Hyperlipidaemia Flow Chart for Clinician Reference in **Figure 1**, and the recommendations for LDL-C targets in **Tables 7 to 9**.

Table 7: Recommendations for LDL-C Therapeutic Targets – Prevention in Very High Risk Group

LDL-C Therapeutic Targets: Very High-Risk Group	Strength of Evidence	Quality of Evidence
In secondary prevention (patients with established ASCVD) for patients at very-high risk, a LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended. For patients with a history of acute coronary syndrome, aim for a LDL-C goal of <1.4 mmol/L (<55 mg/dL).[9,68,74-76]	I	A
For FH patients with ASCVD or additional CV risk factors (such as DM, smoking, HPT, > 40 years) , treatment to achieve a LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended. If the goal cannot be achieved, a drug combination is recommended.[75-78]	I	C
Lipid levels should be re-evaluated 4 to 6 weeks after ACS to determine whether a LDL-C goal of <1.4 mmol/L (<55 mg/dL) has been achieved. Safety issues need to be assessed at this time and statin treatment doses adapted accordingly.[75,76,79,80]	IIa	C

Table 8: Recommendations for LDL-C Therapeutic Targets - Primary Prevention in High Risk and Intermediate Risk Groups

LDL-C Therapeutic Targets: High Risk and Intermediate Risk Group	Strength of Evidence	Quality of Evidence
In patients at high risk, a LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.[9,68]	I	A
For FH patients with no known ASCVD or other major risk factors, a LDL-C goal of <2.6 mmol/L (<100 mg/dL) is recommended. [75-78]	I	C
In patients with DM at high risk (CKD, multiple microvascular complications, DM duration ≥ 10 years, or glycaemic level persistently above the target despite optimal treatment), a LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.[86]	I	A
In individuals at intermediate risk, a LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.[68]	IIa	A

Table 9: Recommendations for LDL-C Therapeutic Targets - Primary Prevention in Borderline Risk and Low Risk Groups

LDL-C Therapeutic Targets: Borderline Risk and Low Risk Groups	Strength of Evidence	Quality of Evidence
In individuals at borderline risk, a LDL-C goal < 3.4 mmol/L (< 130 mg/dl) can be considered. If risk enhancers are present, a risk-benefit discussion for statin can be considered. [10,71-73]	IIb	A
In individuals at low risk, focus on lifestyle intervention, and a risk-benefit discussion for statin can be considered if the LDL-C is persistently > 4.1 mmol/L (160 mg/dl). Ideally, an LDL-C of < 3.4 mmol/L (130 mg/dl) can be considered. [10,71-73]	IIb	A

Key Summary points: LDL-C therapeutic targets
Cardiovascular risk by medical condition
In very high-risk group with established ASCVD, LDL goal <1.8 mmol/L (<70 mg/dL) is recommended. Consider LDL-C goal of <1.4 mmol/L (<55 mg/dL) in patients with acute coronary syndrome
For FH patients with ASCVD or additional CV risk factors (such as DM, smoking, HPT, > 40 years) , treatment to achieve a LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.
For FH patients with no known ASCVD or other major risk factors, a LDL-C goal of <2.6 mmol/L (<100 mg/dL) is recommended.
In patients with DM at high risk (CKD, multiple microvascular complications, DM duration ≥ 10 years, or glycaemic level persistently above the target despite optimal treatment), a LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.
Otherwise healthy patients without the above conditions: CV risk by 10-year risk scoring
In high-risk patients, an LDL goal <1.8 mmol/L (<70 mg/dL) is recommended.
In individuals at intermediate risk, consider an LDL-C goal of <2.6 mmol/L (<100 mg/dL).
In individuals at borderline risk, a LDL-C goal < 3.4 mmol/L (< 130 mg/dl) can be considered.
Re-evaluate LDL levels 4-6 weeks after therapy initiation to determine if target is achieved and address other safety issues during follow-up.

4.2 Other Lipid Therapeutic Targets

Although there is currently no strong clinical data to support specific therapeutic targets for TG, there is data to show that there is increased ASCVD risk when fasting TGs are >1.7 mmol/L (>150 mg/dL). [87]

Current data shows that lowering TGs in at risk patients is associated with a reduction in cardiovascular risk. A meta-analysis of 10 trials using various therapeutic agents to lower TG demonstrated a 12% reduction in cardiovascular outcomes. [88]

For very high risk and high-risk patients whose TGs are >4.5 mmol/L (>400 mg/dL) after lifestyle measures, drug therapy may be considered.

In situations where the LDL-C may not adequately reflect the CV risk, ApoB can be used as a secondary target. ApoB targets in the very-high, high, and intermediate risk categories are <65 mg/dL, <80 mg/dL, and <100 mg/dL respectively.[89,90] See **Table 10**.

Table 10: Recommendations on Secondary Target: ApoB

ApoB Therapeutic Targets	Strength of Evidence	Quality of Evidence
In situations where the LDL-C may not adequately reflect the CV risk , ApoB can be used as a secondary target. ApoB targets in the very-high, high, and intermediate risk categories are <1.3 umol/L (<65 mg/dL), < 1.6 umol/L (<80 mg/dL), and <2.0 umol/L (<100 mg/dL) respectively.[89,90]	I	A

5. MANAGEMENT OF HYPERLIPIDEMIA

5.1 Lifestyle Modification

Appropriate lifestyle modification is an integral part of the management of hyperlipidaemia. Lifestyle interventions, including dietary choices, can reduce risk of cardiovascular disease directly or through its impact on risk factors such as blood pressure, glucose levels and lipid levels. Refer to **Table 11** for recommendations on lifestyle modification.[91-96]

5.1.1 Use of Tobacco

Use of tobacco in any form, including smoking and vaping, should stop. Smoking cessation has clear benefits on overall cardiovascular disease risk and on HDL cholesterol.[97-100]

5.1.2 Weight Management

Weight reduction reduces fasting TG and increases HDL cholesterol, with a small effect on lowering of TC and LDL cholesterol. For obese individuals, a weight reduction of 10 kg is associated with a reduction of LDL-C level of 0.2 mmol/L (8 mg/dL). Weight loss has an impact on risk factors such as hypertension and diabetes mellitus. Weight reduction improves insulin sensitivity and also decreases the level of TG.[101,102]

5.1.3 Exercise

Regular exercise is an important part of lifestyle management and should be performed unless there are any underlying contraindications. Regular physical exercise reduces TG levels over and above the effect of weight reduction.[103-105]

The "Singapore Physical Activity Guidelines" published by the Health Promotion Board and Sport Singapore, Revised Edition 2022, recommend that for substantial health benefits, adults should do at

least 150 minutes (2 hours and 30 minutes) to 300 minutes (5 hours) a week of moderate-intensity, or 75 minutes (1 hour and 15 minutes) to 150 minutes (2 hours and 30 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity, spread over 5 to 7 days in a week. In addition, adults should also do muscle-strengthening activities of moderate- or vigorous-intensity that target major muscle groups at least twice a week, as these activities provide additional health benefits. For adults with chronic conditions, the same recommendations and tips are still applicable but healthcare professionals should provide advice on a suitable exercise regime if individuals are unsure on how to begin.

5.1.4 Alcohol Consumption

A standard drink is 10g of alcohol which is the equivalent of 2/3 can of 220ml beer, one small 100ml glass of wine or 1 nip (30ml) of spirits. Earlier studies have reported a J-shaped distribution of outcomes with the lowest rates of heart attacks in those with low to moderate alcohol consumption (12.5 to 30 gm) and higher rates in those who did not drink or have high alcohol consumption. Hence, moderate alcohol consumption of $\leq$2 standard drinks for men and $\leq$1 standard drink for women has been considered as being acceptable for those who consume alcohol, if TG levels are not elevated.[106-108]

However, this perceived benefit has not been validated in any randomised controlled trial. [109,110] Furthermore, this J shape effect has not been seen in studies in Chinese and Indian cohorts. [111,112]
The 2022 World Heart Federation (WHF) released a policy brief in 2022, "The impact of alcohol consumption on cardiovascular health: myths and measures", which challenged the perception that low to moderate alcohol consumption is cardioprotective. The WHF brief stated that the regular consumption of alcohol raises blood pressure, increases the risk for cardiomyopathy, precipitates the onset of atrial fibrillation/flutter and elevates stroke risk. There is a linear association between regular alcohol consumption of at least 100gm/ week and an increased risk of stroke, heart failure, fatal hypertensive disease and fatal aortic aneurysm. Alcohol intake (> 60 gm) can have a major impact on TG levels, particularly in individuals with hypertriglyceridaemia.[109,113] In patients with severe hypertriglyceridaemia, consumption of alcohol is associated with an increased risk of pancreatitis.

Given the data, we recommend that individuals who do not currently drink should not start. As Chinese and Indians form a large segment of the local population and the studies on Chinese and Indian cohorts have not demonstrated a J-shape curve for outcomes, we do not recommend the consumption of alcohol for the purpose of obtaining purported cardioprotective effects.

5.1.5 Dietary Sugars

Regular consumption of "fruit sugar" fructose in amounts contributing >10% total daily energy needs will lead to TG elevation. There is correlation between quantity of fructose intake and level of TG elevation. Fructose intake between 15 to 20% of total energy intake can increase the TG by 30-40%. Not surprisingly, "table sugar" sucrose, is the commonest source of fructose. Hence, for those with elevated TG, intake of simple sugars (fructose or sucrose) should be limited to < 10 % of total dietary energy intake, or in severely elevated individuals, elimination of added sugars. [114-117]

5.1.6 Dietary Fats

There is correlation between consumption of saturated fatty acids (SFAs) with LDL-C levels. For each additional 1% energy intake from SFAs, there is an increase in 0.02-0.04 mmol/L or 0.8-1.6 mg/dL of LDL-C.[118] Dietary trans fatty acids also contribute to LDL-C elevation, but unlike SFAs which increase HDL-C levels , trans fat decrease the HDL-C.[119] Trans-fat intake should be limited to < 1% of total energy or < 2 grams per day.[120] Given the negative effects of SFAs and trans-fat, a diet rich in wholegrain foods, vegetables, fruit, legumes, nuts, fish and unsaturated oils and low in saturated and trans-fat, refined grains and cholesterol should be encouraged.[121]

Saturated fat should be replaced with mono and polyunsaturated fats to lower TC and LDL cholesterol (without lowering HDL cholesterol)[122,123] and lower risk of CAD.[96] For those with hyperlipidemia, saturated fat intake should be reduced to <7% of total caloric intake 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 these targets.[5]

The recommended cholesterol intake in the diet should be reduced to <300 mg/day.[124,125]

5.1.7 Dietary Fiber Intake

Foods such as barley and oats contain the fibre b-glucan which has been shown to lower LDL-C. Hence, the consumption of foods or supplements containing b-glucan is recommended for LDL-C lowering.[126] The quantity of each fibre type to be taken to achieve a meaningful 3 to 5% LDL-C reduction varies with the fibre type.[127] In general, dietary fibre intake should be 20 to 30 grams per day by increasing consumption of whole-grains, fruit and vegetables and reducing consumption of processed grains and sugar.[115,128]

Table 11: Recommendations on Lifestyle Modification

Lifestyle Modification	Strength of Evidence	Quality of Evidence
Tobacco use Use of tobacco in any form, including smoking and vaping, should stop.[7,97-100]	I	A
Weight Management If body mass index is above 23 kg/m2, weight reduction through diet modification and exercise is recommended.[7,101]	I	A
Exercise Persons with hyperlipidaemia should undertake 150 to 300 minutes per week (about 30 to 60 minutes per day) of moderate intensity aerobic activity spread out over 5 to 7 days per week.[7,103-105]	I	A
Alcohol consumption For good overall health, individuals who do not currently drink should not start.[7,109,110]	I	C
Dietary sugars	IIa	C

For patients with high TG levels, intake of simple sugars (fructose and sucrose) should be limited to <10% of total energy intake, or in severely elevated individuals, elimination of added sugars.[7,114-117]		
Dietary Fat 1. A diet rich in wholegrain foods, vegetables, fruit, legumes, nuts, fish and unsaturated oils and low in saturated and trans-fat, refined grains and cholesterol should be encouraged.[7,121] 2. Saturated fat should be replaced with mono and polyunsaturated fats to lower TC and LDL cholesterol (without lowering HDL cholesterol)[7,122] to lower risk of CAD.[96] 3. Trans fat intake should be limited to < 1% of total energy or < 2 grams per day.[7,120] 4. For those with hypercholesterolaemia, saturated fat intake should be reduced to <7% of total caloric intake 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 these targets.[5,7] 5. Cholesterol intake should be reduced to less than 300mg per day as this reduces serum LDL cholesterol levels.[7,124,125]	I I I I I	A A A C A
Dietary fibre intake Dietary fibre intake should be 20-30 grams per day by increasing consumption of whole-grains, fruit and vegetables and reducing consumption of processed grains and sugar.[7,115,127,128]	I	C

Key Summary points: Lifestyle modifications
Tobacco use in any form should be avoided
Moderate intensity aerobic activity of 150 to 300 minutes per week (about 30 to 60 minutes per day) or vigorous-intensity aerobic physical activity of 75 minutes (1 hour and 15 minutes) to 150 minutes (2 hours and 30 minutes) per week spread out over 5 to 7 days
Saturated fat should be <7% of total caloric intake
Polyunsaturated fat intake should be around 10% of total calories
Dietary fibre intake should be 20-30 grams per day by increasing consumption of whole-grains, fruit and vegetables

6. DRUG THERAPY

6.1 Statins

Statins differ in their pharmacologic characteristics. Most currently available statins are in their active forms except for simvastatin and lovastatin which are prodrugs. While evening administration is usually recommended, this has to be balanced with the likelihood of adherence and hence the timing has to be individualised to ensure the highest likelihood of compliance. Many statins undergo a first-pass effect in the liver with significant metabolism via the cytochrome P450 (CYP) isoenzymes, except for pravastatin, rosuvastatin, and pitavastatin. Drugs such as erythromycin, clarithromycin, azole

antifungal agents and cyclosporine that are also metabolised by the same enzyme pathway may elevate the serum level of these statins which undergo a first-pass effect (eg, simvastatin, atorvastatin, and lovastatin) when administered concomitantly and therefore may increase the risk of toxicity.

Current evidence supports the view that benefits derived from statin therapy are a class effect that is primarily related to the level of LDL-C reduction.

6.1.1 Statin Therapy

Statins are very effective in lowering both TC and LDL cholesterol. Multiple large trials and meta-analyses have shown that statins are beneficial for both secondary as well as primary prevention of CAD.[9,10,68,129-147]

The approximate equipotency of the different statins is as follows: 10 mg atorvastatin = 5 mg rosuvastatin = 20 mg simvastatin = 40 mg lovastatin / pravastatin = 80 mg fluvastatin.[148,149]

By definition, a high intensity statin therapy lowers LDL-C by 50% or more, and moderate intensity statin therapy lowers LDL-C by 30 to less than 50%. High intensity statin therapy in very high-risk group includes atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily. Moderate intensity statin therapy in high risk group includes 10 to 20 mg atorvastatin, 5 to 10 mg rosuvastatin, 20 mg to 40 mg simvastatin, 40 mg to 80 mg pravastatin, 40 mg lovastatin or 80 mg fluvastatin. Pitavastatin with dose range between 1 mg to 16 mg per day lowered LDL-C by 33.3% to 54.7%. For lowering LDL cholesterol, pitavastatin is 6 times stronger than atorvastatin, 1.7-times stronger than rosuvastatin, 77-times stronger than Fluvastatin.[150,151] See **Table 12** for average LDL-C reductions with different statins.

Table 12 : Expected average LDL-C reduction by total daily dosages for statins (adapted from ACC/AHA) [6] (Table reproduced from the ACE Clinical Guidance "Lipid Management: Focus on Cardiovascular Risk"[1] with permission from Agency for Care Effectiveness (ACE), Ministry of Health, Singapore. The classification was originally published by the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines)

Statin	Low-density dose (LDL-C reduction < 30%)	Moderate-intensity dose (LDL-C reduction 30-49%)	High-intensity dose (LDL-C reduction ≥ 50%)
Atorvastatin		**10-20 mg**	**40-80 mg**
Lovastatin	**20 mg**	**40-80 mg**	
Pitavastatin		**1-4 mg**	
Pravastatin	**10-20 mg**	**40-80 mg**	
Rosuvastatin		**5-10 mg**	**20-40 mg**
Simvastatin	**10 mg**	**20-40 mg**	*

ACC, American College of Cardiology; AHA, American Heart Association

*Simvastatin 80 mg is not recommended due to high risk of myopathy; use should be restricted to those who have been taking 80 mg long-term without evidence of myopathy

There is variation in the response to statins between individuals. Higher statin sensitivity may be present in Asian patients and hence, clinicians who are up-titrating the dose for therapy in the local population should monitor patients for side effects.[152] This is especially so when high dose statins such

as rosuvastatin at doses higher than 20 mg , are being considered.[153] Among the Chinese, a higher incidence of myopathy has been noted at lower statin doses (simvastatin 40mg daily) in studies such as Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS THRIVE).[154] These data do not preclude the use of statins at high doses in appropriately selected cases.

In addition to LDL-C lowering , statins can reduce TG levels by 10 to 20% from baseline values.[155] Statins have minimal effect on HDL-C and Lp(a).

In patients where statin therapy is recommended but daily statin therapy is not possible, considerable LDL-C -lowering can be achieved with alternative dosing with potent statins , such as every other day or twice a week with atorvastatin or rosuvastatin.[156]

Before commencing patients on statin therapy, go through the following checklist in **Table 13**.

Table 13: Checklist prior to Statin Therapy

Check for the following before commencement of statin therapy

- **Pregnancy, planning conception, or breastfeeding**
  - contraindicated
- **Hepatic impairment**
  - contraindicated in decompensated cirrhosis and acute liver failure
  - check baseline liver transaminases prior to initiation
- **Renal function**
  - dose adjustment
  - Predisposition to adverse effects
- **Concurrent treatment that may interact with statins**
  - Avoid drug-drug interaction
- **Risk factors for myopathy**
  - Dose adjustment for those at increased risk for myopathy such as elderly, thyroid disorders, excessive alcohol consumption, family history of myopathy to statins, renal or hepatic impairment
  - Higher risk of severe myopathy or rhabdomyolysis, although rare

6.1.2 Statin Side Effects

The incidence of side effects from statin therapy is low, consisting mainly of a rise in the liver enzymes and myopathy. There is a small risk of new onset type 2 diabetes mellitus (T2DM) with statin therapy but the absolute risk reduction in the risk of cardiovascular disease in high risk patients outweighs the possible adverse effects of a small increase in the incidence of diabetes.[157] Refer to **Table 14** for recommendations on statin side effects.

Despite the small risk of side effects, misperceptions by the public about the potential adverse side effects of statins are commonly encountered. In some cases, these are believed to be “nocebo effects” or “misattribution”, rather than a real side effect of therapy.[158-162]

6.1.2.1 Myopathy

High dosages of statins are more likely to result in myopathy and rhabdomyolysis. Although considerably rarer, rhabdomyolysis is a much more serious complication which can lead to renal

failure and death.[163,164] Due to risk of myopathy and rhabdomyolysis, high dosages of statins should be prescribed with caution, especially in elderly patients, in those with impaired renal function and when a statin is combined with a fibrate.[153,165-167] When using simvastatin, the highest dose should be 40 mg. However, in patients who have been taking 80 mg for more than 12 months without any evidence of myopathy or other side effects, it is acceptable to continue the dose.[153,165-167]

Combination of statins with gemfibrozil enhances the risk of myopathy, and hence it should not be prescribed together with statins. Use of other fibrates (fenofibrate, bezafibrate, or pemafibrate) in combination with statins is safe with no or minimal risk.[168,169]

6.1.2.2 Elevated Liver Enzymes

Mild elevation of liver enzymes, as measured by alanine aminotransferase, ALT, (also termed as serum glutamic pyruvic transferase, SGPT) occurs in 0.5 to 2.0% of patients on statin therapy, in particular those who are on high dose statins. This has not been shown to have any long term effects on liver function.[170-172] In patients with pre-existing elevation of transaminases due to steatosis or due to non-alcoholic fatty liver disease, statin therapy does not worsen liver disease.[161] A clinically significant elevation of ALT $\geq$ 3 x upper limit of normal range on 2 consecutive occasions is rarely ever seen.[173] Based on meta-analyses of RCTs, clinically relevant transaminase elevation with statin therapy is rare.[174,175]

Severe statin induced liver injury is very rare with an incidence of <2 per million patient years according to the US FDA database, and an incidence of around 1.2 per 100,000 as per Swedish adverse drug reactions advisory committee.[176,177] Hence, the risk of liver injury with statins is very rare. Mild elevations of transaminases in isolation in asymptomatic statin users is not clinically relevant.

6.1.2.3 Risk of New-Onset Diabetes Mellitus

Statin therapy has been shown to be associated with a small increase in the incidence of new onset of type 2 diabetes mellitus (T2DM). It has been proposed that statins due to their action on HMG CoA reductase can be associated with risk of DM by either a direct effect on pancreatic beta cell or by increased insulin resistance.[161] This risk of developing T2DM is higher in those on potent statins at high doses, in the elderly, and in those with features of metabolic syndrome. However, numerous randomized controlled trials have shown that the risk of developing DM is low.[157,178,179]

The risk of new onset DM is estimated at 1 new case per 1000 patients per year of statin exposure but statin therapy also has been estimated to prevent, for example, 5 new CV deaths per 1000 patients per year.[161] For low risk individuals, the lesser benefits of statins should be weighed against this low risk of new onset diabetes.

6.1.2.4 Neurocognition

Statins have been anecdotally linked with transient cognitive impairment. There have been case reports and studies which have reported acute short term reversible memory impairment with statin therapy. This brain fog reportedly resolves upon cessation of the statin therapy.[180-190]

However numerous RCTs have shown that statins had no adverse effects on long term neurocognition.[191-193] In addition, the incidence of neurocognitive adverse events did not increase with very low LDL-C levels (<0.50 mmol/L or < 20 mg/dl).[194]

Statins as a group do not appear to have any long-term effects on neurocognition, although we cannot exclude the possibility that there may be a very low incidence of acute memory impairment in susceptible individuals on statin therapy which resolve upon cessation of the statin.

6.1.2.5 Chronic Kidney Disease

Statins reduce risk of CV events by 20% in patients with CKD. However, there appears to be no evidence of benefit from statins for patients on haemodialysis. Meta-analyses in CKD patients showed no increase in progression of CKD or acute renal events on statin therapy.[195]

There has been a higher incidence of proteinuria reported with the use of rosuvastatin. An incidence of 12% has been reported for rosuvastatin 80 mg and at doses of < 40 mg daily, the incidence is consistent with other statins. The statin related proteinuria is transient and thought to be due to reduced tubular reabsorption and not glomerular dysfunction. The reported incidence is low and, mostly not higher than for the incidence seen in placebo arm.[196]

6.1.2.6 Stroke Risk

It was hypothesized that statins may tend to cause higher risk of haemorrhagic stroke. The SPARCL study showed that there was a small increase in haemorrhagic stroke in subjects with prior stroke but this was not been confirmed by other RCTs.[10,68,197] Statin therapy does reduce the risk of first or subsequent ischemic strokes by 15 to 35% per mmol/L reduction in LDL-C cholesterol.[161]

6.1.3 Monitoring of Adverse Side Effects of Statins

Baseline measurements of serum aspartate/alanine transaminase and creatine kinase are recommended to establish patient's baseline prior to starting statin therapy. A second measurement can be performed 3 to 6 months after starting statin therapy. Where there is an escalation in the dosage of the statin, another measurement can be performed 3 to 6 months later. Routine repeat measurement of these is not required for patients whose subsequent follow up results are not elevated beyond the baseline and are asymptomatic. Monitoring of creatinine kinase is necessary in patients with muscle symptoms such as pain, tenderness, cramping, or weakness.

Table 14: Recommendations on Statin Side Effects

Statin Side Effects	Strength of Evidence	Quality of Evidence
Myopathy 1. Due to risk of myopathy and rhabdomyolysis, high dosages of statins should be prescribed with caution, especially in elderly patients, in those with impaired renal function and when a statin is combined with a fibrate.[7,153,165-167]	IIa	C

2. When using simvastatin, the highest dose should be 40mg. However, in patients who have been taking 80mg for more than 12 months without any evidence of myopathy or other side effects, it is acceptable to continue the dose.[7,153,165-167]	IIa	C
3. Combination of statins with gemfibrozil enhances the risk of myopathy, and hence it should not be prescribed together with statins.[168,169]	I	C
4. When using statins, it is recommended that serum creatinine kinase be monitored in patients with muscle symptoms (e.g. pain, tenderness, cramping, weakness).[7,153,198]	I	C
Liver transaminases elevation When using statins, monitor ALT and AST in patients developing symptoms suggestive of hepatotoxicity (e.g. fatigue, weakness, loss of appetite, jaundice).[7,153,198]	I	C
When using statins, patients should be advised to report promptly to their doctors if they develop any of the above liver or muscle symptoms.[7,153,198]	I	C

Key Summary points: Statins side effects
Avoid combination of statins with gemfibrozil
Caution with combination of statins with fibrates especially in renal impairment
Check Creatine kinase (CK) in those with muscle symptoms
Monitor liver enzymes for those with symptoms suggestive of hepatotoxicity

6.1.4 Clinical definition of statin intolerance

The National Lipid Association 2022 Scientific Statement's updated definition of statin intolerance defines statin intolerance as one or more adverse effects associated with statin therapy which resolves or improves with dose reduction or discontinuation and can be classified as a complete inability to tolerate any dose of a statin or partial intolerance with inability to tolerate the dose necessary to achieve the patient-specific therapeutic objective. To classify a patient as having statin intolerance, a minimum of two statins should have been attempted, including at least one at the lowest approved daily dosage. See **Table 15**.

Table 15 : National Lipid Association 2022 definition of Statin Intolerance[199]

Statin intolerance and classification	
Statin intolerance is defined as one or more adverse effects associated with statin therapy, which resolves or improves with dose reduction or discontinuation, and can be classified as complete inability to tolerate any dose of statin, or partial intolerance, with inability to tolerate the dose necessary to achieve the patient-specific therapeutic objective. To classify a patient as having statin intolerance, a minimum of two statins should have been attempted, including at least one at the lowest approved daily dosage.	
Complete statin intolerance	Inability to tolerate any dose or regime of a statin
Partial statin intolerance	Ability to tolerate a lower dose of statin than is required to achieve the desired therapeutic objective

Placebo-controlled studies suggest that statin related muscle complaints may be partially due to the "nocebo" effect, in which the expectation of harm results in perceived side effects that may be unrelated to the pharmacological effects of the drug.[160]

For patients with suspected statin intolerance, multiple strategies should be attempted to identify a tolerable statin regimen (e.g., lower dose, switching statins, non-daily dosing), as complete statin intolerance is uncommon (<5% of patients).

In the "very high risk" and "high risk" patients who have statin intolerance, non-statin therapy should be initiated while additional attempts are made to identify a tolerable statin to manage the elevated levels of atherogenic lipoproteins.[199]

6.1.5 Statin Drug-Drug Interactions

Understanding the mechanisms of drug interactions with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) is important as there is potential for serious side effects as discussed in the earlier sections. Current evidence points towards Cytochrome P450 3A4 (CYP3A4) as an important pathway in many of these drug interactions. Statins can broadly be divided into those that that undergo metabolism by the CYP3A4 isoenzyme (atorvastatin, lovastatin and simvastatin) and those that do not undergo metabolism by the CYP3A4 isoenzyme (pravastatin, pitavastatin and rosuvastatin). Hence drugs that inhibit CYP3A4 will prevent CYP3A4 isoenzymes from metabolising statins using this pathway. This will result in elevation of the plasma levels of these statins thereby increasing the risk of serious statin toxicity. [200]

Other metabolic pathways involving statins include organic anion transporting polypeptides (OATPs) and P-glycoprotein (P-gp). OATPs are membrane influx transporters that regulate cellular uptake of drugs. In the liver, OATPs extract drug substrates from the portal blood into hepatocytes. After metabolism, other drug transporters such as P-glycoprotein may be important in efflux of the metabolite from the hepatocyte. Most statins that use OATPs pathway for hepatic uptake and hence inhibition of the OATPs pathway may increase statin toxicity. Whilst the P-gp pathway plays a role in

the transportation of atorvastatin , lovastatin and simvastatin , this pathway does not appear to play a major role in the transport of pitavastatin , pravastatin and rosuvastatin.[200]

In addition, statins can also be divided into 2 broad groups depending on whether they are predominantly lipophilic (simvastatin, pitavastatin, lovastatin and atorvastatin) or predominantly hydrophilic (rosuvastatin and pravastatin). In general, it is considered that the risk of myopathy is lower with hydrophilic statins because of their inability to enter muscle cells.[201]

The American Heart Association has a scientific statement on drug-drug interactions with statins. [202] For example, the statement recommends that the use of lovastatin, pitavastatin, and simvastatin should be avoided in patients receiving cyclosporine, tacrolimus, everolimus, or sirolimus. Combination therapy of cyclosporine, everolimus, or sirolimus with lovastatin, simvastatin, and pitavastatin is potentially harmful and should be avoided. The statement recommends that when using a statin in such situations, the dose of atorvastatin >10 mg/d when co-administered with cyclosporine, tacrolimus, everolimus, or sirolimus is not recommended without close monitoring of creatinine kinase and signs or symptoms of muscle-related toxicity. Statins should be started at the lowest possible dose and the doses should be gradually titrated . In particular attention should be paid towards the risk of myopathy. Refer to **Annex C** for a table on selected statin related interactions with medications commonly used in primary care that may increase the risk of side effects of statins.

6.1.6 Indications for Stopping Statins

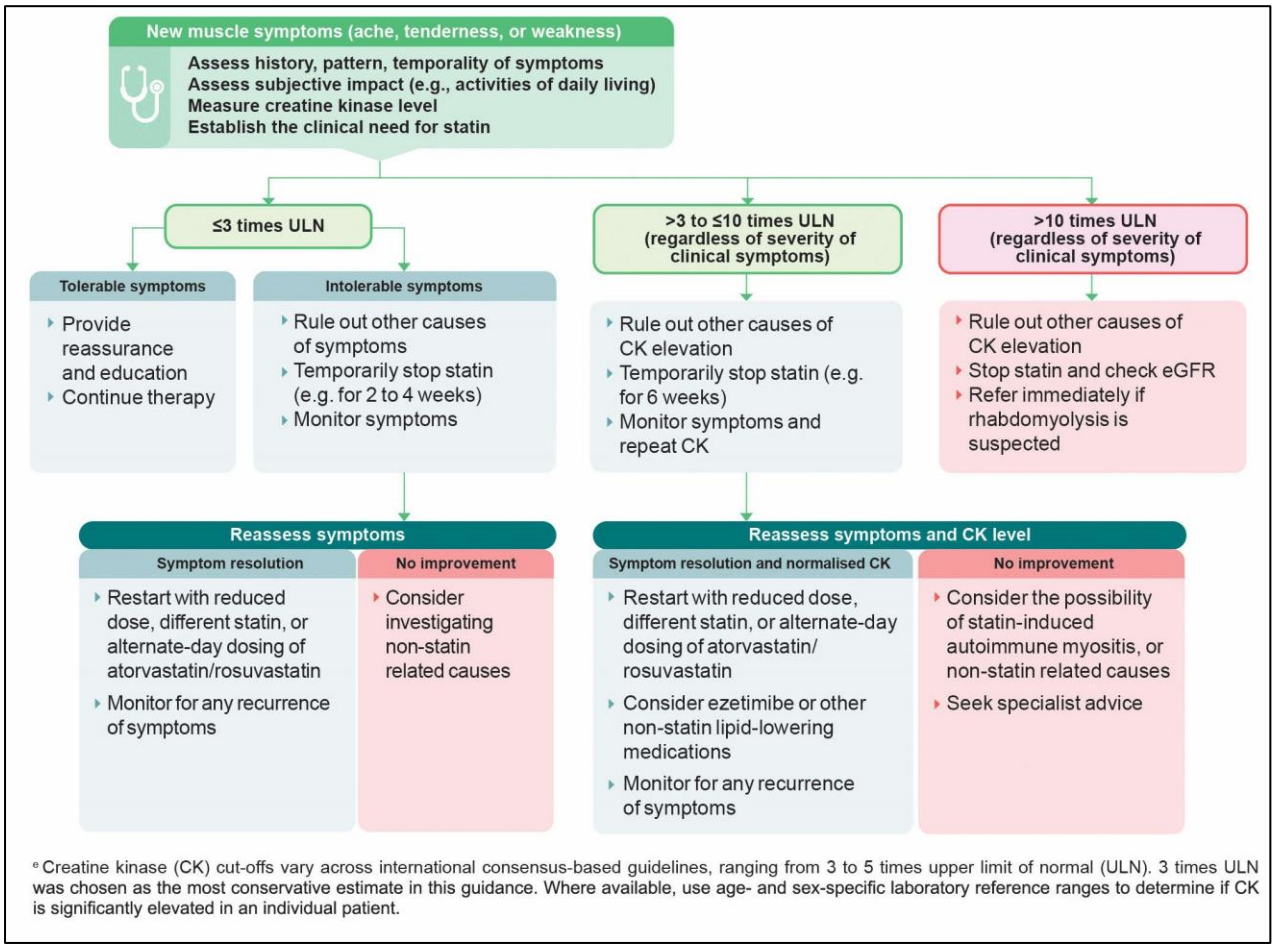
Severe statin induced liver injury is very rare but an elevation of liver transaminases greater than 3 x the upper limit of normal reference range should prompt the physician to stop statin therapy and review therapy after the liver enzymes return to normal.[203] Refer to **Table 16** for recommendations on cessation of statins.

Elevation of serum creatine kinase greater than 3 to 10 times the upper limit of the normal range, when associated with muscle pain is an indication to stop statins, at least temporarily, rule out other causes and monitor. Elevations of > 10 times upper limit of normal should be an indication to stop regardless of severity of symptoms and to check eGFR with immediate referral if rhabdomyolysis is suspected. Some patients who experience muscle symptoms without elevations of creatine kinase may experience a reduction in symptoms when switched to an alternative statin.[198] A flowchart for management of muscle symptoms from the Ministry of Health ACG for Lipid Management 2023 is shown in **Figure 2**.

Table 16: Recommendations for Cessation of Statins

Cessation of statins	Strength of Evidence	Quality of Evidence
Elevation in the levels of serum transaminases above 3 times the upper limit of the normal range is an indication to stop statins. The drugs can be reintroduced at a lower dose when liver function has returned to normal.[7,203]	I	C
Elevation of serum creatine kinase greater than 3 to 10 times the upper limit of the normal range, when associated with muscle pain is an indication to stop statins at least temporarily, rule out other causes and monitor. Patients who are troubled by muscle pain, even in the absence of a raised serum creatine kinase, may benefit from either: 1. stopping the statin therapy or 2. reducing the dosage.[7,201]	I	C

Figure 2: Flowchart for management of muscle symptoms (Figure reproduced from the ACE Clinical Guidance "Lipid Management: Focus on Cardiovascular Risk"[1] with permission from Agency for Care Effectiveness (ACE), Ministry of Health, Singapore)



6.2 Ezetimibe

Ezetimibe is a lipid lowering agent that selectively inhibits the intestinal absorption of cholesterol and related plant sterols. A meta-analysis comparing ezetimibe monotherapy with placebo reported an 18.5% reduction in LDL-C, 3% increase in HDL-C, an 8% reduction in TGs, and a 13% reduction in TC. When added to a statin (e.g., simvastatin), 10 mg of ezetimibe will produce a further 18% lowering of the LDL-C cholesterol. This effect is similar to doubling the dose of the statin three times (e.g. increasing 10 mg simvastatin to 80 mg).[204]

Ezetimibe is also available as a statin and ezetimibe combination tablet. The combination of simvastatin and ezetimibe has been shown to reduce cardiovascular events in patients with chronic kidney disease, compared to placebo. In patients with established coronary artery disease, ezetimibe, when added to a statin, produces further lowering of LDL-C cholesterol and cardiovascular events.[74,195,205]

Ezetimibe given as 10mg/day can be taken in the morning or evening with or without food. The same dosage can be maintained even in those with mild hepatic impairment or mild-to-severe CKD.

6.3 Resins (Bile Acid Sequestrants)

Resins (e.g., cholestyramine) are effective in lowering TC and LDL-C cholesterol. However, they are infrequently used because of side effects.[5,7,206]

6.4 Fibrates

Commonly available fibrates in Singapore include fenofibrate, bezafibrate, pemafibrate and gemfibrozil. Of these fibrates, gemfibrozil increases the risk of myopathy by 5.5- fold as compared with a statin. When used in combination with a statin, gemfibrozil also inhibits statin metabolism leading to increases in plasma statin levels.[207-209]

As fenofibrate uses a different pathway, the risk of myopathy is much lower when using a statin-fibrate combination.[210] The side effects of fibrates include: (i)elevation of liver enzymes (transaminases) (ii) myopathy and (iii) gallstones. Fibrates are generally well tolerated with mild adverse effects'. [209,210]

6.5 Nicotinic Acid

Niacin lowers LDL-C and TG by decreasing secretion of very low density lipoprotein (VLDL) particles and can elevate HDL-C by increasing ApoA1 production.[211] There are two large randomized trials using nicotinic acid which have not only shown no beneficial effect but have also reported a higher incidence of serious adverse effects. Currently, nicotinic acid medications are not approved for use in Europe for lipid lowering.[154,212]

As such, we do not recommend the use of nicotinic acid for lipid lowering except in rare situations where there is no other alternative therapy for lowering TG.

6.6 Omega-3 Fatty Acid

Omega-3 fatty acids derived from fish oils are useful supplements to reduce fasting blood triglyceride levels. It is shown that a dose of 3.25 g of eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) formulations produced a clinically significant reduction of triglycerides, with very slight increases in HDL and LDL, and no changes in total cholesterol.[213]

The omega-3 fatty acids, EPA and DHA are recommended at a dose of 2 to 4 g/day for reducing triglycerides in patients with elevated triglycerides. A combination of EPA and DHA can reduce triglycerides by ≥30% with concurrent increases in LDL, whereas EPA-only formulations did not raise LDL in patients with very high triglycerides. n-3 fatty acids are highly purified oils and do not appear to be allergenic. There is no absolute contraindication in patients allergic to seafood. [214]

6.7 Anti-Proprotein Convertase subtilisin/Kexin type 9 (PCSK9) Therapy

In recent years, a new class of drugs targeting the protein enzyme proprotein convertase subtilisin/kexin type 9 (PCSK9) have been developed. Increased concentration of PCSK9 reduces the availability of LDL receptors (LDLR) and hence decrease binding to plasma LDL-C, leading to an increase in LDL-C level. One class of medications which require the subcutaneous injection of human monoclonal antibodies which bind to PCSK9 and inhibit its activity are called PCSK9 inhibitors, of which two fully human mAbs, alirocumab and evolocumab, are currently approved for use. The use of statins increases PCSK9 level and hence the efficacy of PCSK9 inhibitors is best demonstrated when used in combination with statins.[215-217]

Given the action of this class of drugs, they are effective in all patients except for LDL receptor deficient homozygous familial hyperlipidaemia.[5,218] These drugs are able to reduce LDL-C by an average of 60%,[219,220] and TG by 26%.[221] (Refer to **Table 17)**. Unlike statins which have minimal effect on Lp(a) levels, PCSK9 inhibitors reduce Lp(a) by 30 to 40%.[222,223] They are administered subcutaneously, fortnightly or monthly.

More recently, there is a newer anti-PCSK9 therapy, inclisiran, which is a long-acting, short-chain siRNA directed against PCSK9 protein. Inclisiran works by binding specifically to the mRNA precursor of PCSK9 protein, thereby blocking the expression of PCSK9 and causing its degradation. A recent study that summarized the results of the major studies on inclisiran suggested that when compared to placebo, there was a 51% decrease in LDL-C 37% decrease in total cholesterol, 41% decrease in ApoB, and 24% decrease in CV events, such as cardiac death, cardiac arrest, myocardial infarction, or stroke. The main advantage of inclisiran over the PCSK9 inhibitors (alirocumab and evolocumab) is that at a steady state, it is administered at 6 monthly intervals.[224]

Table 17: Intensity of Lipid Lowering with Drug Therapy[5]

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin + ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor + high intensity statin	≈ 75%
PCSK9 inhibitor + high intensity statin + ezetimibe	≈ 85%

6.8 Recommendations for Management of Elevated LDL-C

The therapeutic drug options for hyperlipidaemia are summarised in **Tables 18, 19 and 20**.

Table 18: Recommendations for Management of Elevated LDL-C

Drug Therapy for Hyperlipidaemia	Strength of Evidence	Quality of Evidence
Statins are the first line drug for both hypercholesterolemia (elevated LDL-C) and mixed hyperlipidaemia when pharmacotherapy is indicated, except when TG > 4.5mmol/L (400mg/dL).[7,10,225]	I	A
It is recommended that a statin is prescribed up to the maximally tolerated dose to reach the therapeutic targets set for the risk group.[68,226,227]	I	A
Ezetimibe can be used as an add-on drug in association with statins when the therapeutic target is not achieved at the maximum tolerated statin dose, or as an alternative to statins in patients who are intolerant of statins or with contraindications to statins.[74]	I	A
For secondary prevention, patients at very-high risk of not achieving their goal (LDL-C < 1.8 mmol/L) on a maximally tolerated dose of a statin and ezetimibe, for at least a minimum of 12 weeks, a combination with an anti-PCSK9 drug is recommended.[75,76]	I	A
For very high risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal of LDL-C < 1.8 mmol/L on a maximally tolerated dose of a statin and ezetimibe, for at least a	I	C

minimum of 12 weeks, a combination with an anti-PCSK9 drug is recommended.[75,76]		
If a statin-based regimen is not tolerated at any dosage (even after re-challenge), ezetimibe should be considered.[228-230]	IIa	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), an anti-PCSK9 drug added to ezetimibe may also be considered if target LDL-C is not achieved in very high risk and high risk patients.[228-230]	IIb	C

Key Summary points: Management of elevated LDL-C
Statins are the first line drug for hyperlipidaemia. Titrate until the target LDL-C is achieved
Ezetimibe can be added on if therapeutic target is not achieved.
In very high-risk patients, who do not achieve their goal of LDL-C < 1.8 mmol/L on a maximally tolerated dose of a statin and ezetimibe, for at least a minimum of 12 weeks, a PCSK-9 inhibitor can be added.

6.9 Recommendations for management of Hypertriglyceridemia

Hypertriglyceridaemia is the cause of about 10% of all cases of pancreatitis. Hence, individuals with very high levels of TG > 4.5mmol/L (400mg/dL) and in particular >10mmol/L (885mg/dL), have an increased risk of acute pancreatitis and should be treated to reduce the risk of pancreatitis.[231-233] Refer to **Table 19** for the recommendations on the management of hypertriglyceridaemia .

Table 19: Recommendations for management of hypertriglyceridaemia

Drug therapy for Hypertriglyceridaemia	Strength of Evidence	Quality of Evidence
For patients in very high risk or high risk groups with hypertriglyceridaemia (TG > 2.3 mmol/L or 200 mg/dl) , statin therapy is recommended as the first line drug therapy.[234]	I	B
Since patients are at increased risk for acute pancreatitis when TG is > 4.5mmol/L (400mg/dL) and the risk is greater with higher TG level, fibrates are the first line drug to reduce the risk of pancreatitis when TG > 4.5mmol/L (400mg/dL).[231-233]	I	C
In primary prevention patients , who are within LDL-C therapeutic targets with elevated TG levels > 4.5 mmol/L (>400 mg/dL), fenofibrate, pemafibrate or bezafibrate may be considered in combination with statins. There is currently no strong evidence that that the addition of fibrates will reduce cardiovascular risk.[235-238] Gemfibrozil should not be given because it significantly increases the level of most statins, and this may increase the risk of complications.[207-209]	IIb	C

6.10 Specific Populations

For lipid management, special considerations should be given to those who are elderly, pregnant women, and those with medical co-morbidities such as renal and liver disease. See **Table 20**.

Table 20: Recommendations for lipid management in specific populations

Drug therapy for Specific Populations	Strength of Evidence	Quality of Evidence
During pregnancy, treatment is indicated only in patients with severe hypertriglyceridemia (e.g. TG >10mmol/L [880mg/dL]). The only therapy recommended is omega 3 fish oils after dietary therapy.[7]	I	C
Statins are contraindicated in women who are pregnant, likely to be pregnant, or who are still breastfeeding.[5,7,153,239] Consider specialist referral.	I	C
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.[5]	I	A
Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤ 75 years.[5]	I	A
In the elderly (age >75 years), the decision to start treatment should take into account the risk group, potential risk-reduction associated with treatment, risk of adverse effects, drug-drug interactions, and patient preferences.[5,7]	IIb	B
For patients on treatment with a statin and LDL-C <1.8mmol/L or 70mg/dL when they turn >75 years of age, there is no need to reduce therapy, if the treatment is well tolerated without any adverse effects.[7]	IIb	C
The starting dose of statins in chronic kidney disease should be low. During therapy, serum creatine kinase and renal function should both be carefully monitored.[5,7]	IIa	C
In dialysis patients without ASCVD, commencement of statin therapy is not recommended.[5,240,241]	III	A
For ASCVD patients on statins, ezetimibe, or a statin/ezetimibe combination at the time of commencement of dialysis, the medication should be continued.[5]	IIa	C
Fibrates can be used in patients with chronic kidney disease in stages 1 to 3 but the dosages should be reduced, with appropriate monitoring for side effects, especially myopathy. When creatinine clearance is less than 30 ml/min (stage 4 or 5), fibrates are contraindicated.[7]	I	C
Screen liver function (especially transaminases) on 2 consecutive occasions in patients with hyperlipidaemia and chronic liver disease.[7]	IIa	C
In patients with hyperlipidaemia and chronic liver disease, if the level of the two transaminases (ALT and AST) is elevated but < 1.5 times the upper limit of the normal range, statins can be given but the starting dose	IIa	C

should be low.[242] Careful monitoring of the serum transaminases and creatine kinase after commencement is recommended.[7]		
In patients with hyperlipidaemia and chronic liver disease, if the level of the two transaminases (ALT and AST) is between 1.5 to 3 times the upper limit of the normal range, statins can still be given but with caution and the starting dose should be low.[249] Careful monitoring of the serum transaminases and creatine kinase after commencement is recommended.[7]	IIa	C
Fibrates can be given in patients whose transaminase levels are elevated < 3 times the upper limit of the normal range, but at a lower starting dosage. Careful monitoring of the serum transaminases and creatine kinase after commencement is recommended.[7]	IIb	C

Key Summary points: Management of lipids in specific populations
Statins are contraindicated in pregnant and breastfeeding women.
In the elderly (age >75 years), the decision to start treatment should consider the risk group, potential risk-reduction, risk of adverse effects, drug-drug interactions, and patient preferences.
In CKD, starting dose of statins should be low. CK and renal function should be carefully monitored.
In dialysis patients without ASCVD, commencement of statin therapy is not recommended.
Fibrates are contraindicated in CKD when creatinine clearance is less than 30 ml/min (stage 4 or 5).
In chronic liver disease, if the level of the two transaminases (ALT and AST) is less than 3 times the upper limit of the normal range, statins to be used with caution and initiated with a lower dose.

6.11 Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is a group of inherited genetic defects resulting in severely elevated serum cholesterol concentrations. In the heterozygous FH, cholesterol levels rise to about two times the normal levels due to a defect in LDL clearance. Affected individuals have a much higher risk (about 20-fold) of premature CAD if untreated. The prevalence of FH is 1 in 300 to 500 in many populations, making FH among the most common of serious genetic disorders. Clinical diagnosis of FH can be made by applying any one of several validated sets of criteria, including the Simon Broome Trust diagnostic criteria[243] provided in **Table 21** and the Dutch Clinic Lipid Network score[244] provided in **Table 22**. For patients with definite FH, primary care physicians can initiate therapy based on the guidelines or refer patients to a specialist to initiate and stabilise the patient on therapy. For patients with possible FH, primary care physicians may want to refer patient to specialists to make a recommendation on the need for therapy and to initiate therapy if required. Refer to **Table 23** for recommendations on drug therapy for patients with FH.

Table 21 : Simon Broome Trust diagnostic criteria for Familial Hypercholesterolemia[243]

Diagnosis	Criteria
Definite Familial hypercholesterolemia	**Cholesterol level:** *Adults:* TC > 7.5 mmol/L (>290 mg/dl) or LDL-C > 4.9 mmol/L (> 190 mg/dl). *Child < 16 years:* TC > 6.7 mmol/L (>260 mg/dl) or LDL-C > 4.0 mmol/L (>160 mg/dl). **In addition:** Tendon xanthomas in patient or in 1st degree relative (parent, sibling, child) or in 2nd degree relative (grandparent, uncle, aunt). **OR** DNA-based evidence of an LDL receptor mutation or familial defective apo B-100 or a PCSK9 mutation.
Possible Familial Hypercholesterolaemia	**Cholesterol level:** *Adults:* TC > 7.5 mmol/L (>290 mg/dl) or LDL-C > 4.9 mmol/L (> 190 mg/dl). *Child < 16 years:* TC > 6.7 mmol/L (>260 mg/dl) or LDL-C > 4.0 mmol/L (>160 mg/dl). **In addition:** Family history of myocardial infarction: younger than 50 years of age in a 2nd degree relative or younger than 60 in a 1st degree relative. **OR** Family history of TC > 7.5mmol/L in adult 1st or 2nd degree relative or greater than 6.7mmol/L in child or sibling aged younger than 16 years.

Table 22 : Dutch Lipid Clinic network criteria for Familial hypercholesterolemia[244]

Criteria	Points
1. Family history • First-degree relative with known premature* coronary and vascular disease, OR First-degree adult relative with known LDL-C level above the 95th percentile • First-degree relative with tendinous xanthomata and/or arcus cornealis, OR First degree relative aged less than 18 years with LDL-C level above the 95th percentile	1 2
2. **Clinical history** • Patient with premature* coronary artery disease • Patient with premature* cerebral or peripheral vascular disease	2 1
3. **Physical examination** • Tendinous xanthomata • Arcus cornealis prior to age 45 years	6 4
4. **LDL-C levels**	
• LDL-C >= 330 mg/dL (≥8.5 mmol/L)	8
• LDL-C 250 – 329 mg/dL (6.5–8.4 mmol/L)	5
• LDL-C 190 – 249 mg/dL (5.0–6.4 mmol/L)	3
• LDL-C 155 – 189 mg/dL (4.0–4.9 mmol/L)	1
5. **DNA analysis** Functional mutation in the LDLR, apo B or PCSK9 gene	8

*****_Premature refers to < 55 yrs in men and < 60 yrs in Women_

Diagnosis (based on the total number of points obtained)	Total points
• **Definite Familial Hypercholesterolemia** • **Probable Familial Hypercholesterolemia** • **Possible Familial Hypercholesterolemia** • **Unlikely Familial Hypercholesterolemia**	**> 8** **6 – 8** **3 – 5** **< 3**

Table 23: Recommendations for drug therapy in Familial Hypercholesterolemia

Drug therapy in Familial Hypercholesterolemia	Strength of Evidence	Quality of Evidence
Screening of all first degree relatives of diagnosed familial hypercholesterolemia patients is recommended.[7]	I	C
For FH patients with ASCVD who are at very high risk, treatment to achieve a LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended.[5]	I	C
Treatment with anti-PCSK9 therapy is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximally tolerated statin plus ezetimibe.[5]	I	C
For FH patients, in the absence of ASCVD or another major risk factor, treatment is recommended to achieve at least an LDL target of <2.6 mmol/L (<100 mg/dL)[5]	I	C

This target may not be achievable despite the use of the maximally tolerated dose of lipid lowering therapy in patients with FH, which may include the use of combination therapy with multiple lipid lowering drugs. However, pharmacotherapy provides some benefit despite not achieving the LDL cholesterol target in such patients. In very high risk ASCVD patients, the use of combination therapy including anti-PCSK9 therapy may help the patient achieve the therapeutic targets for LDL-C.

7. COST-EFFECTIVESS OF LIPID LOWERING THERAPY

One of the factors influencing the choice of lipid modifying drugs is cost and cost-effectiveness. Studies have shown that statins and fibrates are cost effective when used for both secondary as well as primary prevention.[10,68,132-137,245-247] Importantly, most of these studies had been done in countries at a time when generic drugs were unavailable. Today, with the wide availability of generic drugs, statin and fibrate therapy have become even more cost-effective.[246,247] Generic formulations cost less than non-generic drugs and can be considered if they meet prescribed standards.[246-248]

PCSK9 inhibitors (alirocumab and evolocumab) are very effective drugs that can reduce LDL-C and CV events on top of statin and/or ezetimibe treatment. This class of drugs have a good safety profile. The prices of PCSK9 inhibitors have been decreasing and a 2019 cost-effectiveness study concluded that they are cost-effective with recent US costing in the very high risk ASCVD group with LDL > 1.8 mmol/L using the American College of Cardiology guideline definition.[249] In the American College of Cardiology /American Heart Association 2018 guidelines on lipids, the definition of " very high-risk" include those with a history of multiple major ASCVD events (ACS within the past 12 months , history of myocardial infarction, history of ischaemic stroke , symptomatic peripheral arterial disease) or one major ASCVD event and multiple high-risk conditions. This definition differs from the definition of "very high risk" used in this clinical practice guideline.

Based on a recent 2022 publication on the cost-effective analysis on the use of inclisiran, based on the price of inclisran in public hospitals , the use of inclisiran in high risk ASCVD patients appears to be cost-effective in US adults with proven ASCVD and LDL-C $\geq$ 1.8 mmol/l.[250] Nevertheless, PCSK9 therapy remains relatively expensive compared to generic oral lipid lowering therapy and hence in addition to the clinical indications, appropriate consideration has to be given on the financial means of the patient before commencement of anti-PCSK9 therapy.

The economic value of PCSK9 inhibitors is better with higher-risk patients. Hence, for maximal economic value, PCSK9 inhibitors and inclisiran may be used in secondary prevention in those with a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions (as in American College of Cardiology /American Heart Association 2018 guidelines) who are unable to achieve LDL-C therapeutic targets despite oral cholesterol lowering medication. Currently, the economic value of using PCSK9 inhibitors and inclisiran in primary prevention has yet to be proven.[6,251,252]

8. REFERRAL TO SPECIALISTS

Patients who remain outside the LDL cholesterol target values or with TG levels persistently >4.5mmol/L (400mg/dL) despite dietary changes and maximally tolerated drug therapy can be referred to cardiologists or endocrinologists.[7] For those patients who do not reach target LDL-C levels despite maximally tolerated oral medications and anti-PCSK9 therapy is being considered , referral to cardiologists or endocrinologists can be considered. Those with statin intolerance who are unable to achieve target LDL-C with non-statin measures can be referred to cardiologists or endocrinologists. Pregnant women with hypertriglyceridaemia can also be referred to a relevant specialist, such as an endocrinologist, as hypertriglyceridaemia can be accompanied by preeclampsia, hyperviscosity syndrome and pancreatitis.

9. QUALITY INDICATORS FOR LIPID MANAGEMENT

The following clinical quality indicators for recommended LDL cholesterol target levels (**Table 24)** and process indicators for review frequency **(Table 25)** are proposed for lipid management. However, measurement of attainment of these target levels should exclude those whose age is >75 years.

Table 24: Recommendations for LDL-C Therapeutic Targets

Risk Groups	LDL-C Therapeutic Targets
Cardiovascular risk by medical condition	
Very high risk (secondary prevention)	• Ideal LDL-C goal of <1.4 mmol/L (<55 mg/dL) in those with a history of ACS. • At least <1.8 mmol/L (<70 mg/dl) for other types of ASCVD. • Consider lower based on clinical need and tolerability.
Very high risk to high risk (primary prevention)	*Familial hypercholesterolaemia*: • Consider LDL-C goal of <1.8 mmol/L (<70 mg/dL) if age > 40 years, or additional CV risk factor(s) e.g., DM, HPT, smoking, evidence of subclinical atherosclerosis if investigated) • Consider LDL-C goal of <2.6 mmol/L (<100 mg/dL) if age ≤40 years and no additional CV risk factors *Diabetes mellitus:* • Consider LDL-C goal of <1.8 mmol/L (<70 mg/dL) if any additional DM-specific risk factor (CKD, multiple microvascular complications, DM ≥ 10 years, or glycaemic target persistently above target despite optimal treatment • Aim for LDL-C goal of <2.6 mmol/L (<100 mg/dL) if none of the additional risk factor listed above. Consider lower based on clinical need and tolerability. *Chronic kidney disease*: • Aim for LDL-C <2.6 mmol/L (<100mg/dL), consider lower based on clinical need and tolerability.
Otherwise healthy patients without the above conditions*: CV risk by 10-year risk scoring	
High-risk Group	• LDL-C goal of <1.8 mmol/L (<70 mg/dL).
Intermediate Risk Group	• LDL-C goal of <2.6 mmol/L (<100 mg/dL).
Borderline and Low Risk Groups	• LDL-C goal < 3.4 mmol/L (< 130 mg/dl) can be considered for borderline risk; it is an ideal goal for low risk groups. • Focus on lifestyle intervention in the low risk group. • Consider risk-benefit discussion for a statin if LDL-C persistently > 4.1 mmol/L.
*For patients with LDL-C>4.9 mmol/L but not FH, consider calculating 10-year CV risk to determine risk level	

Table 25: Process Indicators and recommended frequency

Performance Parameter	Recommended review frequency
All patients who are on stable lipid modifying drug therapy with LDL-C target levels achieved	Lipid measurement at least every 12 months
Patients who are not on lipid modifying drug therapy (with LDL-C target levels achieved as stated above): (1) Very high risk and high risk (2) Intermediate risk and low risk	 4 to 12 weeks after initiation. This can be repeated every 3-12 months as needed. 12 monthly

In the management of an individual patient, good clinical judgment, which takes into account other factors that may influence overall morbidity or mortality risk, should be exercised in every situation. As such, aiming for 100% attainment of these targets is inappropriate. Furthermore, measurements of attainment of these targets should exclude those age > 75 years.

Therapy can be initiated, and levels monitored 4 to 12 weeks after initiation. This can be repeated every 3 to 12 months as needed.

Annex A: **Summary of recommendations**

Class I recommendations	Quality of Evidence
Recommendations for lipid measurement	
Assessment of a lipid profile should include TC, LDL-C (measured or calculated), HDL-C and TG	C
Cardiovascular risk factor assessment, including, lipid screening should be performed in adults aged 40 years or more	B
Non-fasting lipid samples can be used for general risk assessment, and assessment of baseline lipid profile prior to the commencement of lipid lowering therapy in primary prevention and secondary prevention	B
ApoB measurement is recommended in those with hypertriglyceridaemia, diabetes mellitus, obesity and post-treatment achieved low LDL-C	C
Recommendations for LDL-C Therapeutic Targets	
LDL-C Therapeutic Targets in Very High-Risk Group	
In secondary prevention (patients with established ASCVD) for patients at very-high risk, an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended. For patients with a history of ACS, an LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended	A
For FH patients with ASCVD, treatment to achieve an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended. If the goal cannot be achieved, a drug combination is recommended	C
Primary Prevention in High Risk and Intermediate Risk Groups	
In patients at high risk, an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended	A
For FH patients with no known ASCVD or other major risk factors, a LDL-C goal of <2.6 mmol/L (<100 mg/dL) is recommended	C
In patients with DM at high risk (CKD, multiple microvascular complications, DM duration ≥ 10 years, or glycaemic level persistently above the target despite optimal treatment), a LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended	A
Recommendations on Secondary target: ApoB	
In situations where the LDL-C may not adequately reflect the CV risk, ApoB can be used as a secondary target. ApoB targets in the very-high, high, and moderate groups are <65 mg/dL, <80 mg/dL, and <100 mg/dL respectively	A
Recommendations on Lifestyle Modification	
Tobacco use Use of tobacco in any form, whether by smoking, vaping, or any other means, should stop	A
Weight Management If body mass index is above 23 kg/m2, weight reduction through diet modification and exercise is recommended	A
Exercise Persons with hyperlipidaemia should undertake 150 to 300 minutes per week (about 30 to 60 minutes per day) of moderate intensity aerobic activity spread out over 5 to 7 days per week	A
Alcohol consumption For good overall health, individuals who do not currently drink should not start	C
Dietary Fat	A

A diet rich in wholegrain foods, vegetables, fruit, legumes, nuts, fish, and unsaturated oils and low in saturated and trans-fat, refined grains and cholesterol should be encouraged	
Saturated fat should be replaced with mono and polyunsaturated fats to lower TC and LDL cholesterol (without lowering HDL cholesterol) and lower risk of CAD	A
Trans fat intake should be limited to < 1% of total energy or < 2 grams per day.	A
For those with hypercholesterolaemia, saturated fat intake should be reduced to <7% of total caloric intake, 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 these targets	C
Cholesterol intake should be reduced to less than 300mg per day as this reduces serum LDL cholesterol levels	A
Dietary fibre intake Dietary fibre intake should be 20-30 grams per day by increasing consumption of whole-grains, fruit and vegetables and reducing consumption of processed grains and sugar	C
Recommendations on statin side effects	
Myopathy Combination of statins with gemfibrozil enhances the risk of myopathy, and hence it should not be prescribed together with statins	C
When using statins, it is recommended that serum creatinine kinase be monitored in patients with muscle symptoms (e.g., pain, tenderness, cramping, weakness)	C
Liver transaminases elevation When using statins, monitor ALT and AST in patients developing symptoms suggestive of hepatotoxicity (e.g., fatigue, weakness, loss of appetite, jaundice)	C
When using statins, patients should be advised to report promptly to their doctors if they develop any of the above liver or muscle symptoms	C
Recommendations for cessation of statins	
Elevation in the levels of serum transaminases above 3 times the upper limit of the normal range is an indication to stop statins. The drugs can be reintroduced at a lower dose when liver function has returned to normal	C
Elevation of serum creatine kinase greater than 5 to 10 times the upper limit of the normal range, when associated with muscle pain is an indication to stop statins. Patients who are troubled by muscle pain, even in the absence of a raised serum creatine kinase, may benefit from either: 1. stopping the statin therapy or 2. reducing the dosage	C
Recommendations for management of elevated LDL-C	
Statins are the first line drug for both hypercholesterolemia (elevated LDL cholesterol) and mixed hyperlipidaemia when pharmacotherapy is indicated, except when TG > 4.5mmol/L (400mg/dL)	A
It is recommended that a statin is prescribed up to the highest tolerated dose to reach the therapeutic targets set for the risk group	A
Ezetimibe can be used as an add-on drug in association with statins when the therapeutic target is not achieved at the maximum tolerated statin dose, or as an alternative to statins in patients who are intolerant of statins or with contraindications to statins	A
For secondary prevention, patients at very-high risk not achieving their goal on a maximum tolerated dose of a statin and ezetimibe, a combination with an anti-PCSK9 drug is recommended	A

For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal on a maximum tolerated dose of a statin and ezetimibe, a combination with an anti-PCSK9 drug is recommended	C
Recommendations for management of hypertriglyceridaemia	
For patients in very high risk or high risk groups with hypertriglyceridaemia (TG > 2.3 mmol/L or 200 mg/dl), statin therapy is recommended as the first line drug therapy .	B
Since patients are at increased risk for acute pancreatitis when TG is >4.5mmol/L (400mg/dL) and the risk is greater with higher TG level, fibrates are the first line drug to reduce the risk of pancreatitis when TG > 4.5mmol/L (400mg/dL).	C
Recommendations for Specific Populations	
During pregnancy, treatment is indicated only in patients with severe hypertriglyceridemia (e.g., TG >10mmol/L [880mg/dL]). The only therapy recommended is omega 3 fish oils after dietary therapy	C
Statins are contraindicated in women who are pregnant, likely to be pregnant, or who are still breastfeeding. Consider specialist referral.	C
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients	A
Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤ 75 years	A
Fibrates can be used in patients with chronic kidney disease in stages 1 to 3, but the dosages should be reduced, with appropriate monitoring for side effects, especially myopathy. When creatinine clearance is less than 30 ml/min (stage 4 or 5), fibrates are contraindicated	C
Recommendations for familial hypercholesterolemia	
Screening of all first-degree relatives of diagnosed familial hypercholesterolemia patients is recommended	C
For FH patients with ASCVD who are at very high-risk, treatment to achieve an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended	C
Treatment with an anti-PCSK9 therapy is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe	C
FH patients with high-risk in the absence of ASCVD or another major risk factor, treatment is recommended to achieve an LDL-C target <2.6 mmol/L (<100 mg/dL)	C

Class IIa recommendations	Quality of Evidence
Recommendations for lipid measurement	
Routine lipid screening can be performed in young adults (aged 18 years or more) at least once every 5 years	B
For individuals with screening results within the LDL cholesterol target levels and have low TG levels, screening should be repeated at 3 yearly intervals unless they are in the very high or high risk ASCVD group, in which case screening should be repeated annually	C
Primary Prevention: Recommendations for risk modifiers	
Recommendation for cardiovascular imaging for risk assessment	
In the CV risk assessment of asymptomatic individuals at intermediate risk where the CAC score is measured for the purpose of making a decision on the use of statin, ▪ If the CAC score is zero, it is reasonable to withhold statin therapy and reassess in 5 years in the absence of high-risk factors such as diabetes mellitus, family history of premature CAD, and cigarette smoking ▪ If CAC score is 1 to 99, the incremental value for risk reclassification is modest, and there is variation in international recommendations on how this should influence the decision to start a statin. In general, the decision to start a statin should not be based on a single test or risk factor, but on the individual's global ten year risk ▪ If CAC score is 100 or higher, it is reasonable to commence statin therapy	B
Recommendations for LDL-C Therapeutic Targets	
LDL-C Therapeutic Targets in Very High-Risk Group	
Lipid levels should be re-evaluated 4 to 6 weeks after ACS to determine whether a LDL-C goal of <1.4 mmol/L (<55 mg/dL) has been achieved. Safety issues need to be assessed at this time and statin treatment doses adapted accordingly	C
Primary Prevention in High Risk and Intermediate Risk Groups	
In individuals at intermediate risk, a LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered	A
Primary Prevention in Borderline Risk and Low Risk Groups	
In individuals at intermediate risk, an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered	A
Recommendations on Lifestyle Modification	
Dietary sugars For patients with high TG levels, intake of simple sugars (fructose and sucrose) should be limited to <10% of total energy intake, or in severely elevated individuals, elimination of added sugars	C
Recommendations on statin side effects	
Myopathy	

Due to risk of myopathy and rhabdomyolysis, high dosages of statins should be prescribed with caution, especially in elderly patients, in those with impaired renal function and when a statin is combined with a fibrate	C
When using simvastatin, the highest dose should be 40mg. However, in patients who have been taking 80mg for more than 12 months without any evidence of myopathy or other side effects, it is acceptable to continue the dose	C
Recommendations for management of elevated LDL-C	
If a statin-based regimen is not tolerated at any dosage (even after re-challenge), ezetimibe should be considered.	C
Recommendations for Specific Populations	
The starting dose of statins in chronic kidney disease should be low. During therapy, serum creatine kinase and renal function should both be carefully monitored	C
For ASCVD patients on statins, ezetimibe, or a statin/ezetimibe combination at the time of commencement of dialysis, the medication should be continued	C
Screen liver function (especially transaminases) on 2 consecutive occasions in patients with hyperlipidaemia and chronic liver disease	C
In patients with hyperlipidaemia and chronic liver disease, if the level of the two transaminases (ALT and AST) is elevated but < 1.5 times the upper limit of the normal range, statins can be given but the starting dose should be low. Careful monitoring of the serum transaminases and creatine kinase after commencement is recommended	C
In patients with hyperlipidaemia and chronic liver disease, if the level of the two transaminases (ALT and AST) is between 1.5 to 3 times the upper limit of the normal range, statins can still be given but with caution and the starting dose should be low. Careful monitoring of the serum transaminases and creatine kinase after commencement is recommended	C

Class IIb recommendations	Quality of Evidence
Recommendations for lipid measurement	
For patients with acute febrile illness such as an infection, lipid assessment may be deferred for at least 2 weeks until complete recovery from the acute illness	C
Lp(a) may be considered at least once to identify those with highly elevated Lp(a) and especially in those with a family history of premature cardiovascular disease	C
Primary Prevention: Recommendations for risk modifiers	
Recommendation for cardiovascular imaging for risk assessment	
In the CV risk assessment of asymptomatic individuals at borderline or intermediate risk where the decision about the use of statin is uncertain, it is reasonable to consider the use of CAC score as a risk modifier in making a decision on commencing or withholding statin therapy	B
Recommendations for LDL-C Therapeutic Targets	
Primary Prevention in Borderline Risk and Low Risk Groups	
In individuals at borderline risk, a LDL-C goal < 3.4 mmol/L (< 130 mg/dl) can be considered. If risk enhancers are present, a risk-benefit discussion for statin can be considered	A
In individuals at low risk, focus on lifestyle intervention, and a risk-benefit discussion for statin can be considered if the LDL-C is persistently > 4.1 mmol/L (160 mg/dl). Ideally, a LDL-C of < 3.4 mmol/L (130 mg/dl) can be considered	A
Recommendations for management of elevated LDL-C	
If a statin-based regimen is not tolerated at any dosage (even after re-challenge), an anti-PCSK9 drug added to ezetimibe may also be considered if target LDL-C is not achieved in very high risk and high risk patients	C
Recommendations for management of hypertriglyceridaemia	
In primary prevention patients, who are within LDL-C therapeutic targets with elevated TG levels > 4.5 mmol/L (>400 mg/dL), fenofibrate, pemafibrate or bezafibrate may be considered in combination with statins. There is currently no strong evidence that that the addition of fibrates will reduce cardiovascular risk Gemfibrozil should not be given because it significantly increases the level of most statins, and this may increase the risk of complications	C
Recommendations for Specific Populations	
In the elderly (age >75 years), the decision to start treatment should take into account the risk group, potential risk-reduction associated with treatment, risk of adverse effects, drug-drug interactions, and patient preferences	C
For patients on treatment with a statin and LDL-C <1.8mmol/L or 70mg/dL when they turn >75 years of age, there is no need to reduce therapy, if the treatment is well tolerated without any adverse effects	C
Fibrates can be given in patients whose transaminase levels are elevated < 3 times the upper limit of the normal range, but at a lower starting dosage. Careful monitoring of the serum transaminases and creatine kinase after commencement is recommended	C

Class III recommendations	Quality of Evidence
Recommendation for cardiovascular imaging and other assessment for risk assessment	
The routine collection of other potential modifiers such as genetic risk scores, circulating or urinary biomarkers or vascular tests or imaging methods (other than CAC scoring or carotid ultrasound for plaque determination) is not recommended.[34]	B
Recommendations for specific populations	
In dialysis patients without ASCVD, commencement of statin therapy is not recommended.	A

Annex B: Overview of lipid lowering medication registered in Singapore. (Table reproduced from the ACE Clinical Guidance "Lipid Management: Focus on Cardiovascular Risk"[1] with permission from Agency for Care Effectiveness (ACE), Ministry of Health, Singapore)

Medication*	Dosing recommendations	Dose adjustment in renal impairment^	Common side effects	Additional considerations (contraindications, precautions, monitoring)
Statin: inhibits the HMG-CoA reductase enzyme, increasing the uptake of cholesterol and inhibiting hepatic synthesis				
Atorvastatin	10–80 mg daily	Not required	Headache, myalgia, fatigue, constipation, dizziness, nausea, abdominal pain, hyperglycaemia	Usual dose range applies in patients with mild hepatic impairment (Child-Pugh score class A) Elevated CK at baseline >5x ULN: investigate cause before considering statin initiation *Rosuvastatin:* Regular monitoring of renal function and specialist supervision is recommended if treated with 40 mg dose. **Contraindication**: Decompensated cirrhosis or acute liver failure. The manufacturer advises against use of statin in active liver disease or unexplained persistent transaminase elevations.
Lovastatin	20–80 mg daily, with evening meal	CrCl <30: caution with >20 mg daily		
Pitavastatin	1–4 mg daily	CrCl 15–60: initial 1 mg daily, up to 2 mg daily		
Pravastatin	10–40 mg daily	Moderate to severe renal impairment: initial dose 10 mg daily		
Rosuvastatin	Initial: 5 mg daily for Asian patients Maintenance: up to 20 mg daily Higher doses than 20 mg should be prescribed with caution in Asian patients	Not required for mild renal impairment CrCl <60: doses above 20 mg should not be used CrCl <30: contraindicated		
Simvastatin	5–40 mg daily 80 mg: use should be limited to patients who have been taking 80mg long-term without myopathy.	Not required		
Cholesterol absorption inhibitor: inhibits the absorption of cholesterol, leading to reduced hepatic stores and increasing clearance of cholesterol				
Ezetimibe	10 mg daily	Not required *If eGFR <60 mL/min/1.73 m² and used with simvastatin:* Caution with simvastatin doses >20 mg daily	Arthralgia, dizziness, upper respiratory tract infection, diarrhoea, GGT increased (With statin) AST or ALT increased, myalgia, fatigue, headache	Hepatic impairment: No dosage adjustment is necessary for patients with mild impairment. Not recommended in moderate or severe (Child-Pugh class B and C) hepatic impairment **Co-administration with other lipid-lowering medications**: • Statins: Liver function test should be performed if added on to a statin. • Fibrates: Fenofibrate is the only fibrate that has been co-administered with ezetimibe **Contraindication**: Active liver disease or unexplained persistent transaminase elevations
Fibrate: activation of peroxisome proliferator activated receptor type alpha (PPARα) and increases the lipolysis of triglyceride-rich particles				
Fenofibrate	Multiple formulations exist - refer to institutional formulary when using information below. Fenofibrate 145 mg tablet (nanoparticles): 1 tab daily Fenofibrate (micronised) 160 mg tablet: 1 tab daily with food Fenofibrate capsule (100 mg, 160 mg, 200 mg, 300 mg): refer to product-specific prescribing information as dosing varies	CrCl 30–59: if available, start with 100 mg standard capsule. CrCl <30: contraindicated	Abdominal pain, nausea, vomiting, diarrhoea, flatulence, transaminases increased	Max 200 mg daily if used with a statin **Contraindication**: Not recommended for patients with hepatic impairment **Monitoring**: Transaminases should be monitored periodically. Renal monitoring should be considered for patients at risk of renal impairment.

Medication*	Dosing recommendations	Dose adjustment in renal impairment^	Common side effects	Additional considerations (contraindications, precautions, monitoring)
Choline fenofibrate	MR capsules: 135mg daily for mixed hyperlipidaemia; 45–135 mg daily for severe hypertriglyceridaemia	CrCl 30–80: initial 45 mg daily CrCl <30: contraindicated	Abdominal pain, nausea, vomiting, diarrhea, flatulence, transaminases increased	Hepatic impairment: Not studied in patients with hepatic impairment
Bezafibrate	200 mg TDS	CrCl <15: avoid	Decreased appetite, GI disorder	**Monitoring**: liver function and creatine kinase when used in conjunction with statin
Pemafibrate	0.1–0.2 mg BD	eGFR <30: Use a low starting dose; max 0.2 mg daily	Cholelithiasis	**Contraindication**: Child-Pugh grade B or C, biliary obstruction, cholelithiasis **Monitoring**: liver function
Gemfibrozil	1200 mg daily in 2 divided doses, 30 min before morning and evening meal	eGFR 30–80: initial 900 mg daily eGFR <30: contraindicated	Constipation, diarrhoea, fatigue, flatulence, GI discomfort, headache, nausea, skin reactions, vertigo, vomiting	**Contraindication**: gallbladder or biliary tract disease, use with simvastatin **Monitoring**: blood count for first year of use; liver function; creatine kinase when used in conjunction with statin
PCSK9 inhibitor Monoclonal antibody: inhibits the binding of PCSK9 to LDL-C receptors, increasing LDL-C receptors and enhancing clearance of cholesterol from the blood.				
Evolocumab *(only 140 mg/mL injection registered in Singapore at present)*	SC 140 mg once every 2 weeks or 420 mg once monthly	Not required eGFR <30: Limited experience and data; use with caution	Injection site reactions, upper respiratory tract signs and symptoms, pruritus, arthralgia, back pain	Hepatic impairment: Limited experience in severe hepatic impairment (Child-Pugh class C). No dose adjustment is needed for patients with mild or moderate hepatic impairment. Patient or caregiver should be counselled on subcutaneous injection technique and how to handle missed doses.
Alirocumab *(only 75 mg/mL and 150 mg/mL injections registered in Singapore at present)*	SC 75 mg once every 2 weeks or 300 mg once monthly SC 150 mg once every 2 weeks may be considered for those requiring >60% LDL-C reduction	No dose adjustment is needed for patients with mild or moderate renal impairment eGFR <30: Limited experience and data; use with caution		
PCSK9 inhibitor Double-stranded small interfering ribonucleic acid (SiRNA): directs breakdown of mRNA for PCSK9, increasing LDL-C receptors and enhancing clearance of cholesterol from the blood.				
Inclisiran	SC 284 mg initially, again at 3 months, then every 6 months	Not required eGFR <30: Limited experience	Injection site reactions (pain, rash, erythema)	Hepatic impairment: Limited experience in severe hepatic impairment (Child-Pugh class C). No dose adjustment is needed for patients with mild or moderate hepatic impairment. Inclisiran is to be administered by a healthcare professional.
Bile acid sequestrants: bind bile acids and promote hepatic conversion of cholesterol into bile acids, increasing LDL-C receptors and clearing LDL-C from the blood				
Cholestyramine	Initially 4 g daily, increase to 12–16 g in 1 to 4 divided doses before meals. Max dose may vary depending on product – refer to leaflet.	Not required	Constipation, GI discomfort, headache, nausea, vomiting	**Contraindication**: Complete biliary obstruction Hyperchloraemic acidosis have been reported.

*Includes medications with single active ingredient registered in Singapore. For fixed-dose combination products, refer to information on individual components. Information is referenced from local product inserts or consolidated product monographs; refer to product inserts for full details before prescribing. Information from other references (e.g. international guidelines) may differ. Clinical judgement should be exercised at all times when making decisions for an individual patient.

^Renal dose adjustment in dialysis is excluded from this table.

Abbreviations - ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **CrCl**, creatinine clearance (in mL/min); **eGFR**, estimated glomerular filtration rate (in mL/min/1.73m²); **GGT**, gamma-glutamyl transferase; **ULN**, upper limit of normal

The table includes medications with single active ingredient registered in Singapore. For fixed-dose combination products, refer to information on individual ingredients. Information is referenced from local product inserts or consolidated product monographs; refer to products inserts before prescribing. Information from other references (e.g., international guidelines) may differ. Clinical judgement should be exercised at all times when making decisions for an individual patient. Renal dose adjustment in dialysis is excluded from this table.

Annex C : Selected interactions with commonly used medications that may increase the risk of statin side effects (Table reproduced from the ACE Clinical Guidance "Lipid Management: Focus on Cardiovascular Risk"[1] with permission from Agency for Care Effectiveness (ACE), Ministry of Health, Singapore)

Statin	Medication	Recommendation**
All statins	Colchicine	Monitor signs and symptoms of myopathy
	Gemfibrozil	Avoid; if gemfibrozil must be used, rosuvastatin 10mg daily may be considered
	Fenofibrate	Monitor signs and symptoms of myopathy Max dose of rosuvastatin: 10 mg daily
Atorvastatin	Clarithromycin (oral)	Max dose of atorvastatin 20 mg daily
	Erythromycin (oral)	Monitor signs and symptoms of myopathy
	Fluconazole (oral)	Monitor signs and symptoms of myopathy
	Itraconazole (oral)	Max dose of atorvastatin 20 mg daily
	Sacubitril and valsartan combination	Consider lower doses and monitor signs and symptoms of myopathy, or use other statins
	Verapamil	Consider lower doses of atorvastatin and monitor signs and symptoms of myopathy
Lovastatin	Amlodipine	Monitor signs and symptoms of myopathy; consider limiting lovastatin dose to 20 mg daily
	Amiodarone	Max dose of lovastatin 40 mg daily
	Clarithromycin (oral)	Avoid; stop statin temporarily to complete course of treatment if clarithromycin is needed
	Diltiazem	Max dose of lovastatin 20 mg daily
	Erythromycin (oral)	Avoid
	Fluconazole (oral)	Monitor signs and symptoms of myopathy
	Itraconazole (oral)	Avoid; lovastatin is contraindicated during and for 2 weeks after treatment with itraconazole
	Ticagrelor	Max dose of lovastatin 40 mg daily
	Verapamil	Max dose of lovastatin 20 mg daily
Pitavastatin	Erythromycin (oral)	Max dose of pitavastatin 1 mg daily
Pravastatin	Clarithromycin (oral)	Max dose of pravastatin 40 mg daily
Rosuvastatin	Clopidogrel	Max dose of rosuvastatin 20 mg daily
Simvastatin	Amlodipine	Max dose of simvastatin 20 mg daily
	Amiodarone	Max dose of simvastatin 20 mg daily
	Clarithromycin (oral)	Avoid; stop statin temporarily to complete course of treatment if clarithromycin is needed
	Diltiazem	Avoid using simvastatin doses greater than 10 mg/day and diltiazem doses greater than 240 mg/day
	Erythromycin (oral)	Avoid
	Fluconazole (oral)	Monitor signs and symptoms of myopathy
	Itraconazole (oral)	Avoid; simvastatin is contraindicated during and for 2 weeks after treatment with itraconazole
	Nirmatrelvir and ritonavir combination (Paxlovid)	Stop statin temporarily to complete course of treatment
	Ticagrelor	Max dose of simvastatin 40 mg daily
	Verapamil	Max dose of simvastatin 10 mg daily

**Refer to drug interactions checker for full details on management and other medications.

References

1. Agency for Care Effectiveness (ACE). Lipid management: focus on cardiovascular risk. ACE Clinical Guidance (ACG), Ministry of Health, Singapore. 2023. Available from: go.gov.sg/acg-lipid-management

2. Weir HK, Anderson RN, King SMC, Soman A, Thompson TD, Hong Y, Moller B, Leadbetter S. Heart Disease and Cancer Deaths - Trends and Projections in the United States, 1969-2020. *Prev Chronic Dis* 2016;13:E157.

3. Xu J, Murphy SL, Kochanek KD, Arias E. Mortality in the United States, 2015. *NCHS Data Brief* 2016:1-8.

4. Younus A, Aneni EC, Spatz ES, Osondu CU, Roberson L, Ogunmoroti O, Malik R, Ali SS, Aziz M, Feldman T, Virani SS, Maziak W, Agatston AS, Veledar E, Nasir K. A Systematic Review of the Prevalence and Outcomes of Ideal Cardiovascular Health in US and Non-US Populations. *Mayo Clin Proc* 2016;91:649-670.

5. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, Backer GGD, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen M-R, Tokgozoglu L, Wiklund O. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111-188.

6. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, Ferranti SD, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Sidney C Smith J, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;139:e1082–e1143.

7. Ministry of Health Singapore. Clinical practice guidelines on lipids 2016. *MOH clinical practice guidelines, Singapore* 2016.

8. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Borén J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, Sluis Bvd, Taskinen M-R, Tokgözoglu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017;38:2459-2472.

9. Cholesterol Treatment Trialists' (CTT) Collaboration, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, Simes J, Collins R, Kirby A, Colhoun H, Braunwald E, Rosa JL, Pedersen TR, Tonkin A, Davis B, Sleight P, Franzosi MG, Baigent C, Keech A. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015;385:1397-1405.

10. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;380:581-590.

11. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, Braunwald E, Sabatine MS. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. *JAMA* 2016;316:1289-1297.

12. Navarese EP, Robinson JG, Kowalewski M, Kolodziejczak M, Andreotti F, Bliden K, Tantry U, Kubica J, Raggi P, Gurbel PA. Association Between Baseline LDL-C Level and Total and Cardiovascular Mortality After LDL-C Lowering: A Systematic Review and Meta-analysis. *JAMA* 2018;319:1566-1579.

13. Emerging Risk Factors Collaboration, Angelantonio ED, Gao P, Pennells L, Kaptoge S, Caslake M, Thompson A, Butterworth AS, Sarwar N, Wormser D, Saleheen D, Ballantyne CM, Psaty BM, Sundström J, Ridker PM, Nagel D, Gillum RF, Ford I, Ducimetiere P, Kiechl S, Koenig W, Dullaart RPF, Assmann G, Ralph B D'Agostino Sr, Dagenais GR, Cooper JA, Kromhout D, Onat A, Tipping RW, Gómez-de-la-Cámara A, Rosengren A, Sutherland SE, Gallacher J, Fowkes FGR, Casiglia E, Hofman A, Salomaa V, Barrett-

Connor E, Clarke R, Brunner E, Jukema JW, Simons LA, Sandhu M, Wareham NJ, Khaw K-T, Kauhanen J, Salonen JT, Howard WJ, Nordestgaard BG, Wood AM, Thompson SG, Boekholdt SM, Sattar N, Packard C, Gudnason V, Danesh J. Lipid-Related Markers and Cardiovascular Disease Prediction. *JAMA* 2012;307:2499-2506.

14. Harari G, Green MS, Magid A, Zelber-Sagi S. Usefulness of Non-High-Density Lipoprotein Cholesterol as a Predictor of Cardiovascular Disease Mortality in Men in 22-Year Follow-Up. *Am J Cardiol* 2017;119:1193-1198.

15. van Deventer HE, Miller WG, Myers GL, Sakurabayashi I, Bachmann LM, Caudill SP, Dziekonski A, Edwards S, Kimberly MM, Korzun WJ, Leary ET, Nakajima K, Nakamura M, Shamburek RD, Vetrovec GW, Warnick GR, Remaley AT. Non-HDL cholesterol shows improved accuracy for cardiovascular risk score classification compared to direct or calculated LDL cholesterol in a dyslipidemic population. *Clin Chem* 2011;57:490-501.

16. Johnson NB, Hayes LD, Brown K, Hoo EC, Ethier KA. CDC National Health Report: leading causes of morbidity and mortality and associated behavioral risk and protective factors--United States, 2005-2013. *MMWR Suppl* 2014;63:3-27.

17. US Preventive Services Task Force. Screening adults for lipid disorders: recommendations and rationale. *Am J Prev Med* 2001;20:73-76.

18. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Donald Lloyd-Jones, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC, Virani SS, Williams KA, Yeboah J, Ziaeian B. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;140:e596-e646.

19. Health hub Singapore. ABCs of Health Screening. https://www.healthhub.sg/live-healthy/abcs_of_health_screening and https://www.healthhub.sg/programmes/screen_for_life/sfl-faqs Last accessed online 13/12/2023.

20. Phoon IKY, Koh YLE, Guo X, Usha S, Tan NC. Compatibility between an overnight fasting and random cholesterol tests in Asians. *Sci Rep* 2021;11:6478.

21. Chapman MJ, Ginsberg HN, Amarenco P, Andreotti F, Borén J, Catapano AL, Descamps OS, Fisher E, Kovanen PT, Kuivenhoven JA, Lesnik P, Masana L, Nordestgaard BG, Ray KK, Reiner Z, Taskinen M-R, Tokgözoglu L, Tybjærg-Hansen A, Watts GF, European Atherosclerosis Society Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J* 2011;32:1345-1361.

22. Cartier L-J, Collins C, Lagacé M, Douville P. Comparison of fasting and non-fasting lipid profiles in a large cohort of patients presenting at a community hospital. *Clin Biochem* 2018;52:61-66.

23. National Clinical Guideline Centre (UK). Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease. *National Clinical Guideline Centre (UK)* 2014.

24. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease. *Heart* 2014;100:ii1-ii67.

25. Nordestgaard BG, Langsted A, Mora S, Kolovou G, Baum H, Bruckert E, Watts GF, Sypniewska G, Wiklund O, Borén J, Chapman MJ, Cobbaert C, Descamps OS, Eckardstein Av, Kamstrup PR, Pulkki K, Kronenberg F, Remaley AT, Rifai N, Ros E, Langlois M, European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) joint consensus initiative. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. *Eur Heart J* 2016;37:1944-1958.

26. Sniderman AD, Islam S, Yusuf S, McQueen MJ. Discordance analysis of apolipoprotein B and non-high density lipoprotein cholesterol as markers of cardiovascular risk in the INTERHEART study. *Atherosclerosis* 2012;225:444-449.
27. Tsimikas S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. *J Am Coll Cardiol* 2017;69:692-711.
28. Cook NR, Mora S, Ridker PM. Lipoprotein(a) and Cardiovascular Risk Prediction Among Women. *J Am Coll Cardiol* 2017:287-296.
29. Kamstrup PR, Tybjærg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and improved cardiovascular risk prediction. *J Am Coll Cardiol* 2013;61:1146-1156.
30. Willeit P, Kiechl S, Kronenberg F, Witztum JL, Santer P, Mayr M, Xu Q, Mayr A, Willeit J, Tsimikas S. Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck Study. *J Am Coll Cardiol* 2014;64:851-860.
31. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, Backer GD, Graham I, Taskinen M-R, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D, ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011;32:1769-1818.
32. US Preventive Services Task Force. Screening adults for lipid disorders: recommendations and rationale. *Am J Prev Med* 2001;20:73-76.
33. Ministry of Health Singapore. National Health Survey. Singapore. *Ministry of Health 2010* 2011.
34. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida J-M, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Angelantonio ED, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, Dis Iv, Gelder ICv, Wanner C, Williams B, ESC National Cardiac Societies, ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;42:3227-3337.
35. blog.nus.edu.sg/sphs/files/2023/10/2023_Recalibrated_Singapore-Modified_Framingham_Risk_Score_SG-FRS-2023_report.pdf
36. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-3421.
37. Madsen CM, Varbo A, Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. *Eur Heart J* 2017;38:2478-2486.
38. Patel J, Rifai MA, Scheuner MT, Shea S, Blumenthal RS, Nasir K, Blaha MJ, McEvoy JW. Basic vs More Complex Definitions of Family History in the Prediction of Coronary Heart Disease: The Multi-Ethnic Study of Atherosclerosis. *Mayo Clin Proc* 2018;93:1213-1223.
39. del-Rincón ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001;44:2737-2745.
40. Manzi S, Meilahn EN, Rairie JE, Conte CG, T A Medsger Jr, Jansen-McWilliams L, D'Agostino RB, Kuller LH. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol* 1997;145:408-415.
41. Triant VA, Perez J, Regan S, Massaro JM, Meigs JB, Grinspoon SK, Ralph B D'Agostino Sr. Cardiovascular Risk Prediction Functions Underestimate Risk in HIV Infection. *Circulation* 2018;137:2203-2214.
42. Wellons M, Ouyang P, Schreiner PJ, Herrington DM, Vaidya D. Early menopause predicts future coronary heart disease and stroke: the Multi-Ethnic Study of Atherosclerosis. *Menopause* 2012;19:1081-1087.

43. Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, Zaman A, Fryer AA, Kadam U, Chew-Graham CA, Mamas MA. Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis. *Circ Cardiovasc Qual Outcomes* 2017;10:e003497.
44. Tanz LJ, Stuart JJ, Williams PL, Rimm EB, Missmer SA, Rexrode KM, Mukamal KJ, Rich-Edwards JW. Preterm Delivery and Maternal Cardiovascular Disease in Young and Middle-Aged Adult Women. *Circulation* 2017;135:578-589.
45. Vance MC, Wiitala WL, Sussman JB, Pfeiffer P, Hayward RA. Increased Cardiovascular Disease Risk in Veterans With Mental Illness. *Circ Cardiovasc Quality and Outcomes* 2019;12:e005563.
46. Goldfarb M, Hert MD, Detraux J, Palo KD, Munir H, Music S, Piña I, Ringen PA. Severe Mental Illness and Cardiovascular Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2022;80:918-933.
47. Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, Garcia MJ, Gregson J, Pocock S, Falk E, Fuster V. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. *J Am Coll Cardiol* 2015;65:1065-1074.
48. McDermott MM, Kramer CM, Tian L, Carr J, Guralnik JM, Polonsky T, Carroll T, Kibbe M, Criqui MH, Ferrucci L, Zhao L, Hippe DS, Wilkins J, Xu D, Liao Y, McCarthy W, Yuan C. Plaque Composition in the Proximal Superficial Femoral Artery and Peripheral Artery Disease Events. *JACC Cardiovasc Imaging* 2017;10:1003-1012.
49. Sillesen H, Sartori S, Sandholt B, Baber U, Mehran R, Fuster V. Carotid plaque thickness and carotid plaque burden predict future cardiovascular events in asymptomatic adult Americans. *Eur Heart J Cardiovasc Imaging* 2018;19:1042-1050.
50. Perrone-Filardi P, Achenbach S, Möhlenkamp S, Reiner Z, Sambuceti G, Schuijf JD, Wall EVd, Kaufmann PA, Knuuti J, Schroeder S, Zellweger MJ. Cardiac computed tomography and myocardial perfusion scintigraphy for risk stratification in asymptomatic individuals without known cardiovascular disease: a position statement of the Working Group on Nuclear Cardiology and Cardiac CT of the European Society of Cardiology. *Eur Heart J* 2011;32:1986-1993, 1993a, 1993b.
51. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA* 2012;308:788-795.
52. Ruijter HMD, Peters SAE, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engström G, Evans GW, Graaf Jd, Grobbee DE, Hedblad B, Hofman A, Holewijn S, Ikeda A, Kavousi M, Kitagawa K, Kitamura A, Koffijberg H, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels G, Okazaki S, O'Leary DH, Polak JF, Price JF, Robertson C, Rembold CM, Rosvall M, Rundek T, Salonen JT, Sitzer M, Stehouwer CDA, Witteman JC, Moons KG, Bots ML. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA* 2012;308:796-803.
53. Lorenz MW, Schaefer C, Steinmetz H, Sitzer M. Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS). *Eur Heart J* 2010;31:2041-2048.
54. Kavousi M, Elias-Smale S, Rutten JHW, Leening MJG, Vliegenthart R, Verwoert GC, Krestin GP, Oudkerk M, Maat MPMd, Leebeek FWG, Mattace-Raso FUS, Lindemans J, Hofman A, Steyerberg EW, Lugt Avd, Meiracker AHvd, Witteman JCM. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. *Ann Intern Med* 2012;156:438-444.
55. Mortensen MB, Falk E, Li D, Nasir K, Blaha MJ, Sandfort V, Rodriguez CJ, Ouyang P, Budoff M. Statin Trials, Cardiovascular Events, and Coronary Artery Calcification: Implications for a Trial-Based Approach to Statin Therapy in MESA. *JACC Cardiovasc Imaging* 2018;11:221-230.
56. Garg PK, Jorgensen NW, McClelland RL, Leigh JA, Greenland P, Blaha MJ, Yoon AJ, Wong ND, Yeboah J, Budoff MJ. Use of coronary artery calcium testing to improve coronary heart disease risk assessment in a lung cancer screening population: The Multi-Ethnic Study of Atherosclerosis (MESA). *J Cardiovasc Comput Tomogr* 2018;12:493-499.
57. Hong JC, Blankstein R, Shaw LJ, Padula WV, Arrieta A, Fialkow JA, Blumenthal RS, Blaha MJ, Krumholz HM, Nasir K. Implications of Coronary Artery Calcium Testing for Treatment Decisions

Among Statin Candidates According to the ACC/AHA Cholesterol Management Guidelines: A Cost-Effectiveness Analysis. *JACC Cardiovasc Imaging* 2017;10:938-952.
58. Vlachopoulos C, Xaplanteris P, Aboyans V, Brodmann M, Cífková R, Cosentino F, Carlo MD, Gallino A, Landmesser U, Laurent S, Lekakis J, Mikhailidis DP, Naka KK, Protogerou AD, Rizzoni D, Schmidt-Trucksäss A, Bortel LV, Weber T, Yamashina A, Zimlichman R, Boutouyrie P, Cockcroft J, O'Rourke M, Park JB, Schillaci G, Sillesen H, Townsend RR. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis* 2015;241:507-532.
59. DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, Kronmal RA, McClelland RL, Nasir K, Blaha MJ. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med* 2015;162:266-275.
60. Yeboah J, Young R, McClelland RL, Delaney JC, Polonsky TS, Dawood FZ, Blaha MJ, Miedema MD, Sibley CT, Carr JJ, Burke GL, David C Goff Jr, Psaty BM, Greenland P, Herrington DM. Utility of Nontraditional Risk Markers in Atherosclerotic Cardiovascular Disease Risk Assessment. *J Am Coll Cardiol* 2016;67:139-147.
61. Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, Miedema MD, Sibley CT, Shaw LJ, Blumenthal RS, Budoff MJ, Krumholz HM. Implications of Coronary Artery Calcium Testing Among Statin Candidates According to American College of Cardiology/American Heart Association Cholesterol Management Guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2015;66:1657-1668.
62. Mortensen MB, Fuster V, Muntendam P, Mehran R, Baber U, Sartori S, Falk E. A Simple Disease-Guided Approach to Personalize ACC/AHA-Recommended Statin Allocation in Elderly People: The BioImage Study. *J Am Coll Cardiol* 2016;68:881-891.
63. Cohen R, Budoff M, McClelland RL, Sillau S, Burke G, Blaha M, Szklo M, Uretsky S, Rozanski A, Shea S. Significance of a positive family history for coronary heart disease in patients with a zero coronary artery calcium score (from the Multi-Ethnic Study of Atherosclerosis). *Am J Cardiol* 2014;114:1210-1214.
64. Budoff MJ, McClelland RL, Nasir K, Greenland P, Kronmal RA, Kondos GT, Shea S, Lima JAC, Blumenthal RS. Cardiovascular events with absent or minimal coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J* 2009;158:554-561.
65. Schulman-Marcus J, Valenti V, Hartaigh BÓ, Gransar H, Truong Q, Giambrone A, Callister TQ, Shaw LJ, Lin FY, Min JK. Prognostic utility of coronary artery calcium scoring in active smokers: a 15-year follow-up study. *Int J Cardiol* 2014;177:581-583.
66. Valenti V, Hartaigh BÓ, Cho I, Schulman-Marcus J, Gransar H, Heo R, Truong QA, Shaw LJ, Knapper J, Kelkar AA, Sciarretta S, Chang H-J, Callister TQ, Min JK. Absence of Coronary Artery Calcium Identifies Asymptomatic Diabetic Individuals at Low Near-Term But Not Long-Term Risk of Mortality: A 15-Year Follow-Up Study of 9715 Patients. *Circ Cardiovasc Imaging* 2016;9:e003528.
67. Budoff MJ, Young R, Burke G, Carr JJ, Detrano RC, Folsom AR, Kronmal R, Lima JAC, Liu KJ, McClelland RL, Michos E, Post WS, Shea S, Watson KE, Wong ND. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). *Eur Heart J* 2018;39:2401-2408.
68. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670-1681.
69. Hsia J, MacFadyen JG, Monyak J, Ridker PM. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol <50 mg/dl with rosuvastatin. The JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *J Am Coll Cardiol* 2011;57:1666-1675.
70. McCormack T, Dent R, Blagden M. Very low LDL-C levels may safely provide additional clinical cardiovascular benefit: the evidence to date. *Int J Clin Pract* 2016;70:886-897.

71. Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, Nakaya N, Nishimoto S, Muranaka M, Yamamoto A, Mizuno K, Ohashi Y, MEGA Study Group. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet* 2006;368:1155-1163.
72. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet* 2012;380:565-571.
73. Clearfield M, Whitney EJ, Weis S, Downs JR, Shapiro DR, Stein EA, Watson DJ, Langendörfer A, Beere PA, Stamler J, Jr AMG. Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS): baseline characteristics and comparison with USA population. *J Cardiovasc Risk* 2000;7:125-133.
74. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, Ferrari GMD, Ruzyllo W, Lucca PD, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM, IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015;372:2387-2397.
75. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017;376:1713-1722.
76. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby J-F, Tricoci P, White HD, Zeiher AM, ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* 2018;379:2097-2107.
77. Landmesser U, Chapman MJ, Farnier M, Gencer B, Gielen S, Hovingh GK, Lüscher TF, Sinning D, Tokgözoglu L, Wiklund O, Zamorano JL, Pinto FJ, Catapano AL, European Society of Cardiology (ESC), European Atherosclerosis Society (EAS). European Society of Cardiology/European Atherosclerosis Society Task Force consensus statement on proprotein convertase subtilisin/kexin type 9 inhibitors: practical guidance for use in patients at very high cardiovascular risk. *Eur Heart J* 2017;38:2245-2255.
78. Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, Flather M, Glynn RJ, Gregoire J, Jukema JW, Karpov Y, Kastelein JJP, Koenig W, Lorenzatti A, Manga P, Masiukiewicz U, Miller M, Mosterd A, Murin J, Nicolau JC, Nissen S, Ponikowski P, Santos RD, Schwartz PF, Soran H, White H, Wright RS, Vrablik M, Yunis C, Shear CL, Tardif J-C, SPIRE Cardiovascular Outcome Investigators. Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients. *N Engl J Med* 2017;376:1527-1539.
79. Sabatine MS, Ferrari GMD, Giugliano RP, Huber K, Lewis BS, Ferreira J, Kuder JF, Murphy SA, Wiviott SD, Kurtz CE, Honarpour N, Keech AC, Sever PS, Pedersen TR. Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease: Analysis From FOURIER. *Circulation* 2018;138:756-766.
80. Giugliano RP, Pedersen TR, Park J-G, Ferrari GMD, Gaciong ZA, Ceska R, Toth K, Gouni-Berthold I, Lopez-Miranda J, Schiele F, Mach F, Ott BR, Kanevsky E, Pineda AL, Somaratne R, Wasserman SM, Keech AC, Sever PS, Sabatine MS, FOURIER Investigators. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet* 2017;390:1962-1971.
81. Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, Ose L, Averna M, Boileau C, Borén J, Bruckert E, Catapano AL, Defesche JC, Descamps OS, Hegele RA, Hovingh GK, Humphries SE, Kovanen PT, Kuivenhoven JA, Masana L, Nordestgaard BG, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AFH, Steinhagen-Thiessen E, Stroes ES, Taskinen M-R, Tybjærg-Hansen A, Wiklund O, European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J* 2015;36:2425-2437.
82. Braamskamp MJAM, Langslet G, McCrindle BW, Cassiman D, Francis GA, Gagne C, Gaudet D, Morrison KM, Wiegman A, Turner T, Miller E, Kusters DM, Raichlen JS, Martin PD, Stein EA, Kastelein JJP, Hutten BA. Effect of Rosuvastatin on Carotid Intima-Media Thickness in Children With

Heterozygous Familial Hypercholesterolemia: The CHARON Study (Hypercholesterolemia in Children and Adolescents Taking Rosuvastatin Open Label). *Circulation* 2017;136:359-366.
83. Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Tonstad S, Wiegman A, Drogari E, Ramaswami U. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst Rev* 2019;2019:CD006401.
84. Reiner Ž. Treatment of children with homozygous familial hypercholesterolaemia. *Eur J Prev Cardiol* 2018;25:1095-1097.
85. Watts GF, Gidding S, Wierzbicki AS, Toth PP, Alonso R, Brown WV, Bruckert E, Defesche J, Lin KK, Livingston M, Mata P, Parhofer KG, Raal FJ, Santos RD, Sijbrands EJG, Simpson WG, Sullivan DR, Susekov AV, Tomlinson B, Wiegman A, Yamashita S, Kastelein JJP. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. *Int J Cardiol* 2014;171:309-325.
86. Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008;371:117-125.
87. Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration, Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, Angelantonio ED, Boekholdt SM, Ouwehand W, Watkins H, Samani NJ, Saleheen D, Lawlor D, Reilly MP, Hingorani AD, Talmud PJ, Danesh J. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet* 2010;375:1634-1639.
88. Maki KC, Guyton JR, Orringer CE, Hamilton-Craig I, Alexander DD, Davidson MH. Triglyceride-lowering therapies reduce cardiovascular disease event risk in subjects with hypertriglyceridemia. *J Clin Lipidol* 2016;10:905-914.
89. Charlton-Menys V, Betteridge DJ, Colhoun H, Fuller J, France M, Hitman GA, Livingstone SJ, Neil HAW, Newman CB, Szarek M, DeMicco DA, Durrington PN. Targets of statin therapy: LDL cholesterol, non-HDL cholesterol, and apolipoprotein B in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS). *Clin Chem* 2009;55:473-480.
90. Thanassoulis G, Williams K, Ye K, Brook R, Couture P, Lawler PR, Graaf Jd, Furberg CD, Sniderman A. Relations of change in plasma levels of LDL-C, non-HDL-C and apoB with risk reduction from statin therapy: a meta-analysis of randomized trials. *J Am Heart Assoc* 2014;3:e000759.
91. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med* 2000;343:16-22.
92. Dalen JE, Devries S. Diets to prevent coronary heart disease 1957-2013: what have we learned? *Am J Med* 2014;127:364-369.
93. Eckel RH, Jakicic JM, Ard JD, Jesus JMd, Miller NH, Hubbard VS, Lee I-M, Lichtenstein AH, Loria CM, Millen BE, Nonas CA, Sacks FM, Sidney C Smith Jr, Svetkey LP, Wadden TA, Yanovski SZ, Kendall KA, Morgan LC, Trisolini MG, Velasco G, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen W-K, Sidney C Smith Jr, Tomaselli GF, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129:S76-99.
94. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, Franco OH, Butterworth AS, Forouhi NG, Thompson SG, Khaw K-T, Mozaffarian D, Danesh J, Angelantonio ED. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. *Ann Intern Med* 2014;160:398-406.
95. Mente A, Koning Ld, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med* 2009;169:659-669.
96. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med* 2010;7:e1000252.
97. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004;328:1519.

98. Rabkin SW. Effect of cigarette smoking cessation on risk factors for coronary atherosclerosis. A control clinical trial. *Atherosclerosis* 1984;53:173-184.
99. Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, Naghavi M, Mensah GA, Murray CJL. Demographic and epidemiologic drivers of global cardiovascular mortality. *N Engl J Med* 2015;372:1333-1341.
100. Craig WY, Palomaki GE, Haddow JE. Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data. *BMJ* 1989;298:784-788.
101. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr* 1992;56:320-328.
102. Nordmann AJ, Nordmann A, Briel M, Keller U, William S Yancy Jr, Brehm BJ, Bucher HC. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2006;166:285-293.
103. Kodama S, Tanaka S, Saito K, Shu M, Sone Y, Onitake F, Suzuki E, Shimano H, Yamamoto S, Kondo K, Ohashi Y, Yamada N, Sone H. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. *Arch Intern Med* 2007;167:999-1008.
104. Slentz CA, Houmard JA, Johnson JL, Bateman LA, Tanner CJ, McCartney JS, Duscha BD, Kraus WE. Inactivity, exercise training and detraining, and plasma lipoproteins. STRRIDE: a randomized, controlled study of exercise intensity and amount. *J Appl Physiol (1985)* 2007;103:432-442.
105. Kelley GA, Kelley KS, Roberts S, Haskell W. Comparison of aerobic exercise, diet or both on lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. *Clin Nutr* 2012;31:156-167.
106. Health Hub Singapore. Alcohol and health - set your drinking limits. https://www.healthhub.sg/live-healthy/alcohol-and-health-set-your-drinking-limits. Last accessed online 14/12/2023.
107. GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2018;392:1015-1035.
108. Wood AM, Kaptoge S, Butterworth AS, Willeit P, Warnakula S, Bolton T, Paige E, Paul DS, Sweeting M, Burgess S, Bell S, Astle W, Stevens D, Koulman A, Selmer RM, Verschuren WMM, Sato S, Njølstad I, Woodward M, Salomaa V, Nordestgaard BG, Yeap BB, Fletcher A, Melander O, Kuller LH, Balkau B, Marmot M, Koenig W, Casiglia E, Cooper C, Arndt V, Franco OH, Wennberg P, Gallacher J, Agustín Gómez de la Cámara, Völzke H, Dahm CC, Dale CE, Bergmann MM, Crespo CJ, Schouw YTvd, Kaaks R, Simons LA, Lagiou P, Schoufour JD, Boer JMA, Key TJ, Rodriguez B, Moreno-Iribas C, Davidson KW, Taylor JO, Sacerdote C, Wallace RB, Quiros JR, Tumino R, Dan G Blazer 2nd, Linneberg A, Daimon M, Panico S, Howard B, Skeie G, Strandberg T, Weiderpass E, Nietert PJ, Psaty BM, Kromhout D, Salamanca-Fernandez E, Kiechl S, Krumholz HM, Grioni S, Palli D, Huerta JM, Price J, Sundström J, Arriola L, Arima H, Travis RC, Panagiotakos DB, Karakatsani A, Trichopoulou A, Kühn T, Grobbee DE, Barrett-Connor E, Schoor Nv, Boeing H, Overvad K, Kauhanen J, Wareham N, Langenberg C, Forouhi N, Wennberg M, Després J-P, Cushman M, Cooper JA, Rodriguez CJ, Sakurai M, Shaw JE, Knuiman M, Voortman T, Meisinger C, Tjønneland A, Brenner H, Palmieri L, Dallongeville J, Brunner EJ, Assmann G, Trevisan M, Gillum RF, Ford I, Sattar N, Lazo M, Thompson SG, Ferrari P, Leon DA, Smith GD, Peto R, Jackson R, Banks E, Angelantonio ED, Danesh J, Emerging Risk Factors Collaboration/EPIC-CVD/UK Biobank Alcohol Study Group. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet* 2018;391:1513-1523.
109. Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. *BMJ* 2011;342:d636.
110. Piano MR. Alcohol's Effects on the Cardiovascular System. *Alcohol Res* 2017;38:219-241.
111. Schooling CM, Sun W, Ho SY, Chan WM, Tham MK, Ho KS, Leung GM, Lam TH. Moderate alcohol use and mortality from ischaemic heart disease: a prospective study in older Chinese people. *PLoS One* 2008;3:e2370.

112. Roy A, Prabhakaran D, Jeemon P, Thankappan KR, Mohan V, Ramakrishnan L, Joshi P, Ahmed F, Mohan BVM, Saran RK, Sinha N, Reddy KS, Sentinel Surveillance in Industrial Populations Study Group. Impact of alcohol on coronary heart disease in Indian men. *Atherosclerosis* 2010;210:531-535.
113. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ* 1999;319:1523-1528.
114. Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, Hatcher B, Cox CL, Dyachenko A, Zhang W, McGahan JP, Seibert A, Krauss RM, Chiu S, Schaefer EJ, Ai M, Otokozawa S, Nakajima K, Nakano T, Beysen C, Hellerstein MK, Berglund L, Havel PJ. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest* 2009;119:1322-1334.
115. Stanhope KL, Havel PJ. Fructose consumption: recent results and their potential implications. *Ann N Y Acad Sci* 2010;1190:15-24.
116. Stanhope KL, Medici V, Bremer AA, Lee V, Lam HD, Nunez MV, Chen GX, Keim NL, Havel PJ. A dose-response study of consuming high-fructose corn syrup-sweetened beverages on lipid/lipoprotein risk factors for cardiovascular disease in young adults. *Am J Clin Nutr* 2015;101:1144-1154.
117. Taskinen M-R, Söderlund S, Bogl LH, Hakkarainen A, Matikainen N, Pietiläinen KH, Räsänen S, Lundbom N, Björnson E, Eliasson B, Mancina RM, Romeo S, Alméras N, Pepa GD, Vetrani C, Prinster A, Annuzzi G, Rivellese A, Després J-P, Borén J. Adverse effects of fructose on cardiometabolic risk factors and hepatic lipid metabolism in subjects with abdominal obesity. *J Intern Med* 2017;282:187-201.
118. Lorgeril Md, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 1999;99:779-785.
119. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Martínez-González MA. Retraction and Republication: Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. N Engl J Med 2013;368:1279-90. *N Engl J Med* 2018;378:2441-2442.
120. Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Trans Fatty Acids and Cardiovascular Disease. *N Engl J Med* 2006;354:1601-1613.
121. Yu-Poth S, Zhao G, Etherton T, Naglak M, Jonnalagadda S, Kris-Etherton PM. Effects of the National Cholesterol Education Program's Step I and Step II dietary intervention programs on cardiovascular disease risk factors: a meta-analysis. *Am J Clin Nutr* 1999;69:632-646.
122. Mensink RP, Zock PL, Kester ADM, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr* 2003;77:1146-1155.
123. Schwingshackl L, Bogensberger B, Benčič A, Knüppel S, Boeing H, Hoffmann G. Effects of oils and solid fats on blood lipids: a systematic review and network meta-analysis. *J Lipid Res* 2018;59:1771-1782.
124. Hopkins PN. Effects of dietary cholesterol on serum cholesterol: a meta-analysis and review. *Am J Clin Nutr* 1992;55:1060-1070.
125. U.S. Department of Agriculture, U.S. Department of Health and Human Services. 2010 Dietary Guidelines. *wwwdietaryguidelinesgov* 2010.
126. Hartley L, May MD, Loveman E, Colquitt JL, Rees K. Dietary fibre for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2016;2016:CD011472.
127. Pirro M, Vetrani C, Bianchi C, Mannarino MR, Bernini F, Rivellese AA. Joint position statement on "Nutraceuticals for the treatment of hypercholesterolemia" of the Italian Society of Diabetology (SID) and of the Italian Society for the Study of Arteriosclerosis (SISA). *Nutr Metab Cardiovasc Dis* 2017;27:2-17.
128. Brown L, Rosner B, Willett WW, Sacks FM. Cholesterol-lowering effects of dietary fiber: a meta-analysis. *Am J Clin Nutr* 1999;69:30-42.

129. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart J-C, Gotto AM, Greten H, Kastelein JJP, Shepherd J, Wenger NK, Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425-1435.
130. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R, Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-1278.
131. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH, CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685-696.
132. Hay JW, Yu WM, Ashraf T. Pharmacoeconomics of lipid-lowering agents for primary and secondary prevention of coronary artery disease. *Pharmacoeconomics* 1999;15:47-74.
133. Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R, Heart Protection Study Collaborative Group. Cost-effectiveness of simvastatin in people at different levels of vascular disease risk: economic analysis of a randomised trial in 20,536 individuals. *Lancet* 2005;365:1779-1785.
134. Mitchell AP, Simpson RJ. Statin cost effectiveness in primary prevention: A systematic review of the recent cost-effectiveness literature in the United States. *BMC Res Notes* 2012;5:373.
135. Lazar LD, Pletcher MJ, Coxson PG, Bibbins-Domingo K, Goldman L. Cost-effectiveness of statin therapy for primary prevention in a low-cost statin era. *Circulation* 2011;124:146-153.
136. Wagner M, Lindgren P, Merikle E, Goetghebeur M, Jönsson B. Economic evaluation of high-dose (80 mg/day) atorvastatin treatment compared with standard-dose (20 mg/day to 40 mg/day) simvastatin treatment in Canada based on the Incremental Decrease in End-Points Through Aggressive Lipid-Lowering (IDEAL) trial. *Can J Cardiol* 2009;25:e362-369.
137. Plosker GL, Lyseng-Williamson KA. Atorvastatin: a pharmacoeconomic review of its use in the primary and secondary prevention of cardiovascular events. *Pharmacoeconomics* 2007;25:1031-1053.
138. Shepherd J, Blauw GJ, Murphy MB, Bollen ELEM, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RGJ, PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623-1630.
139. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-1389.
140. Genser B, März W. Low density lipoprotein cholesterol, statins and cardiovascular events: a meta-analysis. *Clin Res Cardiol* 2006;95:393-404.
141. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit. A new look at old data. *Circulation* 1995;91:2274-2282.
142. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. *Circulation* 1998;97:946-952.
143. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999;282:2340-2346.
144. Mills EJ, Wu P, Chong G, Ghement I, Singh S, Akl EA, Eyawo O, Guyatt G, Berwanger O, Briel M. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. *QJM* 2011;104:109-124.
145. Ray KK, Seshasai SRK, Erqou S, Sever P, Jukema JW, Ford I, Sattar N. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. *Arch Intern Med* 2010;170:1024-1031.
146. Taylor F, Huffman MD, Macedo AF, Moore THM, Burke M, Smith GD, Ward K, Ebrahim S. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013;1:CD004816.
147. Cholesterol Treatment Trialists' (CTT) Collaboration, Herrington W, Emberson J, Mihaylova B, Blackwell L, Reith C, Solbu M, Mark P, Fellström B, Jardine A, Wanner C, Holdaas H, Fulcher J, Haynes R, Landray M, Keech A, Simes J, Collins R, Baigent C. Impact of renal function on the effects of LDL

cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. *Lancet Diabetes Endocrinol* 2016;4:829-839.
148. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol* 1998;81:582-587.
149. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, Cain VA, Blasetto JW, STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol* 2003;92:152-160.
150. Adams SP, Alaeiilkhchi N, Wright JM. Pitavastatin for lowering lipids. *Cochrane Database Syst Rev* 2017;2017:CD012735.
151. Karlson BW, Wiklund O, Palmer MK, Nicholls SJ, Lundman P, Barter PJ. Variability of low-density lipoprotein cholesterol response with different doses of atorvastatin, rosuvastatin, and simvastatin: results from VOYAGER. *Eur Heart J Cardiovasc Pharmacother* 2016;2:212-217.
152. Liao JK. Safety and efficacy of statins in Asians. *Am J Cardiol* 2007;99:410-414.
153. Lee E, Ryan S, Birmingham B, Zalikowski J, March R, Ambrose H, Moore R, Lee C, Chen Y, Schneck D. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. *Clin Pharmacol Ther* 2005;78:330-341.
154. HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, Wallendszus K, Craig M, Jiang L, Collins R, Armitage J. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* 2014;371:203-212.
155. Reiner Z. Managing the residual cardiovascular disease risk associated with HDL-cholesterol and triglycerides in statin-treated patients: a clinical update. *Nutr Metab Cardiovasc Dis* 2013;23:799-807.
156. Keating AJ, Campbell KB, Guyton JR. Intermittent nondaily dosing strategies in patients with previous statin-induced myopathy. *Ann Pharmacother* 2013;47:398-404.
157. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, Craen AJMd, Seshasai SRK, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Pressel SL, Marchioli R, Marfisi RM, Maggioni AP, Tavazzi L, Tognoni G, Kjekshus J, Pedersen TR, Cook TJ, Gotto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KK, Ford I. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010;375:735-742.
158. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. *Eur Heart J* 2016;37:908-916.
159. Matthews A, Herrett E, Gasparrini A, Staa TV, Goldacre B, Smeeth L, Bhaskaran K. Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. *BMJ* 2016;353:i3283.
160. Tobert JA, Newman CB. The nocebo effect in the context of statin intolerance. *J Clin Lipidol* 2016;10:739-747.
161. Mach F, Ray KK, Wiklund O, Corsini A, Catapano AL, Bruckert E, Backer GD, Hegele RA, Hovingh GK, Jacobson TA, Krauss RM, Laufs U, Leiter LA, März W, Nordestgaard BG, Raal FJ, Roden M, Santos RD, Stein EA, Stroes ES, Thompson PD, Tokgözoglu L, Vladutiu GD, Gencer B, Stock JK, Ginsberg HN, Chapman MJ, European Atherosclerosis Society Consensus Panel. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *Eur Heart J* 2018;39:2526-2539.
162. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D, Evans S, Law M, MacMahon S, Martin S, Neal B, Poulter N, Preiss D, Ridker P, Roberts I, Rodgers A, Sandercock P, Schulz K, Sever P, Simes J, Smeeth L, Wald N, Yusuf S, Peto R. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016;388:2532-2561.
163. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, Roden M, Stein E, Tokgözoğlu L, Nordestgaard BG, Bruckert E, Backer GD, Krauss RM, Laufs U, Santos RD, Hegele RA, Hovingh GK, Leiter LA, Mach F, März W, Newman CB, Wiklund O, Jacobson TA, Catapano AL, Chapman MJ, Ginsberg HN, European Atherosclerosis Society Consensus Panel. Statin-associated muscle symptoms: impact on

statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management *Eur Heart J* 2015;36:1012–1022.
164. Law M, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol* 2006;97:52C-60C.
165. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage J, Bowman L, Wallendszus K, Bulbulia R, Rahimi K, Haynes R, Parish S, Peto R, Collins R. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet* 2010;376:1658-1669.
166. U.S. Food and Drug Administration. FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. *http://wwwfdagov/Drugs/DrugSafety/ucm256581htm* 2011.
167. Health Sciences Authority Singapore. Safety update on statins. *https://wwwhsagovsg/announcements/safety-alert/safety-updates-on-statins* 2012.
168. Franssen R, Vergeer M, Stroes ESG, Kastelein JJP. Combination statin-fibrate therapy: safety aspects. *Diabetes Obes Metab* 2009;11:89-94.
169. Holoshitz N, Alsheikh-Ali AA, Karas RH. Relative safety of gemfibrozil and fenofibrate in the absence of concomitant cerivastatin use. *Am J Cardiol* 2008;101:95-97.
170. Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with Elevated Liver Enzymes Are Not at Higher Risk for Statin Hepatotoxicity. *Gastroenterology* 2001;126:1287-1292.
171. Dongiovanni P, Petta S, Mannisto V, Mancina RM, Pipitone R, Karja V, Maggioni M, Kakela P, Wiklund O, Mozzi E, Grimaudo S, Kaminska D, Rametta R, Craxi A, Fargion S, Nobili V, Romeo S, Pihlajamaki J, Valenti L. Statin use and non-alcoholic steatohepatitis in at risk individuals. *J Hepatol* 2015;63:705-712.
172. Vuppalanchi R, Teal E, Chalasani N. Patients with elevated baseline liver enzymes do not have higher frequency of hepatotoxicity from lovastatin than those with normal baseline liver enzymes. *Am J Med Sci* 2005;329:62-65.
173. Marcum ZA, Griend JPV, Linnebur SA. FDA drug safety communications: a narrative review and clinical considerations for older adults. *Am J Geriatr Pharmacother* 2012;10:264-271.
174. Naci H, Brugts J, Ades T. Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. *Circ Cardiovasc Qual Outcomes* 2013;6:390-399.
175. Newman C, Tsai J, Szarek M, Luo D, Gibson E. Comparative safety of atorvastatin 80 mg versus 10 mg derived from analysis of 49 completed trials in 14,236 patients. *Am J Cardiol* 2006;97:61-67.
176. Björnsson E, Jacobsen EI, Kalaitzakis E. Hepatotoxicity associated with statins: reports of idiosyncratic liver injury post-marketing. *J Hepatol* 2012;56:374-380.
177. Clarke AT, Johnson PCD, Hall GC, Ford I, Mills PR. High Dose Atorvastatin Associated with Increased Risk of Significant Hepatotoxicity in Comparison to Simvastatin in UK GPRD Cohort. *PLoS One* 2016;11:e0151587.
178. Preiss D, Seshasai SRK, Welsh P, Murphy SA, Ho JE, Waters DD, DeMicco DA, Barter P, Cannon CP, Sabatine MS, Braunwald E, Kastelein JJP, Lemos JAd, Blazing MA, Pedersen TR, Tikkanen MJ, Sattar N, Ray KK. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* 2011;305:2556-2564.
179. Cederberg H, Stančáková A, Yaluri N, Modi S, Kuusisto J, Laakso M. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. *Diabetologia* 2015;58:1109-1117.
180. Orsi A, Sherman O, Woldeselassie Z. Simvastatin-associated memory loss. *Pharmacotherapy* 2001;21:767-769.
181. King DS, Wilburn AJ, Wofford MR, Harrell TK, Lindley BJ, Jones DW. Cognitive impairment associated with atorvastatin and simvastatin. *Pharmacotherapy* 2003;23:1663-1667.
182. Galatti L, Polimeni G, Salvo F, Romani M, Sessa A, Spina E. Short-term memory loss associated with rosuvastatin. *Pharmacotherapy* 2006;26:1190-1192.

183. Padala KP, Padala PR, Potter JF. Simvastatin-induced decline in cognition. *Ann Pharmacother* 2006;40:1880-1883.
184. Okeahialam BN, Isiguzoro I. Statin related memory dysfunction in a Nigerian woman: a case report. *Curr Drug Saf* 2012;7:33-34.
185. McDonagh J. Statin-related cognitive impairment in the real world: you'll live longer, but you might not like it. *JAMA Intern Med* 2014;174:1889.
186. Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. *Pharmacotherapy* 2003;23:871-880.
187. Langsjoen PH, Langsjoen JO, Langsjoen AM, Lucas LA. Treatment of statin adverse effects with supplemental Coenzyme Q10 and statin drug discontinuation. *Biofactors* 2005;25:147-152.
188. Evans MA, Golomb BA. Statin-associated adverse cognitive effects: survey results from 171 patients. *Pharmacotherapy* 2009;29:800-811.
189. Rockwood K, Howlett S, Fisk J, Darvesh S, Tuokko H, Hogan DB, Wolfson C, McDowell I. Lipid-lowering agents and the risk of cognitive impairment that does not meet criteria for dementia, in relation to apolipoprotein E status. *Neuroepidemiology* 2007;29:201-207.
190. Bernick C, Katz R, Smith NL, Rapp S, Bhadelia R, Carlson M, Kuller L, Cardiovascular Health Study Collaborative Research Group. Statins and cognitive function in the elderly: the Cardiovascular Health Study. *Neurology* 2005;65:1388-1394.
191. Song Y, Nie H, Xu Y, Zhang L, Wu Y. Association of statin use with risk of dementia: a meta-analysis of prospective cohort studies. *Geriatr Gerontol Int* 2013;13:817-824.
192. Richardson K, Schoen M, French B, Umscheid CA, Mitchell MD, Arnold SE, Heidenreich PA, Rader DJ, deGoma EM. Statins and cognitive function: a systematic review. *Ann Intern Med* 2013;159:688-697.
193. Ott BR, Daiello LA, Dahabreh IJ, Springate BA, Bixby K, Murali M, Trikalinos TA. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. *J Gen Intern Med* 2015;30:348-358.
194. Giugliano RP, Wiviott SD, Blazing MA, Ferrari GMD, Park J-G, Murphy SA, White JA, Tershakovec AM, Cannon CP, Braunwald E. Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol : A Prespecified Analysis of the IMPROVE-IT Trial. *JAMA Cardiol* 2017;2:547-555.
195. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, Zeeuw Dd, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Yiping Chen D, Chen PZ, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins PR. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;377:2181-2192.
196. Davidson MH. Rosuvastatin safety: lessons from the FDA review and post-approval surveillance. *Expert Opin Drug Saf* 2004;3:547-557.
197. Amarenco P, Bogousslavsky J, Alfred Callahan 3rd, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KMA, Zivin JA, Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;355:549-559.
198. Anderson TJ, Grégoire J, Hegele RA, Couture P, Mancini GBJ, McPherson R, Francis GA, Poirier P, Lau DC, Grover S, Jacques Genest Jr, Carpentier AC, Dufour R, Gupta M, Ward R, Leiter LA, Lonn E, Ng DS, Pearson GJ, Yates GM, Stone JA, Ur E. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol* 2013;29:151-167.
199. Cheeley MK, Saseen JJ, Agarwala A, Ravilla S, Ciffone N, Jacobson TA, Dixon DL, Maki KC. NLA scientific statement on statin intolerance: a new definition and key considerations for ASCVD risk reduction in the statin intolerant patient. *J Clin Lipidol* 2022;16:361-375.

200. Balasubramanian, R; Maideen, NMP. HMG-CoA Reductase Inhibitors (Statins) and their Drug Interactions Involving CYP Enzymes, P-glycoprotein and OATP Transporters-An Overview**.** Current Drug Metabolism, Volume 22, Number 5, 2021, pp. 328-341(14)**.**
201. Tomaszewski M, Stepien KM, Tomaszewska J, et al. 2011. Statin-induced myopathies. *Pharmacological Reports* 63: 859-66.
202. BS Wiggins, JJ Saseen, RL Page, BN Reed, K Sneed, JB Kostis, D Lanfear, S Virani, PB Morris. 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. Circ 2016;134:e468–e495.
203. Mancini GBJ, Baker S, Bergeron J, Fitchett D, Frohlich J, Genest J, Gupta M, Hegele RA, Ng D, Pope J. Diagnosis, prevention, and management of statin adverse effects and intolerance: proceedings of a Canadian Working Group Consensus Conference. *Can J Cardiol* 2011;27:635-662.
204. Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, Suresh R, Sun S, Veltri EP. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002;40:2125-2134.
205. 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* 2010;160:785-794.e710.
206. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984;251:351-364.
207. Prueksaritanont T, Tang C, Qiu Y, Mu L, Subramanian R, Lin JH. Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos* 2002;30:1280-1287.
208. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol* 2005;95:120-122.
209. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, Grenade LL, Gurwitz JH, Chan KA, Goodman MJ, Platt R. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-2590.
210. Davidson MH, Armani A, McKenney JM, Jacobson TA. Safety considerations with fibrate therapy. *Am J Cardiol* 2007;99:3C-18C.
211. Kamanna VS, Kashyap ML. Mechanism of action of niacin. *Am J Cardiol* 2008;101:20B-26B.
212. AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365:2255-2267.
213. Eslick GD, Howe PRC, Smith C, Priest R, Bensoussan A. Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-analysis. *Int J Cardiol* 2009;136:4-16.
214. Skulas-Ray AC, Wilson PWF, Harris WS, Brinton EA, Kris-Etherton PM, Richter CK, Jacobson TA, Engler MB, Miller M, Robinson JG, Blum CB, Rodriguez-Leyva D, Ferranti SDd, Welty FK, American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing and Council on Clinical Cardiology. Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association. *Circulation* 2019;140:e673-e691.
215. Abifadel M, Varret M, Rabès J-P, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D, Derré A, Villéger L, Farnier M, Beucler I, Bruckert E, Chambaz J, Chanu B, Lecerf J-M, Luc G, Moulin P, Weissenbach J, Prat A, Krempf M, Junien C, Seidah NG, Boileau C. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet* 2003;34:154-156.
216. Norata GD, Tibolla G, Catapano AL. Targeting PCSK9 for hypercholesterolemia. *Annu Rev Pharmacol Toxicol* 2014;54:273-293.
217. Nozue T. Lipid Lowering Therapy and Circulating PCSK9 Concentration. *J Atheroscler Thromb* 2017;24:895-907.

218. Thedrez A, Blom DJ, Ramin-Mangata S, Blanchard V, Croyal M, Chemello K, Nativel B, Pichelin M, Cariou B, Bourane S, Tang L, Farnier M, Raal FJ, Lambert G. Homozygous Familial Hypercholesterolemia Patients With Identical Mutations Variably Express the LDLR (Low-Density Lipoprotein Receptor): Implications for the Efficacy of Evolocumab. *Arterioscler Thromb Vasc Biol* 2018;38:592-598.
219. Cho L, Rocco M, Colquhoun D, Sullivan D, Rosenson RS, Dent R, Xue A, Scott R, Wasserman SM, Stroes E. Clinical Profile of Statin Intolerance in the Phase 3 GAUSS-2 Study. *Cardiovasc Drugs Ther* 2016;30:297-304.
220. Schmidt AF, Carter J-PL, Pearce LS, Wilkins JT, Overington JP, Hingorani AD, Casas JP. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2020;10:CD011748.
221. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, Shahawy ME, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJP, ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1489-1499.
222. Gaudet D, Kereiakes DJ, McKenney JM, Roth EM, Hanotin C, Gipe D, Du Y, Ferrand A-C, Ginsberg HN, Stein EA. 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* 2014;114:711-715.
223. Raal FJ, Giugliano RP, Sabatine MS, Koren MJ, Langslet G, Bays H, Blom D, Eriksson M, Dent R, Wasserman SM, Huang F, Xue A, Albizem M, Scott R, Stein EA. Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolocumab (AMG 145): a pooled analysis of more than 1,300 patients in 4 phase II trials. *J Am Coll Cardiol* 2014;63:1278-1288.
224. Khan SA, Naz A, Masood MQ, Shah R. Meta-Analysis of Inclisiran for the Treatment of Hypercholesterolemia. *Am J Cardiol* 2020;134:69-73.
225. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;285:1711-1718.
226. Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RGJ, Craen AJMd, Knopp RH, Nakamura H, Ridker P, Domburg Rv, Deckers JW. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *BMJ* 2009;338:b2376.
227. Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. *J Am Coll Cardiol* 2008;52:1769-1781.
228. Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve FJ, Bruckert E, Jacobson TA, Kopecky SL, Baccara-Dinet MT, Du Y, Pordy R, Gipe DA, ODYSSEY ALTERNATIVE Investigators. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol* 2015;9:758-769.
229. Nissen SE, Stroes E, Dent-Acosta RE, Rosenson RS, Lehman SJ, Sattar N, Preiss D, Bruckert E, Ceška R, Lepor N, Ballantyne CM, Gouni-Berthold I, Elliott M, Brennan DM, Wasserman SM, Somaratne R, Scott R, Stein EA, GAUSS-3 Investigators. Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial. *JAMA* 2016;315:1580-1590.
230. Schreml J, Gouni-Berthold I. Role of Anti-PCSK9 Antibodies in the Treatment of Patients with Statin Intolerance. *Curr Med Chem* 2018;25:1538-1548.
231. Moulin P, Dufour R, Averna M, Arca M, Cefalù AB, Noto D, D'Erasmo L, Costanzo AD, Marçais C, Walther LAA-S, Banach M, Borén J, Cramb R, Gouni-Berthold I, Hughes E, Johnson C, Pintó X, Reiner Ž, Lennep JRv, Soran H, Stefanutti C, Stroes E, Bruckert E. Identification and diagnosis of patients with familial chylomicronaemia syndrome (FCS): Expert panel recommendations and proposal of an "FCS score". *Atherosclerosis* 2018;275:265-272.

232. Meyers CD, Tremblay K, Amer A, Chen J, Jiang L, Gaudet D. Effect of the DGAT1 inhibitor pradigastat on triglyceride and apoB48 levels in patients with familial chylomicronemia syndrome. *Lipids Health Dis* 2015;14:8.
233. Murphy MJ, Sheng X, MacDonald TM, Wei L. Hypertriglyceridemia and acute pancreatitis. *JAMA Intern Med* 2013;173:162-164.
234. Vallejo-Vaz AJ, Fayyad R, Boekholdt SM, Hovingh GK, Kastelein JJ, Melamed S, Barter P, Waters DD, Ray KK. Triglyceride-Rich Lipoprotein Cholesterol and Risk of Cardiovascular Events Among Patients Receiving Statin Therapy in the TNT Trial. *Circulation* 2018;138:770-781.
235. Chapman MJ, Redfern JS, McGovern ME, Giral P. Niacin and fibrates in atherogenic dyslipidemia: pharmacotherapy to reduce cardiovascular risk. *Pharmacol Ther* 2010;126:314-345.
236. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, John R Crouse 3rd, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, David C Goff Jr, Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1563-1574.
237. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M, 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;366:1849-1861.
238. Catapano AL, Farnier M, Foody JM, Toth PP, Tomassini JE, Brudi P, Tershakovec AM. Combination therapy in dyslipidemia: where are we now? *Atherosclerosis* 2014;237:319-335.
239. National Institute for Health and Clinical Excellence (NICE). Cardiovascular disease: risk assessment and reduction, including lipid modification. *NICE Clinical guidelines* 2014;CG181.
240. Wanner C, Krane V, März W, Olschewski M, Mann JFE, Ruf G, Ritz E, German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;353:238-248.
241. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae D-W, Chevaile A, Cobbe SM, Grönhagen-Riska C, Lima JJD, Lins R, Mayer G, McMahon AW, Parving H-H, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Süleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wüthrich RP, Gottlow M, Johnsson E, Zannad F, AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;360:1395-1407.
242. Anfossi G, Massucco P, Bonomo K, Trovati M. Prescription of statins to dyslipidemic patients affected by liver diseases: a subtle balance between risks and benefits. *Nutr Metab Cardiovasc Dis* 2004;14:215-224.
243. Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. . *BMJ* 1991;303:893-896.
244. Defesche JC, Lansberg PJ, Umans-Eckenhausen MAW, Kastelein JJP. Advanced method for the identification of patients with inherited hypercholesterolemia. *Semin Vasc Med* 2004;4:59-65.
245. Carrington M, Stewart S. Is fenofibrate a cost-saving treatment for middle-aged individuals with type II diabetes? An economic analysis of the FIELD Study. *Int J Cardiol* 2008;127:51-56.
246. Plans-Rubió P. The cost effectiveness of statin therapies in Spain in 2010, after the introduction of generics and reference prices. *Am J Cardiovasc Drugs* 2010;10:369-382.
247. Heart Protection Study Collaborative Group. Statin cost-effectiveness in the United States for people at different vascular risk levels. *Circ Cardiovasc Qual Outcomes* 2009;2:65-72.
248. Haas JS, Phillips KA, Gerstenberger EP, Seger AC. Potential savings from substituting generic drugs for brand-name drugs: medical expenditure panel survey, 1997-2000. *Ann Intern Med* 2005;142:891-897.
249. Fonarow GC, Hout Bv, Villa G, Arellano J, Lindgren P. Updated Cost-effectiveness Analysis of Evolocumab in Patients With Very High-risk Atherosclerotic Cardiovascular Disease. *JAMA Cardiol* 2019;4:691-695.
250. Desai NR, Campbell C, Electricwala B, Petrou M, Trueman D, Woodcock F, Cristino J. Cost-effectivess of inclisiran in atherosclerotic cardiovascular disease patients with elevated low-density

lipoprotein chlesetrol despite statin use : a threshold analysis. *Am J Cardiovasc Drugs* 2022;22:545-556.
251. Kazi DS, Moran AE, Coxson PG, Penko J, Ollendorf DA, Pearson SD, Tice JA, Guzman D, Bibbins-Domingo K. Cost-effectiveness of PCSK9 Inhibitor Therapy in Patients With Heterozygous Familial Hypercholesterolemia or Atherosclerotic Cardiovascular Disease. *JAMA* 2016;316:743-753.
252. Gandra SR, Villa G, Fonarow GC, Lothgren M, Lindgren P, Somaratne R, Hout Bv. Cost-Effectiveness of LDL-C Lowering With Evolocumab in Patients With High Cardiovascular Risk in the United States. *Clin Cardiol* 2016;39:313-320.

Workgroup Members

Co-chairpersons:	
(1) Lim Chun Leng, Michael	Chapter of Cardiologists representative and ACG Expert Group member
(2) Mohammed Rizwan Amanullah	Chapter of Cardiologists representative
Committee Members:	
(3) Chua Siang Jin, Terrance	ACG Expert Group Co-chairperson, Cardiologist, NHCS
(4) Koh Si Ya, Natalie	Chapter of Cardiologists representative
(5) Low Lip Ping	Singapore Heart Federation representative
(6) Phoon Kwong Yun, Ian	ACG Expert Group Co-chairperson, Family Medicine Physician, SingHealth Polyclinics
(7) Poh Kian Keong	Singapore Cardiac Society representative, ACG Expert Group member
(8) Sum Chee Fang	ACG Expert Group member and Endocrinologist, NHG group
(9) Tai E Shyong	Chapter of Endocrinologists representative
(10) Tan Wei Chieh, Jack	Singapore Heart Federation representative
(11) Tavintharam, Subramaniam	Chapter of Endocrinologists representative
(12) Yeo Khung Keong	Chapter of Cardiologists representative and Singapore Cardiac Society representative

PUBLISHED: DECEMBER 2023

Chapter of Cardiologists,
College of Physicians, Singapore
Academy of Medicine, Singapore
81 Kim Keat Road
#11-00 NKF Centre
Singapore 328836