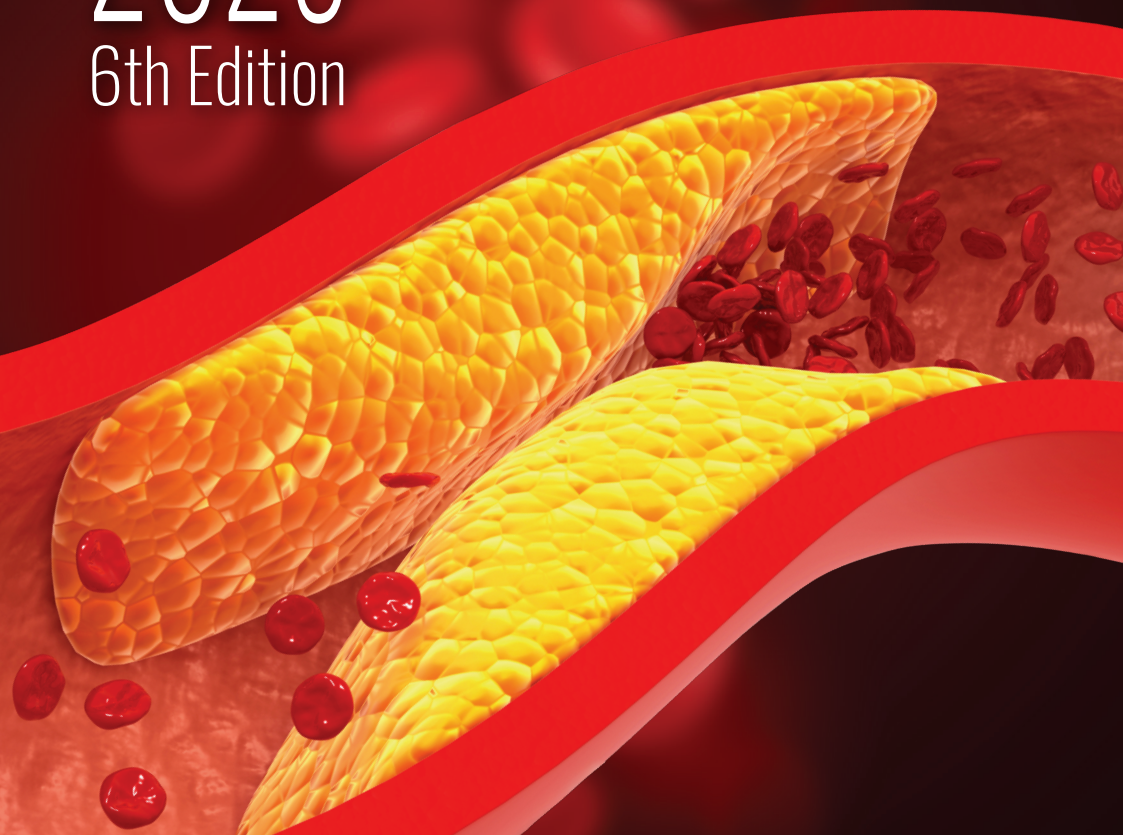
CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF DYSLIPIDEMIA

2023

6th Edition



Ministry of Health Malaysia

Academy of Medicine Malaysia

National Heart Association of Malaysia

PUBLISHED BY:

National Heart Association of Malaysia
D-13A-06, Menara SUEZCAP 1, KL Gateway
No.2 Jalan Kerinchi, Gerbang Kerinchi Lestari
59200 Kuala Lumpur

e ISBN 978-967-11794-7-5

COPYRIGHT

STATEMENT OF INTENT

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

REVIEW OF THE GUIDELINE

This guideline is issued in 2023 and will be reviewed in about 5 years or earlier if important new evidence becomes available.

CPG Secretariat

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

Available on the following websites:
http://www.moh.gov.my
http://www.acadmed.org.my

This is an update to the Clinical Practice Guidelines on Management of Dyslipidaemia, 5th Ed, published in 2017. This CPG supersedes the previous CPG.

MESSAGE FROM THE DIRECTOR GENERAL OF HEALTH

Nearly 30 years since the publication of the first Malaysian Consensus on management of hyperlipidaemia, I am proud to announce the publication of the 6th Clinical Practice Guidelines (CPG) on the management of dyslipidemia. Since the 5th CPG, published in 2017, there has been much development in both diagnosis and treatments of dyslipidemia. This CPG is timely, as Malaysia has seen a rise in the prevalence of hypercholesterolemia in adults - a rise of 31.5% in 2011 to 38.1% in 2019.

Dyslipidemia remains one of the most deadly of the established cardiovascular risk factors. Compared to cigarette smoking, hypertension and diabetes, dyslipidemia is often only diagnosed when patients develop their first acute vascular event, such as a heart attack or stroke. Therefore, with the advent of such new therapeutics now available, with accompanying safety and efficacy clinical data, this CPG is timely to enable all healthcare professionals to optimise the management of their patients with dyslipidemia.

This CPG comes with 13 new key messages and 19 key recommendations, valuable additions from the last CPG. The main aims of this 2023 CPG are to reduce the level of low-density lipoprotein (LDL-C), introduce new medications that can be used, in particularly for secondary preventions; and new updates in the Medical Nutrition therapy section. A significant reduction the LDL-C targets will see a corresponding reduction in serious cardiovascular outcomes. Improved point-of-care diagnostics will lead to more of the population to be diagnosed with dyslipidemia, and an aggressive, multi-aspect management plan being formulated, and administered, to each individual.

I would like to thank the Chairperson of the Writing Committee - Dr Jeyamalar Rajadurai - and her colleagues, and all those who contributed towards the publication of this CPG.

I am certain that, with its dissemination, the burden of cardiovascular disease attributed to dyslipidemia, will be attenuated, and its deadly manifestations in the form of acute vascular events can be mitigated. For a condition so prevalent in Malaysia, this CPG will be a valuable resource from healthcare professionals practising at primary to tertiary care centres, and provide useful guidance to all stakeholders, so that this multidisciplinary approach will translate to improved health outcomes for both patients, and the population as a whole.

Dr Muhammad Radzi Abu Hassan
Director-General of Health Malaysia

MEMBERS OF THE EXPERT PANEL

Chairperson:

Dr. Jeyamalar Rajadurai	Consultant Cardiologist, *Subang Jaya Medical Center, Selangor*

Expert Panel Members (in alphabetical order):

Dr. Abdul Rashid Abdul Rahman	Consultant Physician, *(Specialist in Cardiovascular Medicine),* *An-Nur Specialist Hospital*
Dr. Ahmad Syadi Mahmood Zuhdi	Consultant Cardiologist, *University Malaya Medical Center*
Dr. Al Fazir Omar	Consultant Cardiologist, *Cardiovascular Sentral Kuala Lumpur*
Dr. Alan Fong Yean Yip	Consultant Cardiologist, *Sarawak General Hospital*
Dr. Chan Siew Pheng	Consultant Endocrinologist, *Subang Jaya Medical Center*
Dr. Gnanasegaran Xavier	Klinik Xavier, *633, Bagan Ajam, 13000 Butterworth.*
Dr. Hasliza Abu Hassan	Lecturer & Family Medicine Specialist, *Department of Primary Care Medicine, Faculty of Medicine & Defence Health, National Defence University*
Dr. Mohd Al-Baqlish Mohd Firdaus	Consultant Cardiologist, *International Islamic University Malaysia, Kuantan*
Dr. Mohd Rahal Yusoff	Consultant Cardiologist & Physician, *Universiti Teknologi MARA (UiTM)*
Dr. Narul Aida Salleh	Family Physician, *Klinik Kesihatan Kuala Lumpur*
Ms. Nirmala Jagan	Clinical Pharmacist, *Pharmacy Program, Ministry of Health*
Dr. Ong Mei Lin	Consultant Cardiologist, *Gleneagles Hospital Penang*
Dr. Rokiah Ismail	Head, Department of Dietetics, *University Malaya Medical Center*
Dr. Sahimi Bte Mohamed	Head of Pharmacy, Cardiology Center, *Hospital Sultan Idris Shah*
Dr. Wan Azman Wan Ahmad	Consultant Cardiologist, *University Malaya Medical Center*
Dr. Wong Ping Foo	Family Medicine Specialist, *Klinik Kesihatan Cheras Baru*
Dr. Zanariah Hussein	Consultant Endocrinologist, *Hospital Putrajaya*

EXTERNAL REVIEWERS

Dr. Asri Ranga Abdullah Ramaiah	Consultant Cardiologist, *Hospital Sultan Idris Shah*
Dr. Liew Houng-Bang	Consultant Physician & Cardiologist, Head, Department of Cardiology *Queen Elizabeth Hospital II.*
Dr. Mafauzy Mohamed	Honorary Professor of Medicine & Senior Consultant Endocrinologist, *Universit Sains Malaysia*
Dr. Nik Sherina Haidi Hanafi	Professor, Department of Primary Care Medicine, *Universiti Malaya Medical Center*
Dr. Noel Thomas Ross	Consultant Physician, *Hospital Kuala Lumpur*
Dr. Nor Azmi Kamaruddin	Honorary Professor of Medicine & Senior Consultant Endocrinologist, *Universit Kebangsaan Malaysia*
Dr. Ong Loke Meng	Consultant Physician & Nephrologist, *Island Hospital Penang*
Dr. Sakina Sahuri Suffian Sahuri	Retired Senior Lecturer, *Department of English, Faculty of Languages and Linguistics,* *University Malaya Medical Center*
Dr. Sunita Bavanandan	Consultant Nephrologist, *Hospital Kuala Lumpur*
Dr. Vengketeswara Rao Seetharaman	Family Medicine Specialist, *Klinik Kesihatan Serendah*
Dr. Wardati Mazlan Kepli	Pharmacist & Research Fellow (Cardiovascular), *Universiti Malaya*
Dr. Winnie Chee Siew Swee	Professor, Department of Nutrition & Dietetics, *Pro Vice-Chancellor (Academic),* *International Medical University*
Dr. Yeap Gim Ean	General Practitioner, President, *ASP Medical Group, Penang*
Dr. Zurkurnai Yusof	Professor of Medicine & Consultant Cardiologist, *Universiti Sains Malaysia*

RATIONALE AND PROCESS OF GUIDELINE DEVELOPMENT

Rationale:

In Malaysia, cardiovascular disease (CVD) was the leading cause of death in both men and women till 2021.[3,4] CVD includes coronary heart disease (CHD), cerebrovascular disease and peripheral arterial disease.

The prevalence of the common cardiovascular (CV) risk factors - dyslipidemia, hypertension, diabetes, smoking and overweight/obesity - has been on an increasing trend.[5,7,8] Malaysians develop heart disease at a younger age when compared to people in Thailand, mainland China and western countries.[10] Our local NCVD-ACS Registry (2018-2019) showed that most patients (93.5%) had at least one established CV risk factor-hypertension (61.9%), dyslipidemia (36.7%) or diabetes (44.2%).[10] About 40.3% (2 persons out of 5) had ≥ 3 CV risk factors.[10]

In preventing CVD, efforts should be aimed at reducing the individual's global CV risk. This Clinical Practice Guideline (CPG) is on management of dyslipidemia. The last CPG (5th edition) was published in 2017. Thus, the need for an update.

Objectives:

The objectives of this clinical practice guidelines are to review:

- The clinical evidence linking dyslipidemia and atherosclerosis and determining which lipid parameters should be targeted.
- Strategies for assessing CV risk that is most applicable to our local population.
- Evidence based management of dyslipidemia that translates to CV benefits, utilizing existing healthcare resources wherever possible.

Process:

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

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

"Hyperlipidemia"; "Dyslipidemia"; "Hypercholesterolemia"; "Cholesterol"; "LDL-Cholesterol" "HDL-Cholesterol"; "Triglycerides"; Diabetic dyslipidemia"

The search was filtered to clinical trials and reviews, involving humans, and published in the English language. The relevant articles were carefully selected from this huge list. In addition, the reference lists of all relevant articles retrieved were searched to identify further studies. The search was conducted from 31st August 2016 (date of last review for previous CPG) till 31st August 2022.

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

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

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

The level of recommendation and the grading of evidence used in this guideline was adapted from the American Heart Association and the European Society of Cardiology (ACC/ESC) and outlined on pg. 9. In the text, this is written in black on the left-hand margin.

Clinical Questions Addressed:

In addition to the old clinical questions that were updated, several new clinical questions were formulated using the Population Intervention Comparison Outcome (PICO) method, addressing the diagnosis and therapy of dyslipidemia.

For ***diagnosis:***

Which lipid parameters contribute to CV risk?
Which are the most cost effective to treat considering our resources.?

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

P: Population - Persons

With heart disease (secondary prevention)

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

- Elderly
- Women
- Children and adolescents

I: Intervention:

Total and LDL-Cholesterol lowering

- HDL- Cholesterol raising
- Triglyceride lowering

C: Comparison:

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

O: Outcome:

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

Type of Question - Involves:

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

Type of Study

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

Thus, there were numerous clinical questions formulated.
e.g. of some of these Clinical Questions:

- In persons with CVD (secondary prevention), which lipid parameter is the most beneficial and cost effective to treat leading to a reduction in cardiovascular (CV) event rate, CV mortality and total mortality?
- In persons with CVD (secondary prevention), which means of treatment (therapeutic lifestyle changes vs pharmacotherapy) is the most beneficial and cost effective leading to a reduction in CV event rate, CV mortality and total mortality?
- In persons without CVD but with diabetes, which lipid parameter is the most beneficial and cost effective to treat leading to a reduction in CV event rate, CV mortality and total mortality?
- In persons without CVD and diabetes (primary prevention), which means of treatment (therapeutic lifestyle changes vs pharmacotherapy) is the most beneficial and cost effective leading to a reduction in CV event rate, CV mortality and total mortality?
- How does the decision and strategy change if the person:
  - Has Chronic Kidney Disease (CKD)?
  - Is elderly?
  - Is a woman?
- etc

Target Group:

This guideline is directed at all healthcare providers involved in the management of dyslipidemia - general practitioners, medical officers, pharmacists, general and family physicians, cardiologists, nephrologists, and endocrinologists.

Target Population:

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

Period of Validity of the Guidelines:

These guidelines need to be revised at least every 5 years to keep abreast with recent scientific research and knowledge.

Applicability of the Guidelines and Resource Implications:

These guidelines were developed considering our local health resources.

- Blood chemistry for lipid profiles, liver and kidney function tests can be done in all government health facilities. The use of non-fasting samples to assess lipid profile simplifies workflow and makes it easier for patients.
- Almost all the medications recommended are approved for use in Malaysia and available in public hospitals. Potent statins and ezetimibe are available as generics in the government formulary.
- These guidelines aim to educate health care professionals on strategies to optimize existing resources in the management of dyslipidemia.

Facilitators and Barriers:

The main barriers for successful implementation of this CPG are the lack of knowledge of the:

- role of cholesterol (especially LDL-C) in the pathogenesis of CVD.
- benefits of total cholesterol (especially LDL-C) lowering.
- long-term safety profile of pharmacotherapy among both healthcare professionals and the public.
- Lack of knowledge of the benefits and safety of the very low levels of LDL-C recommended for individuals in secondary prevention.

Implementation of the Guidelines:

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

- Increasing public awareness of CVD in general and educating them on the importance of knowing their individual CV risk.
- Continuous medical education and training of healthcare providers on CV risk assessment tools and the implementation of appropriate preventative strategies depending on everyone's CV risk status. This can be done by road shows, electronic media, and in house training sessions.
- Clinical audit by individual hospitals, units, and general practices to ensure compli ance using the suggested performance measures in Section 14, pg. 87-88.

Dr. Jeyamalar Rajadurai
Chairperson

GRADES OF RECOMMENDATION AND LEVEL OF EVIDENCE

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

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

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

(Available at: http://assets.cardiosource.com/Methodology_Manual_for_ACC_ HA_Writing_Committees and at http://www.escardio.org/guidelines-surveys/escguidelines/about/Pages/rules-writing.aspx).

TABLE OF CONTENTS

WHAT'S NEW IN THE GUIDELINES

1. The LDL-C target in secondary prevention has been lowered. There has been an abundance of evidence in the scientific literature of the safety and benefits of such low levels in persons with established CVD.

2. Introducing new medications that are available to achieve these low LDL-C levels in secondary prevention and for use in statin intolerant individuals:
   - Proprotein Convertase Subtilisin Kexin type 9 (PCSK-9) inhibitors.
   - SiRNA PCSK-9 inhibitors - Inclisiran
   - Bempedoic Acid - Not registered in Malaysia yet

3. The section on Medical Nutrition Therapy has new information and updates.

GLOSSARY

Abbreviation	Description
ABI	Ankle Brachial Index
ACC	American College of Cardiology
ACE-I	Angiotensin Converting Enzyme Inhibitor
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
AHA	American Heart Association
ALA	α-linolenic acid
AMI	Acute Myocardial Infarction
Apo – A1	Apolipoprotein A1
Apo B	Apolipoprotein B
ART	Anti Retroviral therapy
ASCVD	Atherosclerotic Cardiovascular Disease
ATP	Adenosine Triphosphate
Bd	Bis In Die (twice daily)
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCU	Cardiac Care Unit
CHD	Coronary Heart Disease
CHO	Carbohydrates
CIN	Contrast Induced Nephropathy
CK	Creatinine Kinase
CKD	Chronic Kidney Disease
CPG	Clinical Practice Guidelines
CR	Cardiac Rehabilitation

Abbreviation	Description
CrCl	Creatinine Clearance
CT	Computed Tomographic
CV	Cardiovascular
CVD	Cardiovascular Disease
CYP	Cytochrome P 450
DBP	Diastolic Blood Pressure
DHA	Docosahexaenoic Acid
DM	Diabetes Mellitus
eGFR	Estimated Glomerular Filtration Rate
EPA	Eicosapentaenoic acid
ESC	European Society of Cardiology
FRS	Framingham Risk Score
GFR	Glomerular Filtration Rate
HCP	Healthcare Professional
HDL-C	High Density Lipoprotein Cholesterol
HF	Heart Failure
HR	Hazard Ratio
ICD	Implantable Cardioverter-Defibrillator
IDL-C	Intermediate Density Lipoproteins Cholesterols
IHD	Ischaemic Heart Disease
IMT	Intimal Medial Thickness
IPE	Icosapent Ethyl
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
LDL-C	Low Density Lipoprotein Cholesterol
Lp(a)	Lipoprotein (a)
MACE	Major Adverse Cardiovascular Events
mAbs	Monoclonal antibodies
MI	Myocardial Infarction
MOH	Ministry of Health Malaysia
MUFA	Monounsaturated Fatty Acids
OD	Once a Day
NCVD-ACS	National Cardiovascular Disease Database-Acute Coronary Syndrome Registry
NHMS	National Health and Morbidity Survey
Non-HDL-C	Non High Density Lipoprotein Cholesterol
NP	Natriuretic Peptides
NRTI	Nucleoside Reverse Transcriptase Inhibitors
Od	Once daily

Abbreviation	Description
PCSK-9	Proprotein Convertase Subtilisin Kexin type 9 (PCSK9)-
PCI	Percutaneous Coronary Interventions
PI	Protease Inhibitors
PRN	Pro Re Nata
PUFA	Polyunsaturated Fatty Acids
QID	Quater In Die (Four x a day)
RPCE	Revised Pooled Cohort Equation
SBP	Systolic Blood Pressure
SC	Subcutaneous
SCD	Sudden Cardiac Death
Scr	Serum Creatinine
SDB	Sleep Disordered Breathing
SFA	Saturated Fatty Acids
SiRNA	Small interfering RNA
STEMI	ST Segment Elevation Myocardial Infarction
TC	Total Cholesterol
Tds	Ter die sumendus (three times per day)
T2DM	Type 2 diabetes mellitus
TG	Triglycerides
TLC	Therapeutic Lifestyle changes
VLDL	Very Low Density Lipoproteins

KEY MESSAGES

Key Messages #1: Introduction

- Cardiovascular disease (CVD) has been an important cause of morbidity and mortality in both Malaysian men and women for more than a decade.
- Malaysians developed ACS at a mean age of 58.7 years and almost a quarter were below the age of 50 years. This is almost 10 years younger than that seen in Singapore.
- The prevalence of the common cardiovascular (CV) risk factors among adults > 18 years has been on an increasing trend.
- About 40% of patients presenting with Acute Coronary Syndrome have >3 CV risk factors.

Key Message #2: Measurement of Lipids and Apolipoproteins

- A standard lipid profile includes measurement of Plasma or serum total cholesterol (TC), LDL-Cholesterol (LDL-C), HDL-Cholesterol (HDL-C) and Triglycerides (TG).
- TC, HDL-C and TG are measured directly from the serum and LDL-C is calculated using the Friedwald's equation provided TG < 4.5mmol/l.

Key messages #3: Classification of Dyslipidemia

- Dyslipidemias may be primary due to genetic disorders or secondary to nephrotic syndrome, cholestatic liver disease, hypothyroidism, Cushing's syndrome, drugs, alcoholism, and insulin resistance states such as Type 2 diabetes and metabolic syndrome.

Key Messages #4: Dyslipidemia as a CV Risk Factor

- **LDL-C:**
  - ➢ This has been shown to be an important causative factor in the development of atherosclerotic vascular disease based on numerous epidemiological, genetic and clinical interventional trials.
  - ➢ Based on the Malaysian NCVD-ACS Registry 2018-2019:
    - The prevalence of dyslipidemia among individuals admitted with ACS was 36.7%.
    - The mean LDL-C on admission was 3.1mmol/l in males and 3.0mmol/l in females.
- **Non-HDL-C:**
  - ➢ Reflects the concentration of cholesterol within all lipoprotein particles considered atherogenic. This includes chylomicrons, VLDL and their remnants, IDL, LDL and Lp(a).
  - ➢ Studies have demonstrated that non-HDL-C is a better predictor of CV risk than is LDL-C.
- **Atherogenic dyslipidemia:**
  - ➢ This consists of an increase in TG-rich lipoproteins, low HDL-C, lipoprotein remnants (i.e. small VLDL and intermediate-density lipoprotein [IDL]) and a preponderance of numerous small and dense LDL particles and postprandial hyperlipidemia.
  - ➢ It is usually associated with insulin resistance states such as obesity, metabolic syndrome, and type 2 diabetes.
- **Lp(a)**
  - ➢ This has been shown to be an independent risk factor for atherosclerosis, MI, strokes, and aortic stenosis.
  - ➢ The difficulty, to date, has been that there is no standardized assay to measure the Lp(a), the "normal levels" in the different populations is still unknown and the lack of effective therapy specifically targeting it.

Key messages #5: Global Cardiovascular Risk Assessment

- The committee advocates lipid screening in all adults > 30 years of age. Individuals who are at high risk of developing CVD should have a lipid profile earlier in life (> 18 years of age). For individuals at high risk of developing CVD see Table 10, pg.39.
- The intensity of LDL-C lowering should be tailored to the individual's global CV risk.
- In 2 local studies, the FRS-General CVD risk model was shown to be a better discriminator of global CV risk in our local multi-ethnic population.

Key messages #6: Management of Dyslipidemia-Therapeutic Lifestyle Changes

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

Key messages #7: Management of Dyslipidemia- Lipid Modifying Drugs

- Statins are the drug of choice for reducing LDL-C in a wide range of individuals with dyslipidemia in both primary and secondary prevention.
- Some individuals may require combination therapy to achieve LDL-C goals.

Key messages #8: Primary Prevention

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

Key Message #9: Dyslipidemia in Thyroid Disease and Cushing Syndrome

- Thyroid hormones have profound effects on lipoprotein metabolism.
- Dyslipidemia is a common metabolic abnormality in Cushing syndrome, the prevalence ranging from 12% to 72%.

Key Messages #10: Dyslipidemia in Patients with Human Immunodeficiency Virus

- CVD has become an important cause of morbidity and mortality in these patients. This may be due to the:
  - HIV infection itself, which may produce a cardiometabolic type of syndrome.
  - metabolic changes associated with anti-retroviral therapy (ART).
  - associated CV risk factors such as smoking and recreational drug use (e.g. cocaine).

Key Messages #11: Dyslipidemia in Psychiatric Disorders

- Psychiatric patients have a higher risk of developing CVD.
- In addition, antipsychotic drugs also induce a dyslipidemia which increases the risk for developing further metabolic complications and CVD.

Key Messages #12: Dyslipidemia in Women, Children, Adolescents and Elderly

- The goals of lipid lowering therapy is similar in both gender and in the elderly. Target LDL-C levels will depend on the global CV risk (Table 4, pg. 26)
- Children whose lipid levels are significantly elevated may have a genetic dyslipidemia and should be referred to specialists interested in this field.
- When prescribing lipid lowering therapy in the elderly, the presence of co-morbidities and altered pharmacokinetics should be considered. Lipid lowering medication should be started at a lower dose and then titrated with caution to achieve target lipid levels.

Key Messages #13: Adherence to Lifestyle Changes and Medications

- There is a general lack of adherence to cardiovascular preventive therapy.
- To improve adherence to TLC and compliance to medications, efforts should be undertaken looking at:
  - Patient Factors,
  - Healthcare Provider Factors and
  - Health delivery systems.

KEY RECOMMENDATIONS

KEY RECOMMENDATIONS	Grade of Recommendation / Level of Evidence*
Key Recommendations #1: Measurement of Lipids and Apolipoproteins	
• Non-fasting lipid testing is acceptable.	**I,A**
• The difference in values between fasting and non-fasting samples is small and has been shown to have no impact on CV risk estimation.	
• Measurement of TC (and its usual conventional derivatives - HDL-C, LDL-C and TG) is sufficient in most cases for CV risk assessment and treatment, given healthcare cost and the limited ability of most laboratories to measure apolipoproteins.	
• Most of the CV benefits seen, is with LDL-C lowering.	**I,A**
Key Recommendation #2: Secondary Dyslipidemia	
• Treatment of the underlying etiology in secondary dyslipidemia can lead to an improvement in the lipid profile.	**I,C**
Key Recommendations #3: Targets of Therapy	
• LDL-C is the primary target of therapy in both secondary and primary prevention.	**I,A**
• Both the absolute value of LDL-C achieved and the percentage reduction in LDL-C lead to CV benefits.	**I,A**
• The lower the LDL-C achieved, the greater the CV benefit. At levels <1.8mmol/L, less progression of the atherosclerotic plaque is seen and at levels <1.6mmol/L, regression of the plaque has been documented.	**I,A**

Key Recommendations #4: Global Cardiovascular Risk Assessment and Stratification	
• All individuals should be risk stratified. (Table 4, pg. 26)	**I,A**
• Patients with established CVD, CKD and diabetes fall into the **Very High-** and High-Risk **Categories**.	
• All other individuals should be risk stratified at the outset using **the Framingham (FRS)- General CVD risk score** to determine if they are at High, Intermediate (Moderate) or Low Risk. (Tables 1 & 2, pg. 23-24)	
• The intensity of risk factor reduction and target lipid levels will depend on their CV risk. (Table 4, pg. 26)	
Key Recommendations # 5: Targets of therapy	
• LDL-C is the primary target of therapy.	**I,A**
• The target LDL-C level will depend on the individual's CV global risk. (Table 4, pg. 26)	
• Non-HDL-C may be considered as a secondary target when treating patients with: ➢ combined hyperlipidemias ➢ diabetes ➢ cardio metabolic risk ➢ chronic kidney disease	**IIa,B**
• Non-HDL-C becomes the primary target of therapy in individuals where the TG>4.5 mmol/l.	
Key Recommendations #6: Therapeutic Lifestyle Changes (Table 5, pg. 27)	
• The current emphasis is on healthy dietary patterns rather than on individual nutrient composition.	**I,B**
• A heart healthy diet consists of: ➢ primarily fruits and vegetables, ➢ whole grains, ➢ healthy sources of protein (mostly plant based such as tofu, beans, nuts, lentils), fish, and seafood, lean cuts of meat, ➢ liquid plant oils, ➢ minimally processed foods (Appendix 2, pg 92), ➢ low added sugar and salt (<2000mg sodium equivalent to 5gm salt =1 level teaspoon of salt/day)) in beverages and foods ***and*** ➢ nuts.	**I,B** **I,B**
• The duration of exercise for CVD prevention in healthy adults regardless of age is: ➢ at least 150-300 minutes a week of moderate intensity or ➢ 75-150 minutes a week of vigorous-intensity aerobic physical activity or an equivalent combination.	**I,A**
• Smoking should be discouraged, and individuals referred to smoking cessation programmes.	

Key Recommendations #7: Lipid Modifying Drugs	
• Individuals should be on lifelong therapy.	**I,C**
• They should be assessed on a regular basis for: ➢ Response to therapy and achievement of individualized lipid targets. ◆ Lipid profile should be measured at 1 to 3 months following initiation and following a change in the dose of statin therapy. The dose is then adjusted accordingly to achieve LDL-C targets. ➢ Adverse effects ◆ Hepatic transaminases should be measured at baseline and at 1 to 3 months after starting treatment and/or following a change in dose. ◆ CK is measured if myositis is suspected. ◆ Should there be an adverse effect, the dose of the drug should be reduced, or it should be temporarily discontinued. Following an improvement and normalization of symptoms and/or biochemical parameters, the drug can be reintroduced at a lower dose. If the adverse effect recurs, then the drug should be discontinued, and an alternative form of treatment used.	
• Combination therapies may sometimes be necessary to achieve LDL-C targets. These include:	
➢ Statins + Ezetimibe combination	**I,A**
➢ Statins + PCSK-9 Inhibitors	**I,A**
➢ Statins + ezetimibe + PCSK-9 inhibitors	**I,A**
➢ Statins + SiRNA PCSK-9 inhibitors therapies	**IIa,B**
➢ Statins + SiRNA PCSK-9 inhibitors + ezetimibe	**IIa,B**
➢ Ezetimibe + bempedoic Acid (in statin intolerant patients)	**IIa,B**
Key Recommendations #8: Primary Prevention	
• Maintaining a healthy lifestyle should be started early in life.	**I,C**
• We advocate all individuals >30 years old to have a lipid profile.	**I,C**
• Frequency of repeat screening if the LDL-C levels are at target and TG levels are low: ➢ screening should be repeated at 3 yearly intervals. ➢ In individuals who at very high or high risk of CVD, screening should be repeated annually e.g., diabetes, family history of premature CVD etc.	**I,C**
Key Recommendations # 9: Secondary Prevention	
• All patients with CVD should receive lipid lowering therapy.	**I,A**
• Target LDL-C < 1.4 mmo/l and a 50% reduction in LDL-C levels.	**I,A**
• High intensity statins should be started (irrespective of their baseline cholesterol levels):	
➢ on admission in all individuals with ACS.	**I,A**
➢ prior to PCI and CABG and continued indefinitely.	**I,A**
• Lipid lowering therapy with statins should be initiated in all individuals with previous non cardioembolic ischemic stroke or transient ischemic attack.	**I,A**

Key Recommendations #10: Asymptomatic Atherosclerotic Disease	
• Patients with abnormal exercise stress tests, calcified and non-calcified plaques detected by imaging modalities should have: ➢ All their CV risk factors treated to target. ➢ Their LDL-C treated to a target dependent on their CV risk.	**I,A** **I,A**
• In patients at **Intermediate Risk**, the presence of any of the features listed below indicates established atherosclerotic vascular disease and a need to upgrade CV risk, treatment targets and the decision to initiate pharmacotherapy.	
• The presence of the any of the following is indicative of established CVD: ➢ Ankle Brachial Index (ABI): < 0.9 or > 1.40. An ABI > 1.4 indicates calcified non compressible vessels. ➢ Positive exercise stress test at low to moderate workload (≤ 6 METS) ➢ Calcium score: ◆ 0 :- reassess in 5-10 years if diabetes, family history of premature CAD or cigarette smoking is absent. ◆ 1-99:- Agatston units and < 75th percentile for age/sex/race - reasonable to initiate statins if the individual is > 55 years of age. ◆ ≥ 100:- Agatston units or > 75th percentile for age/sex/race - reasonable to initiate statins. ➢ CT coronary angiography with plaques causing > 50% luminal narrowing. ➢ Plaques on carotid ultrasonography - seen as localized thickening encroaching into the arterial lumen by at least 50% or with a thickness > 1.2 mm.	
• In these patients, the LDL-C target should be < 1.4 mmol/l and a 50% reduction from baseline.	**I,A**
Key Recommendations #11: Hypertension	
• For patients with Hypertension, initiate statins for Primary Prevention if they also have elevated cholesterols (LDL-C > 3.4 mmol/L).	**I,A**
• In all other patients assess CV risk using the FRS-General CVD risk score (Tables 1 & 2, pg. 23-24). The target LDL-C would depend upon the individual's CV risk. (Table 4, pg. 26)	
Key Recommendations #12: Diabetes	
• All persons with diabetes above the age of 40 should be treated with a statin regardless of baseline LDL-C level.	**I,A**
• In Type 2 diabetic patients below 21 years of age and without clinical CVD, statin is generally not recommended.	**III,C**
• The target LDL-C levels will depend upon their CV risk (Table 4, pg. 26)	

• Statins are the drugs of first choice.	**I,A**
• If target LDL-C is not achieved, consider combination with:	
➢ Statins + Ezetimibe (selective cholesterol absorption inhibitors)	**I,A**
➢ Statins + PCSK-9 inhibitors	**I,A**
➢ Statins + ezetimibe + PCSK-9 inhibitors	**I,A**
➢ Statins + SiRNA PCSK-9 inhibitors therapies	**IIa,B**
➢ Statins + ezetimibe + SiRNA PCSK-9 inhibitors	**IIa,B**
Key Recommendations #13: Heart Failure	
• All patients with HF due to CAD should be on statins.	**IIa,B**
• Routine use of cholesterol-lowering therapy is not recommended in non-ischemic HF.	**IIa,B**
Key Recommendations #14: Kidney Disease	
• Lipid lowering therapy with statins or ezetimibe/simvastatin combination should be initiated in non-dialysis CKD patients (Stages 3-5) for primary and secondary prevention of CVD.	**I,A**
• Patients with CKD stages 1-2 should be assessed using the FRS-General CVD Risk score.	
• The target LDL-C levels will depend upon their CV risk. (Table 4, pg. 26)	
• Statins should not be commenced for primary prevention of CVD in patients on dialysis. These patients are at very high CV risk but it is of non-atherosclerotic CVD e.g. due to medial calcific arteriosclerosis, LVH, coronary artery calcification, arrhythmias etc. No CV benefits have been demonstrated in clinical trials of lipid lowering therapy in these patients.	**III,B**
• In patients with established CVD or who are already on statins or an ezetimibe/statin combination at the time of initiation of dialysis, these drugs should be continued.	**IIa,C**
• In patients with eGFR < 60mls/min/1.73m^2, the risk of muscle related symptoms is higher. For this reason, statins should be started at a lower dose and the combination with fibrates should be avoided.	**IIa,B**
Key Recommendation #15: Endocrine Disorders	
• Thyroid Disorders:	
➢ Appropriate treatment of hypothyroidism or hyperthyroidism can improve the lipid abnormalities.	**I,A**
➢ The lipid profile should be reassessed after the patient has become euthyroid before initiating lipid lowering therapy.	**I,C**
• Cushing's Disease	
➢ In adults with persistent endogenous Cushing syndrome, irrespective of the CV risk score, statin therapy, as adjunct to lifestyle modification, should be considered to reduce CV risk.	**IIa,C**
➢ LDL-C should be the primary target of therapy. The target should be LDL -C < 1.8 mmol/L.	**I,A**

Key Recommendations #16: Patients with Human Immunodeficiency Viral Infection	
• In patients with HIV, LDL-C is the primary goal of treatment.	**I,A**
• Drug interactions with ART is common and monitoring for adverse effects is important.	**I,C**
Key Recommendations #17: Psychiatric Disorders	
• In patients with psychiatric disorders, LDL-C is the primary target of therapy.	**I,A**
• Drugs of first choice are statins.	**I,A**
Key Recommendations #18: Specific Lipid Disorders	
• In patients with high TG and/or low HDL-C, the primary goal of treatment is lowering LDL-C to target.	**I,A**
Key Recommendations #19: Performance Measures	
• Performance measures are used with the goal of improving quality of care. • This includes audit parameters for the: ➢ Primary Care Clinics - Follow Up patients. ➢ Cardiac clinic/general medical clinic (within 3 months of discharge after an admission for ACS/Stable CHD) • For the Quality indicators, see section 14, pg. 87-88.	

**For Grades of Recommendation and Level of Evidence, refer pg. 9*

Table 1A: Estimation of 10-year Framingham General CVD Risk Score for MEN (FRS- General CVD Risk Score for Men)[110]

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

Grand Total: _____points

Table 1B: FRS- General CVD Risk Score for Men[110]

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

It can also be calculated online at:
https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php

Table 2A: Estimation of 10-year Framingham General CVD Risk Score for WOMEN (FRS-General CVD Risk Scores for Women)[110]

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

Grand Total: _____points

Table 2B: FRS-General CVD Risk Score for Women[110]

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

It can also be calculated online at:
https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php

Table 3A: Heart Age/ Vascular Age for Men[110]

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

Table 3B: Heart Age/ Vascular Age for Women[110]

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

Table 4: Target LDL-C levels

Global Risk	LDL-C Initiate Drug Therapy (mmol/L)	Target LDL-C levels (mmol/L)	Target Non-HDL-C (mmol/l)
Low CV Risk* < 10%10-year CVD risk	clinical judgement**	<3.0	<3.8
Intermediate (Moderate) CV Risk* ➢ 10-20% 10-year CVD risk ➢ Diabetics < 50 years old and < 10-year duration and no CV risk factors	>2.6 **	<2.6	<3.4
High CV Risk ➢ > 20% 10-year CVD risk ➢ diabetes >10-year duration without target organ damage + 1 other CV risk factor ➢ CKD with eGFR 30-< 60ml/min-1/1.73 m^2	> 1.8	≤ 1.8 ***and*** a reduction of > 50% from baseline	≤ 2.6 ***and*** a reduction of > 50% from baseline
Very high CV Risk* ➢ established CVD ➢ diabetes with CVD or other target organ damage or > 3 CV risk factors ➢ CKD with eGFR < 30ml/min-1/1.73 m^2 ****	>1.4	≤ 1.4 ***and*** a reduction of > 50% from baseline	≤ 2.2 ***and*** a reduction of > 50% from baseline
***Those with recurrent CV events within 2 years despite achieving a LDL-C target of <1.4mmol/l		<1.0	

**Low and Moderate CV risk is assessed using the FRS- General CVD Risk Score*
***After a therapeutic trial of 8-12 weeks of TLC and following discussion of the risk: benefit ratio of drug therapy with the patient.*
****All other CV risk factors should be treated to target.*
***** Lipid lowering therapy lowers the risk of atherosclerotic CVD in CKD patients. Those who are on dialysis are at very high CV risk, but it is for non-atherosclerotic CVD e.g. due to medial calcific arteriosclerosis, LVH, coronary artery calcification, arrhythmias etc. Thus, lipid lowering therapy is not initiated in patients on dialysis but if they have CVD or are already on statins before becoming dialysis dependent, then it should be continued.*

Table 5: Recommendations for Therapeutic Lifestyle Changes#

Nutrition	Comments	Grades of Recommendation / Level of Evidence
Saturated Fat	<10% of total calories.I, B SFA should be replaced by PUFA.	I, B
Trans Fat **Dietary Sodium**	<1% of total calories I, A A diet containing reduced amounts of sodium (<2000mg daily equivalent to 5 gm of salt = 1 level teaspoon) can be beneficial to decrease CVD risk.	IIa, B
Carbohydrates (CHO)	Reduced intake of carbohydrates with emphasis on whole grains susch as brown rice and to reduce intake of refined carbohydrates and sweetened beverages. In the presence of high TG and low HDL-C, (atherogenic dyslipidemia) carbohydrate intake should be lower.	I, B I, B
Protein	Emphasis on plant-based protein such as tofu, legumes, beans. A diet emphasizing the intake of legumes, nuts, and fish is recommended to decrease CVD risk factors.	I, B I, B
Dietary Fibre	Incorporate fibre-rich foods that contribute at least 20 to 30 g of fibre per day. Emphasis should be on soluble fibre sources (7 to 13 g) such as fruits**, vegetables**, whole grains, high-fibre cereals, oatmeal, legumes, and beans. A diet emphasizing the intake of vegetables, fruits, and whole grains is recommended to decrease CVD risk factors.	I, B I, B
Weight	Achieve body mass index (BMI) <23 kg/m^2 or	I, B
Reduction	at least a 5-10% reduction in body weight. Maintain waist circumference at: <90 cm for men <80 cm for women	I, B
Exercise	150-300 minutes a week of moderate-intensity or 75-150 minutes a week of vigorous-intensity aerobic phyical activity, or an equivalent combination.	I, A
Smoking	Smoking should be discouraged and individuals referred to smoking cessation programme.	I, B
Alcohol	Advise abstinence whenever possible. If necessary, limit to 1 drink/day (10gm/day) in females and 2 drinks/day (20 gm/day) in males	I, B

#The current emphasis of medical nutrition therapy is on dietary patterns rather than on individual nutrient composition.
*** Juicing removes fibre from whole fruits and vegetables; thus, it is not recommended.*

Table 6: Lipid Modifying Therapy for Dyslipidemia

The Primary Target of Therapy is LDL-C:
The target will depend on the Individuals' CV Risk (Table 4 pg. 26)

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

** After Therapeutic Lifestyle changes*

1. INTRODUCTION

1.1. Epidemiology

In 2019, pre pandemic, non -communicable diseases accounted for 7 of the 10 leading causes of deaths globally.[1,2] This was about 74% of all deaths and the leading cause was cardiovascular deaths- Ischemic heart disease (IHD) and strokes.[2]

In Malaysia, in 2020, ischemic heart disease remained the principal cause of medically certified deaths accounting for 17.0% of all deaths.[3] It had been the leading cause of deaths for more than 2 decades and for the first time in 2021, it was overtaken by Covid-19 infections, and it dropped to second place, accounting for 13.7% of all deaths.[4]

The most recent 2019 National Health and Morbidity Survey (NHMS) reported that among adults aged ≥18 years, the prevalence of some cardiovascular (CV) risk factors - diabetes and overweight/obesity - were on an increasing trend.[5] On the other hand, the prevalence of hypercholesterolemia, hypertension and smoking, although still high, appeared to have stabilized and seemed to be on the downward trend.[5] (Table 7, pg. 30)

The prevalence of hypercholesterolemia in the NHMS VI was 38.1% and was similar in both rural and urban populations.[5-7] Even in young adults aged 30-34 years, the prevalence was as high as 27.9%.[5] The Malaysian Health and Adolescents Longitudinal Research Team study (MyHeARTs) found that among 13-year-old students from selected urban and rural public schools, almost 20-25% had total cholesterols >5.2 mmol/L.[8] The CV health of these adolescents have documented adverse transitions over time as more of these school children appeared to be shifting towards a higher prevalence of CV risk factors.[9]

Data from the most recent National Cardiovascular Disease Darabase - Acute Coronary Syndrome (NCVD-ACS) Registry 2018-2019, indicated that Malaysians developed ACS at a mean age of 58.7 years and almost a quarter were below the age of 50 years.[10] These figures are similar to that in the 10 year NCVD-ACS Registry.[11] This is almost a decade less than that seen in Singapore where the median age of onset of MI was 70.4 years.[12] Among patients admitted with ACS, 61.9% had hypertension, 44.2% had diabetes and 36.7% had dyslipidemia. Risk Factor clustering was common with almost 40% having 3 or more CV risk factors.[10]

1.2. Prevention of Cardiovascular Disease

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

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

There already exist clinical practice guidelines addressing specific CV risk factors. The objectives of this CPG on the Management of Dyslipidemia are to:

- Critically review the role of dyslipidemia as a CV risk factor.
- Provide treatment strategies for managing dyslipidemia, in the following situations:
  - ➢ High risk individuals - these include those who have:
    - Established CVD (i.e., secondary prevention)
    - Diabetes, multiple CV risk factors and/or chronic kidney disease (CKD) (i.e., primary prevention in high-risk individuals).
  - ➢ Individuals who are otherwise healthy (i.e., primary prevention).

- Provide strategies for the successful implementation and dissemination of the recommendations, utilizing and optimizing existing health resources.

Decision making however, should be individualized, and based on sound clinical judgment.

1.3. Definition of Dyslipidemia

Lipid levels are continuous and there is no cut off between "normal" and "abnormal" levels. Arbitrary definitions of dyslipidemia refer to levels which:

- Have been shown in epidemiological studies to be associated with increased CV risk ***and/or***
- Treatment has been shown to reduce CV risk.

Commonly used cut off values for dyslipidemia and which has been adopted in this CPG are:

- Total cholesterol (TC) > 5.2 mmol/l
- HDL-C < 1.0 mmol/l (males) < 1.2 mmol/l (females)
- TG > 1.7 mmol/l
- LDL-C levels - will depend on the patient's CV risk - Tables 4, pg. 26.

Table 7: Prevalence of Cardiovascular Risk Factors among Adults > 18 years of age in Malaysia

Risk Factor	NHMS III (2006)[13]	NHMS IV (2011)[14]	NHMS V (2015)[15]	NHMS VI (2019)[5]
Hypercholesterolaemia*	20.7%	35.1%	47.7%	38.1%
Hypertension**	32.2%	32.7%	30.3%	30.0%
Diabetes***	11.5%	15.2%	17.5%	18.3%
Smoking****	21.5%	23.1%	22.8%	21.3%
Overweight / Obesity BMI >25 kg/m^2	43.1%	44.5%	54.4%	50.1%*****

** total cholesterol >5.2 mmol/L by finger prick test*
***BP > 140/>90mmHg*
****fasting blood glucose >6.1 mmol/L by finger prick*
*****current smokers > 15 years of age*
****** >23 kg/m^2*

Key Messages #1:

- Cardiovascular disease (CVD) has been an important cause of morbidity and mortality in both Malaysian men and women for more than a decade.
- Malaysians developed ACS at a mean age of 58.7 years and almost a quarter are below the age of 50 years. This is almost 10 years younger than that seen in Singapore.
- The prevalence of the common cardiovascular (CV) risk factors among adults ≥ 18 years has been on an increasing trend.
- About 40% of patients presenting with ACS have ≥ 3 CV risk factors.

2. MEASUREMENT OF LIPIDS AND APOLIPOPROTEINS

A standard lipid profile includes measurement of:

- Plasma or serum total cholesterol (TC)
- LDL-Cholesterol (LDL-C)
- HDL-Cholesterol (HDL-C)
- Triglycerides (TG)

TC, HDL-C and TG are measured directly from the serum.

2.1. Low Density Lipoprotein Cholesterol (LDL-C)

This is usually calculated by the Friedewald equation. This equation is not valid if the TG > 4.5 mmol/L. In these cases, it will have to be measured directly. However, the method of measurement is not standardized and for this reason it is not routinely performed.

There have been reports indicating that Friedewald-calculated LDL-C values lose their accuracy in patients with TG ≥1.7mmol/l or LDL-C <1.8mmol/l.[16,17] A large analysis, however, comparing the different methods of LDL-C calculation - the Friedewald, Martin-Hopkins, NIH equation 2 and BQ-derived methods - found that the correlation between all methods was good and the differences small and clinically insignificant.[18]

Friedewald equation:

LDL-C (mmol/L) = TC - HDL-C - TG/2.2
(If TG> 4.5 mmol/L, this formula is not valid.)

2.2. Non-High Density Lipoprotein Cholesterol (Non-HDL-C)

Non-HDL-C (mmol/L) = TC - HDL-C

- Non-HDL-C estimates the total amount of atherogenic lipoproteins (VLDL, VLDL remnants, IDL, LDL-C and lipoprotein(a)) present in plasma. It can be used to:
  - Evaluate CV risk when the TG > 4.5 mmol/L.[19]
  - Predict CV risk.[20]
- If non-HDL-C is used as a treatment target, the value is **0.8 mmol/L higher** than the corresponding LDL-C target level.

2.3. Triglycerides

Non-fasting TG measurements are more predictive of CV risk than fasting TG.[21] Non-fasting TG more accurately reflects the presence of atherogenic remnant lipoproteins compared to fasting TG measurements. There is however a lack of a standardized protocol for quantitation of post-prandial hypertriglyceridemia. This limits its clinical applicability.[21]

2.4. Fasting vs Non-fasting Lipid Measurement

I, A

Non-fasting lipid testing is acceptable.[22] The difference in values between fasting and non-fasting samples is small and has been shown to have no impact on CV risk estimation even in diabetics.[23] Concentrations of HDL-C, apolipoprotein A1 (Apo-AI), apolipoprotein B (Apo B), and Lipoprotein (a) (Lp(a)) are not affected by fasting/non-fasting status.

The use of a non-fasting sample, simplifies blood sampling, improves compliance to testing, helps workflow in laboratories and facilitates clinical decision making.

However, fasting lipid profile should be considered or preferred:

- If the non-fasting TG is > 4.5 mmol/L or > 2.3 mmol/l in diabetics.[24]
- In cases of familial dyslipidemia/hypertriglyceridemia.
- Following recovery of hypertriglyceridemia induced pancreatitis.
- When initiating medications that may cause hypertriglyceridemia (e.g., steroids, anti-retroviral therapy).

2.5. Other Lipid Parameters

- Other lipid measures that can be considered include Apo B, Apo B/ Apo A-1 ratio and Lp(a). Studies, however, indicate that measuring other lipid measures beyond the traditional lipid parameters offer little, or at the most modest, improvement in CVD risk prediction.[25,26]

2.5.1. Apo B

- Apo B is found in each of the atherogenic lipoprotein particles - chylomicrons, VLDL-C, intermediate density lipoprotein cholesterol (IDL), LDL-C and Lp(a).
- It is a better measure of the total atherogenic burden of the individual.
- Where appropriate laboratory facilities exist, apo B/ apo A-1 ratio should be measured given the importance of apo B/ Apo A-1 ratio as a risk factor for MI and ischemic stroke.[27,28]
- IIa, B It is important and realistic to note that the measurement of TC (and its usual conventional derivatives) is sufficient for most regions, given healthcare cost and the limited ability of most laboratories to measure apolipoproteins.[29]

2.5.2. Lp (a)

- Lp(a) has undergone a revival as a biomarker of CV risk, independent from other classical risk factors such as LDL.[30]
- Higher Lp(a) levels contribute significantly to “residual risk” in patients treated with statins and/or proprotein convertase subtilisin/kexin type- 9 (PCSK-9) inhibitors.[31,32]
- There are however challenges in the measurement and interpretation of Lp(a). There is a need for:[33]
  - standardization and harmonization of the currently available assays.
  - standardization of reporting units. Lp(a) measurements can be expressed in molecular mass (mg/dl), or molar concentration nmol/L, however the most appropriate units for measurement of Lp(a) are nmol/L.[34] Conversion between mass and molar units is inherently inaccurate and should be avoided.
  - evidence-based information on the cut points for “high CV risk” based on age, sex, and ethnicity and certain comorbid conditions.

Key Message #2:

- A standard lipid profile includes measurement of Plasma or serum total cholesterol (TC), LDL-Cholesterol (LDL-C), HDL-Cholesterol (HDL-C) and Triglycerides (TG).
- TC, HDL-C and TG are measured directly from the serum and LDL-C is calculated using the Friedwald’s equation provided TG<4.5 mmol/l.

Key Recommendations #1:

- Non-fasting lipid testing is acceptable.
- The difference in values between fasting and non-fasting samples is small and has been shown to have no impact on CV risk estimation.
- Measurement of TC (and its usual conventional derivatives - HDL-C, LDL-C and TG) is sufficient in most cases for CV risk assessment and treatment, given healthcare cost and the limited ability of most laboratories to measure apolipoproteins.
- Most of the CV benefits seen is with LDL-C lowering.

3. CLASSIFICATION OF DYSLIPIDEMIA

Dyslipidemias may be primary or secondary. (Tables 8 & 9, pg. 34-35)

3.1. Primary Dyslipidemia

- Primary Dyslipidemia is due to genetic disorders resulting in an isolated increase in LDL-C levels or a combination of elevation of LDL-C and TG.
- It is usually due to the complex interaction of multiple genes although occasionally it may be due to single gene defects. e.g., Familial Hypercholesterolemia.
- The commonest genetic disorder is Common Polygenic Hypercholesterolemia which is caused by a combination of multiple gene defects and environmental factors such as an atherogenic diet, sedentary lifestyle, and obesity.[35]

3.2. Secondary Dyslipidemia

In the following situations, secondary causes of dyslipidemia should be considered. For management of these patients, refer to sections 10.3, 10.6 and 11.

- When TC exceeds 7.0 mmol/L, exclude conditions such as primary hypothyroidism, nephrosis, and cholestatic liver disease. Hypothyroidism is more prevalent in the elderly in whom a high index of suspicion may be necessary for diagnosis.[36,37]
- Cushing's syndrome (including subclinical disease) can lead to lipid abnormalities in 40-70% of patients.[38] Patients on exogenous steroids may also develop secondary dyslipidemias.
- When TG exceeds 4.5 mmol/L, exclude secondary causes such as alcoholism.
- When there is high TG with low HDL-C, insulin resistance states such as type 2 diabetes and metabolic syndrome should be considered.
- Failure to respond to anti-lipid therapy.
- In patients with a family history of Type 2 diabetes or a previous history of thyroid disease.
- The effect of drugs on lipid levels is generally small and insignificant except for anabolic steroids that can cause almost a 50% reduction in levels of HDL-C and Lp (a). [39-41]

Key Message #3:

- Dyslipidemias may be primary due to genetic disorders or secondary to nephrotic syndrome, cholestatic liver disease, hypothyroidism, Cushing's syndrome, drugs, alcoholism and insulin resistance states such as Type 2 diabetes and metabolic syndrome.

Key Recommendations #2:

- Treatment of the underlying etiology in secondary dyslipidemia can lead to an improvement in the lipid profile.

Table 8: Primary (Genetic) Dyslipidemias

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

Key: ↑ Increased ↔ No change ↓ Decreased

Table 9: Effects of Secondary Causes of Dyslipidemias

CAUSES	CHOLESTEROL	TRIGLYCERIDES	HDL-CHOLESTEROL
Lifestyle Factors			
Alcohol	↔	↑↑	↑
Saturated fat/ trans-fat	↑	↑	↓
Cardio metabolic risk	↔	↑↑	↓
Smoking	↔	↔	↓
Physical inactivity	↔	↑	↓
Metabolic / Endocrine			
Hypothyroidism	↑↑	↔	↔
Type 2 Diabetes (T2DM)	↑	↑↑	↓
Cushing's Syndrome	↑	↑↑	↓
Kidney			
Chronic Kidney Disease	↔or ↓	↑	↓
Nephrotic syndrome	↑↑	↑↑	↓
Hepatic			
Obstructive liver disease	↑↑	↔	↓
Primary biliary cirrhosis	↑↑	↔	↑
Drugs*			
Thiazide diuretics	↔	↑↑	↓
β -blockers (non-cardioselective)[39]	↔	↑	↓
Anabolic steroids[40]	↔	↑	↓↓
Glucocorticoids[41]	↔	↔	↓*↑**

** < 60 years ** > 60 years*
Weir MR, Moser M. Diuretics and β-blockers: Is there a risk for dyslipidaemia?. Am Heart J. 2000;139(1) : 174-184.[39]
Hartgens F, Rietjens G, Keizer HA, et al Effects of androgenic-anabolic steroids on apolipoproteins and lipoprotein (a)British Journal of Sports Medicine 2004;38:253-259.[40]
Choi HK, Seegar JD. Glucocorticoid Use and Serum Lipid Levels in US Adults: The Third National Health and Nutrition Examination Survey. Arthritis & Rheumatism (Arthritis Care & Research) 2005: 53: 528-535[41]

Key: ↑ Increased ↔ No change ↓ Decreased

4. DYSLIPIDEMIA AS A CV RISK FACTOR

Dyslipidemia is recognized as one of the major risk factors for CVD. According to the Malaysian NCVD-ACS Registry 2018-2019, the prevalence of dyslipidemia among individuals admitted with Acute Coronary Syndrome was 36.7%.[10] The mean LDL-C on admission was 3.1 mmol/l in males and 3.0 mmol/l in females.[10]

I, A Reducing LDL-C has been shown in numerous secondary and primary prevention trials to reduce CVD events and mortality.[42-45]

The evidence of the CV benefits of reducing TG and/or increasing HDL-C has been less robust.

TC, HDL-C and TG are measured directly from the serum.

4.1. Low Density Lipoprotein Cholesterol (LDL-C)

LDL-C plays a major causal role in the development of CVD. This role has been demonstrated in many epidemiological and mendelian studies and in randomized controlled trials of LDL-C lowering.[46-57] Mendelian disorders such as Familial Hypercholesterolemia, where LDL levels are high, lead to a high incidence of premature CVD.[58]

The risk of CVD is also determined by the duration of exposure to high levels of LDL-C. Studies have shown that young adults with elevated LDL-C have significant long-term risk for CVD.[59,60] In Familial Hypercholesterolemia, manifestations of premature CVD become apparent early in the third decade of life.[61-65] On the other hand, there is a near absence of clinical CHD in populations with very low levels of serum cholesterol throughout their life- (TC < 3.9 mmol/L or LDL-C < 2.6 mmol/L).[66,67] The risk of CHD appears to increase progressively above these levels.

In the secondary prevention trials, LDL-C reduction by lipid lowering therapy and lifestyle modifications led to a reduction in CV events and mortality. A 1 mmol/L reduction in LDL-C resulted in a relative risk reduction of major CV events by 22% and all-cause mortality by 10%.[42] A meta regression analysis showed that the reduction of LDL-C by 1 mmol/L, by whatever mechanism, resulted in a similar reduction in major CV events.[44] The achieved absolute LDL-C level was significantly associated with the absolute rate of major coronary events.[44] For each 1 mmol/L lower LDL-C level, there was a 1.5% lower event rate in the primary prevention trials and a 4.6% lower event rate in the secondary prevention trials.[44]

I, A For these reasons, LDL-C is the primary target of therapy in both secondary and primary prevention.[42-45] Both the absolute value of LDL-C achieved and the percentage reduction in LDL-C lead to CV benefits.[44,68-84]

Lowering TC and LDL-C lowers CV risk, the absolute benefit is greater in high-risk Individuals.[42-45] The lower the LDL-C achieved, the greater the CV benefit.[72-80] At levels <1.8mmol/L, less progression of the atherosclerotic plaque is seen and at levels <1.6mmol/L, regression of the plaque has been documented.[81-84]

4.2. High Density Lipoprotein Cholesterol (HDL-C)

Isolated Low HDL-C is more common among Asians than non-Asians (33.1% vs 27.0%).[85] It is associated with a sedentary lifestyle, obesity, and avoidance of alcohol intake.[85] A low HDL-C especially when combined with high LDL-C and high TG is associated with an increase in CV risk.[86,87]

Despite this, increasing HDL-C levels by pharmacotherapy or by genetic techniques have not shown an improvement in CV outcomes.[88]

4.3. Triglycerides (TG)

In some people, despite achieving low LDL-C levels, the rate of CV events is still significantly high. This residual CV risk is partly contributed by cholesterol remnant particles - TG and TG-rich lipoproteins.[89,90]

An increase in TG levels is due to multiple factors. These include genetic factors, systemic illnesses e.g., hypothyroidism, poorly control diabetes, systemic lupus erythematosus, a high calorie diet and certain medications.[90]

Recent epidemiological and mendelian studies have shown that high TG levels may have a direct causal effect on CVD and is associated with an increase in all-cause mortality among persons with established CVD.[91,92]

Previously, reducing TG levels by pharmacotherapy has not demonstrated an improvement in CV outcomes. More recently however, the use of newer agents, specifically icosapent ethyl (IPE) at 4 grams per day, has shown promising results.[93-96] The observed CV benefits with this preparation of omega 3 fatty acids, however, appeared not to be consistent with the amount of TG lowering that occurred.

4.4. Non-HDL-C

Non-HDL-C reflects the concentration of cholesterol within all lipoprotein particles considered atherogenic. This includes chylomicrons, VLDL and their remnants, IDL, LDL and Lp(a).

Studies have demonstrated that non-HDL-C is a better predictor of CV risk than is LDL-C and may be especially true in statin-treated patients.[97-103] A 1% reduction in Non-HDL-C by lipid modifying drugs has been shown to be associated with a 1% reduction in CHD.[104]

Non-HDL-C is the secondary target of therapy. In cases where the TG>4.5 mmol/l, Non-HDL-C becomes the primary target of therapy.

4.5. Atherogenic Dyslipidemia

Atherogenic dyslipidemia consists of an increase in TG-rich lipoproteins, low HDL-C, lipoprotein remnants (i.e. small VLDL and IDL) and a preponderance of numerous small and dense LDL particles and postprandial hyperlipidemia.

Atherogenic dyslipidemia is usually associated with insulin resistance states such as obesity, metabolic syndrome and type 2 diabetes.

It has been shown to be causally linked to the development and progression of CVD.[105] It also contributes to the residual CV risk seen in statin treated patients.[105]

4.5. Lipoprotein (a) (Lp(a)

Lp(a) is a LDL-C like particle bound to apolipoprotein(a). It is inherited as an autosomal dominant trait.[106] Lp(a) has been shown to be an independent risk factor for atherosclerosis, MI, strokes, and aortic stenosis.[33,106,107]

The difficulty, to date, has been that there is no standardized assay to measure the Lp(a), the "normal levels" in the different populations is still unknown and the lack of effective therapy targeting it.[33,106,107]

Key Message #4:

- **According to the Malaysian NCVD-ACS Registry 2018-2019:**
  - The prevalence of dyslipidemia among individuals admitted with ACS was 36.7%.
  - The mean LDL-C on admission was 3.1 mmol/l in males and 3.0 mmol/l in females.
- **Non-HDL-C:**
  - Reflects the concentration of cholesterol within all lipoprotein particles considered atherogenic. This includes chylomicrons, VLDL and their remnants, IDL, LDL and Lp(a).
  - Studies have demonstrated that non-HDL-C is a better predictor of CV risk than is LDL-C.
- **Atherogenic dyslipidemia:**
  - Consists of an increase in TG-rich lipoproteins, low HDL-C, lipoprotein remnants (i.e., small VLDL and intermediate-density lipoprotein [IDL]) and a preponderance of numerous small and dense LDL particles and postprandial hyperlipidemia.
  - It is usually associated with insulin resistance states such as obesity, metabolic syndrome and type 2 diabetes.
- **Lp(a)**
  - Has been shown to be an independent risk factor for atherosclerosis, MI, strokes, and aortic stenosis.
  - The difficulty, to date, has been that there is no standardized assay to measure the Lp(a), the "normal levels" in the different populations is still unknown and the lack of effective therapy targeting it.

Key Recommendations #3:

- LDL-C is the primary target of therapy in both secondary and primary prevention.
- Both the absolute value of LDL-C achieved and the percentage reduction in LDL-C lead to CV benefits.
- The lower the LDL-C achieved, the greater the CV benefit. At levels <1.8mmol/L, less progression of the atherosclerotic plaque is seen and at levels <1.6mmol/L, regression of the plaque has been documented.

5. GLOBAL CARDIOVASCULAR RISK ASSESSMENT

5.1. Lipid Screening

According to NHMS VI, about 1 in 7 young adults aged 18-19 years (13.6%) have TC > 5.2 mmol/L.[5] All the CV risk factors- diabetes, hypertension, hypercholesterolemia, overweight/obesity and smoking- stratified by age, showed a sharp increase in prevalence from the age group 25-29 years.[5]

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

If available, in patients with recurrent CV events, Lp(a) levels should be measured.

I, C Individuals who are at high risk of developing CVD should have a lipid profile earlier in life. (Table 10, pg. 39)

Table 10: Individuals Who are at High Risk of Developing CVD

- Clinical evidence of atherosclerosis - CHD, CVA, atherosclerotic aortic aneurysm, peripheral vascular disease
- A family history of premature CVD - males (father and/or brother(s)) < 55 years of age and females (mothers and/or sister(s)) < 65 years of age
- A family history of genetic dyslipidemias
- Stigmata of dyslipidemia (corneal arcus, xanthelasma, xanthoma)
- CV Risk factors such as:
  - Metabolic syndrome
  - Diabetes mellitus
  - Abdominal obesity
  - Hypertension
  - Current cigarette smokers
- Inflammatory diseases such as Rheumatoid Arthritis, Systemic Lupus Erythematosus, Polyarteritis nodosa
- Chronic Kidney Disease (eGFR ≤ 60 mL/min/1.73 m2 or ACR ≥ 3 mg/mmol)
- Human Immunodeficiency Viral infection
- Erectile Dysfunction
- A history of hypertensive disorders of pregnancy
- Chronic Obstructive Airway Disease

5.2. Assessment of CV Risk

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

5.2.1. CV Risk Equations

- There are several risk equations that may be used to determine CV risk. (Appendix 1, pg. 90-91) The cut-off points that are used in these risk models to define risk categories are in part arbitrary. They are based on the risk levels at which the stipulated CV end points was seen in the population studied and the levels at which benefit was demonstrated in clinical trials.
- All risk models have limitations and difficulty when extrapolated to our local population. Ideally, the CV risk model used should be based on data derived from our local population. Currently, we do not have such a CV risk score. Both Thailand and Singapore have their own CV risk score which is based on the older Framingham Risk Score (10-year risk of CHD deaths, Non-fatal MI only) adapted to the local populations.[108,109]
- The risk score that is widely used in Malaysia is the Framingham General CVD risk score tool (FRS-General CVD) for primary care that assesses the 10-year risk of developing CVD (heart disease, strokes, PAD and Heart Failure).[110] (Tables 1 & 2 pg. 23-24) It can also be calculated online at https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php
- The earlier version of the Framingham Risk Score CHD (2002) provided a risk estimate of "hard" CHD events only i.e. cardiac death and nonfatal myocardial infarction unlike the FRS-General CVD Risk Score.
- The FRS - General CVD has the advantage of being derived from a population that had received no or little treatment at the start and during the study.[110,111] It is also simple and easy to use - an important feature if healthcare providers are to use it routinely.
- In 2 local studies, the FRS-General CVD risk model was a better discriminator of CV risk in our local multi-ethnic population.[112,113]
- The 2013 ACC / AHA risk calculator overestimated CV risk in the Malaysian population.[114]
- Based on a dataset from a longitudinal Malaysian community-based study of 12, 573 participants aged ≥18 years, it was shown, in a recent study, that both the FRS-General CVD and the Revised Pooled Cohort Equations (RPCE) showed good discrimination in CVD risk prediction.[115] Based on calibration however, the authors felt that RPCE would be the most clinically useful model to predict CVD risk in the Malaysian population.[115] Discrimination is the ability to accurately rank individuals from low to high risk and calibration is the ability to accurately predict the absolute risk level.

I, C

- Currently, the committee still recommends the FRS-General CVD risk score for primary prevention since it has been well validated.

5.2.2. Calculation of CV Risk

- All apparently healthy individuals should be risk stratified using the FRS-General CVD Risk Score[110] (Tables 1 & 2 pg. 23-24) or online at: https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php
- The 10-year risk calculation is to be performed at the outset to help guide the intensity of lipid lowering therapy. It cannot be used to track changes in risk over time as risk factors are modified.
- Risk assessment is not a one-time event; it should be repeated, for example, every 5 years, although there are no empirical data to guide intervals.

- In calculating the risk scores:
  - the TC and HDL-C should be the average of at least 2 measurements.
  - The average baseline blood pressure should be obtained from an average of several readings.
  - A "smoker" means any cigarette smoking in the past month.
- Based on the 10-year CV risk, individuals may be:
  - ≥ 20% - High CV Risk
  - ≥ 10 - <20 % - Intermediate (Moderate) CV risk
  - < 10% - Low CV risk

5.2.3. Classification of CV Risk

Individuals may be classified as:

- **Very High Risk -individuals with:**
  - **Established CVD** - Patients who already had a CV event are at highest risk for a recurrent event.
    - In the contemporary era, pooled results from phase III trials of high-risk ACS patients show that 4.1% and 8.3% of patients developed a recurrent major adverse CV event (MACE) - i.e., CV death, MI, or stroke - at 90 days and 360 days, respectively.[116]
    - Registry data, however, indicate that these figures are higher - 1-year post index MI rate for MACE was 18.3%, and the 5-year event rate was 33.4%.[117,118]
    - In patients with stable established atherosclerotic disease or risk factors for atherosclerosis, however, the risk is lower-1-year and 4-year rate of MACE was 1.4% and 6.9% respectively.[119]
    - Following a stroke, the risk of MACE (ACS, MI, incident CAD, coronary revascularization procedures, incident heart failure, or CV death) is also increased. The data from a registry of elderly stroke survivors (> 66 years), showed that the risk was time-dependent, highest within 30 days.[120] The risk of incident MACE associated with first ever ischemic stroke at 30 days was 25-fold in women and a 23-fold higher in men. This decreases but remains significant between 31 and 90 days (HR 4.2-4.8) and 91 to 365 days (HR, 2.0-2.1).[120] The risk of a recurrent stroke and the risk of death at 1 year was 8-11%[121,122] and 24.5%[121] respectively.
  - **Atherosclerosis in other vascular beds** - aorta including atherosclerotic aortic aneurysms, carotid, cerebral and peripheral vessels.
  - **Asymptomatic significant atherosclerotic plaques** detected on Computed Tomography (CT) coronary angiogram and carotid ultrasound. (refer Section 10.1)
  - **Diabetes with proteinuria**[24,123-128] or with a major risk factor such as smoking, hypertension or dyslipidemia.
  - **Chronic kidney disease (CKD)** - Estimated Glomerular Filtration Rate (eGFR) <30 ml/min^{-1} /1.73 m^2 (Stage 4 & 5) - There is an independent, graded association between reduced eGFR and the risk of death, CV events, and hospitalization.[129,130] The risk begins to increase with eGFR <60 ml / min^{-1} / 1.73 m^2 and escalates as the eGFR drops below <30 ml/min^{-1} / 1.73 m^2.[129]
- **High Risk individuals** include those with (Table 4, pg. 26):
  - **Chronic kidney disease** (CKD) - eGFR ≥30 - <60 ml / min−1 /1.73 m^2 (Stage 3)
  - **Diabetes without target organ damage**[24,131]
  - **Very high levels of individual risk factors** (e.g. LDL-C > 4.9 mmol/l or BP ≥180/110mmHg[71])
  - **Multiple risk factors that confer a 10-year risk for CVD > 20%** based on the FRS-General CVD Risk Score[110]

Individuals who belong to the above **Very High Risk and High-Risk categories**, do not need to be risk stratified using the FRS-General CVD Risk Score.

They should be encouraged to have:

- **a healthy lifestyle** (stop smoking, regular exercise, and a healthy diet) ***in addition to***
- **pharmacotherapy**, to ensure that all their CV risk factors are treated to targets.

I, A These individuals derive the greatest benefit from risk factor reduction and lipid lowering therapy.[42-44]

The risk of recurrent events in stable CVD patients is influenced mainly by the classical CV risk factors, vascular disease site, and kidney function. In these individuals, the following **risk stratification tools for secondary prevention** may be used. These include:

- Secondary Manifestations of Arterial Disease **(SMART) risk score** for estimating 10-year residual CVD risk.[132]
- European Action on Secondary and Primary Prevention by Intervention to Reduce Events **(EUROASPIRE) risk model** which estimates 2-year risk of recurrent CVD.[133]

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

- **Low risk** - 10-year CV risk <10%.
  - Low-risk individuals should be given advice to help them maintain this status.
  - The relative risk reduction of lipid lowering therapy is similar in all individuals irrespective of their CV risk status. However, in low-risk individuals the absolute benefit may be less.[45,134-136]
  - Many young individuals may fall into this category of **low absolute risk of CVD** but they may have **a high lifetime risk** if their individual risk factors are high. These include individuals with:
    - BP > 180/110 mmHg
    - LDL-C > 4.9 mmol/L
    - In these individuals using Vascular Age (Tables 3A & B, pg. 25), may be helpful in defining CV Risk and guiding management strategies.[137-139] This risk model has not been validated in our local population.
- **Intermediate (Moderate) Risk** - 10-year CV risk >10 - <20%
  - In these individuals, other risk factors not included in the FRS-General CVD Risk Score may influence treatment targets and the decision to initiate pharmacotherapy.
  - Additional factors that may support upgrading of CV risk include[140,141]
    - Family history of premature CVD - males (father and/or brother(s)) < 55 years of age and females (mothers and/or sister(s)) < 65 years of age[142-146]
    - Ankle: brachial (ABI) index < 0.9- this indicates PAD, the lower the index, the more severe the disease.[140]
    - hs-CRP levels ≥ 2mg/L[140,141]
    - Coronary artery calcium score of ≥ 100 Agatston units or coronary artery calcium ≥ 75th percentile for a patient of the same sex and age.[140,147-151] Coronary Calcium score:
      - can be low or even zero in patients with soft plaques.
      - does not provide information on plaque burden or stenosis.

III, B

- Routine measurement of carotid intima media thickness (CIMT) for risk assessment is not recommended due to the lack of methodological standardization, and the absence of added value of IMT in predicting future CVD events, even in the intermediate-risk group.[141,152]
- It has not yet been demonstrated that with upgrading of the risk category of patients at **Intermediate (Moderate) Risk** and subjecting them to aggressive risk factor reduction, it would lead to reduction in CV risk and improvement in CV outcomes.

These risk models help guide risk assessment and management. They do not replace sound clinical judgement in the assessment of global risk and management strategies. They also do not consider **risk modifiers** such as:

- **Psycho-social stressors** such as work or family stress, depression, anxiety etc. These can increase CV risk and mortality.[141,153-155]
- **Frailty** - This, by itself, has been associated with both high CV and non-CV morbidity and mortality.[156,157]

I, C

The intensity of preventive actions should be tailored to the patient's total CV risk. The risks (side effects, costs etc.) should be weighed against the benefits of each intervention.

In subjects who are at **Low or Intermediate (Moderate)** risk, the decision to initiate pharmacotherapy should be individualized following a mutual discussion with the patient.

Key Messages #5:

- The committee advocates lipid screening all adults > 30 years of age. Individuals who are at high risk of developing CVD should have a lipid profile earlier in life (> 18 years of age).
- The intensity of LDL-C lowering should be tailored to the individual's global CV risk.
- In 2 local studies, the FRS-General CVD risk model was a better discriminator of CV risk in our local multi-ethnic population.

Key Recommendations #4:

- All individuals should be risk stratified. (Table 4, pg. 26)
- Patients with established CVD, CKD and diabetes fall into the Very High - and High-Risk Categories.
- All other individuals should be risk stratified at the outset using the FRS-General CVD risk score to determine if they are at High, Intermediate (Moderate) or Low Risk. (Tables 1 & 2, pg. 23-24)

6. TARGET LIPID LEVELS

6.1. LDL-C Goals

I, A — LDL-C is the primary target of therapy.[42-45,134-136]

I, A — The target LDL-C level will depend on the individual's CV global risk. (Table 4, pg. 26 & 45)

I, A — Both the absolute on treatment LDL-C level and the percentage LDL-C reduction achieved have been found to correlate with the observed CV benefits.[42-44,68-84]

6.2. Non-HDL-C Goals

IIa, B
- Non-HDL-C may be considered as a secondary target when treating patients with:
  - Combined hyperlipidemias
  - Diabetes[24]
  - Cardio metabolic risk
  - Chronic kidney disease
- The targets for non-HDL-C are **0.8 mmol/L higher** than the corresponding LDL-C goal.
- Adjusting lipid lowering therapy to achieve these secondary goals may be considered after achieving LDL-C targets in patients with **Very High and High CV risk**.
- Although increases in HDL-C predict atherosclerosis regression and low HDL-C is associated with excess events in CHD patients, clinical trial evidence using pharmacotherapy to increase HDL-C has not shown any CV benefits.[88,158-160]

Table 4: Target LDL-C levels

Global Risk	LDL-C Initiate Drug Therapy (mmol/L)	Target LDL-C levels (mmol/L)	Target Non-HDL-C (mmol/l)
Low CV Risk* <10%10-year CVD risk	clinical judgement**	<3.0	<3.8
Intermediate (Moderate) CV Risk* ➢ 10-20% 10-year CVD risk ➢ Diabetics < 50 years old and< 10-year duration and no CV risk factors	>2.6 **	<2.6	<3.4
High CV Risk ➢ > 20% 10-year CVD risk ➢ diabetes >10-year duration without target organ damage + 1 other CV risk factor ➢ CKD with eGFR 30-<60ml/min-1/1.73 m^2	> 1.8	≤ 1.8 ***and*** a reduction of >50% from baseline	≤ 2.6 ***and*** a reduction of >50% from baseline
Very high CV Risk* ➢ established CVD ➢ diabetes with CVD or other target organ damage or > 3 CV risk factors ➢ CKD with eGFR <30ml/min-1/1.73 m^2 ****	>1.4	≤ 1.4 ***and*** a reduction of > 50% from baseline	≤ 2.2 ***and*** a reduction of >50% from baseline
***Those with recurrent CV events within 2 years despite achieving a LDL-C target of <1.4mmol/l		<1.0	

**Low and Moderate CV risk is assessed using the FRS- General CVD Risk Score*
***After a therapeutic trial of 8-12 weeks of TLC and following discussion of the risk: benefit ratio of drug therapy with the patient.*
****All other CV risk factors should be treated to target.*
***** Lipid lowering therapy lowers the risk of atherosclerotic CVD in CKD patients. Those who are on dialysis are at very high CV risk, but it is for non-atherosclerotic CVD e.g. due to medial calcific arteriosclerosis, LVH, coronary artery calcification, arrhythmias etc. Thus, lipid lowering therapy is not initiated in patients on dialysis but if they have CVD or are already on statins before becoming dialysis dependent, then it should be continued.*

Key Recommendations #5:

- LDL-C is the primary target of therapy.
- The target LDL-C level will depend on the individual's CV global risk. (Table 4, pg. 26 & 45)
- Non-HDL-C may be considered as a secondary target when treating patients with:
  - combined hyperlipidemias
  - diabetes
  - cardio metabolic risk
  - chronic kidney disease
- Non-HDL-C however, becomes the primary target of therapy in situations where the TG >4.5 mmol/l.

7. MANAGEMENT OF DYSLIPIDEMIA

7.1. Therapeutic Lifestyle Changes (Table 5, pg. 27)

I, C

- Therapeutic lifestyle changes (TLC) are a critical component of health promotion and CV risk reduction efforts both prior to and after commencement of lipid-lowering therapies in all individuals.
- These measures should be promoted as a population-based strategy for the primary prevention of CVD.[161]
- TLC refers to:
  - Adhering to healthy dietary patterns,
  - Regular exercise - ≥ 150 minutes of moderate intensity exercise per week or 75 minutes a week of vigorous-intensity exercise or an equivalent combination,
  - Avoidance of tobacco smoking,
  - Alcohol restriction ***and***
  - Maintenance of an ideal weight - BMI 20 - 23.5 kg/m^2 and waist circumference < 90 cm (men), < 80 cm (women).

7.1.1. Medical Nutrition Therapy (MNT)

I, C

- MNT should be emphasized in both primary and secondary prevention of CVD. (Table 5, pg. 27).
- MNT is aimed at:
  - Optimizing lipid levels while maintaining a balanced diet.
  - Weight management - weight loss (5%-10% of body weight) for those who are overweight or obese.
  - Empowering the individual to manage their stages of change to achieve their nutritional goal.
- All patients with CVD and individuals with elevated lipids should be referred, where available, to a dietitian for MNT. Motivational interviews, usually conducted by the dietitian, are important and have been shown to optimize outcomes.[162]

- Studies have shown that MNT by a trained dietitian with multiple visits over six to twelve weeks can result in reduction in TC by 7% to 21%, LDL-C by 7% to 22% and TG by 11% to 31%.[163-165] The challenge, however, is long term adherence to the dietary advice.[165]
- The **current emphasis is on dietary patterns** rather than on individual nutrients. Dietary patterns refer to the balance, variety, and combination of foods and beverages habitually consumed.[166]
- Poor diet quality is strongly associated with an elevated risk of CVD morbidity and mortality.[166]
- In general, **heart-healthy dietary patterns** which are associated with low CV risk, should be encouraged in all individuals. Energy intake and expenditure should be adjusted to achieve and maintain a healthy body weight. A healthy diet consists of:[166]
  - Primarily fruits and vegetables.
  - Foods made with whole grains such as brown rice rather than refined rice.
  - Healthy sources of protein:
    - Mostly plant based such as tofu, beans, lentils, chickpeas, and other legumes.
    - Fish, and seafood. Eating ≥2 fish meals per week is beneficial. However, preparing fish by deep frying is not associated with CV benefits.[167,168] It is healthier to pan fry, bake or boil rather than deep fry the fish.[169]
    - Low-fat or fat-free dairy products.
    - If meat or poultry are desired, use lean cuts and avoid processed meats such as burgers and sausages.
  - Liquid plant oils such as sunflower oil, rapeseed oil, corn oil etc.
  - Minimally processed foods - (Appendix 2, pg. 92)
  - Low added sugar and salt in beverages and foods.
  - Nuts - Consuming ½ to 1 cup of nuts per day as part of a heart healthy diet, lowers TC by 4% to 21% and LDL-C by 6% to 29%.[163,170,171] This, however, contributes significant calories to the diet.[163] A higher nut intake has been associated with lower risk of incidence and mortality from CVD, CHD, and strokes.[166,172,173]
- **A plant-based diet**, along with increased fruit, nut, vegetable, legumes, and lean meat or animal protein (preferably fish) consumption, with the inherent soluble and insoluble fibre present in the food, has consistently been associated with a lower risk of all-cause mortality than control or standard diets.[174-177]
  - Replacing animal proteins of different origins with plant proteins has been shown to be associated with a lower all cause and CV mortality rate.[178] Caution is necessary with the use of some plant-based meat alternatives. These may be ultra-processed and contain added sugar, saturated fat, salt, stabilizers, and other preservatives.[166] (Appendix 2, pg. 92)
- The **Malaysian Healthy Plate guideline recommends the #QuarterQuarterHalf diet** which consists of:[161]
  - Quarter of the plate being carbohydrates - rice, noodles, bread, cereals and other cereal products and/or tubers.
  - Quarter of the plate being protein - fish, poultry, meat and/or legumes.
  - Half of the plate being fruits and vegetables.
  - Drinking plain water.

7.1.1.1 Dietary Cholesterol

- The role of serum cholesterol (especially LDL-C) in the pathogenesis of atherosclerosis and CVD is consistent and robust. (Section 4)
- The contribution of dietary cholesterols to blood cholesterol levels is, however, more complex, and controversial. The question is whether eating food high in cholesterol leads

to high serum cholesterol and LDL-C, and whether limiting dietary cholesterol intake lowers serum LDL-C.[179-181]

- Blood cholesterol is mainly synthesized by the body especially in the liver. Dietary sources only contribute about 15-20% and there is, under normal circumstances, a balance between the 2 sources to maintain cholesterol homeostasis.
- Data indicates that the impact of dietary cholesterol on serum cholesterol levels is weak.[179-181] However, many high-cholesterol foods also contain high levels of saturated fats (SFA). This includes dairy products, meat, and most processed foods.
- Dietary guidance, at present, tend to focus on healthy dietary patterns rather than specific dietary cholesterol targets.[166,182]

7.1.1.2. Total Fats - Saturated and Unsaturated Fats

- Fats in the diet consist of TG which is made up of three fatty acids and a glycerol backbone.
- Fatty acids differ in the length of their aliphatic tails, ranging from short chain (≤ 5) to very long chain (≥ 22) fatty acids. Depending on the number of double bonds, fatty acids can be further categorized as:
  - Saturated fatty acids (SFA) : no double bonds
  - Unsaturated fats which may occur as either:
    - polyunsaturated fats (PUFA) : 2 or more double bonds
    - monounsaturated fatty acids (MUFA) : 1 double bond
- Oils are mixtures of fatty acids. For fatty acid composition of common dietary oils and selected Malaysian food, refer to Appendix 3 & 4, pg. 93-95).[183]
- Omega fatty acids are PUFA and include:
  - Omega-6 fatty acids - linoleic acid found in vegetable oils such as sunflower, safflower, soybean, corn, grapeseed, peanut, and canola oils as well as nuts and seeds.[184]
  - Omega-3 fatty acids which consist of:
    - α-linolenic acid (ALA) - found in plant oils, canola oil, flaxseed oil, soybean, chia seed, linseed and rapeseed oils, walnuts, and leafy green vegetables.[185-187]
    - Eicosapentaenoic acid (EPA) - present in marine oils such as fish oils.[188]
    - Docosahexaenoic acid (DHA) - present in marine oils such as fish oils.[188,189]
- The rate of conversion of omega-6 fatty acids to omega-3 fatty acids in the body is low.[187] Thus it is important to increase the intake of omega-3 fatty acids in the diet. Sources of omega-3 fatty acids (DHA and EPA) are fatty fish (e.g., salmon, ikan kembung, ikan jelawat, siakap, keli, patin, senangin, white pomfret).[186,188,189] For prescription omega-3-fatty acid supplements and its effect on lipids and CVD, refer Section 7.2.6.3.
- The body can produce all the required fatty acids except for the essential fatty acids -linoleic acid and alpha-linolenic acid.[190] These must come from the diet e.g., corn, sunflower, and soybean, flaxseed walnuts, and dark leafy vegetables (e.g., spinach, kailan).
- Excess intake of SFA has been implicated with an increased risk of CVD in several epidemiological studies.[191] Increasingly however, there has been controversy about associations between total SFA and CV risk.[192-200] It is also being recognized that the health effects of foods cannot be predicted by their content of any nutrient group without considering the overall macronutrient composition.[166,201]

I, A

- Older guidelines recommend that the intake of SFA should not exceed 10% of energy intake.[140,141,161,191] (Table 5, pg. 27) The current 2020-2025 Dietary Guidelines for Americans, however, recommends a dietary pattern low in SFA without specifying targets.[166,202]
- A central issue in the relationship between SFA and CVD is the specific macronutrients that are used to replace it in the diet. When SFA is replaced with:

I, B
- **PUFA** - results in a reduction in TC and CV events. However, there was no significant effect on all-cause, CVD, or CV mortality.[192]

IIb, B
- **MUFA or Carbohydrates** - will not have any effect on blood lipids.[192]

- Taking PUFA or MUFA (e.g.,1 teaspoon of olive oil) without cutting down SFA intake will not confer CV benefit. Virgin coconut oil is rich in SFA.

7.1.1.3. Trans Fat

- Trans fat (TFA) may be:[203]
  - "Industrially produced" TFA- these are man-made fats added to foods such as shortening and baked goods.
  - "Ruminant" TFA- these occur naturally in small amounts in foods such as butter and beef.
- Trans fats are created through a process of partial hydrogenation.[203] The presence of TFA makes oils more solid and extends their shelf life. Major sources of TFA are deep-fried fast foods, margarine, commercially baked cookies, cakes, crackers, and some bread.[203] Repeated / prolonged heating of MUFA and PUFA may convert them to trans-fat.[204,205]
- Intake of TFA raises levels of LDL-C, reduces HDL-C, and increases the ratio of TC to HDL-C.[203] Prospective cohort studies showed that TFA was also associated with an increase in the incidence of diabetes.[206-208]
- TFA appears to increase the risk of CVD more than any other macronutrient on a per-calorie basis.[203] Even at low levels of consumption of 1-3% of total energy intake, CV risk is substantially increased.[203]
- Total TFA fat intake was associated with all-cause mortality, CHD mortality, and total CHD.[203] Industrial, but not ruminant, TFA fats were associated with CHD mortality and CHD.[209]
- A 2 percent increase in energy intake from trans fats was associated with a 23 percent increase in the incidence of CHD.[210] It was estimated that substituting 2% of energy from trans fats with SFA, MUFA and PUFA would reduce CV risk by 17%, 21% and 24% respectively.[210]
- There has been no consistent scientific evidence of a relationship between TFA with BP or cancer.

I, A
- TFA intake should be kept at <1% of total energy.[140,141,161] (Table 5, pg. 27)
- The TFA content in commonly available commercial food sold in Malaysian supermarkets is generally very low (<1mg/100gm of weight of the food).[211]

7.1.1.4. Carbohydrates

- There are many types of diet. Some of these are:
  - **Low carbohydrate diet** where the proportion of calories from carbohydrates are reduced and replaced with protein and/or fats. The calories in these diets may be reduced or be maintained.
  - **Low fat diet** where the proportion of calories from fats are reduced and replaced with either carbohydrates and/or protein. Again, the total calorie intake may be maintained or reduced.
  - **Low calorie diet** where total calorie intake is reduced and the proportion of carbohy drates, fats and protein may be maintained or reduced e.g., low-fat, low-calorie diet or low carbohydrate, low calorie diet.
- A low-quality carbohydrate diet has been associated with an increased risk of CVD and death.[212,213] This consists of:
  - Low amounts of fibre,
  - High amounts of refined grains ***and***

- A high glycemic index (a measure of how much a given carbohydrate raises blood glucose levels).

- Carbohydrate restriction has been shown to:[214]
  - Improve glycemic control and reverse Type 2 diabetes and the metabolic syndrome even without significant weight loss.[215-217]
  - Result in weight loss. A low carbohydrate, high fat, unrestricted calorie diet has been shown to result in a better glycemic control and weight loss when compared to a low fat, high carbohydrate diet at 6 months. The changes seen were however non sustained at 3-month post intervention.[218]
  - Significantly decrease TG and increase HDL-C.[219]
  - Result in minimal change in LDL-C levels. There has been concern because in these diets, carbohydrates are being replaced with protein and SFA. Studies, however, seem to indicate that carbohydrate restriction results in decreased small, dense LDL particles and an increase in large particles with no significant change in total LDL particles or po B-containing lipoproteins.[220]
  - Significantly reduce blood pressure although this may be secondary to the weight loss seen in the study.[221]
- **The low carbohydrate, high fat diets are not encouraged** because:
  - Most of these studies have been of short duration (< 2 years) and long-term data on safety and sustainability of these diets is lacking.[222]
  - A Cochrane review however, found little to no difference in weight reduction and changes in CV risk factors up to two years' follow-up, when overweight and obese participants without and with Type 2 Diabetes were randomized to either low-carbohydrate or balanced-carbohydrate weight-reducing diets.[223]
  - A recent observational study showed that individuals on a low carbohydrate, high fat diet had significantly higher levels of LDL-C, apo B levels and higher new CV events (9.8% vs 4.3%) compared with participants on a standard diet after 11.8 years of follow up.[224] This was a “keto-like” diet consisting of no more than 25% of calories from carbohydrates and >45% of total daily calories from fat.[224]
- In patients with Type 2 diabetes, low-carbohydrate diets have been advised as the first approach in management.[225] However, the type of carbohydrates consumed is also important. Diets that emphasized:
  - Plant-based foods and high-quality carbohydrates, such as fruits, vegetables, and whole grains were associated with a lower CV event rate and cancer mortality.[226]
  - Animal products and low-quality carbohydrates, such as potatoes, added sugars, and refined grains, were not significantly associated with lower mortality.[226]
- There is no clear consensus on what defines a low-carbohydrate diet. Commonly used definitions:
  - A Low-Carbohydrate diet where carbohydrates are reduced to 26-45% of total calories. (<225 g/day of a 2000 calorie diet).[215]
  - Very Low-Carbohydrate diets where carbohydrate content varies from <10% to <26% of daily caloric intake.[215,225]
  - A keto diet has substantially lower intakes of carbohydrate (eg, <10% of daily calories). This has been shown to induce nutritional ketosis. The body uses fat as its main fuel source instead of carbohydrates. This results in significant weight loss but the diet itself is usually non sustainable. There is inadequate data on long-term safety of keto diets.[227] For most individuals, **the risks of ketogenic diets may outweigh the benefits**.[227]

7.1.1.5. Atherogenic Dyslipidemia

- In patients with an atherogenic dyslipidemia, a low carbohydrate diet (< 26% of total energy intake) results in a significant reduction in TG levels, an increase in HDL-C levels, and a shift from small dense LDL-C to the larger buoyant LDL-C even in the absence of weight loss.[228-233]
- A meta - analysis found that compared with participants on low-fat diets, persons on low-carbohydrate diets experienced a slightly but statistically significant lower reduction in TC and LDL-C but a greater increase in HDL-C and a greater decrease in TG.[234]
- There were no significant differences in weight loss between the low-fat vs the low carbohydrate diet.[234]

I, B
- In patients with atherogenic dyslipidemia, a low carbohydrate diet emphasizing plant based and high-quality carbohydrates together with weight loss and regular exercise should be encouraged.[228-234]

7.1.1.6. Sodium

IIa, B
- Dietary sodium reduction has been shown to reduce BP and CV events.[235,236]
- Reducing salt to 2.5 g/day (1/2 teaspoon of salt/day) results in a 20% reduction of CV events.[237]
- High consumption of sodium (>2000 mg daily equivalent to 5 g of salt or 1 leveled teaspoon), red meat (>14g a day), sugar-sweetened beverages and processed red meat consumption were all associated with increased CV mortality.[238]

7.1.1.7. Alcohol

- Alcohol has diverse effects on the CV system depending on the amount and type of alcohol consumed, patterns of drinking (e.g., binge drinking), age, sex, and ethnicity of the individual.[239]
- There is J shaped curve between alcohol intake and a variety of adverse health outcomes.[239]
- Low levels of alcohol intake have been shown to reduce all-cause mortality in both men and women.[240]
- Moderate consumption of alcohol (30 gm ethanol/day) increases the concentration of HDL-C, apoA-I and TG.[241]

I, C
- The recommendation is one should not start drinking alcohol for health benefits.[166]

I, C
- Those individuals who do drink, should not exceed 1 drink/day (10gm/day) in non-pregnant females or 2 drinks/day (20gm/day) in males. Binge drinking should be avoided.[166,202]

7.1.2. Exercise

- Regular exercise reduces the risk of all-cause and CVD mortality in both healthy individuals and patients with CVD by 20–30%.[242-244]
- However, there is still a lack of data on how much and type of exercise that is required to improve the lipid profile and reduce CV risk.[245,246]
- In general, the effect of exercise on lipids will depend on:[247]
  - Type of exercise - aerobic or resistance training or a combination.
  - Duration of exercise.
  - Intensity of exercise.
- Studies show that regular aerobic exercise can:[247-252]
  - Increase HDL-C by 3–13% -up to 0.16 mmol/L.
  - Reduce TG by about 11% (up to 0.34 mmol/L).

- Vigorous aerobic and resistance exercises improve HDL-C more than less-intense exercise.[248,252]
- The decrease in TG with exercise is acute and short-lived, becomes evident 12-18 hours after a single bout of exercise and lasts for 2-3 days.[253] It requires that a certain amount of energy (a threshold) be expended during exercise, independent of duration or intensity. More exercise above that threshold does not seem to result in greater reductions in plasma TG concentrations.[253]
- A meta-analysis showed that pharmacotherapy (statins) and exercise interventions showed similar reductions in post prandial TG but statins lowered fasting TG levels more than exercise.[254]

I, A
- The recommended duration of exercise for CVD prevention in healthy adults, regardless of age is:[140,141,161,255]
  - At least 150-300 minutes a week of moderate-intensity or
  - 75-150 minutes a week of vigorous-intensity aerobic physical activity exercise or an equivalent combination

I, B
- For weight loss, increased exercise of approximately 250 to 450 minutes of moderate-intensity exercise per week, including strength training 2 to 3 times per week is required.[256] This should be accompanied by a calorie-restricted diet.

7.1.3 Weight Loss

- A 5% weight loss has been shown to decrease TC, LDL-C, TG and increase HDL-C levels.[257]
- In most patients, however, the changes in lipid levels with weight loss are small and proportional to the change in weight.[258] A meta-analysis showed that for every 10 kg weight loss, TC decreases by 0.23 mmol/L during long term follow-up in persons suffering from obesity or who are grossly overweight.[259]

7.1.4. Smoking

- Smoking is a strong and independent risk factor for CVD.[260] It accelerates coronary plaque development and may lead to plaque rupture.
- Smoking has:[261,262]
  - An adverse effect on TG - heavy smokers had a significantly higher concentration.
  - The concentration of HDL-C was inversely related to smoking, non-smokers having the highest concentration.
- The concentrations of TC, fasting blood glucose and uric acid were correlated with body mass index (BMI) rather than smoking.[261,262]
- Cigarette smoking cessation increases serum levels of HDL-C, especially in women, but has no effect on TC, LDL-C, and TG.[263-265] This improvement in HDL-C levels may be offset by the weight increase that occurs after quitting. Strategies should be taken to minimize the weight gain following smoking cessation.
- There is significant reduction in CV morbidity within the first 6 months of smoking cessation.[260] The CV risk decreases gradually after smoking cessation and reaches that of non-smokers after 15 years.[260] This benefit occurs independent of its effect on lipids.

I, B
- Smoking should be discouraged, and individuals referred to smoking cessation programmes. One such service is the mQuit which is a collaborative effort by the Ministry of Health, Malaysian Academy of Pharmacy, Malaysian Pharmacists Society, and various other partners and involves both public and private sectors. More information is available at www.JomQuit.com.my

Key Message #6:

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

Key Recommendations #6:

- The current emphasis is on healthy dietary patterns rather than on individual nutrients.
- A heart healthy diet consists of:
  - Primarily fruits and vegetables,
  - Whole grains,
  - Healthy sources of protein (mostly plant based such as tofu, beans, lentils), fish, and seafood, lean cuts of meat,
  - Liquid plant oils,
  - Minimally processed foods (Appendix, pg 92),
  - Low added sugar and salt (<2000mg sodium equivalent to 5 gm of salt /day = 1 level teaspoon of salt) in beverages and foods ***and***
  - Nuts.
- The duration of exercise for CVD prevention in healthy adults regardless of age is:
  - At least 150-300 minutes a week of moderate intensity or
  - 75-150 minutes a week of vigorous intensity aerobic PA or an equivalent combination.
- Weight loss causes a small but significant decrease in TC, LDL-C and TG on long term follow up.
- Smoking should be discouraged, and individuals referred to smoking cessation programmes.

7.2. Lipid Modifying Drugs

I, C

- Most individuals at Low and Intermediate (Moderate) Risk can be managed by Therapeutic Lifestyle Changes. Occasionally, lipid modifying agents may be necessary to achieve target lipid levels. Only statins have been studied in primary prevention.
- In those at Very High and High CV Risk, it is recommended that drug treatment be initiated early, simultaneously with TLC. There are eight major groups of lipid modifying drugs. (Tables 11, pg. 56)

7.2.1. HMG CoA Reductase Inhibitors (Statins)

- Statins are inhibitors of HMG CoA reductase, the rate limiting enzyme in hepatic cholesterol synthesis. This results in a reduction in intracellular cholesterol which leads to an increase in LDL receptor expression at the surface of the hepatocytes. This in turn, results in an increase in clearance of LDL- and other Apo B-containing lipoproteins, including TG-rich particles from the plasma.

I, A

- LDL-C reduction with statin treatment remains the cornerstone of lipid lowering therapy to reduce risk of CVD.[42-45,134,135,266] They are the drugs of choice in reducing LDL-C because of the consistent results of numerous randomized primary and secondary prevention clinical trials.[42-45,134,135,266]

- The amount of CV risk reduction seen will depend:[42-45,68-84]
  - on the absolute risk of the individual - In primary prevention, the absolute benefit from statin treatment is lower since these individuals are typically at lower risk.
  - the degree of LDL-C lowering that is achieved (level of LDL-C achieved and/or the percentage reduction).
- Depending on the treatment level of LDL-C level achieved, lipid modifying agents can slow the progression and even promote regression of coronary atherosclerotic plaques.[81-84,267,268]
- An achieved on-treatment LDL-C level of < 1.6 mmol/L appears to significantly slow down progression of atherosclerosis.[81-84,267,268]

7.2.1.1. Lipid Lowering Effects of Statins

- The degree of LDL-C reduction seen with the different statins is dose-dependent. (Table 12, pg.59)[269]
  - A high intensity statin (i.e atorvastatin 40-80mg, rosuvastatin 20 mg) can, on average, reduce LDL-C by > 50%.
  - A moderate-intensity statin reduces LDL-C by about 30-50%.
- Statins reduce TG levels by 10-20% from baseline values.[270] High intensity Statins have moderate effect in lowering TG and in elevating HDL-C. (Table 12, pg.59)
- Statins have either no effect or result in a small increase in Lp(a) levels.[271] The magnitude of relative risk reduction in CV events with statin therapy was, however, similar among participants with high or low Lp(a).[271]
- Statins also have other pleiotropic effects - anti-inflammatory and antioxidant effects - that are potentially relevant for the prevention of CVD.[272-274]

7.2.1.2. Initiating Statin Therapy

- Since cholesterol is biosynthesized in the early morning hours, statins with shorter half-lives (pravastatin 1-3 hours, lovastatin 2 hours, simvastatin < 5 hours, and fluvastatin < 3 hours) should be administered in the evening. In contrast, statins with longer half-lives (atorvastatin 14 hours, rosuvastatin 19 hours, and pitavastatin 22 hours) can be administered during the day.[275,276]
- Treatment is initiated at the recommended starting dose with the evening meal or at bedtime especially with simvastatin.[275] Small short term clinical studies indicated that the LDL-C fell significantly by 5-8% when simvastatin was taken in the evening rather than in the morning.[277-281]
- In initiating statin therapy, the following steps are proposed:
  - Evaluate the total CV risk of the individual. (Table 4, pg. 26)
  - The total CV risk will help determine the LDL-C treatment target.
  - Involve the patient in the decision-making process on managing his/her CV risk.
  - Choose a statin regimen that is likely to reach the target LDL-C level. (Table 12, pg 59) This practice will help overcome both doctor and patient inertia of starting low and then up titrating to reach the target dose.
  - Response to statin treatment is variable, therefore monitoring of the statin dose is required before additional LDL-lowering treatments are started.
- If the LDL-C treatment target is not achieved, additional treatment (s) may be necessary to achieve both absolute on treatment value and percentage LDL-C reduction. This includes:
  - ezetimibe and/or
  - PCSK9 inhibitors or
  - Inclisiran

III, C

- Statin therapy should be avoided in pregnancy and lactation unless there is strong clinical indication. It should not be prescribed to women of childbearing potential unless adequate contraception is taken.

7.2.1.3. Monitoring Statin Therapy

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

  A) Response to therapy and achievement of lipid targets.

  B) Safety/Adverse effects

A) Response to therapy and achievement of lipid targets.

- The degree of LDL-C reduction is dose dependent and varies between the different statins.[282] There is considerable inter-individual variation in LDL-C reduction with the same dose of drug.[283]
- Inadequate response to statin treatment may be due to poor compliance and/or genetic variations of cholesterol and statin metabolism in the liver.[284,285]
- Lipid profile should be measured at 1 to 3 months following initiation and following a change in the dose of statin therapy.
- The dose is then adjusted accordingly to achieve LDL-C levels.
- If LDL-C targets have been achieved, the same dose of statin should be maintained. The drug should not be stopped.
- The lipid profile can be repeated at 6-to-12-month intervals.
- If LDL-C target is not achieved, the dose of statin should be up titrated to the maximal tolerated dose. If target level is still not achieved, then a non-statin drug can be added.
- The frequency of repeat testing while on stable lipid therapy, will depend on individual adherence to therapy and lipid profile consistency. If adherence is a concern or the lipid profile is unstable, then more frequent assessments may be necessary.[286]

B) Safety/Adverse Effects

B.1. Liver Function

- Hepatic transaminases should be measured at baseline and at 1 to 3 months after starting treatment and/or following a change in dose.
- If levels are elevated prior to therapy, other causes (e.g., fatty liver, hepatitis) should be excluded. If due to fatty liver, lipid lowering therapy is not contraindicated.
- Mild elevation of ALT occurs in < 3% of patients on statin treatment, more commonly with potent statins or at high doses.[287]
- Mild elevation of ALT has not been shown to be associated with true hepatotoxicity or changes in liver function.[288-290]
- When transaminase levels (especially ALT) are > 3 times the upper limit of normal (ULN) on 2 occasions, the drug should be stopped. The transaminase levels tend to decrease and may even normalize with reduction of the dose or cessation of the drug.
- Cautious reintroduction of therapy may be considered under close monitoring after ALT values have returned to normal.
- Progression to liver failure is exceedingly rare. Routine monitoring of ALT during long term statin treatment is no longer recommended.[291]
- Mild elevation of transaminases at baseline is not a contraindication for statin therapy.

Table 11: Major Lipid Modifying Drug Classes#

Drug Class	Lipid Effects	Side Effects	Contraindications
HMG-CoA Reductase Inhibitors (Statins)	LDL-C ↓ 21-55% HDL-C ↑ 2-10% TG ↓ 6-30%	• Myopathy • Increased liver enzymes	Absolute: • Active or chronic liver disease Relative: • Concomitant use of certain drugs*
Fibric-Acid Derivatives (Fibrates)	LDL-C ↓ 20-35% (fenofibrate) HDL-C ↑6-18% Primarily TG↓20-35%+	• Dyspepsia • Cholelithiasis • Myopathy	Absolute: • Severe hepatic disease • Severe kidney disease Relative: • Concomitant use of certain drugs**
PCSK 9 (Proprotein convertase subtilisin/kesin type 9) inhibitors	LDL-C ↓ 48-71% Non- HDL-C ↑ 49-58% TC ↓ 36-42%	• Injection site swelling or rash • Nasopharyngitis • Limb pain • Fatigue	Absolute • Hypersensitivity
Bile-Acid Sequestrants (Anion exchange resins)	LDL-C ↓15-25% HDL-C ↑3-5% TG ↔/ ↑	• GIT distress • Constipation • Reduce absorption of folic acid and fat-soluble vitamins (A, D & K) • ***Decreased absorption of certain drugs	Absolute: • Dysbetalipoproteinemia • TG > 4.5 mmol/L Relative: • TG > 2.3 mmol/L
Nicotinic Acid (Niacin)	LDL-C ↓ 10-25% HDL-C ↑10-35% TG ↓ 20-30%	• Flushing • Hyperglycaemia • Hyperuricemia (or gout) • Upper-GIT distress • Hepatotoxicity (rare but may be severe)	Absolute: • Chronic-liver disease • Severe gout Relative: • Diabetes (high doses only) • Peptic Ulcer Disease
Cholesterol Absorption Inhibitors****	Primarily LDL-C ↓ 10-18% (monotherapy) In combination with the following an additional: (a) statins: ↓25% (b) fenofibrate: ↓20-22%	• Headache • Abdominal pain • Diarrhoea	Absolute: Hypersensitivity Relative: Active liver disease or unexplained persistent elevations in hepatic transaminase levels
Inclisiran	LDL-C ↓ 50%	• Injection site reaction • Arthralgia • Urinary tract infection • Headache	None
Bempedoic Acid	LDL-C ↓ 25-30% (monotherapy) In combination with (a) statins: ↓20% (b) ezetimibe: ↓40%	• Hyperuricemia	Absolute: Concurrent use with simvastatin >20mg and pravastatin >40mg Relative: Hyperuricemia Tendon rupture

#Adapted from American Association of Clinical Endocrinologists 2017[286]
**cyclosporin, macrolide antibiotics, antifungal agents, protease inhibitors and cytochrome P-450 inhibitors (fibrates and nicotinic acid should be used with appropriate caution)*
***gemfibrozil and repaglinide[292]*
****Paracetamol, NSAIDs, anticoagulant, valproate, digitalis, thiazides, thyroxine, raloxifene, propranolol and tricyclic antidepressants.*
*****usually used in combination with statins.*
+maybe upto 60% with fenofibrate[293]
These data are derived from short-term clinical trials meant for drug registration. In real-life long-term use, the amount of lipid change achieved may be less than this.

B.2. Muscle Symptoms

- In clinical practice and in registries, 10-30% of patients report statin-associated muscle symptoms (SAMS).[294,295] This includes myalgia (CK normal), myositis (CK > ULN) and rhabdomyolysis (CK > 10X of ULN).
- The incidence of SAMS is much lower in clinical trials, and only differs slightly from placebo.[296-298] In observational studies, however, the frequency varies between 10 and 15%.[299,300]
- In a study by Parker designed specifically to study the effects of statins on muscle symptoms, the frequency of muscle-related complaints was approximately 9%.[301]
- Myalgia (without CK elevation) occurs in 5-10% of patients in clinical practice.[301] If the symptoms are not tolerable or are progressive, the dose of statin should be reduced, or the drug stopped.
- The incidence of myopathy (myositis and rhabdomyolysis) is low and is more likely to occur in persons with complex medical problems (especially chronic kidney disease) and/or who are taking multiple medications, or in elderly persons, especially women.
- Creatine kinase (CK) is not routinely measured unless myositis is suspected. If the level is more than 5 times the ULN on 2 occasions, the drug should be discontinued. Measurement should not be done after vigorous physical exertion.
- There is no uniform definition for statin intolerance. In certain trials, 'statin intolerant' patients were defined as patients unable to tolerate at least two different statins because of unexplained skeletal muscle-related symptoms (pain, aches, weakness, or cramping) that began or increased during statin therapy and symptoms improved when statin therapy was discontinued.[296]
- When SAMS or statin myopathy is suspected:
  - ➢ the first step is statin discontinuation for 2-3 weeks.
    - ◆ If symptoms have not resolved, it is unlikely to be statin related and the patient should be continued on the same dose of statin.
    - ◆ If symptoms have resolved, then the following strategies may be considered:
      - ❑ Lowering the dose or decreasing the frequency to less than daily.[302]
      - ❑ An alternative dosing such as every other day or twice a week with atorvastatin or rosuvastatin[303] can be used.
      - ❑ Treatment with the highest tolerable dose of statin in combination with a cholesterol absorption inhibitor (ezetimibe)
      - ❑ If indicated, a PCSK9 inhibitor may be considered.[304,305]
- 92% of statin intolerant patients do well with a second statin.[302]
- 73% will tolerate a re-challenge with a third statin.[302]
- An alternative approach is to consider co-enzyme Q10 to alleviate the symptoms of myalgia. he relationship between co-enzyme Q10 and statin related muscle symptoms is circumstantial. However, the risk of side effects from co-enzyme Q10 is low. Thus, a trial of co-enzyme Q10 in patients with possible statin related muscle side effects may be considered. The response rate is variable.[306-308]

III, C
- The routine use of Co- enzyme Q 10 together with statins is unproven and therefore not recommended.[306-308]

IIa, B
- Care should be taken when prescribing high doses of simvastatin (> 20mg/daily) together with certain other medications that inhibit the cytochrome P450 pathway. It has the potential of increasing the risk of muscle injury.[309,310]
- The combination of statins with gemfibrozil enhances the risk of myopathy and should be avoided. There is no or very little increased risk for myopathy when combining statins with other fibrates, such as fenofibrate, bezafibrate, or ciprofibrate.[311,312]

- Patients with CKD stages 1-2 with eGFR >60 mL/min/1.73 m^2, can be treated in the same way as the general population.
- For patients with CKD and eGFR <60 mL/min/1.73 m^2, refer to section 10.5.

B.3. Diabetes

- Statins have been associated with a slight increase in dysglycemia and new-onset diabetes (9-12%).[313,314] It occurs with all statins and is a dose related effect. The risk is higher with the more potent statins at high doses.[314]

I, A

- The CV reduction benefits seen with statins far outweigh the risk of developing diabetes. In fact, statins have been proven to prevent CV events in persons with diabetes with no overt CVD.[43,69,70]
- Screening for diabetes should be considered at 6 - 12 monthly intervals in patients at high risk of developing diabetes. These include the following individuals/conditions:
  - elderly
  - metabolic syndrome
  - obesity or signs of insulin resistance
  - family history of diabetes (parents and siblings)

B.4. Kidney Effects

- An increased frequency of proteinuria has been reported for all statins, more so for rosuvastatin.
- The proteinuria induced by statins is of tubular origin and is due to reduced tubular reabsorption and not to glomerular dysfunction.[315]
- In clinical trials the frequency of proteinuria is in general, low and in most cases is not higher than for placebo.[316] It is reversible on stopping the medication.

III, B

- As such, we do not recommend routine monitoring of kidney function or proteinuria.[316]
- Statins do not have any deleterious impact on the kidneys and, in fact, has been shown to reduce CVD and mortality in patients with CKD. (refer Section 10.5)

B.5. Neurocognitive function

- Regulatory bodies have required that a statement be added to the drug label for all statins indicating that there is a potential for cognitive side-effects (such as memory loss and confusion).[317]
- Clinical studies designed to assess the effect of statins on cognitive function have, however, found little to no evidence that statins are associated with adverse effects on memory or cognition or Alzheimer's disease.[318-320] Furthermore, neurocognitive functions were extensively investigated in the Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS) and no excess risk was observed among patients on a statin regimen randomized to a PCSK9 inhibitor.[321]

B.6. Others

- There is no evidence that patients on statins have increased risk of non-CV mortality e.g., cancers, suicides or other conditions, such as hepatic steatosis, venous thromboembolism, atrial fibrillation, and cataracts.[322-327]
- In patients with a history of prior stroke, statins clearly decreased the risk of ischemic stroke and major CV events.[328-330] The benefit was not different among the LDL-C-low ering strategies.[330] The risk of intracerebral hemorrhage in these individuals, however, appears to be increased.[331-333]

7.2.1.4. Optimizing Statin Therapy

- The therapeutic doses of statins used in clinical practice should be similar between Asian and Caucasian populations. Studies conducted among Asian and Caucasian subjects concluded that systemic exposure to atorvastatin did not differ between the two groups.[334,335]

I, A
- High-intensity statin therapy produces a greater percentage LDL-C reduction and thus reduces CV events more than moderate-intensity statin therapy.[42-45] (Table 12, pg.59)

I, A
- Lower-intensity statin therapy has also been shown to reduce CV events, but to a lesser degree.[42-45]

I, A
- **Very High Risk** and **High-Risk** individuals should be treated with a maximally tolerated dose of statins.[42,43,76-88]

Table 12: Recommended Doses of Statin Therapy#++

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

#Adapted from: Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S76-S99269
**High intensity statin therapy is for patients who are at Very High and High Risk*
***Low intensity statin therapy is generally used for primary prevention after TLC and following a discussion with the patient of the risk: benefit ratio.*
++For patients with CKD, refer to Table 14 for the recommended doses according to KDIGO.

7.2.1.5. Adhering to Statin Therapy

- The importance of LDL-C lowering to prevent CVD should be strongly emphasized. There appears to be a dose-dependent reduction in CVD with LDL-C lowering; the greater the LDL-C reduction, the greater the CV risk reduction.[42,43,336,337]
- The benefits related to LDL-C reduction are not specific for statin therapy.[44]
- The benefits of LDL-C lowering have been documented even in individuals whose baseline levels of LDL-C are low (e.g., <1 mmol/l).[42,44]
- CV risk reduction should be individualized, and this can be more specific if goals are defined. The use of goals can also aid patient - doctor communication and facilitate adherence to treatment.
- If available, plasma levels of statins may be checked for compliance.

I, A
- We advocate LDL-C treatment goals and percentage LDL-C reduction.[42-45,68-84] (Table 4, pg. 26)

7.2.2. Cholesterol Absorption Inhibitors

- Cholesterol absorption inhibitors selectively block intestinal absorption of both dietary and biliary cholesterols without altering the absorption of fat-soluble nutrients. This leads to a reduction in hepatic cholesterol delivery - a mechanism which complements the action of statins.
- It cab be used in combination with any dose of statin to further lower LDL-C if targets are not achieved with the maximum tolerated statin dose.

I, A

- Ezetimibe-statin combination therapy was found to have CV benefits in individuals with CKD and following vascular surgery and acute coronary syndromes.[76,83,338-341]

7.2.2.1. Lipid Lowering Effects of Cholesterol Absorption Inhibitors

- Ezetimibe monotherapy can result in:[342]
  - ➢ Reduction of 18.58% in LDL-C
  - ➢ Reduction of 13.46% in TC
  - ➢ Increase of 3.0% in HDL-C
  - ➢ Reduction of 8.06% in TG levels.
- When used in combination with a statin there is significantly greater LDL-C reduction. When ezetimibe (10 mg) was administered with any dose of a statin, LDL-C levels was reduced by an additional 25%. This is far greater than the 6% obtained when the dose of statin is doubled.[343] This is because of dual cholesterol inhibition - liver production and absorption from the gut.
- It may be considered as monotherapy in patients who cannot tolerate statins.[342]
- No major adverse effects have been reported with ezetimibe monotherapy.[342] As add-on therapy, ezetimibe resulted in little or no difference in adverse events.[344]
- No dose adjustment is necessary in patients with mild hepatic impairment or mild to moderate kidney disease.
- It is not recommended in patients with moderate to severe hepatic impairment.[345]
- Recommended Dose:
  - ➢ Ezetimibe 10 mg daily

7.2.3. Proprotein Convertase Subtilisin Kexin type 9 (PCSK9)- Inhibitors

- This group of drugs work by inhibiting the binding of PCSK9 to the LDL-receptors. This interaction decreases the degradation of the LDL-receptors, resulting in higher LDL-receptor density at the cell surface. The higher expression of LDL-receptors at the cell surface leads to increased clearance with resulting decrease in LDL-C levels.[346,347]
- Monoclonal antibodies (mAbs)have been developed against PCSK9 that have been shown to reduce LDL-C, irrespective of the background lipid-lowering therapy. [77,78,84,304,305,345,348,349]
- The 2 mAbs that have been approved in Malaysia are alirocumab and evolocumab.

7.2.3.1. Lipid Lowering Effects of PCSK9- inhibitors.

- In clinical trials, alirocumab and evolocumab, either alone or in combination with statins, and/or other lipid-lowering therapies, have been shown to significantly reduce LDL-C levels on average by 60%, depending on the dose.[350]
- Both alirocumab and evolocumab have been shown to effectively lower LDL-C levels in patients who are at high CV risk, including those with DM.[350]

- PCSK9 inhibitors have also been shown to:[351-354]
  - Reduce TG levels by 26%
  - Increase HDL-C by 9%
  - Reduce Lp(a) by 30-40%.
- In general, patients with more extensive atherosclerotic disease who were at higher risk of MACE, obtained greater risk reduction from a lower LDL-C level achieved with the PCSK9-inhibitors.[78,355-358] This would include patients with recent MI< 1-year, diabetes and polyvascular disease.

7.2.3.2. Initiating PCSK9-Inhibitor Therapy

- Currently, these agents are only available as an injection administered subcutaneously every other week or once a month, at different doses depending on the agent used.
- Recommended Dose:
  - Dose of evolucumab: 140mg SC every two weeks or 420mg SC monthly.
  - Dose of alirocumab: 75-150mg SC every two weeks or 300 mg SC monthly.
- The most frequently reported side effects are:[359]
  - Itching at the site of injection and
  - Flu-like symptoms

III, C
- PCSK9 - inhibitors cross the placenta and should not be used in pregnancy and are not licensed for use in children.
- PCSK-9 inhibitors do not have adverse effects on the liver. Less than < 2% of individuals had elevation of liver function tests >3x the upper limit of normal.[360] They are also safe in individuals with mild and moderate CKD.[361] It has not been studied in patients with eGFR < 20ml/min/1.73m^2.

7.2.4. Fibric Acid Derivatives (Fibrates)

- Fibrates are Peroxisome Proliferator Activated Receptor (PPAR) - α agonist which have an important role in fatty acid oxidation. They reduce serum TG effectively and increase HDL-C modestly. The initial lipid level has a significant impact on the size of the effect.[362]
- Fibrates reduce the risk of CV and coronary events in primary prevention, according to moderate-quality evidence, however the absolute treatment effect is limited with absolute risk reductions of about 1%.[363]
- Fibrates have not been shown to reduce CVD events in the secondary prevention trials.[364-366]

IIa, C
- Its use is limited to the treatment of patients with very high TG levels who do not respond to non-pharmacological measures to prevent pancreatitis.[367] (Table 13, pg.62)

IIb, B
- In persons with diabetes already on maximally tolerated statins, and who have low HDL-C (≤ 0.88 mmol/L) and high TG (≥2.3 mmol/L), fibrates may be considered to reduce CV events.[368,369] A more recent trial in this group of patients, was however neutral.[370]
- Dosage adjustment of fibrates is required in the presence of CKD. Serum alanine aminotransferase should be monitored when starting therapy or when doses are increased. (Table 13, pg. 62)

Table 13: Recommended Dosages for Fibrates*#

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

** As stated in MIMS, (2016-2017) Malaysia*
***not recommended for use in combination with statins*
#For patients with CKD, refer to Table14 for recommended doses according to KDIGO.

7.2.5. Newer Lipid Lowering Agents

7.2.5.1. Small interfering RNA (siRNA) PCSK-9 Inhibitors (Inclisiran)

- Small interfering RNA (siRNA) molecules also block the hepatic production of PCSK9. Inclisiran is a long-acting, synthetic siRNA molecule that binds to a RNA-induced silencing complex (RISC), thereby inhibiting the translation of PCSK9 messenger RNA (mRNA) causing a marked reduction in LDL-C levels.[371,372]
- Inclisiran is a first in this class of therapeutic agents.

7.2.5.1.1. Lipid lowering Effects siRNA PCSK-9 Inhibitors (Inclisiran)

- Inclisiran can reduce LDL-C by ≈50%.[372-374]

IIa, B

- Current evidence suggests a good safety profile with total and serious adverse events approximating that of placebo.[373,374]
- No serious hepatic or renal effects were seen. Elevation of liver enzymes to >3x the upper limit of normal was seen in about 1% of individuals.[372-374] It was also found to be safe in patients with mild to moderate CKD.[374]
- It, however, still lacks clinical evidence for the expected reduction in atherosclerotic CVD events when added to statin therapy. Clinical studies are still ongoing. (ClinicalTrials.gov Identifier: NCT05030428)
- Inclisiran is administered subcutaneously.
- Recommended dose:
  - ➢ Dose of inclisiran: 284mg administered as a single SC injection, initially repeated at 3 months after the 1st dose and then followed by every 6 months.
- Inclisiran should not be used in combination with PCSK-9 inhibitors since there is no evidence of additive LDL lowering.[345]

7.2.5.2. Bempedoic acid

- Bempedoic acid antagonizes ATP-citrate lyase, which is a rate-limiting component of the cholesterol synthesis pathway.[375]
- It reduces LDL-C[376] when given alone (by 20-24%)[375,376] and in combination with a statin (an additional 18% reduction)[376] or ezetimibe (by as much as 38-40%).[376,377]

IIa, B

- The combination of bempodoic acid and ezetimibe has been shown to significantly reduce major CV events in statin intolerant patients.[378,379]

- No dosage adjustment required in patients with mild to moderate kidney or liver impairment.
- The risk of myalgia and myopathy is minimal.[377-379]
- Recommended dose: 180mg daily.
- It is not yet registered in Malaysia.

7.2.6. Other Lipid Lowering Agents

7.2.6.1. Bile Acid Sequestrants (Anion exchange resins)

- Bile acid sequestrants bind to bile acids to promote their secretion into the intestines. This leads to bile acid depletion resulting in the liver generating more hepatic cholesterol. This raises the hepatic demand for cholesterol and lowers the level of LDL in the blood.

IIb, B
- Monotherapy has a modest effect on CHD in primary prevention trials done in the pre statin era.[380-382]
- There is no significant impact on HDL-C. In some individuals who are susceptible however, TGs may rise.[383] Its use is discouraged in patients with TG ≥ 3.4mmol/L.[345]
- Bile acid sequestrants provide a practical add-on option with extra LDL-C-lowering for those who are unable to tolerate a guideline directed statin dose.[384]
- Even at low doses, these medications frequently cause gastrointestinal side effects such as flatulence, constipation, and dyspepsia, which restricts their usefulness.
- Due to major drug interactions, other medications should be taken 1 hour before and / or 4 hours after resins. Cholestyramine may be taken before a meal and/or at bedtime to minimise the drug interactions.
- **Recommended Dose:**
  - Cholestyramine: 4gm/d increased by 4gm at weekly intervals to 12-24gm/day in 1-4 divided doses, Max: 24gm/day

7.2.6.2. Nicotinic Acid (Niacin) and its derivatives

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

IIb, B
- An earlier trial showed mortality benefits with niacin during long term follow up.[385] More contemporary clinical studies, however, have not shown any CV benefits.[160,386]

IIa, B
- It may be considered as an alternative therapy to fibrates in individuals with elevated TG not responsive to other pharmacological options.[387]
- **Recommended Dosages:**
  - Nicotinic acid (Niacin) is available as tablets of 50mg, capsules of 100mg and 250mg.
  - Starting dose: 150-300mg daily in divided doses, titration of dose up to 2g/day (usual dose). It should be taken with meals to reduce gastrointestinal side effects.

7.2.6.3 . Omega-3 Fatty Acids supplements

- Omega-3 fatty acids supplements are present as:
  - Mixtures of EPA and DHA - as omega-3 ethyl esters and as carboxylic acids.
  - Purified EPA- as icosapent ethyl (IPE).
- In individuals whose LDL-C is already at target, Omega-3 Fatty Acids has a role in:
  - Reducing TG usually in combination with other lipid lowering agents.[21,96] (section 11, Specific Lipid Disorders).

➢ Improving CV outcomes in individuals with residual CV risk. Only the preparation icosapent ethyl (IPE) at 4gms per day, has shown promising results.[93-96,388] The other preparation of Omega-3 Fatty Acids, although having similar effects on lipids, did not demonstrate the same clinical benefits.[389-391]

7.2.7. Combination therapy

- There is sufficient evidence to show that the addition of non-statin therapies to statins is both safe and effective in further lowering LDL-C and improving CV outcomes.[76-78,84,338-341,345,392,393]
- Combination therapy is used when LDL-C targets are not achieved despite optimal statin dose or the use of maximally tolerated guideline-directed statin dose.

A. Achieving LDL-C target

The combinations that may be used are:

I, A
- **Statin + cholesterol absorption inhibitors (ezetimibe)**[76,83,338-340,342,345] In comparison to statin monotherapy, the addition of ezetimibe to statin therapy resulted in a modest additional decrease in LDL-C. However, for some ASCVD patients who have particularly high LDL-C values despite receiving adequate statin medication, this might not be adequate.[341,345]

I, A
- **Statin + PCSK-9 inhibitors +/- Ezetimibe**[77,78,84,345,348-351,355-358]

IIa, B
- **Statins + SiRNA PCSK-9 Inhibitors +/- Ezetimibe**[372-374]

IIa, B
- **Bempedoic Acid +/- Ezetimibe (in statin intolerant patients)**[376-379]

B. Low HDL-C, High TG after LDL-C target is achieved.

I, A
- **Achieving LDL-C target is the priority.**
- Occasionally combination therapy may be used if LDL-C target is achieved but HDL-C is low, and TG is high.
  - ➢ There is no data that drug therapy in this subset of individuals will reduce CV events.

IIb, B
  - ➢ Subgroup analysis suggest a small benefit with the addition of fibrates to statins.[368,393] When using a statin - fibrate combination:
    - Fibrates increase the risk of myopathy with statins, and the risk is highest for gemfibrozil.
    - The risk with gemfibrozil is 15 times higher when compared to fenofibrate because it interferes with statin glucuronidation.[394-396]
    - The combination of statins and gemfibrozil is discouraged. The myopathy risk is minimal with pravastatin combination.[397]
    - The risk of myopathy when combining statins with fenofibrate seems to be small.[398]
    - Fibrates should preferably be taken in the morning and statins in the evening to minimize peak dose concentrations and decrease the risk of myopathy.

Key Message #7:

- **Statins are the drug of choice for reducing LDL-C** in a wide range of individuals with dyslipidemia in both primary and secondary prevention.
- Some individuals may require combination therapy to achieve LDL-C goals.

Key Recommendations #7:

- Individuals should be on lifelong therapy.
- They should be assessed on a regular basis for:
  - Response to therapy and achievement of lipid targets.
  - Lipid profile should be measured at 1 to 3 months following initiation and following a change in the dose of statin therapy. The dose is then adjusted accordingly to achieve LDL-C levels.
  - Adverse effects
  - Hepatic transaminases should be measured at baseline and at 1 to 3 months after starting treatment and/or following a change in dose.
  - CK is measured if myositis is suspected.
  - Should there be an adverse effect, the dose of the drug should be reduced, or it should be temporarily discontinued. Following an improvement and normalization of symptoms and/or biochemical parameters, the drug can be reintroduced at a lower dose. If the adverse effect recurs, then the drug should be discontinued, and an alternative form of treatment used.
- Combination therapies may sometimes be necessary to achieve LDL-C targets. These include:
  - Statins + Ezetimibe combination
  - Statins + PCSK-9 Inhibitors+/- Ezetimibe
  - Statins + SiRNA PCSK-9 Inhibitors +/- Ezetimibe
  - Bempedoic Acid + Ezetimibe (in statin intolerant patients)

8. PRIMARY PREVENTION

- Primary prevention refers to all efforts aimed at either populations or individuals to prevent or delay the onset of CVD.
- The FRS General CVD Risk Score is used to assess the 10-year risk of developing CVD and guide risk reduction efforts.[110]

Primary prevention strategies are:

- **Population based strategies:**
  - This is aimed at educating the public concerning CVD, its presentation and complications, cardiac risk factors, and the importance of healthy behaviour modifications, which include:
    - A healthy diet: 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.
    - Achieving and maintaining a healthy body weight.
    - Increased exercise.
    - Avoidance or cessation of smoking
    - Limiting alcohol consumption
    - Ensuring a sufficient duration of sleep (7-9 hours)
  - These measures should be started early in life.
  - Mass screening for dyslipidemia is not advocated as it is not cost effective and there may be inadequate follow-up and counselling.

- **Individual based strategies:**
  - The aim is to identify individuals at risk of developing CVD and modifying their risk factors. See Section 5.1 and Table 10, pg. 39.
  - How to screen for dyslipidemia:
    - The committee advocates screening all adults > 30 years of age. This is because there is a sharp increase in prevalence of the common CV risk factors from the age group 25-29 years according to NHMS VI.5
    - Following a good history taking and physical examination, a non-fasting lipid profile is recommended in most adults for screening.
    - For individuals noted to have or with a history of high TG > 4.5mmol/L, measurement of fasting lipid levels is recommended. (Section 2)
  - When to repeat screening if the LDL-C levels are at target and TG levels are low:
    - Screening should be repeated at 3 yearly intervals.
    - In individuals who at very high or high risk of CVD, screening should be repeated annually.

Public education is paramount for the success of CVD prevention efforts. In addition to information about CVD and the primary preventive strategies mentioned earlier, the public should also be educated of the benefits and safety profiles of the commonly used medications for treating dyslipidemia particularly statin therapy. This is important since there is a lot of misconceptions and myths about this class of medications.

Key Message #8:

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

Key Recommendations #8:

- Maintaining a healthy lifestyle should be started early in life.
- The committee advocates screening all adults > 30 years of age with a non fasting lipid profile. This is because there is a sharp increase in prevalence of the common CV risk factors from the age group 25-29 years according to NHMS VI.
- TWhen to repeat screening if the LDL-C levels are at target and TG levels are low:
  - Screening should be repeated at 3 yearly intervals.
  - In individuals who at very high or high risk of CVD, screening should be repeated annually.

9. SECONDARY PREVENTION

I, A Lipid lowering therapy has been shown to improve CV outcomes in individuals with:

- Coronary Heart Disease-
  - Stable CAD[68,74,399]
  - Acute Coronary Syndromes[72,73,75-78]
  - Peri procedure - Percutaneous Coronary Intervention (PCI)[400-405]

I, A
- Ischemic Strokes[328-333,406-409]

I, A
- Peripheral Vascular Disease[410-412]

Important considerations:

- **Timing of initiation of lipid lowering therapy in patients with:**

I, A
  - **ACS:**
    - Initiation of high dose statin therapy <24 hours after admission was associated with improved CV outcomes.[73,413-418]
    - In patients who are already on statins, the dose should be up titrated, or a high intensity statin should be used.[418]
    - Statin treatment should not be delayed until lipid levels are available or for the management of other modifiable risk factors.
    - Lipids should be re-tested about 4-6 weeks after ACS to determine if target LDL-C have been achieved.

IIa, B
  - **Undergoing PCI:**
    - Pre-treatment with statins prior to elective PCI has been shown to reduce post-pro cedure MI.[418-421]

I, A
- **Target LDL-C:**
  - **Secondary Prevention:** < 1.4mmo/l and a 50% reduction in LDL-C levels.[42-44,76-80,82-84]

IIa, B
  - **Individuals with recurrent events within 2 years while taking maximally tolerated statin therapy:** <1.0mmol/L.[255]

Key Recommendations #9:

- All patients with CVD should receive lipid lowering therapy, the target LDL-C:
  - Target LDL-C < 1.4mmo/l and a 50% reduction in LDL-C levels.
- High intensity statins should be started (irrespective of their baseline cholesterol levels):
  - On admission in all individuals with ACS.
  - Prior to PCI and CABG and continued indefinitely.
- Lipid lowering therapy with statins should be considered in all individuals with previous non cardioembolic ischemic stroke or transient ischemic attack.

10. MANAGEMENT OF DYSLIPIDEMIA IN SPECIFIC CONDITIONS

10.1 Asymptomatic Atherosclerotic Disease

Asymptomatic atherosclerotic disease may be detected by:

- Ankle Brachial Index.
- Exercise stress tests/stress imaging.
- Calcium score.
- Computed Tomographic (CT) coronary angiography.
- Carotid ultrasonography (excluding carotid intimal medial thickness).

Patients with abnormal exercise stress tests, calcified and non-calcified plaques detected by imaging modalities should have:

- All their CV risk factors treated to target.
- Their LDL-C treated to a target dependent on their CV risk. Table 4, pg. 26. In patients at **Intermediate Risk**, the presence of any of of the features listed below may support upgrading of CV risk, the decision to initiate pharmacotherapy and treatment targets. (Section 5.2.3)

The following **high-risk features** is indicative of the presence of significant atherosclerotic disease. These include:

- Ankle Brachial Index: < 0.9 or > 1.40[422]
- Positive exercise stress test at low to moderate workload (≤ 6 METS)
- Calcium score:[345]
  - 0 - reassess in 5-10 years if diabetes, family history of premature CAD or cigarette smoking is absent.
  - 1-99 Agatston units and < 75th percentile for age/sex/race - reasonable to initiate statins if the individual is > 55 years of age.
  - ≥ 100 Agatston units or > 75th percentile for age/sex/race - reasonable to initiate statins.
- CT coronary angiography with plaques causing > 50% luminal narrowing[423-426]
- Plaques on carotid ultrasonography - seen as localized thickening encroaching into the arterial lumen by at least 50% or with a thickness > 1.2 mm.[427]

I, A Patients with these **high-risk feature**s have **subclinical established CVD**. In these patients, **the LDL-C target should be < 1.4 mmol/l and a 50% reduction from baseline**.[42-44,76-80,82-84]

Key Recommendations #10:

- Patients with abnormal exercise stress tests, calcified and non-calcified plaques detected by imaging modalities should have:
  - All their CV risk factors treated to target.
  - Their LDL-C treated to a target dependent on their CV risk. In patients at Intermediate Risk, the presence of any of these features may support upgrading of CV risk, the decision to initiate pharmacotherapy and treatment targets.
- The presence of the any of the following is indicative of established CVD:
  - Ankle Brachial Index: < 0.9 or > 1.40.
  - Positive exercise stress test at low to moderate workload (≤ 6 METS).
  - Calcium score:
    - 0 - reassess in 5-10 years if diabetes, family history of premature CAD or cigarette smoking is absent.
    - 1-99 Agatston units and < 75th percentile for age/sex/race - reasonable to initiate statins if the individual is > 55 years of age.
    - ≥ 100 Agatston units or >75th percentile for age/sex/race - reasonable to initiate statins.
  - CT coronary angiography with plaques causing > 50% luminal narrowing.
  - Plaques on carotid ultrasonography - seen as localized thickening encroaching into the arterial lumen by at least 50% or with a thickness >1.2 mm.
- In these patients, the LDL-C target should be < 1.4 mmol/l and a 50% reduction from baseline.

10.2. Hypertension

- The benefits of statins in patients with **established CVD with or without hypertension** is well established.[42-45,68,72-84]
- For the **primary prevention of CVD in hypertensive patients**, studies of the benefits of statins have been mixed.
  - In the ALLHAT study, high dose pravastatin failed to show any mortality and CV benefits in high-risk hypertensive with mildly elevated BP even after long term follow up.[428,429] The lipid lowering achieved was however very modest (from LDL C of 3.4mmo/L to 2.7mmol/L).
  - In the ASCOT-LLA study, low dose atorvastatin in medium risk hypertensive patients with moderately elevated BP and baseline LDL C of 3.4mmol/L reduced to 2.1mmol/L showed significant reduction in CV events.[71] However in this study, there was no mortality benefits.[71] On long term follow up however, there was a reduction in all-cause mortality, suggesting a legacy effect.[430]
  - In HOPE 3 - LLA trial, patients with a baseline BP of 138/81mmHg and with an intermediate baseline CV risk were randomized to 10mg daily rosuvastatin or placebo. The LDL-C was reduced from 3.4mmol/L at baseline to 2.3mmol/L. This significantly reduced the primary endpoint by 25% although there was no mortality reduction seen.[431] In HOPE 3 the best clinical outcome was seen in patients taking both antihypertensive and lipid lowering therapy.[432] In patients taking antihypertensive drugs alone, no reduction in CV events were seen.

I, A
- These observations support the analysis **that the lower the absolute LDL-C achieved and the greater the percentage LDL-C reduction, the greater the magnitude of the CV benefits.**[42-44]

I, A
- A meta regression analysis showed that **statin therapy** effectively **decreased CV morbidity and mortality to the same extent in both hypertensive and non-hypertensive patients.**[433]
- In patient with concurrent hypertension and dyslipidemia, **combination therapy** has been shown to **not only improve medication adherence but also improvement in CV risk factor control**.[434-436]
- In patients with hypertension and dyslipidemia who refuse to take lipid lowering drugs, the use of therapeutic lifestyle changes (non-pharmacological approaches) with a favourable effect on BP and lipids, has been shown to reduce CV events.[437]

Key Recommendations #11:
- For patients with Hypertension, initiate statins for Primary Prevention if they also have elevated cholesterols (LDL-C > 3.4mmol/L).
- In all other patients assess CV risk using the FRS-General CVD risk score (Table 1 &2, pg. 23-24). The target LDL-C would depend upon the individual's CV risk. (Table 4, pg. 26)

10.3. Diabetes Mellitus

- Patients with diabetes and impaired glucose tolerance (IGT) are at high risk of CVD.[438,439] These patients have higher mortality and a higher incidence of recurrent CV events.[439] This is especially in individuals with diabetes of more than 10 years duration.[440-442]
- Dyslipidemia is one of the key risk factors contributing to CVD in patients with diabetes.

- **Lipid abnormalities differ in type 1 diabetes (T1DM) and Type 2 diabetes (T2DM).**
  - Type 1 diabetes - high TG is common. HDL-C levels are often normal and even high unless glycemic control is poor, or nephropathy is present.
  - Type 2 diabetes - high plasma TG concentration, reduced HDL-C and increased levels of small dense LDL particles is the usual pattern.

I, A
- **Statin therapy has been proven to reduce CV events in patients > 40 years with Type 2 diabetes irrespective of the baseline LDL-C.**[43,69,70]

- Among individuals with **Type 1 diabetes** without a history of CVD, **registry data showed that statins are associated with a 22 - 44% reduction in risk of CVD and CV death.**[443]
- The **Malaysian National Diabetes Registry Report (NDR 2020)** consisted mainly of patients seen at public primary care clinics.444 Majority of the patients had Type 2 diabetes (99.33%), followed by Type 1 diabetes (0.59%) and others (0.06%). Of the Type 2 diabetic patients:
  - The prevalence of dyslipidemia was 75.72%.
  - Mean LDL-C levels was 2.9mmol/L.
  - Mean HDL-C levels was 1.2mmol/L for men and 1.4mmol/L for women.
  - Achievement of targets:
    - About 39.78% of patients achieved TC < 4.5mmol/L.
    - 45.68% achieved LDLC target < 2.6mmol/L.
    - 66.79% achieved TG < 1.7mmol/L.
  - Types of pharmacotherapies:
    - About 81.96 % were receiving statins.
    - 1.54% received fibrates.

10.3.1. Screening

- In adult patients with diabetes, a lipid profile should be measured at least annually and more often if needed to achieve goals.[24]
  - Non-fasting sample can be used for assessment of lipid parameters.
  - If non-fasting TG is elevated (>2.3mmol/L), a fasting sample is required.[24]
- In adults with low-risk lipid values (LDL-C < 2.6mmol/L, HDL-C >1.0mmol/L in males and > 1.3mmol/L in females and TG <1.7mmol/L), lipid assessments may be repeated every year.[24]
- In adolescents with Type 2 diabetes, screening for lipid disorders should be done at diagnosis after glycemic control is achieved. If normal lipid values are obtained, screening should be repeated every 2 years.[24,445]
- CV risk calculators for primary prevention are not recommended as individuals with Type 2 diabetes are already considered high risk and all CV risk factors should be aggressively managed.

10.3.2. Lipid Targets in Diabetes

I, A
- The primary target of therapy is LDL-C.[42,69,70] (Table 4, pg.26 & 71).

I, A
- Lowering LDL-C is the main aim of treatment and statins are the first-line lipid lowering drug.[42,69,70]
- The LDL-C target depends on the patient's CV risk category. (Table 4, pg. 26 & 71)

Table 4: Target LDL-C Levels

Global Risk	LDL-C Levels to Initiate Drug Therapy (mmol/L)	Target LDL-C levels (mmol/L)	Target Non-HDL -C (mmol/l)
Low CV Risk* <10%10-year CVD risk	Clinical Judgement**	< 3.0	< 3.8
Intermediate (Moderate) CV Risk* ➢ 10-20% 10-year CVD risk ➢ Diabetics < 50 years old and< 10-year duration and no CV risk factors	> 2.6 **	< 2.6	< 3.4
High CV risk ➢ > 20% 10-year CVD risk ➢ Diabetes ≥10-year duration without target organ damage **+** 1 other CV risk factor ➢ CKD with eGFR 30-<60ml/min-1/1.73 m^2	> 1.8	≤ 1.8 ***and*** a reduction of > 50% from baseline	≤ 2.6 ***and*** a reduction of > 50% from baseline
Very high CV risk* ➢ Established CVD ➢ Diabetes with CVD or other target organ damage ***or*** ≥ 3 CV risk factors ➢ CKD with eGFR <30ml/min-1/1.73 m^2	> 1.4	< 1.4 ***and*** a reduction of > 50% from baseline	≤ 2.2 ***and*** a reduction of >50% from baseline
***Those with recurrent CV events within 2 years despite achieving a target of < 1.4mmol/l		< 1.0	

**Low and Moderate CV risk is assessed using the FRS-General CVD Risk Score*
***After a therapeutic trial of 8-12 weeks of TLC and following discussion of the risk: benefit ratio of drug therapy with the patient*
****All other CV risk factors should be treated to target.*

In patients who have achieved LDL-C targets, the following are secondary targets of therapy.[127]

Parameter	Target
Non -HDL-C	0.8mmol/L higher than the LDL-C Target for that risk category (See Table)
HDL-C	> 1.0 mmol/l for males and >1.3 mmol/l for females
TG	< 1.7 mmol/l

In patients with high TG>4.5mmol/L, when the LDL-C cannot be calculated, non-HDL level is a target of therapy and can be calculated from a non-fasting serum.

10.3.3. Management

10.3.3.1 Elevated LDL-C (or Non-HDL-C)

I, A
- All persons with diabetes above the age of 40 should be treated with a statin regardless of baseline LDL-C level.[42,69,70]

III, C
- In type 2 diabetes patients who are below 21-years of age and without clinical CVD, statin is generally not recommended.[446-448]
- All persons with diabetes and CVD should be on a high intensity statins from the time of the CV event.[42,69,70,449]
- Statin therapy should be intensified to achieve LDL-C goal before considering combination therapy.

I, A
- If the target LDL-C is not achieved with maximal tolerated dose of statin therapy, combination therapy with ezetimibe is recommended.[76,450]

I, A
- For very high-risk patients, PCSK9 -i should be considered if maximal tolerated dose of statin and ezetimibe fail to achieve LDL-C targets.[77,78,348-351,451]
- Very low LDL-C level achieved by newer lipid lowering drugs had shown further CV risk reduction in large scale clinical trials proportionate to the degree of LDL-C lowering. The absolute risk reduction is most evident in patients with higher CV risk.[42-44,79,80]

10.3.3.2. Hypertriglyceridemia (See Section 11)

- The primary objective is to achieve target LDL-C.
- Investigate for secondary causes if fasting TG > 5.7mmol/L.[24]
- Improving diabetes control. Lifestyle modification should be emphasized.
- Consider pharmacological therapy with fibrate and/or fish oil (2-4 g/day) to reduce the risk of pancreatitis. A dose of 3-4 gm/day of omega - 3 - fatty acids decrease TG by about 30% (range 16-45%).[452]

IIb, B
- In patients at target LDL-C, but with TG > 2.3 mmol/l and a low HDL-C, fibrates maybe considered in combination with statin.[368,453-455]

IIa, B
- In patients with established diabetic retinopathy, fenofibrate reduces progression of diabetic retinopathy, irrespective of baseline TG/HDL-C level.[456,457]

IIa, B
- In patients with CVD or high CV risk and in whom the LDL-C is already at target, but with elevated TG, the addition of icosapent ethyl 4 mg/day to statins has been shown to reduce CV risk by 25%.[93-96]

IIa, B
- Nicotinic acid should only be used in patients with high risk of pancreatitis with a TG level of > 10 mmol/L and in those who do not respond adequately to fibrates and/or fish oil.[458-460]

Key Recommendations #12 :
- All persons with diabetes above the age of 40 should be treated with a statin regardless of baseline LDL-C level.
- In Type 2 diabetes patients below 21-years of age and without clinical CVD, statin is generally not recommended.
- The target LDL-C levels will depend upon their CV risk (Table 4 pg. 26 & 71)
- Statins are the drugs of first choice. If target LDL-C is not achieved, consider combination with:
  - Ezetimibe **and/or**
  - PCSK-9 inhibitors.

10.4 Heart Failure (HF)

- In patients with established atherosclerotic CAD (without HF), cholesterol lowering with statin reduced the incidence of HF, mainly by preventing MI.[141]
- Meta analysis seem to show that statins should probably be continued in patients with CAD who develop HF although a beneficial effect on CV outcomes is at the most, modest.[461-463] 2 randomized clinical trials have shown conflicting results. In 1 trial rosuvastatin reduced the rate of first and repeat hospitalizations in older patients (> 60 years) with systolic HF of ischemic etiology.[464,465] In another trial with the same agent, there was no effect on clinical outcomes in patients with chronic HF of any cause.[466]
- Patients with advanced chronic HF may have a low TC which is associated with a poor prognosis.[467,468] In these patients, especially if they have a short life expectancy, it may not be unreasonable to discontinue statin therapy to reduce costs and polypharmacy.

IIa, B
- All patients with HF due to an ischemic etiology, should be on statins unless there are contraindications.[461-463]

IIb, B
- Routine use of cholesterol-lowering therapy is not recommended in non-ischemic HF.[466]
- Patients with HF do not appear to benefit from PCSK-9 inhibition after ACS.[469,470]

Key Recommendations #13 :

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

10.5. Kidney Disease

- Individuals with Chronic Kidney Disease (CKD) are at high risk for CVD.[129,471-473] It is the most common cause of death in these patients, accounting for 40-50% of all deaths in End Stage Kidney Disease (ESKD), with CVD mortality rates approximately 15 times that seen in the general population.[474]
- All patients with CKD should be screened for the traditional CV risk factors and treated appropriately. They benefit similar to non-CKD patients from therapies targeting hypertension, glucose control and smoking cessation.[475-477] These have been shown to slow down the atherosclerotic process, improve their CV outcomes and also slow down the progression of CKD.[475-477]
- The main lipid abnormality in CKD is elevated TG, small dense LDL- particles and low HDL-C. TC is usually normal or low.[478-480] (Table 14, pg. 74)
- Dyslipidemia can occur in all stages of CKD, on dialysis, after kidney transplantation and in nephrotic syndrome. As CKD progresses, the dyslipidemia often worsens.[481] The excess risk associated with increased LDL-C decreases in parallel with eGFR despite higher absolute risk of MI.[482]

Table 14: Abnormalities of lipid profile by target population

	Nephrotic (Stages 1-2)	Syndrome CKD	CKD (Stages 3–4)	HD	PD	KTR
Total Cholesterol	↑↑	=	=	= or ↓	↑	↑
LDL	↑↑	=	= or ↓	= or ↓	↑	↑
HDL	↓	↓	↓	↓	↓	= or ↓
Triglycerides	↑↑	↑↑	↑↑	= or ↑	↑↑	↑ or ↑↑

Adapted from:
Weiner DE, Sarnak MJ. Managing Dyslipidemia in Chronic Kidney Disease. J Gen Intern Med. 2004;19:1045–1052.[478]
Lo JC, Go AS, Chandra M, Fan D, Kaysen GA. GFR, body mass index, and low high-density lipoprotein concentration in adults with and without CKD. Am J Kidney Dis. 2007;50:552–558[483]
HD:haemodialysis, KTR kidney transplant recipient, PD peritoneal dialysis
Key: *↑ increase; ↓ decrease; = No change*

10.5.1 Managing Lipid Disorders in Kidney Disease

- All adults and adolescents with CKD should have a lipid profile (TC, LDL-C, HDL-C, TG)
- Targets of Therapy: see Table 4, pg.26.

10.5.1.1. Pharmacotherapy

I, A
- In patients with CKD, statins significantly reduced the risk of all-cause mortality, CV mortality and non-fatal CV events in primary and secondary prevention.[484-486]
- Lipid lowering therapy is safe in patients with CKD. However, when initiating it in patients with CKD, the initiating dose of statin should be lower.[338,339,487,488] These patients are at high risk of medication-related adverse events especially muscle related symptoms due to multiple reasons such as reduced kidney excretion, polypharmacy etc.

I, A
- The combination of simvastatin plus ezetimibe was found to be safe in CKD patients with no history of MI or coronary revascularization. There was a significant reduction in major atherosclerotic events seen in patients in Stage 3A-5.[338-340,486] (Table 15, pg. 75)
- Niacin and fibrates are effective in lipid lowering in CKD.

III, B
  - ➢ Fibrates, however, are not recommended in CKD patients because of increased risk of side effects when it is combined with statins.[487]

III,C
  - ➢ Niacin has not been well studied in advanced CKD and therefore, not recommended.

IIA,C
- Hypertriglyceridemia in CKD patients is best treated with lifestyle changes rather than with drug therapy.[487]

IIb, B
- In patients with markedly elevated fasting levels of TG > 11.3 mmol/l, fibrates may be considered. The dose should be adjusted according to kidney function.[487]

III, B
- In patients with CKD (eGFR <60 mL/min/1.73 m^2), the combination of statins and fibrates and ezetimibe monotherapy is not recommended due to risk of drug toxicity.[487,488]
- PCSK 9 inhibitors, bempedoic acid, and inclisiran have all been shown to decrease LDL-C but there is currently limited data for reduction of CV events or mortality in patients with CKD/ESKD.[361,489]

10.5.1.2. Specific Kidney Disorders

A) Nephrotic Syndrome

- In nephrotic syndrome, both TC and LDL-C are elevated.
- The lipid abnormalities may improve or resolve when the underlying kidney disease is successfully treated.
- If dyslipidemia persists, drug therapy should be considered.
- There is limited data available on the use of lipid lowering therapies in nephrotic syndrome. Data is only available for statins and fibrates. However, no CV outcome data is available.[490,491]

B) CKD (Pre- dialysis)

- In general, lipid modifying therapy has not been shown to retard the progression of CKD or reduce proteinuria.[492,493]

C) ESKF- Dialysis

- End stage kidney disease patients on dialysis have not had similar benefits of lipid lowering therapy.[494,495] The relative impact of dyslipidemia on CVD development and progression in these patients may be less than in other CKD and non-CKD patients.

III, B
- Statins should not be commenced for primary prevention of CVD in patients on dialysis.[487,494,495] These patients are at very high CV risk, but it is for non-atherosclerotic CVD e.g., due to medial calcific arteriosclerosis, LVH, coronary artery calcification, arrhythmias etc. No CV benefits have been demonstrated in these patients in clinical trials of lipid lowering therapy.

IIa, C
- In patients with established CVD or who are already on statins or an ezetimibe/statin combination at the time of initiation of dialysis, these drugs should be continued.[487]

D) Post-transplant

IIa, A
- All adul t kidney transplant recipients should be treated with a statin, regardless of age.[487,496,497]

Table 15: Dosing modifications for lipid-lowering drugs in CKD

Agent	Stage 3A - 5mg/day
Atorvastatin	20
Fluvastatin	80
Lovastatin	Not studied
Pravastatin	40
Rosuvastatin	10
Simvastatin	40
Simvastatin/Ezetimibe	20/10

From :Adapted KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney DiseaseKidney International Supplements 2013;volume 3(3)487

Key Recommendations #14 :

- Lipid lowering therapy with statins or ezetimibe/simvastatin combination should be initiated in non dialysis CKD patients for primary and secondary prevention of CVD.
- The target LDL-C levels will depend upon their CV risk (Table 4, pg. 26).
- Statins should not be commenced for primary prevention of CVD in patients on dialysis. These patients are at very high CV risk, but it is for non-atherosclerotic CVD e.g., due to medial calcific arteriosclerosis, LVH, coronary artery calcification, arrythmias etc. No CV benefits have been demonstrated in clinical trials of lipid lowering therapy.
- In patients with established CVD already on statins or an ezetimibe/statin combination at the time of initiation of dialysis, these drugs should be continued.

10.6. Other Endocrine Disorders

10.6.1 Thyroid Disease

- Thyroid hormones have profound effects on lipoprotein metabolism. [498-500]

10.6.1.1. Hypothyroidism

- Hypothyroidism is associated with altered lipid metabolism that may lead to the following lipid abnormalities:[498-500]
  - Elevation in total cholesterol, TG, LDL-C, and apo-B.
  - Elevated Lp(a).
- This dyslipidemia together with the hypercoagulable state and reduced endothelial function contribute to the increased CV risk seen in these patients.[498]
- In patients with dyslipidemia, hypothyroidism is an important secondary cause that needs to be excluded before treatment with lipid- lowering medications.

I, C

- Treatment of hypothyroidism with thyroid hormone replacement can improve the lipid abnormalities. In patients with overt hypothyroidism, treatment for dyslipidemia is usually not initiated until the patient becomes euthyroid to assess the lipid profile more accurately.
- In patients with subclinical hypothyroidism (thyroid-stimulating hormone <10 mIU/L) with associated dyslipidemia, thyroxine treatment can be considered as a means of reducing LDL-C levels.[498]

10.6.1.2. Hyperthyroidism

- Hyperthyroidism, unless transient:[498,500]
  - Accelerates lipid metabolism and results in decreased levels of TC, LDL-C, Lp(a), apoA-1, and apoB. The effects on TG are variable.

I, C

  - Treatment of overt hyperthyroidism significantly increases TC, LDL-C and HDL-C.
  - Changes in LDL cholesterol have been observed as early as 3 months after the patient is euthyroid.[498] Re-evaluation of lipid parameters is recommended after the patient becomes euthyroid.
  - Treatment of subclinical hyperthyroidism did not alter lipid parameters.

10.6.2. Cushing Syndrome

- Chronic hypercortisolism due to Cushing syndrome is associated with the development of metabolic syndrome with hypertension, insulin resistance, dyslipidemia, a prothrombotic state, and visceral obesity. All these contribute to the increased CV risk seen in these patients. Even patients with subclinical Cushing syndrome, have been found to be at increased CV risk.[501]
- Dyslipidemia is a common metabolic abnormality in Cushing syndrome. Estimates for the prevalence of dyslipidemia in active Cushing disease ranges from 12% to 72%.[502] The dyslipidemia in Cushing syndrome:[502,503]
  - Is characterized by elevated plasma TC and TG due to increased circulating VLDL and LDL particles, and variable levels of HDL-C.
  - The severity can be influenced by the severity and duration of hypercortisolemia, presence of diabetes, and degree of visceral obesity.
- Patients who achieve successful remission of Cushing syndrome after treatment do experience improvement in dyslipidemia and other CV risk factors such as obesity, hypertension, and diabetes. However, these risk factors persist after cure in a significant proportion of patients.[502-505] Therefore, patients may require monitoring and treatment for dyslipidemia after successful biochemical remission of Cushing disease.

10.6.2.1 Management

- In adult patients with Cushing syndrome, it is recommended to monitor lipid profile at the time of diagnosis and periodically afterwards.

IIa, C

- In adults with persistent endogenous Cushing syndrome, irrespective of the CV risk score, **statin therapy**, as adjunct to lifestyle modification, should be considered to reduce CV risk.[498]
- LDL-C should be the primary target of therapy. The target should be LDL -C < 1.8 mmol/L.[498]
- Several medications used for the treatment of Cushing syndrome have important effects on lipids.
  - Ketoconazole inhibits cortisol biosynthesis and is also an inhibitor of cholesterol biosynthesis, and treatment can lead to an approximately 25% reduction in apoB and LDL-C levels.
  - Ketoconazole is a potent inhibitor of cytochrome P450 3A4 (CYP3A4) and can markedly increase plasma levels of certain statins, specifically simvastatin, lovastatin, and, to a lesser extent, atorvastatin. This can significantly increase the risk of myotoxicity from statin therapy. Therefore, statins not metabolized by the CYP3A4 system (including fluvastatin, pravastatin, and rosuvastatin) should be used when cholesterol-lowering therapy is required in the setting of ketoconazole therapy.
  - Mitotane, commonly used in the treatment of Cushing syndrome, by itself can contribute to a secondary dyslipidemia.[498,506]

Key Message #9 :

- Thyroid hormones have profound effects on lipoprotein metabolism.
- Dyslipidemia is a common metabolic abnormality in Cushing syndrome, ranging from 12% to 72%.

Key Recommendations #15 :

- Thyroid Disorders:
  - Treatment of hypothyroidism or hyperthyroidism appropriately can improve the lipid abnormalities.
  - The lipid profile should be reassessed after the patient has become euthyroid before initiating lipid lowering therapy.
- Cushing's Disorder:
  - In adults with persistent endogenous Cushing syndrome, irrespective of the CV risk score, statin therapy, as adjunct to lifestyle modification, should be considered to reduce CV risk.
  - LDL-C should be the primary target of therapy. The target should be LDL -C < 1.8mmol/L.

10.7. Patients with Human Immunodeficiency Virus (HIV) Infection

- With the advent of good and improved access to effective therapy for HIV, life expectancy has increased, and CVD has become an important cause of morbidity and mortality in these patients.[507] This may be due to:[508]
  - HIV infection itself, which may produce a cardiometabolic type of syndrome.
  - Metabolic changes associated with anti-retroviral therapy (ART), such as protease inhibitors (PI) and nucleoside or nucleotide reverse transcriptase inhibitors (NRTI).
  - Associated CV risk factors such as smoking and recreational drug use (e.g. cocaine)
- When treating dyslipidemia in patients living with HIV, the following are important:
  - I, A **LDL-C remains the primary target of therapy**.[508,509]
  - **Drug therapy:**
    - Suggested **statin therapy**:[508-511]
      - IIa, B Pravastatin has a good safety profile, has limited interaction with ART and is currently the longest used statin in these patients.
      - Other potential options are fluvastatin and pitavastatin because of minimal cytochrome P 450 (CYP 450) metabolism.
      - IIa, B Atorvastatin and rosuvastatin are recommended if a greater reduction in LDL-C levels is needed, but atorvastatin has a more significant interaction with ART.
      - IIa, B A lower dose (10-20 mg) of these high-intensity statins is recommended when co-administered with ART in combination with a pharmacokinetic booster such as cobicistat. This booster inhibits CYP 450 3A and increases the effect of the statins. Therefore, statin dose should be adjusted according to the current ART and medication regime.
      - III,B Both simvastatin and lovastatin are extensively metabolised by the CYP 450 system and thus should be avoided, especially in patients on a CYP 450 inhibitors, such as protease inhibitors (PI).
    - IIa, B If the **patient is statin intolerant or LDL-C target has not been achieved** despite maximally tolerated dose, ezetimibe, +/- PCSK9 inhibitor can be considered.[508,509,512]
  - Monitoring for side effects is vital. Liver function test must be done regularly. Symptoms of muscle soreness or myopathy, neurologic complications, blood sugar and diabetes should be routinely evaluated.
  - Hepatitis C co-infection is common in HIV patients, and care must be taken regarding the interactions between statins and Hepatitis C medication.
  - IIa, B TG may be very high in these patients because of ART. Suggested drug therapy:
    - Fenofibrates are preferred because there is no significant interaction with ART.[508]
    - IIa, B Gemfibrozil may have a lower efficacy due to interaction with CYP 450 inhibitors, such as protease inhibitors.[508]

Key Message #10 :

- CVD has become an important cause of morbidity and mortality in HIV patients. This may be due to the:
  - HIV infection itself, which may produce a cardiometabolic type of syndrome.
  - Metabolic changes associated with anti-retroviral therapy (ART).
  - Associated CV risk factors such as smoking and recreational drug use (e.g. cocaine).

Key Recommendations #16 :

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

10.8. Psychiatric Disorders

- Metabolic syndrome and dyslipidemia are typical disorders in patients with schizophrenia. [513,514]
- The prevalence of dyslipidemia among persons with severe and persistent mental illness ranges from 25% to 70%.[515]
- These patients have a higher risk of developing CVD, and they are twice as likely to die from CVD. In psychotic patients, dyslipidemia may develop due to: [516,517]
  - The pathophysiology of schizophrenia,
  - Sedentary lifestyle,
  - Poor diet and
  - Use of antipsychotics
- Antipsychotic-induced dyslipidemia increases risk for developing further metabolic complications and CVD.[518]
- Olanzapine and quetiapine induced dyslipidemias significantly increase the risk of CVD in patients with schizophrenia.[515,519]
- When treating dyslipidemia in psychiatric patient's, the following are important:
  - LDL-C remains the primary target of therapy.[42] (Table 4, pg. 26)
  - There is an increase in risperidone blood levels after addition of a statin and there have been case reports of rhabdomyolysis and compartment syndrome in a patient on risperidone after the addition of a statin.[513]
  - The effect of statins in lowering of TC, LDL-C and TG among dyslipidemic psychiatric patients that were treated with antipsychotics was similar to the effectiveness of statin therapy in other clinical trial settings and should be used when they are indicated.[520]
  - Before statin initiation in general the transaminase level should be checked, and this is especially important in psychiatric patients as many antipsychotics (eg, olanzapine, quetiapine, and clozapine) can also cause transaminitis.[521]
  - Clozapine, loxapine, haloperidol, melperone, risperidone, and olanzapine have been known to cause significant CK elevations and checking CK levels before starting a statin would be prudent.[522]
  - After initiation of statin therapy routine CK or ALT testing is not recommended but should be done if the patient develops signs of hepatotoxicity (ALT) or muscle symptoms (CK).

Key Message #11 :

- Antipsychotic drug induced dyslipidemia increases risk for developing further metabolic complications and CVD.

Key Recommendations #17 :

- In patients with psychosis, LDL-C is the primary target of therapy.
- Drugs of first choice are statins.

11. SPECIFIC LIPID DISORDERS

11.1 Elevated TG

- Hypertriglyceridemia has a modest association as a CV risk factor, but the association is far weaker than for hypercholesterolaemia.[523-527]
- In contrast to the established reduction in CV risk with LDL-C lowering, the efficacy of TG lowering in decreasing CV risk has not been established.
- Hypertriglyceridemia is associated with increased numbers of atherogenic small, dense LDL particles and apo B-100-associated Tg-rich lipoprotein remnant cholesterol, which increase CV risk.[528,529]
- Data from large prospective studies, have found that non-fasting TG predicts CV risk and mortality, more strongly than fasting TG.[524-527,530,531] This is indicative of insulin resistance and atherogenic remnant lipoproteins.
- Associations were strongest with postprandial TG taken 2 to 4 h after the meal.
- Unfortunately, the lack of standardization and reference ranges impedes the general implementation of non-fasting TG as a target for control.[532]
- At present, fasting TG >1.7 mmol/L continues to be considered a marker of increased risk, but concentrations ≤1.7 mmol/L are not evidence-based target levels for therapy.

11.1.1 Targets of therapy

- In individuals with elevated TG, the primary target of therapy remains achieving LDL-C goal depending upon the individual's global CV risk.[42-45]
- When TG levels are > 1.5mmol/L, reported LDL-C levels do not reliably indicate LDL particle number.[533]
- Individuals with a TG > 4.5mmol/L should have a repeat lipid panel tested in the fasting state.
- In individuals where the TG > 2.3mmol/L, non-HDL-C and apo-B levels are more representative of all atherogenic lipoproteins than LDL-C. In these individuals, the secondary target of therapy is non-HDL-C.[24,141,534] (Table 4, pg. 26).
- In individuals where the TG > 4.5mmol/L, non-HDL-C is the primary target of therapy.[24,141,535] (Table 4, pg. 26).

A) Mild-to-moderate elevations in TG (> 1.7 – < 10.0 mmol/L)

Treatment should include:

- **Lifestyle changes** of weight reduction, low carbohydrate diet reducing intake of simple carbohydrates, eg. high-glycemic and high-fructose foods and beverages, control of diabetes or insulin resistance, exercise, reduction of alcohol intake and cessation of smoking.[166,536-542] Dietary fat does not raise fasting plasma TG levels in most people. However, reducing SFA is recommended.[543]
- After 4-12 weeks of lifestyle measures, assess need for further TG-lowering therapy with the goal to reduce CVD risk.
- Ensure diabetes, if present, is controlled.
- Drug therapy should be considered in high CV risk individuals. (Refer Table 11, pg. 56) In stepwise fashion:
  - **Statins:**
    - Intensifying statin therapy, especially if LDL-C target is not achieved.[544]
    - Statins have significant effects on mortality and most CV outcome parameters.
    - These drugs are the first choice to reduce both total CV risk and moderately elevated TG levels.
    - More potent statins (atorvastatin, rosuvastatin, and pitavastatin) demonstrate a robust lowering of TG levels, especially at high doses.
  - **+ Fibrates:**
    - Failure to achieve adequate TG lowering despite lifestyle interventions and optimal therapy to lower LDL-C, adding fibrates is the next option as a combination therapy to statin.[368,545,546]
    - Fibrates are generally considered the most potent TG agents, with reductions of 45 to 55%.[286,293,365,547]
    - Caution should be exercised when gemfibrozil is used in combination with statins because of the significant risk of rhabdomyolysis (particularly in the setting of concomitant kidney dysfunction).[394,395]
  - **+ Omega 3 Fatty Acids:**
    - The CV benefits of omega-3 fish oils remains uncertain.
    - 2 trials with high-dose Fish oils have shown CV benefit.[94,95] Another 4 trials, however, were neutral.[389-391,548]
    - The mechanisms for the reduction in CV events with high-dose omega-3 FA (Icosapent ethyl) are uncertain, as there was a lack of correlation between TG lowering and CV outcomes.
    - The preparation used in the REDUCE-IT trial that was shown to have CV benefits, is currently not available in Malaysia.
    - There appears to be a dose-related risk of Atrial Fibrillation (AF) with omega-3 fatty acid.[549]
      - At a dose of 4.0gm/day, there is a highly statistically significant nearly doubling increase in risk.
      - With the intermediate dose (1.8 gm/day) and standard dose (840mg/day), there is an increase in risk which did not achieve statistical significance.
      - Patients who choose to take high doses of omega-3 fatty acids, should be informed of the risk of AF, and followed up for the possible development of this potentially hazardous arrhythmia.
- Currently, there is still no outcome data that show a reduction in CV events with the use of drug therapy to reduce TG.[160,366,367]

B) Severe elevations in TG (>10mmol/L)

In asymptomatic individuals:

- **Repeat fasting TG** (after an interval of 5 days, but within 2 weeks) and review for potential secondary causes of dyslipidemia. Seek specialist advice if the TG remains above 10 mmol/L.[550]
- In these individuals:
  - **Dietary Modification**: Very low carbohydrate (<10%) and low-fat diets (≤10-15%, preferably < 5% of calorie intake), avoidance of alcohol and lifestyle changes.[166,537,551] **(Section 7.1).**
  - **Drug therapy**:
    - **Statins**:
      - These are drugs of choice.
    - **Combination therapy**:
      - Consider a combination of a fibrate, high dose Omega-3 Fatty Acids and/or niacin in severe hypertriglyceridemia (>5.6 mmmol/L).[286,293,365,547]
      - The higher the baseline TG level, the greater the percent and absolute TG lowering that can be achieved by drug therapy.
      - However, despite this, it is less likely any single agent will sufficiently reduce TG to goal.
    - **Omega- 3 Fatty Acids**:
      - A dose of 4gm/day (eicosapentaenoic acid ethyl ester) appears to be efficacious, often given as part of combination therapy.[21,96,552,553]
    - **IV insulin**:
      - Severe hypertriglyceridemia associated with uncontrolled diabetes warrants initiation of IV insulin infusion.[553]
      - IV insulin stimulates intravascular lipoprotein lipase that helps to clear TG at a faster rate.
      - The TG level will improve within 2-5 days but may not normalize.
  - **In patients who have suspected pancreatitis**, treatment includes:
    - **Fibrate or nicotinic acid**
      - Gemfibrozil and Fenofibrate lower TG by about 20-35%.[286]
      - Nicotinic acid at doses of above 1.5gm per day can reduce TG by 40%.[554] However. nicotinic acid is not routinely recommended given its limited benefit, and risk of adverse effects, including a worsening of insulin resistance.
    - **Omega-3 Fatty Acids**,
      - When administered in the early phase (within 48 hours) of acute pancreatitis and sepsis, omega 3 Fatty Acids, appear to be safe, and potentially reduce the incidence of new onset organ failure, infectious complications, and mortality.[555]
      - Omega-3 Fatty Acid administration appears to affect inflammatory markers, potentially resulting in better clinical outcome. Caution is recommended when interpreting these beneficial results due to the limited number of patients and studies.

11.2 Low HDL-C and High TG

- Low HDL-C and high TG are seen in insulin resistance states (e.g., Type 2 diabetes, abdominal obesity), physical inactivity and high carbohydrate intakes. This lipid pattern is associated with atherogenic dyslipidemia and small dense LDL-particles.
- HDL-C < 1.0mmol/L (men) and < 1.3mmol/L (women) is considered a marker of increased CV risk.[24]
- Treatment of this dyslipidemia in individuals with high/very high CV risk is aimed at lowering LDL-C to target.[556]

- Pharmacological manipulation of HDL-C has not improved CV outcomes.
  - At present, there is inadequate data to recommend the use of additional lipid-modifying therapies beyond statins.[160]
  - Fibrates have shown reductions in CV events primarily in the subset of patients with high TG (>2.2mmol/L) and/or low HDL-C (<1mmol/L).[365,366,557-559]
  - A meta-analysis of 18 fibrate trials (45,058 participants) conducted over a mean of 4.1 years found no effect on all-cause mortality or cardiovascular mortality.[366]
  - In the PROMINENT trial, use of pemafibrate in individuals with Type 2 diabetes and established / high CV risk, with moderately elevated TG, and low HDL and LDL-C, did not lower CV events.[370]

11.3 Low HDL-C

- For increasing HDL-C levels, modifying lifestyle with increased exercise[250,540] and dietary modification (reduction in simple carbohydrate, sucrose/fructose consumption), weight reduction, smoking cessation[560], rather than drug treatment, is recommended.

Key Recommendations #18:

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

12. MANAGEMENT IN SPECIAL GROUPS

12.1 Women

- Women develop heart disease about 10 to 15 years later than men.[561-563]
- There are no gender differences in the risk factors that predispose to CVD although women with Type 2 diabetes are at higher risk of CVD than men.[564-567]
- In premenopausal women, CVD tends to occur in those with Type 2 diabetes and multiple CV risk factors.
- Pregnancy related conditions (hypertensive disorders of pregnancy, gestational diabetes, preterm birth, stillbirth, low birth weight infant, or placental abruption and other related complications is associated with an increased risk of developing pre-menopausal CVD.[568]
- Although statins were previously considered teratogenic on the basis of earlier animal studies, this has not been consistently shown in recent human studies.[569,570] Most cases of congenital malformations have been seen among infants whose mothers took lipophilic compounds (eg, atorvastatin, lovastatin, simvastatin) as opposed to hydrophilic compounds (eg, pravastatin, rosuvastatin).[571,572]

12.1.1. Management of Lipid Disorders

- In secondary prevention:
  - Women have similar benefits on CV outcomes as men.[42,43,134,135]
  - Statins should be the drug of first choice.[42,43,134,135]
  - Statins should be avoided in women who are pregnant, planning pregnancy or breast feeding. However, if indicated, a hydrophilic compound (e.g. rosuvastatin) is preferred.[571,572]
- In primary prevention:
  - The cornerstone of management is lifestyle modification with advice on a healthy diet and exercise.
  - Women at high risk who do not achieve their target LDL-C levels should be treated with statins for primary prevention.[134,135] Benefits are similar in both gender.

12.2. Children and Adolescents

- The atherosclerotic process begins in childhood and is progressive. As the number of CV risk factors increase, so does the severity of asymptomatic coronary and aortic atherosclerosis in the young.[573]
- Lipid levels, (TC, LDL-C and non-HDL-C) are low at birth, increase in the first two years of life and then remain stable till adolescence. Thereafter, serum lipid levels fluctuate with growth and sexual maturation and differ between the sexes.[574]
- Risk factors for atherosclerosis in the pediatric age group include:
  - Dyslipidemia especially genetic disorders such as familial hypercholesterolemia
  - Overweight / obesity and the metabolic syndrome
  - Kawasaki's disease
  - Nephrotic syndrome
  - Chronic kidney disease
  - Type 1 and 2 diabetes
  - Chronic inflammatory diseases such as Systemic Lupus Erythematosis
  - HIV
  - Post organ transplantation - in adult transplantation trials, therapy with statins has been shown to reduce the development of graft coronary artery disease.[575] Therefore, most pediatric heart transplantation patients are recommended to receive drug therapy with a statin regardless of the baseline lipoprotein levels.
  - Cigarette smoking
- These high-risk patients should have a full lipid profile.
- In the young, it is sometimes difficult to communicate to them about CV risk. They may have a low absolute risk but if they have high levels of CV risk factors, then their relative risk is high. Instead of looking at thresholds and absolute risk, some useful parameters include:[576,577]
  - CV risk age - The risk age of a person with several CV risk factors is the age of a person with the same level of risk but with ideal levels of risk factors.
  - Lifetime risk - The greater the burden of risk factors, the higher the lifetime risk.

12.2.1 Management of Lipid Disorders

- The main approach in children and adolescents is a healthy lifestyle with appropriate diet, maintenance of "desirable weight" and regular exercise.
- Children whose lipid levels are significantly elevated may have a genetic dyslipidemia and should be referred to specialists interested in this field.
- Targets of therapy:[577]
  - For children and adolescents aged 10 and over: LDL-C < 4.9mmol/l.
  - For children and adolescents with a clinical presentation consistent with FH and who do not adequately respond to lifestyle change after 3-6 months: < 4.2mmol/l.

IIa, B

- Pharmacotherapy:
  - When prescribing drugs in children, the following need to be considered:
    - Need for lifelong therapy and its associated health risks.
    - Drug exposure during unplanned pregnancy in individuals of childbearing age.
    - Risk of new onset diabetes should also be considered when prescribing statins in children with risk factors for diabetes.
  - Patients should be extensively counselled prior to initiation of drug therapy. They should be counselled on how to integrate therapy into their social norms and daily practices to achieve compliance to both pharmacotherapy as well as lifestyle modifications.

- Statins:
  - In patients with FH, statins are the drug of choice.
  - All statins can be used as an adjunct to diet, in children > 10 years of age.[578]
  - Pravastatin and rosuvastatin can be used in > 8 years of age.[578]
- Bile acid sequestrants are difficult to ingest due to their unpalatability.
- Fibric acid derivatives, niacin and omega-3 fish oils lack pediatric safety and efficacy data.
- Ezetimibe provides clinicians with an alternative adjunct therapy option when synergistically paired with a statin or used as monotherapy for patient's intolerant to statins and bile acid sequestrants.[579]

12.3. Elderly

- Increasing age is a major risk factor for CVD and death. The functional status, co-morbidities and cognitive function of the elderly make it imperative that lipid lowering therapy should be individualized.
- For **secondary prevention:**
  - The elderly derive a greater absolute benefit from lipid lowering therapy.[42,43,580-582]
  - Thus, they should not be deprived from lipid lowering therapy solely based on their age although there is limited clinical trial data in patients over the age of 80 years.
- In **primary prevention:**
  - The results appear mixed.
  - A meta-analysis of subjects > 65 years of age showed that statin treatment reduced MI and stroke with no effect on mortality.[583]
  - Statin therapy should be considered in older adults (< 80 years) free from CVD, particularly in the presence of hypertension, smoking, diabetes and dyslipidemia.[583-586]
  - A more recent meta - analysis however, concluded that the benefit of statins in primary prevention for much older patients (> 80 years) is not certain.[587]
  - This underscores the importance of individualizing lipid lowering therapy in those > 80 years.
- Lipid lowering therapy in the elderly has its challenges. The benefits and harm should be carefully considered, particularly in primary prevention, and there should be a discussion with the patient and family.
- Some important considerations include:
  - Functional status and frailty of the patient.
  - Higher risk of adverse side effects.
  - Polypharmacy and risk of drug interactions.
  - Nonadherence to therapy.
- Since older people have co-morbidities and have altered pharmacokinetics, lipid lowering medication should be started at a lower dose and then titrated with caution to achieve target lipid levels.
- The recommendations of cholesterol-lowering treatment in the elderly should be followed with caution and common sense, adverse effects should be monitored closely, and treatment should be reconsidered periodically.

Key Message #12 :

- The goals of lipid lowering therapy is similar in both gender and in the elderly. Target LDL-C levels will depend on the global CV risk (Table 4, pg. 26)
- Children whose lipid levels are significantly elevated may have a genetic dyslipidemia and should be referred to specialists interested in this field.
- When prescribing lipid lowering therapy in the elderly, the presence of co-morbidities and altered pharmacokinetics should be considered. Lipid lowering medication should be started at a lower dose and then titrated with caution to achieve target lipid levels.

13. ADHERENCE TO LIFESTYLE CHANGES AND MEDICATIONS

- It has been well documented that there is a lack of adherence to cardiovascular preventive therapy. Several scientific studies have shown that adherence among patients with chronic disease is only about 50%.[588]
- Lack of adherence threatens the success of the guideline recommendations and implementation. The amount of risk reduction achieved is related to the level of adherence to treatment. Compared with poor adherence, good adherence was associated with lower mortality.[589]
- More importantly, lack of adherence leads to missed opportunity for the risk reducing benefits of the treatment, thus creating enormous costs to the health system for treating CV events that could have been prevented.[590]
- The reasons for the high discontinuation rate and missed doses are complex and multifactorial and may include both intentional and unintentional non-adherence.[591-594] They include:
  - Affordability and accessibility to healthcare facilities.
  - Cost of medication.
  - Unclear label instructions.
  - Adverse effects from medication.
  - Polypharmacy and complexity of regimen.
  - Patient forgetfulness.
  - Patient does not like the idea of having to take medication.
  - Patient does not understand the importance of a given medication for a condition for which he or she has no symptoms.
  - Paternalistic relationship between patient and health care provider (HCP).
- To improve adherence and compliance the following are recommended:[593-595]

A) Patient factors

- Give clear instructions on therapeutic lifestyle changes and medication administration.
- Simplify medication regimens using wherever possible medications with a single daily or twice daily dosing.
- Reduce pill burden by using combination pills.
- Prompt medication-taking reminders (phone alarm/ notifications, mobile health applications).
- Encourage the support of the family/ caregivers.
- Involve patients in their care through self-monitoring and shared decision making.
- Remind patients that lipid modifying drugs are not a substitute for dietary and lifestyle interventions.

B) Healthcare Provider Factors

- Educate HCP to implement lipid treatment guidelines.
- Empower patients through patient education.
- Engage patients to initiate preventive care.
- Remind patients of appointments and follow-up missed appointments.

C) Health Delivery Systems

- Improve availability of and accessibility to guideline recommended medications (home delivery of medications).
- Promote multidisciplinary team-based care approach in patient management.
- Disseminate clinical guidelines and clinical pathways to HCPs.
- Refer patients to medication therapy adherence clinic (MTAC).
- Use mass media for patient education.
- Standardize reference values in all laboratories to recommended Malaysian guidelines.

Key Message #13 :

- There is a general lack of adherence to cardiovascular preventive therapy.
- To improve adherence to TLC and compliance to medications, efforts should be undertaken looking at:
  - Patient Factors,
  - Healthcare Provider Factors ***and***
  - Health delivery systems.

14. QUALITY INDICATORS & PERFORMANCE MEASURES

This CPG recommends the following audit parameters:

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

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

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

- Is the patient on a statin?
  Numerator: number of patients who were discharged on statins .
  Denominator: number of patients seen at that clinic session who had ACS/Stable CHD.

- **Did the individual attain the LDL-C target?**
  Numerator: number of patients who achieved the LDL-C target.
  Denominator: number of patients seen at that clinic session who had ACS/Stable CHD.
- An initial audit should be performed to determine baseline performance indicators.
- Suggest an initial target of 60% with an incremental improvement in performance indicators when reassessed at yearly intervals.
- Reasons for non-achievement of the above targets should also be determined. Based on the reasons, corrective measures should be taken.

FAQs on Lipids

What is the Role of Non-Statin Therapy in Dyslipidemia	Evidence	Grade of Recommendtion /Level of Evidence*
Cholesterol and Heart Disease	The role of serum cholesterol in the pathogenesis of atherosclerosis and CVD is unequivocal and irrefutable. The question is whether eating food high in cholesterol leads to high serum cholesterol and LDL-C, and whether limiting dietary cholesterol intake lowers serum LDL-C. Recent data indicate that the impact of dietary cholesterol on serum cholesterol levels is weak.	
Statins Safety	Statins are safe. Side effects are uncommon, self-limiting, reversible, and have no long-term sequelae.	**I, A**
Fish Oil Supplements	It may be useful in the treatment of elevated triglycerides. Fish oils is not a replacement for statins in the treatment of elevated LDL-C.	**IIa, B** **III, A**
Coenzyme Q10	No definitive evidence to support the use of Coenzyme Q10 on the reduction of cholesterol levels and primary prevention of cardiovascular disease.[596,597]	**III, A**
Complementary and Alternative Therapies:		
Estrogen and Progestins	Hormone replacement is not indicated for primary or secondary prevention of cardiovascular disease.	**III, A**
Red Yeast Rice	Red yeast rice contains substances that are structurally identical to statins. Unlike statins, there is no data on its safety in long term use.	**IIb, C**
Garlic	Natural Medicine Comprehensive Database recently downgraded garlic to a rating of “Possibly ineffective”. Garlic can also cause drug interactions and increased risk of bleeding.[598,599]	**IIb, B**
Apple Cider Vinegar	There is no evidence at present for CV protection.	**III,C**
Virgin Coconut Oil, or Coconutl Oil	Not supported by robust scientific evidence when taken on its own. It worsens the lipid profile. The saturated fatty acids in coconut oil increase total-C, LDL-C, and HDL-C.[600] One tablespoon of coconut oil contains 12gm of saturated fat and 1 tablespoon of virgin coconut oil contains 13gm of saturated fat.[601] This would contribute a significant portion of the recommended total daily saturated fat limit of < 10% of energy. If coconut oil is used as part of a daily eating plan and/or in food preparation, it is recommended that it be used within the context of a healthy dietary pattern.	**III,B** **IIb, B**

**For Grades of Recommendation and Level of Evidence, refer pg. 9.*

Appendix 1: Comparison of Cardiovascular Risk Scores

	FRS (Framingham Risk Score)	SCORE2 (Systematic Coronary Risk Evaluation	RPCE (Revised Pooled Cohort Equations)	WHO CVD (World Health Organization Cardiovascular Disease)	SCORE (Systematic Coronary Risk Evaluation)	PCE (Pooled Cohort Equations)
Population	8491 participants from Framingham, Massachusetts.	45 prospective cohorts, 677684 participants, from 13 European countries.	6 U.S. cohorts, 26689 participants.	85 cohorts, 376 177 individuals from European countries, North America, Japan and Australia.	12 European cohort studies, 205 178 participants, from 12 European countries.	20338 white and 4288 African American participants from NHLBI - sponsored cohort studies and from the Framingham Original and Offspring Study cohort.
Endpoints	Composite of CHD (coronary death, myocardial infarction, coronary insufficiency, angina), cerebrovascular events (ischemic stroke, hemorrhagic stroke, transient ischemic attack), PAD, heart failure.	Fatal cardiovascular disease (ICD10 - codes I10-16, I20-25, I46-52, I60-69, I70-73, R96·0-96·1, and excluding I51·4, I60, I62, I67·1, I68·2, I67·5). Non-fatal cardiovascular disease (ICD10 - codes I21-I23, I60-69, and excluding I60, I62, I67·1, I68·2, I67·5).	Non-fatal myocardial infarction, death from coronary heart disease, or fatal or non-fatal stroke over a 10-year period.	Fatal or non-fatal myocardial infarction or coronary heart disease (ICD10 - codes I21-23). Fatal myocardial or coronary heart disease (ICD10 - codes I24-25). Stroke (ICD10 - codes 160-69).	Cardiovascular mortality (ICD9 - codes 401-414, 426-443, 798·1, 798·2, and excluding non-atherosclerotic deaths - 426·7,429·0, 430·0, 432·1, 437·3, 437·4, 437·5).	Non-fatal myocardial infarction, death from coronaryd. heart disease, or fatal or non-fatal stroke over a 10-year period.
Target Age Range	30 - 74	40 - 69	40 - 79	40 - 80	40 - 85	40 - 79
Target Patient Criteria	No history of CVD.	No history of CVD or diabetes.	No history of CVD.	No history of CVD.	No history of heart attack.	No history of non-fatal MI, stroke, heart failure, percutaneous coronary intervention.

Adapted from:
Kassim SS et al. Validation of the general Framingham Risk Score (FRS), SCORE2, revised PCE and WHO CVD risk scores in an Asian population.The Lancet. Regional Health Western Pacific.
DOI: https://doi.org/10.1016/j.lanwpc.2023.100742

Appendix 1: Comparison of Cardiovascular Risk Scores cont'd

	FRS (Framingham Risk Score)	SCORE2 (Systematic Coronary Risk Evaluation	RPCE (Revised Pooled Cohort Equations)	WHO CVD (World Health Organization Cardiovascular Disease)	SCORE (Systematic Coronary Risk Evaluation)	PCE (Pooled Cohort Equations)
Population	Gender, age, smoking status, systolic blood pressure, total cholesterol, HDL cholesterol, on hypertensive medication, diabetes mellitus.	Gender, age, systolic blood pressure, total cholesterol, HDL cholesterol.	Gender, age, smoking status, systolic blood pressure, total cholesterol, HDL cholesterol, on hypertensive medication, diabetes mellitus.	Gender, age, smoking status, systolic blood pressure, total cholesterol	Gender, age, smoking status, systolic blood pressure, total cholesterol.	Gender, age, smoking status, systolic blood pressure, total cholesterol, HDL cholesterol, on hypertensive medication, diabetes mellitus.
Outputs	10-year risk of CV events	10-year fatal and non-fatal CVD risk	10-year risk of atherosclerotic CVD	10-year risk of fatal and non-fatal CVD.	10-year fatal CV risk	10-year risk of atherosclerotic CVD
Risk Thresholds	**Low:** <10% **Intermediate:** ≥10% to <20% **High:** ≥20%	***Age <50 :*** **Low:** <2·5% **Intermediate:** 2·5% to <7·5% **High:** ≥7·5% **Age 50-69** **Low:** <5% **Intermediate:** 5% to <10% **High:** ≥10%	**Low:** <5% **Intermediate:** ≥5% to <7·5% **High:** ≥7·5%	**Low:** <5% **Intermediate:** 5% to <20% **High:** ≥20%	**Low:** <1% **Intermediate:** ≥1% to <5% **High:** ≥5%	**Low:** <7·5% **Elevated:** ≥7·5%

Adapted from:
Kassim SS et al. Validation of the general Framingham Risk Score (FRS), SCORE2, revised PCE and WHO CVD risk scores in an Asian population.The Lancet. Regional Health Western Pacific.
DOI: https://doi.org/10.1016/j.lanwpc.2023.100742

Appendix 2: NOVA Food Classification system

GROUP	CATEGORY	DESCRIPTION & EXAMPLES
1	**Unprocessed**	**Unprocessed Foods:** or minimally These are obtained directly from plants or processed foodsanimals and do not undergo any alteration following their removal from nature. **Minimally processed foods:** These are natural foods that have been submitted to cleaning, removal of inedible or unwanted parts, fractioning, grinding, drying, fermentation, pasteurization, cooling, freezing, or other processes that may subtract part of the food, but which do not add oils, fats, sugar, salt or other substances to the original food..e.g., fresh fruits, vegetables such as carrots, whole grains, brown rice, granola, roasted nuts, chopped vegetables, vegetable or fruit juices with no added sugar or other substances, eggs.
2	**Processed culinary ingredients**	These are products extracted from natural foods or from nature by processes such as pressing, grinding, crushing, pulverizing, and refining. e.g., butter, lard, oils, sugar, or salts.
3	**Processed foods**	These are products manufactured by industry with the use of salt, sugar, oil or other substances (Group 2) added to natural or minimally processed foods (Group 1) to preserve or to make them more palatable. They are derived directly from foods and are recognized as versions of the original foods. They are usually consumed as a part of or as a side dish in culinary preparations made using natural or minimally processed foods. Most processed foods have two or three ingredients.e.g., canned fish, fruits in syrup, bottled vegetables, salted or sugared nuts and seeds.
4	**Ultra-processed food and drink products**	These are industrial formulations made entirely or mostly from substances extracted from foods (oils, fats, sugar, starch, and proteins), derived from food constituents (hydrogenated fat and modified starch), or synthesized in laboratories from food substrates, or other organic sources (flavor enhancers, colors, and several food additives used to make the product hyper-palatable) e.g. carbonated drinks, pre-prepared burgers, hot dogs, sausages, chocolates, candies, pre-prepared poultry and fish 'nuggets.

Adapted from:
Food, Nutrition & Fitness I: The Digestion Journey Begins with Food Choices. Compiled in 2018 by EduChange with guidance from NUPENS, Sao Paulo. [online] https://educhange.com/wp-content/uploads/2018/09/NOVA-Classification-Reference-Sheet.pdf

Appendix 3 : Fatty acid composition of selected dietary fats and oils[183]

Type of Fats and Oils	SFA	MUFA	PUFA	P/S Ratio	<12:0	12:0	14:0	16:0	16:1	18:0	18:1	18:2	18:3	Others
Coconut Oil	91.9	6.5	1.5	0.02	14.9	48.5	17.6	8.4	-	2.5	6.5	1.5	-	0.1
Palm Kernel Oil	84.2	13.7	2.0	0.02	8.2	49.6	16.0	8.0	-	2.4	13.7	2.0	-	0.1
Cocoa Butter	60.4	35.6	2.9	0.05	-	-	0.1	25.8	0.3	34.5	35.3	2.9	-	1.1
Beef Fat	50.6	42.1	2.8	0.06	0.1	0.1	3.3	25.5	3.4	21.6	38.7	2.2	0.6	4.6
Shea Butter	46.0	48.0	5.1	0.11	-	-	-	5.0	-	41.0	48.0	5.1	-	0.9
Palm Oil	44.9	43.4	10.8	0.24	-	0.3	0.8	39.5	0.3	4.3	43.1	10.5	0.3	0.5
Palm Olein	42.4	44.0	11.8	0.28	-	0.2	0.8	37.2	0.4	4.2	43.6	11.5	0.3	0.3
Lard	38.7	48.2	11.0	0.28	0-.1	0.1	1.4	24.8	3.1	12.3	45.1	9.9	1.1	30
Olive Oil	18.8	68.2	14.6	0.78	-	-	-	16.5	1.8	2.3	66.4	13.0	1.6	0
Groundnut Oil	9.6	71.2	18.2	1.89	-	-	0.04	7.5	0.1	2.1	71.1	18.2	-	0.9
Corn Oil	14.2	27.8	57.1	4.02	-	-	-	12.3	0.1	1.9	27.7	56.1	1.0	0.9
Soybean Oil	14.8	24.1	59.9	4.05	-	-	0.1	10.8	0.2	3.9	23.9	52.1	7.8	1.2
Canola oil	7.4	56.0	35.6	4.81	-	-	-	5.6	-	1.8	56.0	25.8	9.8	1.0
Sunflower Oil	9.1	28.1	62.4	6.85	-	0.02	0.09	6.2	0.12	2.8	28.0	62.2	0.16	0.4
Safflower Oil	9.2	11.6	78.2	8.60	-	-	0.1	6.7	0.1	2.4	11.5	79.0	0.15	0.1

Notes: Values represent %/100g edible fat.
Sources: Dubois *et at.*(2007), Grundy & Denke (1990), Kris-Etherton *et al.* (1988), Orsavova et al. (2015), Gunstone *et al.* (2007) and Karupaiah *et al.* (2005)

[183].National Coordinating Committee on Food and Nutrition. Ministry of Health Malaysia . RNI Recommended Nutrient Intakes for Malaysia. A report of the technical Working Group on Nutritional Guideline. 2017.

Appendix 4: Fatty acid composition of selected Malaysian Food[183]

Type of Fats	Total Fat	SFA	MUFA	PUFA	TEA*
Fishes					
Black Pomfret (Bawal Hitam)	2.3	0.94	0.14	0.71	N/A
Giant Seaperch (Siakap)	2.7	0.13	0.23	0.93	N/A
Gold Snapper (Jenahak)	1.3	0.42	0.94	0.51	N/A
Indian Mackerel (Kembong)	1.8	0.59	0.3	0.19	N/A
Silver Pomfret (Bawal Putih)	2.1	0.88	0.15	0.57	N/A
Yellowstripe Scad (Selar Kuning)	2.1	0.,83	0.29	0.14	N/A
Shellfish					
Cockles (Kerang)	1.9	0.64	0.40	0.61	N/A
Cuttlefish (Sotong)	1.4	0.57	0.11	0.50	N/A
Oyster (Tiram)	1.2	0.56	0.82	0.34	N/A
Prawn (Udang)	1.1	0.31	0.11	0.46	N/A
Nuts and Seeds					
Almond	49.4	3.7	30.9	12.1	-
Hazelnut	62.4	4.5	46.6	8.5	-
Peanut	49.7	6.9	24.6	15.7	-
Walnut	59.0	3.4	15.0	35.1	-
Confectionary					
Chocolate Wafer	27.3	62.3	27.9	6.4	2.72
Cooking Chocolate	33.1	80.7	15.64	2.0	1.27
Fats, Oils, Spreads, Dressing					
Butter	80.6	57.8	31.7	5.9	1.32
Fat Spread	73.4	36.3	39.4	23.2	0.22
Ghee	99.8	61.5	29.7	3.3	1.04
Margarine	77	46.5	36.3	16.8	0.36
Peanut Butter	42	20.3	48.6	26.9	0.52
Salad Dressing	45	14.5	22.7	61	0.18
Shortening	99.8	57	33.6	8.8	0.2
Vanaspati	99.8	50.6	37.9	10.7	0.43
Dairy-Based Products					
Adult Milk Powder	25.6	58.9	30.8	5.2	1.65
Cheese	21.5	59.8	31.6	4.6	0.78
Children's Milk > 3 years	17.8	44.7	36.8	16.4	0.93
Children's Milk < 1 year	27.4	39.6	40.7	18.3	0.14
Ice Cream	11.0	68.3	23.4	4.8	2.09

Source: Tee et al. (1997), Karupaiah et al. (2014), Abd. Aziz et al. (2013)
**relates to total TFA content as a sum of 18:1 n9t; 18:2 n6t; cis-9 t-12; t-9, cis-12; 18:3t1; 18:3t2; 18:3t4; and 18:3t5 excluding natural isomers of conjugated linoleic acid (cis-9,t-11).*
N/A=not available

Appendix 4: Fatty acid composition of selected Malaysian Food[183]

Type of Fats	Total Fat	SFA	MUFA	PUFA	TEA*
Soups					
Soup, Canned	45.8	10.7	54.6	32.3	0.09
Soup, Concentrates	17.0	52.0	36.3	9.0	1.94
Snacks					
French Fries	2.55	51.3	36.9	10.8	0.26
Frozen Chappati/Paratha	9.1	52.1	34.3	12.2	0.64
Frozen Dough	5.5	48.9	37.8	12.2	0.28
Potato Chips	32.7	38.3	45.3	15.1	0.24
Meat & Products					
Beef Lean	1.1	0.6	0.4	0	N/A
Burger Patties	13	40.9	43.3	12.3	0.08
Chcken Thigh, Farm with Skin	3.7	1.1	1.8	0.8	N/A
Chicken Thigh, Farm without Skin	0.5	0.1	0.2	0.1	N/A
Hen Egg	8.1	2.6	4.7	0.8	N/A
Mutton	4.6	2	2.4	0.2	N/A
Nuggets	15	43.5	42.1	13.1	0.18
Pork Fat	89.3	37.8	45.9	5.5	N/A
Pork Lean	21	7.9	11	2.1	N/A
Prawn	0.3	0.1	0.1	0.1	N/A
Sausages	13.8	31.1	45.9	21.3	0.15
Polular Street Foods					
Char Siew Pau	15.4	7.2	7	1.2	N/A
Chicken Rice	4.6	1.8	2.1	0.7	N/A
Curry Laksa	6.4	4.4	1.4	0.6	N/A
Dosai	0.7	0.4	0.2	0	N/A
Fried Kueh Tiau	9.7	3.9	4.5	1.2	N/A
Fried Mee - Hokkien	6.6	2.7	3	0.9	N/A
Fried Mee - Indian Style	9	5.6	2.3	1.1	N/A
Lor Mai Kai	5	1.9	2.4	0.7	N/A
Nasi Goreng Cina	13.2	5.3	6.5	1.4	N/A
Nasi Lemak	3.6	2	1.1	0.5	N/A
Satay	10.8	3.6	4.6	2.6	N/A

Source: Tee et al. (1997), Karupaiah et al. (2014)
**relates to total TFA content as a sum of 18:1 n9t; 18:2 n6t; cis-9 t-12; t-9, cis-12; 18:3t1; 18:3t2; 18:3t4; and 18:3t5 excluding natural isomers of conjugated linoleic acid (cis-9,trans-11).*
N/A=not available

[183] National Coordinating Committee on Food and Nutrition. Ministry of Health Malaysia . RNI Recommended Nutrient Intakes for Malaysia. A report of the technical Working Group on Nutritional Guideline. 2017.

REFERENCES

1. World Health Organization. The Top 10 causes of death. Available at https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. [Online Resource] Accessed on 3rd March 2023.
2. Roser M. (7th Dec 2021) - "Causes of Death". Published online at OurWorldInData.org. Retrieved from: 'https://ourworldindata.org/causes-of-death' [Online Resource]. Acessed on 20th November 2021.
3. Department of Statistics Malaysia. Available at https://www.dosm.gov.my. Online Resource. Released on 16th November 2021. Accessed on 3rd March 2023.
4. Department of Statistics Malaysia. Available at https://www.dosm.gov.my. Online Resource. Released on 27th Oct 2022. Accessed on 3rd March 2023.
5. Institute for Public Health (IPH), National Institutes of Health, Ministry of Health Malaysia. 2020. National Health and Morbidity Survey (NHMS) 2019: Vol. I: NCDs - Non-Communicable Diseases: Risk Factors and other Health Problems.
6. Ismail NH, Rosli NM, Mahat D, Yusof KH, Ismail R. Cardiovascular risk assessment between urban and rural population in Malaysia. Med J Malaysia 2016: 71 (6): 331-337.
7. Mohd Nor, N.S., Chua, YA., Abdul Razak, S. et al. Identification of cardiovascular risk factors among urban and rural Malaysian youths. BMC Cardiovasc Disord 2022: 22, 70. https://doi.org/10.1186/s12872-021-02447-y
8. Hazreen MA, Su TT, Jalaludin MY, Dahlui M, Chinna K, Ismail M, Murray L, Cantwell M, Sadat NA. An exploratory study on risk factors for chronic non-communicable diseases among adolescents in Malaysia: overview of the Malaysian Health and Adolescents Longitudinal Research Team study (The MyHeART study). BMC Public Health. 2014;14:S6.
9. Thangiah N, Chinna K, Su TT, Jalaludin MY, Al-Sadat N, Majid HA. Clustering and Tracking the Stability of Biological CVD Risk Factors in Adolescents: The Malaysian Health and Adolescents Longitudinal Research Team Study (MyHeARTs). Front Public Health. 2020 Mar 17;8:69. doi: 10.3389/fpubh.2020.00069.
10. W.A Wan Ahmad. (Ed). Annual Report of the NCVD-ACS Registry, 2018-2019. Kuala Lumpur, Malaysia: National Cardiovascular Disease Database, 2022. [Internet]. Available from: www. https://www.malaysianheart.org
11. W.A Wan Ahmad (Ed). Annual report of the NCVD-ACS Registry, 2016-2017, Kuala Lumpur, Malaysia: National Cardiovascular Disease Database, 2019.
12. Ministry of Health Singapore. Singapore Myocardial Infarction Registry Annual Report 2019. National Registry of Diseases Office. 30 Jul 2021. [Internet]. Available from: www.nrdo.gov.sg/docs/librariesprovider3/default-document-library/smir-web-report-2019.pdf?sfvrsn=a0d1988b_0
13. Institute for Public Health (IPH), Ministry of Health, Malaysia. The Third National Health and Morbidity Survey 2006: (NHMS III). Executive Summary. 2008.
14. Institute for Public Health (IPH). National Health and Morbidity Survey 2011 (NHMS 2011). Vol. II: NonCommunicable Diseases. 2011.
15. Institute for Public Health (IPH). National Health and Morbidity Survey 2015 (NHMS 2015). Vol. II: Non-Communicable Diseases, Risk Factors & Other Health Problems. 2015.
16. Martin S.S., Blaha M.J., Elshazly M.B., Brinton E.A., Toth P.P., McEvoy J.W., Joshi P.H., Kulkarni K.R., Mize P.D., Kwiterovich P.O., Defilippis A.P., Blumenthal R.S., Jones S.R. Friedewald-estimated versus directly measured low-density lipoprotein cholesterol and treatment implications. J. Am. Coll. Cardiol. 2013;62:732-739
17. Sampson M., Ling C., Sun Q., Harb R., Ashmaig M., Warnick R., Sethi A., Fleming J.K., Otvos J.D., Meeusen J.W., Delaney S.R., Jaffe A.S., Shamburek R., Amar M., Remaley A.T. A New Equation for Calculation of Low-Density Lipoprotein Cholesterol in Patients With Normolipidemia and/or Hypertriglyceridemia. JAMA Cardiol. 2020;5:540-548
18. Ginsberg HN, Rosenson RS, Hovingh GK, Letierce A, Samuel R, Poulouin Y, Cannon CP. LDL-C calculated by Friedewald, Martin-Hopkins, or NIH equation 2 versus beta-quantification: pooled alirocumab trials. J Lipid Res. 2022 Jan;63(1):100148
19. Brunzell JD, Davidson M, Furberg CD et al. Lipoprotein management in patients with cardiometabolic risk. Diabetes care 2009:31;811-822.
20. Chapman MJ, Ginsberg HN, Amarenco P et al. Triglyceride rich lipoprotein and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. EHJ 2011;32:1345-1361
21. Ginsberg HN, Packard CJ, Chapman MJ, Borén J et al. Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies-a consensus statement from the European Atherosclerosis Society, Eur Heart J 2021: 42, (47):m4791-4806,
22. Langsted A Freiburg JJ, Nordestgaard BG et al. fasting and non-fasting lipid levels: influence of normal food intake on lipids, lipoprotein, apolipoproteins, and cardiovascular risk prediction. Circ 2008;118:2047-2056.
23. Nordestgaard BG, Langsted A, Mora S et al. Fasting is not routinely required for determination of lipid profile: a clinical and laboratory implications including flagging at desirable concentration cut-points. EHJ 2016;37:1944
24. Malaysian Clinical Practice Guidelines on Type 2 Diabetes Mellitus 2020. 6Th Ed. Available at www.acadmed.org. my
25. Welsh C, Celis-Morales CA, Brown R, Mackay DF, Lewsey J, Mark PB, Gray SR, Ferguson LD, Anderson JJ, Lyall DM, Cleland JG, Jhund PS, Gill JMR, Pell JP, Sattar N, Welsh P. Comparison of Conventional Lipoprotein Tests and Apolipoproteins in the Prediction of Cardiovascular Disease. Circulation. 2019 Aug 13;140(7):542-552.
26. The Emerging Risk Factors Collaboration. Lipid-related markers and cardiovascular disease prediction. JAMA. 2012;307:2499-2506.
27. Yusuf S, Hawken S, Ounpuu S, et al. Effects of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case control study. Lancet 2004:364;937-52.
28. O'Donnell MJ, Xavier D, Liu L et al. Risk factors for ischemic and intracerebral hemorrhagic stroke in 22 countries (the INTERHEART study). A case control study. Lancet 2010:376;112-123.
29. Murphy A, Faria-Neto JR, Al-Rasadi K et al. World Heart Federation Cholesterol Roadmap. Global Heart 2017. 12(3), 179-197

30. Nordestgaard BG, Chapman MJ, Ray K et al. Lipoprotein (a) as a cardiovascular risk factor: current status. EHJ 2010;31(23):2844-53
31. Willeit P, Ridker PM, Nestel PJ et al. baseline and on statin treatment lipoprotein (a) levels for predicting of cardiovascular events: individual patient data meta-analysis of statin outcome trials. Lancet 2018;392;1311-20.
32. O'Donoghue ML. Fazio S, Giugliano RP et al. Lipoprotein (a). PCSK9 inhibition, and cardiovascular risk, Circ 2019;139(12):1483-92
33. Wilson DP, Jacobson TA, Jones PH, McNeal CJ, Nordestgaard BG et al. Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association. J Clin Lipidology 2019: 13: 374–392
34. Cegla J, France M, Marcovina SM et al. Lp(a): When and how to measure it. Annals of Clinical Biochem 2021:Vol 58(1): , 16-21
35. Rader DJ. Chapter 5: Lipid Disorders. In: Textbook of Cardiovascular Medicine. 3rd Ed. Lippincott Williams & Wilkins; 2007.
36. Peppa M, Betsi G, Dimitriadis G. Lipid Abnormalities and Cardiometabolic Risk in Patients with Overt and Subclinical Thyroid Disease. J Lipids. 2011;e575840.
37. Walsh JP, Bremner AP, Bulsara MK, O'leary P, Leedman PJ, Feddema P, Michelangeli V. Thyroid dysfunction and serum lipids: a community-based study. Clin Endocrinol. 2005;63:670-675.
38. Colao A, Gaillard R. Novel insights in the management of Cushing's syndrome. Neuroendocrinology. 2010;92:6-132.
39. Weir MR, Moser M. Diuretics and β-blockers: Is there a risk for dyslipidemia?. Am Heart J. 2000;139(1) : 174-184.
40. Hartgens F, Rietjens G, Keizer HA, et al Effects of androgenic-anabolic steroids on apolipoproteins and lipoprotein (a)British Journal of Sports Medicine 2004;38:253-259.
41. Choi HK, Seegar JD. Glucocorticoid Use and Serum Lipid Levels in US Adults: The Third National Health and Nutrition Examination Survey. Arthritis & Rheumatism (Arthritis Care & Research) 2005: 53: 528-535
42. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhalla N et al for the Cholesterol Treatment Trialists' (CTT) Collaboration,. 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 ;376:1670-81.
43. Collins R, Reith C, Emberson J, Armitage J, Baigent C et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016; 388: 2532-61
44. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, et al. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. JAMA. 2016; 316:1289-97.
45. Taylor F, Huffman MD, Macedo AF, Moore THM, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013;:CD004816.
46. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, et 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(32): 2459-72.
47. Keys A, ed. Coronary heart disease in seven countries: American Heart Association Monograph 29. Circulation. 1970;41:1-211.
48. Verschuren WM, Jacobs DR, Bloemberg BP, Kromhout D, Menotti A, Aravanis C, Blackburn H, Buzina R, Dontas AS, Fidanza F. Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study. JAMA. 1995;274:131-136.
49. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J. Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study. Ann Intern Med. 1961;55:33-50.
50. Kannel WB, Neaton JD, Wentworth D, Thomas HE, Stamler J, Hulley SB, Kjelsberg MO. Overall and coronary heart disease mortality rates in relation to major risk factors in 325,348 men screened for the MRFIT. Multiple Risk Factor Intervention Trial. Am Heart J. 1986;112:825-836.
51. Smith GD, Shipley MJ, Marmot MG, Rose G. Plasma cholesterol concentration and mortality. The Whitehall Study. JAMA. 1992;267:70-76.
52. Assmann G, Schulte H. The Prospective Cardiovascular Münster Study: prevalence and prognostic significance of hyperlipidemia in men with systemic hypertension. Am J Cardiol. 1987;59:9G-17G.
53. Smith, G. D., Shipley, M. J., Marmot, M. G. & Rose, G. Plasma cholesterol concentration and mortality. The Whitehall Study. JAMA 1992; 267, 70-76.
54. Kuulasmaa K, Tunstall-Pedoe H, Dobson A, Fortmann S, Sans S, Tolonen H, Evans A, Ferrario M, Tuomilehto J. Estimation of contribution of changes in classic risk factors to trends in coronary-event rates across the WHO MONICA Project populations. Lancet. 2000;355:675-687.
55. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L, INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937-952.
56. Wong ND. Epidemiological studies of CHD and the evolution of preventive cardiology. Nat Rev Cardiol. 2014;11:276-289.
57. Stamler J, Daviglus ML, Garside DB, Dyer AR, Greenland P, Neaton JD. Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. JAMA. 2000;284:311-318.
58. Strong A, Rader DJ. Clinical Implications of Lipid Genetics for Cardiovascular Disease. Curr Cardiovasc Risk Rep. 2010;4:461-468.
59. Zhang Y, Vittinghoff E, Pletcher MJ, Allen NB, Zeki Al Hazzouri A, Yaffe K, Balte PP, Alonso A, Newman AB, Ives DG, et al. Associations of blood pressure and cholesterol levels during young adulthood with later cardiovascular events. J Am Coll Cardiol. 2019;74(3):330-41.

60. Abdullah SM, Defina LF, Leonard D, Barlow CE, Radford NB, Willis BL, Rohatgi A, McGuire DK, de Lemos JA, Grundy SM, et al. Long-term association of low-density lipoprotein cholesterol with cardiovascular mortality in individuals at low 10-year risk of atherosclerotic cardiovascular disease. Circulation. 2018;138(21):2315-25.
61. Virmani R, Robinowitz M, Geer JC, Breslin PP, Beyer JC, McAllister HA. Coronary artery atherosclerosis revisited in Korean war combat casualties. Arch Pathol Lab Med. 1987;111(10):972-6.
62. McNamara JJ, Molot MA, Stremple JF, Cutting RT. Coronary artery disease in combat casualties in Vietnam. JAMA. 1971;216(7):1185-7.
63. Joseph A, Ackerman D, Talley JD, Johnstone J, Kupersmith J. Manifestations of coronary atherosclerosis in young trauma victims-an autopsy study. J Am Coll Cardiol. 1993;22(2):459-67.
64. Enos WF Jr, Beyer JC, Holmes RH. Pathogenesis of coronary disease in American soldiers killed in Korea. J Am Med Assoc. 1955;158(11):912-4.
65. Miettinen TA, Gylling H. Mortality and cholesterol metabolism in familial hypercholesterolemia. Long-term follow-up of 96 patients. Arteriosclerosis. 1988;8(2):163-7.
66. Keys AB. Seven countries: a multivariate analysis of death and coronary heart disease. Cambridge, Mass: Harvard University Press; 1980.
67. An epidemiological study of cardiovascular and cardiopulmonary disease risk factors in four populations in the People's Republic of China. Baseline report from the P.R.C.-U.S.A. Collaborative Study. People's Republic of China-United States Cardiovascular and Cardiopulmonary Epidemiology Research Group. Circulation. 1992;85:1083-1096.
68. 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.
69. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, W Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH. 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.
70. Collins R, Armitage J, Parish S, Sleigh P, Peto R for the Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:7-22.
71. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Östergren J. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavi an Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003;361:1149-1158.
72. Pedersen TR, Faergeman O, Kastelein JJP, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendiksen FS, Lindahl C, Szarek M, Tsai J, Group for the ID in EPTALL (IDEAL) S. High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction: The IDEAL Study: A Randomized Controlled Trial. JAMA. 2005;294:2437-2445.
73. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. N Engl J Med. 2004;350:1495-1504.
74. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart J-C, Gotto AM, Greten H, Kastelein JJP, Shepherd J, Wenger NK. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. N Engl J Med. 2005;352:1425-1435.
75. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO, Wun C-C, Davis BR, Braunwald E. The Effect of Pravastatin on Coronary Events after Myocardial Infarction in Patients with Average Cholesterol Levels. N Engl J Med. 1996;335:1001-1009.
76. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015;372:2387-2397.
77. 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;376:1713-22.
78. 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 JF, Tricoci P, White HD, Zeiher AM; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med. 2018;379:2097-107.
79. Robinson JG, Stone NJ. Identifying Patients for Aggressive Cholesterol Lowering: The Risk Curve Concept. Am J Cardiol. 2006;98:1405-1408.
80. Ridker PM, Mora S, Rose L. Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. Eur Heart J. 2016;37:1373-1379.
81. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004;291:1071-80.
82. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006;295:1556-65.
83. Tsujita K, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K, et al. Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention: The Multicenter Randomized Controlled PRECISE-IVUS Trial. J Am Coll Cardiol. 2015 ; 66:495-507.

84. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJP, et al. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. JAMA. 2016;316:2373-84.
85. Huxley RR, Barzi F, Lam TH, Czernichow S, Fang X, Welborn T, et al. Isolated low levels of high-density lipoprotein cholesterol are associated with an increased risk of coronary heart disease: An individual participant data meta-analysis of 23 studies in the asia-pacific region. Circulation. 2011;124(19):2056-64.
86. Bartlett J, Predazzi IM, Williams SM, Bush WS, Kim Y, Havas S, et al. Is isolated low high-density lipoprotein cholesterol a cardiovascular disease risk factor? Circ Cardiovasc Qual Outcomes. 2016;9(3):206-12.
87. Nam GE, Huh Y, Jung J-H, Han K, Kim SM. Association of High-Density Lipoprotein Cholesterol Phenotypes with the Risk of Cardiovascular Diseases and Mortality: A Cohort Study in Korea. Endocrinol Metab. 2022;37(2):261-71.
88. Harrison SC, Holmes MV, Humphries SE. Mendelian randomisation, lipids, and cardiovascular disease.Lancet. 2012; 380:543-545.
89. Hoogeveen RC, Ballantyne CM. Residual Cardiovascular Risk at Low LDL: Remnants, Lipoprotein(a), and Inflammation. Clin Chem. 2021;67(1):143-53.
90. Sandesara PB, Virani SS, Fazio S, Shapiro MD. The forgotten lipids: Triglycerides, remnant cholesterol, and atherosclerotic cardiovascular disease risk. Endocr Rev. 2019;40(2):537-57.
91. Holmes M V., Asselbergs FW, Palmer TM, Drenos F, Lanktree MB, Nelson CP, et al. Mendelian randomization of blood lipids for coronary heart disease. Eur Heart J. 2015;36(9):539-50.
92. Klempfner R, Erez A, Sagit BZ, Goldenberg I, Fisman E, Kopel E, et al. Elevated Triglyceride Level Is Independently Associated with Increased All-Cause Mortality in Patients with Established Coronary Heart Disease: wenty-Two-Year Follow-Up of the Bezafibrate Infarction Prevention Study and Registry. Circ Cardiovasc Qual Outcomes. 2016;9(2):100-8.
93. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med. 2019;380(1):11-22.
94. Peterson BE, Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, et al. Treatment With Icosapent Ethyl to Reduce Ischemic Events in Patients With Prior Percutaneous Coronary Intervention: Insights From REDUCE-IT PCI. J Am Heart Assoc. 2022;11(6).
95. Verma S, Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, et al. Icosapent Ethyl Reduces Ischemic Events in Patients With a History of Previous Coronary Artery Bypass Grafting: REDUCE-IT CABG. Circulation. 2021;144(23):1845-55.
96. Virani S, Morris P, Agarwala A, et al. 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia. J Am Coll Cardiol. 2021 Aug, 78 (9) 960-993.
97. Brunner FJ, Waldeyer C, Ojeda F, et al. Application of Non-HDL Cholesterol for Population-Based Cardiovascular Risk Stratification: Results From the Multinational Cardiovascular Risk Consortium. Lancet 2019; 394 (10215): 2173-2183
98. Liu J., Sempos C., Donahue R.P.: Joint distribution of non-HDL and LDL cholesterol and coronary heart disease risk prediction among individuals with and without diabetes. Diab Care 2005, 28, 8, 1916-1921
99. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, Simes RJ, Durrington P, Hitman GA, Welch KMA, DeMicco DA, Zwinderman AH, Clearfield MB, Downs JR, Tonkin AM, Colhoun HM, Gotto AM, Ridker PM, Kastelein JJP. Association of LDL Cholesterol, Non–HDL Cholesterol, and Apolipoprotein B Levels With Risk of Cardiovascular Events Among Patients Treated With Statins: A Meta-analysis. JAMA. 2012;307:1302-1309.
100. Kastelein JJP, Steeg WA van der, Holme I, Gaffney M, Cater NB, Barter P, Deedwania P, Olsson AG, Boekholdt SM, Demicco DA, Szarek M, LaRosa JC, Pedersen TR, Grundy SM. Lipids, Apolipoproteins, and Their Ratios in Relation to Cardiovascular Events With Statin Treatment. Circulation. 2008;117:3002-3009.
101. van den Berg MJ, van der Graaf Y, de Borst GJ, Kappelle LJ, Nathoe HM, Visseren FLJ, van Petersen R, van Dinther BGF, Algra A, van der Graaf Y, Grobbee DE, Rutten GEHM, Visseren FLJ, de Borst GJ, Kappelle LJ, Leiner T, Nathoe HM. Low-Density Lipoprotein Cholesterol, Non–High-Density Lipoprotein Cholesterol, Triglycerides, and Apolipoprotein B and Cardiovascular Risk in Patients With Manifest Arterial Disease. Am J Cardiol. 2016;118:804–810.
102. Mora S, Glynn RJ, Boekholdt SM, Nordestgaard BG, Kastelein JJP, Ridker PM. On-Treatment Non-HDL Cholesterol, Apolipoprotein B, Triglycerides, and Lipid Ratios in Relation to Residual Vascular Risk after Treatment with Potent Statin Therapy: The JUPITER Trial. J Am Coll Cardiol. 2012;59:1521-1528.
103. Arsenault BJ, Rana JS, Stroes ESG, Després J-P, Shah PK, Kastelein JJP, Wareham NJ, Boekholdt SM, Khaw K-T. Beyond Low-Density Lipoprotein Cholesterol: Respective Contributions of Non-High-Density Lipoprotein Cholesterol Levels, Triglycerides, and the Total Cholesterol/High-Density Lipoprotein Cholesterol Ratio to Coronary Heart Disease Risk in Apparently Healthy Men and Women. J Am Coll Cardiol. 2009;55:35-41.
104. Robinson J. G., Wang S. Smith B.J. et al.: Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. J Am Coll Cardiol. 2009, 53, 316-322
105. Lorenzatti A, Toth PP. New Perspectives on Atherogenic Dyslipidaemia and Cardiovascular Disease. European Cardiology Review 2020;15:e04.
106. Ugovšek S, Šebeštjen M. Lipoprotein(A)-the crossroads of atherosclerosis, atherothrombosis and inflammation. Biomolecules. 2022;12(1):1-14.
107. Reyes-Soffer G, Ginsberg HN, Berglund L, Duell PB, Heffron SP, Kamstrup PR, et al. Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement from the American Heart Association. Arterioscler Thromb Vasc Biol. 2022;42(1):E48-60.
108. Vathesatogkit P, Woodward M, Tanomsup S, Ratanachaiwong W, Vanavanan S, Yamwong S. et al. Cohort profile: the electricity generating authority of Thailand study. Int J Epidemiol. 2012;41(2):359-365.
109. Ministry of Health. Singapore. Clinical Practice Guidelines. Lipids. 2/2016.December 2016.
110. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General Cardiovascular Risk Profile for Use in Primary Care. Circulation. 2008;117:743-753.
111. Liew SM, Doust J, Glasziou P. Cardiovascular risk scores do not account for the effect of treatment: a review. Heart. 2011;97:689-697

112. Chia YC, Gray SYW, Ching SM, Lim HM, Chinna K. Validation of the Framingham general cardiovascular risk score in a multiethnic Asian population: a retrospective cohort study. BMJ Open. 2015;5:e007324.
113. Selvarajah S, Kaur G, Haniff J, Cheong KC, Hiong TG, van der Graaf Y, Bots ML. Comparison of the Framingham Risk Score, SCORE and WHO/ISH cardiovascular risk prediction models in an Asian population. Int J Cardiol. 2014;176:211-218
114. Chia YC, Lim HM, Ching SM. Does use of pooled cohort risk score overestimate the use of statin?: a retrospective cohort study in a primary care setting. BMC Fam Pract. 2014;15:172.
115. Kasim SS, Ibrahim N, Malek S, Ibrahim KS, Aziz MF et al. Validation of the general Framingham Risk Score (FRS), SCORE2, revised PCE and WHO CVD risk scores in an Asian population.The Lancet. Regional Health Western Pacific. DOI: https://doi.org/10.1016/j.lanwpc.2023.100742
116. Chi G, Lee JJ, Kazmi SHA, Fitzgerald C, Montazerin SM eat al. Early and late recurrent cardiovascular events among high-risk patients with an acute coronary syndrome: Meta-analysis of phase III studies and implications on trial design. Clin Cardiol. 2022 Mar;45(3):299-307
117. Steen DL, Khan I, Andrade K, Koumas A, Giugliano RP. Event Rates and Risk Factors for Recurrent Cardiovascular Events and Mortality in a Contemporary Post Acute Coronary Syndrome Population. JAHA 2022;11:e022198
118. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. Eur Heart J 2015: 36 (19); 1163-1170
119. Miao B, Hernandez AV, Alberts MJ, Mangiafico N, Roman YM, Coleman CI. Incidence and Predictors of Major Adverse Cardiovascular Events in Patients With Established Atherosclerotic Disease or Multiple Risk Factors. JAHA 2020;9:e014402
120. Sposato LA, Lam M, Allen B, Shariff SZ, Saposnik Gand on behalf of the PARADISE Study Group. First-Ever Ischemic Stroke and Incident Major Adverse Cardiovascular Events in 93 627 Older Women and Men. Stroke. 2020;51:387-394
121. Feng W, Hendry RM, Adams RJ. Risk of recurrent stroke, myocardial infarction, or death in hospitalized stroke patients. Neurology. 2010;74:588-593.
122. Mohan KM, Wolfe CDA, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and Cumulative Risk of Stroke Recurrence. Stroke. 2011;42:1489-1494.
123. Soejima H, Ogawa H, Morimoto T, Okada S, Matsumoto C et al for the JPAD Trial. Proteinuria is independently associated with the incidence of primary cardiovascular events in diabetic patients. J of Cardiol 2020; 75 (4): 387-393
124. Dinneen SF, Gerstein HC. The Association of Microalbuminuria and Mortality in Non-Insulin-Dependent Diabetes Mellitus: A Systematic Overview of the Literature. Arch Intern Med. 1997;157:1413-1418.
125. Xu J, Lee ET, Best LG, Begum M, Knowler WC, Fabsitz RR, Howard BV. Association of albuminuria with all-cause and cardiovascular disease mortality in diabetes: the Strong Heart Study. Br J Diabetes Vasc Dis. 2005;5:334–340.
126. Arnold J, Evans JC, Meigs JB, Wang TJ, Fox CS, Levy D, et al. Low-grade albuminuria and incidence of cardiovas cular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. Circulation 2005: 112 : 969-975
127. Yuyun MF, Khaw KT, Luben R, Welch A, Bingham S, Day NE, et al. Microalbuminuria independently predicts all-cause and cardiovascular mortality in a British population: the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. Int J Epidemiol, 2004:33: 189-198
128. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. Circulation 2004: 110: 32-35
129. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. N Engl J Med. 2004;351:1296-1305.
130. Ortiz A, Wanner C, Gansevoort R; ERA Council. Chronic kidney disease as cardiovascular risk factor in routine clinical practice: a position statement by the Council of the European Renal Association. Eur J Prev Cardiol. 2022 Dec 7;29(17):2211-2215
131. Dal Canto E, Ceriello A, Rydén L, et al. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications. European Journal of Preventive Cardiology. 2019;26(2_suppl):25-32.
132. Dorresteijn JA, Visseren FL, Wassink AM, et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. Heart. 2013 Jun;99(12):866-72.
133. De Bacquer D, Ueda P, Reiner Ž, De Sutter J, De Smedt D, Lovic D, Gotcheva N, Fras Z, Pogosova N, Mirrakhimov E, Lehto S, Jernberg T, Kotseva K, Rydén L, Wood D, De Backer G; EUROASPIRE IV and V National Coordinators. Prediction of recurrent event in patients with coronary heart disease: the EUROASPIRE Risk Model. Eur J Prev Cardiol. 2022 Mar 11;29(2):328-339.
134. 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.
135. Tonelli M, Lloyd A, Clement F, Conly J, Husereau D, Hemmelgarn B, Klarenbach S, McAlister FA, Wiebe N, Manns B. Efficacy of statins for primary prevention in people at low cardiovascular risk: a meta-analysis. Can Med Assoc J. 2011;183(16): e1189-e1202.
136. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D et al.for the HOPE-3 Investigators. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. N Engl J Med 2016; 374:2021-2031

137. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation 2005;111:3384-90
138. Kucharska-Newton AM, Stoner L, Meyer ML. Determinants of Vascular Age: An Epidemiological Perspective. Clin Chem. 2019 Jan;65(1):108-118
139. Bruno RM, Nilsson PM, Engström G, Wadström BN, Empana J-P et al. Early and Supernormal Vascular Aging. Clinical Characteristics and Association With Incident Cardiovascular Events. Hypertension. 2020;76:1616-1624
140. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD et al. 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
141. Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk.The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J 2020: 41:111-188
142. Lloyd-Jones DM, Nam B-H, Ralph B. D'Agostino S, Levy D, Murabito JM, Wang TJ, Wilson PWF, O'Donnell CJ. Parental Cardiovascular Disease as a Risk Factor for Cardiovascular Disease in Middle-aged Adults: A Prospective Study of Parents and Offspring. JAMA. 2004;291:2204-2211.
143. Murabito JM, Pencina MJ, Nam B-H, D'Agostino RB, Wang TJ, Lloyd-Jones D, Wilson PWF, O'Donnell CJ. Sibling Cardiovascular Disease as a Risk Factor for Cardiovascular Disease in Middle-aged Adults. JAMA. 2005;294:3117-3123.
144. Jousilahti P, Puska P, Vartiainen E, Pekkanen J, Tuomilehto J. Parental history of premature coronary heart disease: An independent risk factor of myocardial infarction. J Clin Epidemiol. 1996;49:497-503.
145. Marenberg ME, Risch N, Berkman LF, Floderus B, de Faire U. Genetic Susceptibility to Death from Coronary Heart Disease in a Study of Twins. N Engl J Med. 1994;330:1041-1046.
146. Chow CK, Islam S, Bautista L, Rumboldt Z, Yusufali A, Xie C, Anand SS, Engert JC, Rangarajan S, Yusuf S. Parental History and Myocardial Infarction Risk Across the World. J Am Coll Cardiol. 2011;57:619-627.
147. Kolossváry M, Mayrhofer T, Ferencik M, Karády J, Pagidipati NJ et al. Are risk factors necessary for pretest probability assessment of coronary artery disease? A patient similarity network analysis of the PROMISE trial. J Cardiovascular Computed Tomography 2022: 16(5) :397-403
148. Alashi A, Lang R, Seballos R, et al. Reclassification of coronary heart disease risk in a primary prevention setting: traditional risk factor assessment vs. coronary artery calcium scoring. Cardiovasc Diagn Ther 2019;9:214-20.
149. Erbel R, Möhlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, Dragano N, Grönemeyer D, Seibel R, Kälsch H, Bröcker-Preuss M, Mann K, Siegrist J, Jöckel K-H, Heinz Nixdorf Recall Study Investigative Group. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. J Am Coll Cardiol. 2010;56:1397–1406.
150. McClelland RL, Jorgensen NW, Budoff M, Blaha MJ, Post WS, Kronmal RA, Bild DE, Shea S, Liu K, Watson KE, Folsom AR, Khera A, Ayers C, Mahabadi A-A, Lehmann N, Jöckel K-H, Moebus S, Carr JJ, Erbel R, Burke GL. 10-Year Coronary Heart Disease Risk Prediction Using Coronary Artery Calcium and Traditional Risk Factors: Derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) With Validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study). J Am Coll Cardiol. 2015;66:1643-1653.
151. Peters SAE, den Ruijter HM, Bots ML, Moons KGM. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. Heart Br Card Soc. 2012;98:177-184.
152. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM et al. Common carotid intimamedia thickness measurements in cardiovascular risk prediction: a meta-analysis.JAMA 2012;308:796-803.
153. Dar T, Radfar A, Abohashem S, Pitman RK, Tawakol A, Osborne MT. Psychosocial Stress and Cardiovascular Disease. Curr Treat Options Cardiovasc Med. 2019 Apr 26;21(5):23.
154. Santosa A, Rosengren A, Ramasundarahettige C, et al. Psychosocial Risk Factors and Cardiovascular Disease and Death in a Population-Based Cohort From 21 Low-, Middle-, and High-Income Countries. JAMA Netw Open. 2021;4(12):e2138920
155. Levine GN. Psychological Stress and Heart Disease: Fact or Folklore? Am J Med 2022: 135 (6) : 688-696
156. Higueras-Fresnillo S, Cabanas-Sanchez V, Lopez-Garcia E, Esteban-Cornejo I, Banegas JR et al. Physical Activity and Association Between Frailty and All-Cause and Cardiovascular Mortality in Older Adults: Population-Based Prospective Cohort Study. J Am Geriatr Soc 2018;66:20972103.
157. Vaes B, Depoortere D, Van Pottelbergh G, Mathei C, Neto J, Degryse J. Association between traditional cardiovascular risk factors and mortality in the oldest old: untangling the role of frailty. BMC Geriatr 2017;17:234.
158. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJP, Komajda M, Lopez-Sendon J, Mosca L, Tardif J-C, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B. Effects of Torcetrapib in Patients at High Risk for Coronary Events. N Engl J Med. 2007;357:2109-2122.
159. Cannon CP, Shah S, Dansky HM, Davidson M, Brinton EA, Gotto AMJ, Stepanavage M, Liu SX, Gibbons P, Ashraf TB, Zafarino J, Mitchel Y, Barter P. Safety of Anacetrapib in Patients with or at High Risk for Coronary Heart Disease. N Engl J Med. 2010;363:2406-2415.
160. The HPS2-THRIVE Collaborative Group. Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients. N Engl J Med. 2014;371:203-212.
161. Ministry of Health Malaysia. Clinical Practice Guidelines. Primary and Secondary Prevention of Cardiovascular Disease 2017, 1 st Ed.
162. Shahar S, Fakhruddin NNINM, Hui KJ,Suhaimi NFS,Zulkepli NYF et al. Family Support and Self-Motivation Influence Dietary Compliance and Glycaemic Control among Type 2 Diabetes Mellitus Outpatients. M J Health Sciences 2016: 14: 39-47

163. Evidence Analysis Library. Academy of Nutrition and Dietetics. Disoders of Lipid Metabolism. Executive Summary of Recommendations 2011. Available at https://www.andeal.org/
164. Sikand G, Kashyap ML, Yang I. Medical nutrition therapy lowers serum cholesterol and saves medication costs in men with hypercholesterolemia. J Am Diet Assoc. 1998; 98: 889-894.
165. Henkin Y, Shai I, Zuk R, Brickner D, Zuilli I, Neumann L, Shany S. Dietary treatment of hypercholesterolemia: do dietitians do it better? A randomized, controlled trial. Am J Med. 2000 Nov;109(7):549-55.
166. Lichtenstein AH, Appel LJ, Vadiveloo M, et al., on behalf of the American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; and Stroke Council. 2021 Dietary Guidance to Improve Cardiovascular Health: A Scientific Statement From the American Heart Association. Circulation 2021. 144:e472-e487.
167. Krittanawong C, Isath A, Hahn J, Wang Z, Narasimhan B, Kaplin SL, Jneid H, Virani SS, Tang WHW. Fish consumption and cardiovascular health: a systematic review.Am J Med. 2021; 134:713-720
168. Belin RJ, Greenland P, Martin L, Oberman A, Tinker L, Robinson J, Larson J, Van Horn L, Lloyd-Jones D. Fish intake and the risk of incident heart failure: the Women's Health Initiative. Circ Heart Fail. 2011 Jul;4(4):404-13.
169. NurSyahirah, S, Rozzamri A. Effects of frying on fish, fish products and frying oil - a review. Food Research 2022: 6 (5):14 - 32
170. Mukuddem-Petersen J, Oosthuizen W, Jerling JC. A systematic review of the effects of nuts on blood lipid profiles in humans. 2005. In: Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]. York (UK): Centre for Reviews and Dissemination (UK); 1995-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK72156/
171. Sabaté J, Oda K, Ros E. Nut Consumption and Blood Lipid Levels: A Pooled Analysis of 25 Intervention Trials. Arch Intern Med. 2010;170(9):821-827
172. Becerra-Tomás N, Paz-Graniel I, Kendall CWC, Kahleova H, Rahelić D, Sievenpiper JL, Salas-Salvadó J. Nut consumption and incidence of cardiovascular diseases and cardiovascular disease mortality: a meta-analysis of prospective cohort studies.Nutr Rev. 2019; 77:691-709
173. Kim Y, Keogh JB, Clifton PM. Does nut consumption reduce mortality and/or risk of cardiometabolic disease? An updated review based on meta-analyses.Int J Environ Res Public Health. 2019; 16:4957
174. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med. 2018;378:e34.
175. Tharrey M, Mariotti F, Mashchak A, et al. Patterns of plant and animal protein intake are strongly associated with cardiovascular mortality: the Adventist Health Study-2 cohort. Int J Epidemiol. 2018;47:1603-12.
176. Van Horn L, Carson JAS, Appel LJ, et al. Recommended dietary pattern to achieve adherence to the American Heart Association/American College of Cardiology (AHA/ACC) guidelines: a scientific statement from the American Heart Association. Circulation.2016;134:e505-29.
177. Rimm EB, Appel LJ, Chiuve SE, et al. Seafood long-chain n-3 polyunsaturated fatty acids and cardiovascular disease: a science advisory from the American Heart Association. Circulation. 2018;138:e35-47.
178. Song M, Fung TT, Hu FB, et al. Association of animal and plant protein intake with all-cause and cause-specific mortality. JAMA Intern Med. 2016;176:1453-63.
179. United States Department of Agriculture. Scientific Report of the 2015 Dietary Guidelines Advisory Committee [Internet]. 2015 [cited 2016 Dec 23]. Available from: https://health.gov/dietaryguidelines/2015-scientific-report/pdfs/scientific-report-of-the-2015-dietary-guidelines-advisory-committee.pdf
180. Soliman GA. Dietary Cholesterol and the Lack of Evidence in Cardiovascular Disease. Nutrients. 2018;10(6):780. Published 2018 Jun 16. doi:10.3390/nu10060780
181. Kanter MM, Kris-Etherton PM, Fernandez ML, Vickers KC, Katz DL. Exploring the Factors That Affect Blood Cholesterol and Heart Disease Risk: Is Dietary Cholesterol as Bad for You as History Leads Us to Believe? Adv Nutr Int Rev J. 2012;3:711-717.
182. Carson JAS, Lichtenstein AH, Anderson CAM, Appel LJ, Kris-Etherton PM et al. Dietary Cholesterol and Cardiovascular Risk: A Science Advisory From the American Heart Association. Circulation. 2020;141:e39-e53
183. National Coordinating Committee on Food and Nutrition. Ministry of Health Malaysia . RNI Recommended Nutrient Intakes for Malaysia. A report of the technical Working Group on Nutritional Guideline. 2017.
184. Mestrovic T. Oils-Rich-in-Linoleic-Acid. Available at www.news-medical.net/health/Oils-Rich-in-Linoleic-Acid.aspx.Accessed on 1st April 2017
185. Kostik V, Memeti S , Bauer B. Fatty Acid composition of Edible Oils and Fats. J Hygienic Engineering and Design .UDC 664.3:577.115.3: 112-116
186. Harris WS. Omega-3 fatty acids. In: Coates PM, Betz JM, Blackman MR, et al., eds. Encyclopedia of Dietary Supplements. 2nd ed. London and New York: Informa Healthcare; 2010:577-86
187. Byelashov OA, Sinclair AJ, Kaur G. Dietary sources, current intakes, and nutritional role of omega-3 docosapentaenoic acid. Lipid Technol. 2015 Apr; 27: 79-82.
188. Muhamad NA, Mohamad J. Fatty acids composition of selected Malaysian fishes (Komposisi asid lemak ikan terpilih Malaysia). Sains Malays. 2012;41:81-94.
189. Ng TKW. Omega-3 Fatty Acids: Potential Sources in the Malaysian Diet with the Goal Towards Achieving Recommended Nutrient Intakes. Mal J Nutr 2006; 12: 181-188, 2006
190. Jones PJH, Papamandjaris AA. Lipids: cellular metabolism. In: Erdman JW, Macdonald IA, Zeisel SH, eds. Present Knowledge in Nutrition. 10th ed. Washington, DC: Wiley-Blackwell; 2012:132-48.
191. Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, Creager MA et al. American Heart Association. Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association. Circulation 2017;136:e1e23.
192. Evidence Analysis Library. Academy of Nutrition and Dietetics. Disoders of Lipid Metabolism. Saturated Fats. Executive Summary of Recommendations 2023. Available at https://www.andeal.org/.Accessed on 20th March 2023

193. Steur M, Johnson L, Sharp SJ, Imamura F et al. Dietary Fatty Acids, Macronutrient Substitutions, Food Sources and Incidence of Coronary Heart Disease: Findings From the EPIC-CVD Case-Cohort Study Across Nine European Countries. Journal of the American Heart Association. 2021;10:e019814
194. de Souza RJ, Mente A, Maroleanu A, Cozma AI, Ha V, Kishibe T, Uleryk E, Budylowski P, Schünemann H, Beyene J, Anand SS. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. BMJ. 2015;351:h3978
195. Bergeron N, Chiu S, Williams PT, Sarah MK,Krauss RM. Effects of red meat, white meat, and nonmeat protein sources on atherogenic lipoprotein measures in the context of low compared with high saturated fat intake: a randomized controlled trial. Am J Clin Nutr 2019;110:24-33
196. Boren J, Chapman MJ, Krauss RM, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2020;41: 2313-30.
197. Grasgruber P, Sebra M, Hrazdira E, Hrebickova S, Cacek J. Food consumption and the actual statistics of cardiovascular disease: an epidemiological comparison of 42 European countries. Food Nutr Res. 2016;60:31694.
198. Dhghan M, Mente A, Zhang X, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Lancet. 2017;S0140-6736(17):1-13.
199. Astrup A, Magkos F, Bier DM et al. Saturated fats and health: a reassessment and proposal for food-based recommendations: JACC state-of-the-art review. J Am Coll Cardiol. 2020; 76: 844-857
200. Hooper L, Martin N, Jimoh OF, et al. Reduction in saturated fat intake for cardiovascular disease. Cochrane Database Syst Rev 2020; 5:CD011737.
201. Bajželj B, Laguzzi F, Röös E. The role of fats in the transition to sustainable diets. The Lancet, Planetary Health. Open Access. Published September, 2021. DOI:https://doi.org/10.1016/S2542-5196(21)00194-7
202. U.S. Department of Agriculture and U.S. Department of health and Human Services. Dietary Guidelines for Americans, 2020-2025. 9th Ed. https://www.dietaryguidelines.gov. Published 2020. Accessed March 20, 2023.
203. Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Trans fatty acids and cardiovascular disease. N Engl J Med. 2006;354:1601-1613
204. Szabo Z, Marosvölgyi T, Szabo E, Koczka V, Verzar Z, Figler M, Decsi T. Effects of Repeated Heating on Fatty Acid Composition of Plant-Based Cooking Oils. Foods. 2022 Jan 12;11(2):192.
205. Brühl, Ludger. Fatty acid alterations in oils and fats during heating and frying. Eur J Lipid Science and Technology. 2014: 116. 10.1002/ejlt.201300273.
206. Salmeron J, Hu FB, Manson JE, Stampfer MJ, Colditz GA, Rimm EB, Willett WC. Dietary fat intake and risk of type 2 diabetes in women. Am J Clin Nutr. 2001;73:1019–1026
207. Cahill LE, Pan A, Chiuve SE, Sun Q, Willett WC, Hu FB, Rimm EB. Fried-food consumption and risk of type 2 diabetes and coronary artery disease: a prospective study in 2 cohorts of US women and men. Am J Clin Nutr. 2014; 100:667-75.
208. Odegaard AO, Koh WP, Yuan JM, Gross MD,Pereira MA. Western-style fast food intake and cardiometabolic risk in an Eastern country. Circulation2012;126:182-8.
209. Bendsen NT, Christensen R, Bartels EM, Astrup A. Consumption of industrial and ruminant trans fatty acids and risk of coronary heart disease: a systematic review and meta-analysis of cohort studies. Eur J Clin Nutr. 2011;65:773-783.
210. Mozaffarian D, Clarke R. Quantitative effects on cardiovascular risk factors and coronary heart disease risk of replacing partially hydrogenated vegetable oils with other fats and oils. Eur J Clin Nutr. 2009;63 Suppl 2:S22-33.
211. Karupaiah T, Tan HK, Ong WW, Tan CH, Sundram K.2014. Trans fatty acid content in Malaysian supermarket foods: a field-to-laboratory approach in assessing food risk, Food Additives & Contaminants: Part A, 2014: 31(8). DOI: 10.1080/19440049.2014.929183.
212. Jenkins DJA , Dehghan M, Mente A, Bangdiwala SI, Rangarajan S et al., for the PURE Study Investigators* et al. Glycemic index, glycemic load, and cardiovascular disease and mortality. N Engl J Med 2021; 384:1312-1322.
213. McKeown NM, Meigs JB, Liu S, Rogers G, Yoshida M, Saltzman E, Jacques PF. Dietary carbohydrates and cardiovascular disease risk factors in the Framingham offspring cohort. J Am Coll Nutr. 2009 Apr;28(2):150-8.
214. Berger, Amya; Thorn, Ericb. Can low-carbohydrate diets be recommended for reducing cardiovascular risk?. Current Opinion in Endocrinology & Diabetes and Obesity 2022; 29(5): 413-419.
215. Evert, A. B. , Dennison, M. , Gardner, C. D. , Garvey, T. W. , Lau, K. H. et al. Diabetes Care. 2019: 42 (5), 731-754.
216. Joshua J. Joseph JJ, Deedwania P, Acharya T, Aguilar D, Bhatt DL et al. on behalf of the American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Clinical Cardiology; and Council on Hypertension. Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes: A Scientific Statement From the American Heart Association Circulation. 2022;145:e722-e759.
217. Hyde PN, Sapper TN, Crabtree CD, et al. Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss. JCI Insight 2019; 4:e128308.
218. Hansen CD, Gram-Kampmann E-M, Hansen JK, Hugger MB, Madsen, BS et al. Effect of Calorie-Unrestricted Low-Carbohydrate, High-Fat Diet Versus High-Carbohydrate, Low-Fat Diet on Type 2 Diabetes and Nonalcoholic Fatty Liver Disease. Ann Int Med: 2023; https://doi.org/10.7326/M22-1787.
219. Unwin D, Khalid AA, Unwin J, et al. Insights from a general practice service evaluation supporting a lower carbohydrate diet in patients with type 2 diabetes mellitus and prediabetes: a secondary analysis of routine clinic data including HbA1c, weight and prescribing over 6 years. BMJ Nutr Prev Health 2020; 3:285-294.
220. Athinarayanan SJ, Hallberg SJ, McKenzie AL, et al. Impact of a 2-year trial of nutritional ketosis on indices of cardiovascular disease risk in patients with type 2 diabetes. Cardiovasc Diabetol 2020; 19:208.
221. Bhanpuri NH, Hallberg SJ, Williams PT, et al. Cardiovascular disease risk factor responses to a type 2 diabetes care

model including nutritional ketosis induced by sustained carbohydrate restriction at 1 year: an open label, nonrand omized, controlled study. Cardiovasc Diabetol 2018; 17:56.
222. Fung TT,van Dam RM,Hankinson SE,Stampfer M, Willet WC,Hu FB. Low-carbohydrate diets and all-cause and cause-specific mortality: Two cohort Studies. Ann Intern Med. 2010 Sep 7; 153(5): 289-298.
223. Naude CE, Brand A, Schoonees A, Nguyen KA, Chaplin M, Volmink J. Low-carbohydrate versus balanced-carbohydrate diets for reducing weight and cardiovascular risk. Cochrane Database of Systematic Reviews 2022, Issue 1. Art. No.: CD013334
224. Iatan J et al. Low-Carbohydrate High-Fat "Keto-Like" Diet Associated With Increased Risk of CVD.Presented at the ACC Annual Scientific Session, March 2023
225. Feinman RD, Pogozelski WK, Astrup A, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutrition2015;31:1-13.
226. Hu Y, Liu G, Yu E, Wang B, Wittenbecher C et al. Low-Carbohydrate Diet Scores and Mortality Among Adults With Incident Type 2 Diabetes," Diabetes Care, April 2023, doi: 10.2337/dc22-2310
227. Crosby L, Davis B, Joshi S, Jardine M, Paul J et al. Ketogenic Diets and Chronic Disease: Weighing the Benefits Against the Risks. Front. Nutr.2021: 8: https://doi.org/10.3389/fnut.2021.702802
228. Krauss RM, Blanche PJ, Rawlings RS, Fernstrom HS, Williams PT: Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. Am J Clin Nutr 2006,83(5):1025-1031.
229. Westman EC, Mavropoulos J, Yancy WS, Volek JS: A review of low carbohydrate ketogenic diets. Curr Atheroscler Rep 2003, 5(6):476-483.
230. Volek JS, Sharman MJ, Forsythe CE: Modification of lipoproteins by very low-carbohydrate diets. J Nutr 2005, 135(6):1339-1342
231. Feinmann RD, Volek JS. Low carbohydrate diets improve atherogenic dyslipidemia even in the absence of weight loss. Nutrition & Metabolism 2006, 3:24
232. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, et al., Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med. 2008;359:229-241.
233. Santos FL, Esteves SS, da Costa Pereira A, Yancy WS, Nunes JPL. Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. Obes Rev. 2012;13:1048-1066.
234. Hu T, Mills KT, Yao L, Demanelis K, Eloustaz M, Yancy WS Jr, Kelly TN, He J, Bazzano LA. Effects of low-carbohy drate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials. Am J Epidemiol. 2012 Oct 1;176 Suppl 7(Suppl 7):S44-54
235. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001;344:3-10.
236. Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). BMJ.2007;334:885-8.
237. He FJ, Tan M, Ma Y, MacGregor GA. Salt Reduction to Prevent Hypertension and Cardiovascular Disease: JACC State-of-the-Art Review. J Am Coll Cardiol2020;75:632-647.
238. Micha R, Penalvo JL, Cudhea F, et al. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. JAMA. 2017;317:912-924.
239. Piano MR. Alcohol's effect on the cardiovascular system. Alcohol Res 2017:38(2): 219-241.
240. Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, et al. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. Arch Intern Med. 2006;166:2437-2445.
241. Toffolo M., Aguiar-Nemer A., Silva-Fonseca V. Alcohol: Effects on Nutritional Status, Lipid Profile and Blood Pressure. Journal of Endocrinology and Metabolism, North America, 2, Jan. 2013. Available at: https://www.jofem.org/index.php/jofem/article/view/150/177>. Date accessed: 25 Mar. 2023.
242. Sattelmair J, Pertman J, Ding EL, Kohl HW, Haskell W, Lee I-M. Dose Response Between Physical Activity and Risk of Coronary Heart Disease: A Meta-Analysis. Circulation. 2011;124:789-795.
243. Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose–response meta-analysis of cohort studies. Int J Epidemiol. 2011;40:1382-1400.
244. Löllgen H, Böckenhoff A, Knapp G. Physical Activity and All-cause Mortality: An Updated Meta-analysis with Different Intensity Categories. Int J Sports Med. 2009;30:213-224.
245. Vanhees L, Geladas N, Hansen D, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors: recommendations from the EACPR. Part II. Eur J Prev Cardiol. 2012;19(5):1005-1033.
246. Pattyn N, Cornelissen VA, Eshghi SR, et al. The effect of exercise on the cardiovascular risk factors constituting the metabolic syndrome: a meta-analysis of controlled trials. Sports Med. 2013;43(2):121-133.
247. Mann S, Beedie C, Jimenez A. Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: review, synthesis and recommendations. Sports Med. 2014 Feb;44(2):211-21.
248. Kelley GA, Kelley KS, Franklin B. Aerobic Exercise and Lipids and Lipoproteins in Patients With Cardiovascular Disease. J Cardpulm Rehabil. 2006;26:131-144.
249. Kelley GA, Kelley KS, Vu Tran Z. Aerobic exercise, lipids and lipoproteins in overweight and obese adults: a meta-analysis of randomized controlled trials. Int J Obes. 2005;29:881-893.
250. Kodama S, Tanaka S, Saito K, et al. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. Arch Intern Med. 2007;167:999-1008.
251. Banz W, Maher M, Thompson W, et al. Effects of resistance versus aerobic training on coronary artery disease risk factors. Exp Biol Med (Maywood) 2003;228(4):434-440.

252. Kelley GA, Kelley KS. Impact of progressive resistance training on lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. Prev. Med. 2009; 48: 9-19.
253. Magkos F. Basal very low-density lipoprotein metabolism in response to exercise: Mechanisms of hypotriacylglycerolemia. Prog Lipid Res. 2009;48:171-190.
254. Alvarez-Jimenez L, Moreno-Cabañas A, Ramirez-Jimenez M, Morales-Palomo F, Ortega JF, Mora-Rodriguez R. Effectiveness of statins vs. exercise on reducing postprandial hypertriglyceridemia in dyslipidemic population: A systematic review and network meta-analysis. J Sport and Health Science 2022; 11 (5); 567-577
255. Visseren FLJ, Mach FO, Smulders YM, Carballo D, Koskinas KC et al for the ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies. With the special contribution of the European Association of Preventive Cardiology (EAPC). Eur J Preventive Cardiol 2022: 29: 5-115
256. Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK, American College of Sports Medicine. American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. Med Sci Sports Exerc. 2009;41:459-471
257. Kiriyama H, Kaneko H, Itoh H, Kamon T, Mizuno Y et al. Association between changes in body weight and lipid profile in the general population: a community-based cohort study, Eur Heart J - Quality of Care and Clinical Outcomes 2021: 7(1): 109-110
258. Feingold KR. Obesity and Dyslipidemia. [Updated 2020 Nov 2]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK3058
259. A. Poobalan, L. Aucott, W. C. S. Smith, A. Avenell, R. Jung, J. Broom, A. M. Grant. Effects of weight loss in overweight/obese individuals and long-term lipid outcomes - a systematic review. Obesity Reviews 2004: 5(1):43-50.
260. United States Public Health Service Office of the Surgeon General; National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health.Washington (DC): US Department of Health and Human Services; 2020.
261. Jain RB, Ducatman A. Associations between smoking and lipid/lipoprotein concentrations among US adults aged ≥ 20 years. J Circ Biomark. 2018 May 31;7:184945441877931.
262. Chun, W., Sano, A., Nishida, H., Urano, S., Sakagami, K. (2000). Effect of cigarette smoking on lipid profile: Analysis of mass screening of 29 519 middle-aged Japanese men. In: Lu, R., Mackay, J., Niu, S., Peto, R. (eds) Tobacco: The Growing Epidemic. Springer, London. https://doi.org/10.1007/978-1-4471-0769-9_51.
263. Gepner AD, Piper ME, Johnson HM, Fiore MC, Baker TB, Stein JH. Effects of smoking and smoking cessation on lipids and lipoproteins: Outcomes from a randomized clinical trial. Am Heart J. 2011;161:145-151.
264. Maeda K, Noguchi Y, Fukui T. The effects of cessation from cigarette smoking on the lipid and lipoprotein profiles: a meta-analysis. Prev Med. 2003;37:283-290.
265. Forey, B.A., Fry, J.S., Lee, P.N. et al. The effect of quitting smoking on HDL-cholesterol - a review based on within-subject changes. Biomark Res 1, 26 (2013). https://doi.org/10.1186/2050-7771-1-26
266. Naci H, Brugts JJ, Fleurence R, Tsoi B, Toor H, Ades AE. Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. Eur J Prev Cardiol 2013;20:641657.
267. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, Raichlen JS, Uno K, Borgman M, Wolski K, Nissen SE. Effect of Two Intensive Statin Regimens on Progression of Coronary Disease. N Engl J Med. 2011;365:2078-2087.
268. Shin S, Park H-B, Chang H-J, Arsanjani R, Min JK, Kim Y-J, Lee BK, Choi J-H, Hong G-R, Chung N. Impact of Intensive LDL Cholesterol Lowering on Coronary Artery Atherosclerosis Progression: A Serial CT Angiography Study. JACC Cardiovasc Imaging. 2016;10.1016/j.jcmg.2016.04.013
269. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S76-S99
270. 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.
271. Khera AV, Everett BM, Caulfield MP, Hantash FM, Wohlgemuth J, Ridker PM, Mora S. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). Circulation 2014;129:635-642.
272. Tsimikas S, Witztum JL, Miller ER, Sasiela WJ, Szarek M, Olsson AG, Schwartz GG; Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. High-dose atorvastatin reduces total plasma levels of oxidized phospholipids and immune complexes present on apolipoprotein B-100 in patients with acute coronary syndromes in the MIRACL trial. Circulation 2004;110:1406-1412.
273. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. Circulation 2004;109:III39-III43.
274. Oesterle A, Laufs U, Liao JK. Pleiotropic effects of statins on the cardiovascular system. Circ Res 2017;120:229-243
275. Plakogiannis R, Cohen H. Optimal low-density lipoprotein cholesterol lowering-morning versus evening statin administration. Ann Pharmacother. 2007;41:106-110.
276. Kaur G, Phillips CL, Wong K, McLachlan AJ, Saini B. Timing of Administration: For Commonly-Prescribed Medicines in Australia. Pharmaceutics. 2016 Apr 15;8(2). pii: E13. doi: 10.3390/pharmaceutics8020013
277. Tharavanij T, Wongtanakarn S, Lerdvuthisopon N, Teeraaunkul S, Youngsriphithak P, Sritipsukho P. Lipid lowering efficacy between morning and evening simvastatin treatment: a randomized double-blind study. J Med Assoc Thai 2010;93((Suppl 7)):S109-S113.

278. Lund TM, Tors ik H, Falch D, Christophersen B, Skardal R, Gullestad L. Effect of morning versus evening intake of simvastatin on the serum cholesterol level in patients with coronary artery disease. Am J Cardiol 2002;90:784-6.
279. Haffner S, Orchard T, Stein E, Schmidt D, LeBelle P. Effect of simvastatin on Lp(a) concentrations. Clin Cardiol 1995:18:261-7.
280. Wallace A, Chinn D, Rubin G. Taking simvastatin in the morning compared with in the evening; randomised controlled trial. BMJ. 2003 ; 327(7418): 788
281. Saito Y, Yoshida S, Nakaya N, Hata Y, Goto Y. Comparison between morning and evening doses of simvastatin in hyperlipidemic subjects: A double-blind comparative study. Arterioscler Thromb 1991;11:816-189
282. Weng T-C, Yang Y-HK, Lin S-J, Tai S-H. A systematic review and meta-analysis on the therapeutic equivalence of statins. J Clin Pharm Ther. 2010;35:139-151
283. Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarenco P, Pedersen TR, LaRosa JC, Waters DD, DeMicco DA, Simes RJ, Keech AC, Colquhoun D, Hitman GA, Betteridge DJ, Clearfield MB, Downs JR, Colhoun HM, Gotto Jr. AM, Ridker PM, Grundy SM, Kastelein JJP. Very Low Levels of Atherogenic Lipoproteins and the Risk for Cardiovascular Events: A Meta-Analysis of Statin Trials. J Am Coll Cardiol. 2014;64:485-494.
284. Chasman DI, Giulianini F, MacFadyen J, Barratt BJ, Nyberg F, Ridker PM. Genetic determinants of statin-induced low-density lipoprotein cholesterol reduction: the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. Circ Cardiovasc Genet. 2012;5:257-264.
285. Reiner Ž. Resistance and intolerance to statins. Nutr Metab Cardiovasc Dis. 2014;24:1057-1066.
286. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. Endocr Pract. 2017; DOI:10.4158/EP171764.GL
287. Calderon RM, Cubeddu LX, Goldberg RB, Schiff ER. Statins in the Treatment of Dyslipidemia in the Presence of Elevated Liver Aminotransferase Levels: A Therapeutic Dilemma. Mayo Clin Proc. 2010;85:349-356.
288. Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology 2004;126:1287-1292.
289. 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 nonalcoholic steatohepatitis in at risk individuals. J Hepatol 2015;63:705712.
290. 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.
291. Marcum ZA, Vande Griend JP, Linnebur SA. FDA Drug Safety Communications: A Narrative Review and Clinical Considerations for Older Adults. Am J Geriatr Pharmacother. 2012;10:264-271.
292. Niemi M, Backman JT, Neuvonen M, Neuvonen PJ. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. Diabetologia. 2003;46:347-351.
293. Woo Y, Shin JS, Shim CY, et al. Effect of fenofibrate in 1113 patients at low-density lipoprotein cholesterol goal but high triglyceride levels: Real-world results and factors associated with triglyceride reduction. PLoS One. 2018;13:e0205006.
294. Laufs U,Scharnagl H, Halle M, Windler E, Endres M, März W. Treatment Options for Statin-Associated Muscle Symptoms. Dtsch Arztebl Int. 2015 Oct; 112(44): 748-755.
295. Stroes ES, Thompson PD,Corsini A, Vladutiu GD, Raal FJ et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J (2015) 36 (17): 1012-1022.
296. Laufs U, Scharnagl H, März W. Statin intolerance. Curr Opin Lipidol. 2015;26:492-501.
297. Finegold JA, Francis DP. What proportion of symptomatic side-effects in patients taking statins are genuinely caused by the drug? A response to letters. Eur J Prev Cardiol. 2015;22:1328-1330.
298. 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.
299. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to Moderate Muscular Symptoms with High-Dosage Statin Therapy in Hyperlipidemic Patients - The PRIMO Study. Cardiovasc Drugs Ther. 2005;19:403-414.
300. Davidson MH, Clark JA, Glass LM, Kanumalla A. Statin safety: an appraisal from the adverse event reporting system. Am J Cardiol. 2006;97:32C-43C.
301. Parker BA, Capizzi JA, Grimaldi AS, Clarkson PM, Cole SM, Keadle J, Chipkin S, Pescatello LS, Simpson K, White CM, Thompson PD. Effect of Statins on Skeletal Muscle Function. Circulation. 2013;127:96–103.
302. Miller PE, Martin SS. Approach to Statin Use in 2016: an Update. Curr Atheroscler Rep. 2016;18:20.
303. Keating AJ, Campbell KB, Guyton JR. Intermittent Nondaily Dosing Strategies in Patients with Previous Statin-Induced Myopathy. Ann Pharmacother. 2013;47:398-404.
304. Moriarty PM, Jacobson TA, Bruckert E, Thompson PD, Guyton JR, Baccara-Dinet MT, Gipe D. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: Design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. J Clin Lipidol. 2014;8:554-561.
305. Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, Bruckert E, Cho L, Dent R, Knusel B, Xue A, Scott R, Wasserman SM, Rocco M. Anti-PCSK9 Antibody Effectively Lowers Cholesterol in Patients With Statin Intolerance: The GAUSS-2 Randomized, Placebo-Controlled Phase 3 Clinical Trial of Evolocumab. J Am Coll Cardiol. 2014;63:2541-2548.
306. Marcoff L, Thompson PD. The Role of Coenzyme Q10 in Statin-Associated Myopathy: A Systematic Review. J Am Coll Cardiol. 2007;49:2231-2237.
307. Banach M, Serban C, Ursoniu S, Rysz J, Muntner P, Toth PP, Jones SR, Rizzo M, Glasser SP, Watts GF, Blumenthal RS, Lip GYH, Mikhailidis DP, Sahebkar A. Statin therapy and plasma coenzyme Q10 concentrations-A systematic review and meta-analysis of placebo-controlled trials. Pharmacol Res. 2015;99:329-336.

308. Banach M, Serban C, Sahebkar A, Ursoniu S, Rysz J, Muntner P, Toth PP, Jones SR, Rizzo M, Glasser SP, Lip GYH, Dragan S, Mikhailidis DP, Lipid and Blood Pressure Meta-analysis Collaboration Group. Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials. Mayo Clin Proc. 2015;90:24-34.
309. U.S Food & Drug Administration. FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury [Internet]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm
310. UK Medicines and Healthcare products Regulatory Agency. Simvastatin: updated advice on drug interactions [Internet]. Available from: https://www.gov.uk/drug-safety-update/simvastatin-updated-advice-on-drug-interactions
311. Franssen R, Vergeer M, Stroes ES, Kastelein JJ. Combination statin-fibrate therapy: safety aspects. Diabetes Obes Metab 2009;11:89-94.
312. 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.
313. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, 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, D owns 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.
314. 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 JA de, 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.
315. Vidt DG. Statins and proteinuria. Curr Atheroscler Rep. 2005;7:351-357.
316. Davidson MH. Rosuvastatin safety: lessons from the FDA review and post-approval surveillance. Expert Opin Drug Saf. 2004;3:547-557.
317. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-Associated Side Effects. J Am Coll Cardiol. 2016;67:2395-2410.
318. Strom BL, Schinnar R, Karlawish J, Hennessy S, Teal V, Bilker WB. Statin Therapy and Risk of Acute Memory Impairment. JAMA Intern Med. 2015;175:1399-1405.
319. Swiger KJ, Manalac RJ, Blumenthal RS, Blaha MJ, Martin SS. Statins and Cognition: A Systematic Review and Meta-analysis of Short- and Long-term Cognitive Effects. Mayo Clin Proc. 2013;88:1213-1221.
320. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. Cochrane Database Syst Rev 2016;1:CD003160.
321. Giugliano RP, Mach F, Zavitz K, Kurtz C, Im K, Kanevsky E, Schneider J, Wang H, Keech A, Pedersen TR, Sabatine MS, Sever PS, Robinson JG, Honarpour N, Wasserman SM, Ott BR; EBBINGHAUS Investigators. Cognitive function in a randomized trial of evolocumab. N Engl J Med 2017;377:633-643
322. Cholesterol Treatment Trialists Collaboration, Emberson JR, Kearney PM, Blackwell L, Newman C, Reith C, Bhala N, Holland L, Peto R, Keech A, Collins R, Simes J, Baigent C. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS One 2012;7:e29849.
323. Eslami L, Merat S, Malekzadeh R, Nasseri-Moghaddam S, Aramin H. Statins for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Cochrane Database Syst Rev 2013;12:CD008623.
324. Rahimi K, Bhala N, Kamphuisen P, Emberson J, Biere-Rafi S, Krane V, Robertson M, Wikstrand J, McMurray J. Effect of statins on venous thromboembolic events: a meta-analysis of published and unpublished evidence from randomised controlled trials. PLoS Med 2012;9:e1001310. doi: 10.1371/journal.pmed.1001310. Epub 18 September 2012.
325. Rahimi K, Emberson J, McGale P, Majoni W, Merhi A, Asselbergs FW, Krane V, Macfarlane PW; PROSPER Executive. Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials. BMJ 2011;342:d1250.
326. Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li Q, Du J, Guarguagli S, Hill M, Chen Z, Collins R, Casadei B. Perioperative rosuvastatin in cardiac surgery. N Engl J Med 2016;374:17441753.
327. Yu S, Chu Y, Li G, Ren L, Zhang Q, Wu L. Statin Use and the Risk of Cataracts: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2017 Mar 20;6(3):e004180.
328. Amarenco P, Bogousslavsky J, Callahan AI III, et al. Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549-59.
329. Ribe AR, Vestergaard CH, Vestergaard M, Pedersen HS, Prior A, Lietzen LW, Brynningsen PK, Fenger-Grøn M. Statins and Risk of Intracerebral Hemorrhage in Individuals With a History of Stroke. Stroke. 2020 Apr;51(4):1111-1119.
330. Lee M, Cheng CY, Wu YL, Lee JD, Hsu CY, Ovbiagele B. Association between intensity of low-density lipoprotein cholesterol reduction with statin-based therapies and secondary stroke prevention: A meta-analysis of randomized clinical trials. JAMA Neurol 2022;79:349-358.
331. Mervyn D.I. Vergouwen MDI, de Haan RJ, Vermeulen M, Roos YBWEM. Statin Treatment and the Occurrence of Hemorrhagic Stroke in Patients With a History of Cerebrovascular Disease. Stroke. 2008;39:497-502.
332. Lin CK, Chen PY, Wu YY, Wu CC , Chen HJ, Liang CL, Lee YC , Lin CW, Hung CM, Wang HK. Adjunctive Statin Therapy Reduces Mortality After Acute Hemorrhagic Stroke. Risk Management and Healthcare Policy 2021:14 177-183
333. Teoh RJJ, Huang C-J, Chan CP, et al. Does statin increase the risk of intracerebral hemorrhage in stroke survivors? A meta-analysis and trial sequential analysis. Therapeutic Advances in Neurological Disorders. 2019;12.
334. Gandelman K, Fung GL, Messig M, Laskey R. Systemic exposure to atorvastatin between Asian and Caucasian subjects: a combined analysis of 22 studies. Am J Ther. 2012;19:164-173.
335. Tan CE, Loh LM, Tai ES. Do Singapore patients require lower doses of statins? The SGH Lipid Clinic experience. Singapore Med J. 2003;44:635-638.

336. Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet. 2007;370:1829-1839.
337. 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, La Rosa J, 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.
338. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC et al. 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.
339. Lin, Y.-C., Lai, T.-S., Wu, H.-Y., Chou, Y.-H., Chiang, W.-C., Lin, S.-L., Chen, Y.-M., Chu, T.-S. and Tu, Y.-K. Effects and Safety of Statin and Ezetimibe Combination Therapy in Patients with Chronic Kidney Disease: A Systematic Review and Meta-Analysis. Clin. Pharmacol. Ther.2020;, 108: 833-843. https://doi.org/10.1002/cpt.1859.
340. Zhan S, Tang M, Liu F, Xia P, Shu M, Wu X. Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events. Cochrane Database of Systematic Reviews 2018, Issue 11. Art. No.: CD012502. DOI: 10.1002/14651858.CD012502.pub2. Accessed 25 November 2022.
341. Pradhan, A., Bhandari, M., & Sethi, R. Ezetimibe and Improving Cardiovascular Outcomes: Current Evidence and Perspectives. Cardiology research and practice, 2020, 9815016. https://doi.org/10.1155/2020/9815016.
342. Pandor A, Ara RM, Tumur I, Wilkinson AJ, Paisley S, Duenas A, Durrington PN, Chilcott J. Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. J Intern Med 2009;265:568-580.
343. Ambegaonkar BM, Tipping D, Polis A, Tomassini J, Tershakovec A. Achieving goal lipid levels with ezetimibe plus statin add-on or switch therapy compared with doubling the statin dose. A pooled analysis. Atherosclerosis. 2014;237:829-37.
344. Wang Y, Zhan S, Du H, et al Safety of ezetimibe in lipid-lowering treatment: systematic review and meta-analysis of randomised controlled trials and cohort studies BMJ Medicine 2022;1:e000134. doi: 10.1136/bmjmed-2022-000134.
345. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Covington AM, DePalma SM, Minissian MB, Orringer CE, Smith SC Jr, Waring AA, Wilkins JT. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2022 Oct 4;80(14):1366-1418.
346. 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, Weissen bach J, Prat A, Krempf M, Junien C, Seidah NG, Boileau C. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet. 2003;34:154-156.
347. Norata GD, Tibolla G, Catapano AL. Targeting PCSK9 for hypercholesterolemia. Annu Rev Pharmacol Toxicol. 2014;54:273-293.
348. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somaratne R, Legg J, Wasserman SM, Scott R, Koren MJ, Stein EA, Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1500-1509.
349. Navarese EP, Kolodziejczak M, Schulze V, Gurbel PA, Tantry U, Lin Y, Brockmeyer M, Kandzari DE, Kubica JM, D'Agostino RB, Kubica J, Volpe M, Agewall S, Kereiakes DJ, Kelm M. Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis. Ann Intern Med. 2015;163:40-51.
350. Schmidt AF, 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 2017;4:CD011748.
351. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJ; ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372:1489-1499.
352. Stein EA, Turner TA. Are the PCSK9 inhibitors the panacea of atherosclerosis treatment? Expert Rev Cardiovasc Ther 2017;15:491-494.
353. Gaudet D, Kereiakes DJ, McKenney JM, Roth EM, Hanotin C, Gipe D, Du Y, Ferrand AC, 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.
354. 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.
355. Gencer B, Mach F, Murphy SA, De Ferrari GM, Huber K, Lewis BS, et al. Efficacy of evolocumab on cardiovascular outcomes in patients with recent myocardial infarction: a prespecified secondary analysis from the FOURIER trial. J AMA Cardiol 2020;5:952-7.
356. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER Trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk). Circulation 2018;137:338-50.
357. Jukema JW, Szarek M, Zijlstra LE, de Silva HA, Bhatt DL, Bittner VA, et al. Alirocumab in patients with polyvascular disease and recent acute coronary syndrome: ODYSSEY OUTCOMES Trial. J Am Coll Cardiol 2019;74:1167-76.

358. Ray KK, Colhoun HM, Szarek M, Baccara-Dinet M, Bhatt DL, Bittner VA, et al. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. Lancet Diabetes Endocrinol 2019;7:618-28.
359. Cicero AF, Tartagni E, Ertek S. Safety and tolerability of injectable lipid-lowering drugs: a review of available clinical data. Expert Opin Drug Saf 2014;13:10231030
360. Shimada YJ, Cannon CP. PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitors: past, present, and the future, Eur Heart J 2015:36(36): 2415-2424
361. Igweonu-Nwakile EO, Ali S, Paul S, Yakkali S, Teresa Selvin S, Thomas S, Bikeyeva V, Abdullah A, Radivojevic A, Abu Jad AA, Ravanavena A, Ravindra C, Balani P. A Systematic Review on the Safety and Efficacy of PCSK9 Inhibitors in Lowering Cardiovascular Risks in Patients With Chronic Kidney Disease. Cureus. 2022 Sep 13;14(9):e29140.
362. Chapman MJ, Redfern JS, McGovern ME, Giral P. Niacin and fibrates in atherogenic dyslipidemia: pharmacotherapy to reduce cardiovascular risk. Pharmacol Ther 2010;126:314345.
363. Jakob T, Nordmann AJ, Schandelmaier S, Ferreira-González I, Briel M. Fibrates for primary prevention of cardiovascular disease events. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD009753. DOI: 10.1002/14651858.CD009753.pub2.
364. Wang D, Liu B, Tao W, Hao Z, Liu M. Fibrates for secondary prevention of cardiovascular disease and stroke. Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD009580. DOI: 10.1002/14651858.CD009580.pub2.
365. 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.
366. Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls SJ, et al. Effects of fibrates on cardiovascular outcomes: A systematic review and meta-analysis. Lancet. 2010;375:1875-84
367. Abourbih S, Filion KB, Joseph L, Schiffrin EL, Rinfret S, Poirier P, Pilote L, Genest J, Eisenberg MJ. Effect of fibrates on lipid profiles and cardiovascular outcomes: a systematic review. Am J Med. 2009;122:962.e1-8.
368. Ginsberg HN, Elam MB, Lovato LC, Crouse JR, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC, Cushman WC, Simons-Morton DG, Byington RP, for the ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563-1574.
369. Saha SA, Kizhakepunnur LG, Bahekar A, Arora RR. The role of fibrates in the prevention of cardiovascular disease-a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. Am Heart J. 2007;154:943-953.
370. Pradhan AD, Glynn RJ, Fruchart J-C, MacFadyen JG, Zaharris ES et al for the PROMINENT Investigators. Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk. N Engl J Med 2022; 387:1923-1934
371. Kosmas CE, Muñoz Estrella A, Sourlas A, Silverio D, Hilario E, Montan PD, et al. Inclisiran: A New Promising Agent in the Management of Hypercholesterolemia. Diseases. 2018;6(3).
372. Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N Engl J Med 2017;376(15):1430-40. doi: 10.1056/ NEJMoa1615758.
373. Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Engl J Med 2020;382:1520-30.
374. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med 2020;382:1507-19
375. U. Laufs, M. Banach, G. J. Mancini et al., Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance, Journal of the American Heart Association , vol. 8, no. 7, article e011662, 2019.
376. Ruscica, M., Sirtori, C.R., Carugo, S. et al. Bempedoic Acid: for Whom and When. Curr Atheroscler Rep 24, 791-801 (2022). https://doi.org/10.1007/s11883-022-01054-2
377. Ray KK, Bays HE, Catapano AL, Lalwani ND, Bloedon LT, Sterling LR, Robinson PL, Ballantyne CM; CLEAR Harmony Trial. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. N Engl J Med 2019;380:10221032. 343. S
378. Ballantyne CM, Banach M, Mancini GBJ, Lepor NE, Hanselman JC, Zhao X, Leiter LA. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. Atherosclerosis 2018; 277:195-203.
379. Nissen SE, Lincoff AM, Brennan D, Ray KK, Mason D et al.for the CLEAR Outcomes Investigators. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. N Engl J Med 2023; 388:1353-1364
380. The Lipid Research Clinics Coronary Primary Prevention Trial Results. I. Reduction in incidence of coronary heart disease. JAMA. 1984;251:351-364.
381. The Lipid Research Clinics Coronary Primary Prevention Trial Results: II. The Relationship of Reduction in Incidence of Coronary Heart Disease to Cholesterol Lowering. JAMA. 1984;251:365-374.
382. The Lipid Research Clinics Coronary Primary Prevention Trial. Results of 6 years of post-trial follow-up. The Lipid Research Clinics Investigators. Arch Intern Med. 1992;152:1399-1410.
383. Mazidi M, Rezaie P, Karimi E, Kengne AP. The effects of bile acid sequestrants on lipid profile and blood glucose concentrations: a systematic review and meta-analysis of randomized controlled trials. Int J Cardiol 2017;227:850-857.
384. Alder, M., Bavishi, A., Zumpf, K., Peterson, J., & Stone, N. J. A Meta-Analysis Assessing Additional LDL-C Reduction from Addition of a Bile Acid Sequestrant to Statin Therapy. The American journal of medicine, 2020: 33(11):, 1322-1327.
385. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W. Fifteen year mortality in Coronary Drug Project patients: Long-term benefit with niacin. J Am Coll Cardiol. 1986;8:1245-1255.
386. The AIM-HIGH Investigators. Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy. N Engl J Med. 2011;365:2255-2267.

387. D'Andrea E, Hey SP, Ramirez CL, Kesselheim AS. Assessment of the Role of Niacin in Managing Cardiovascular Disease Outcomes: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(4):e192224. doi:10.1001/jamanetworkopen.2019.2224.
388. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007; 369:1090.
389. Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial. JAMA 2020; 324:2268.
390. J.E. Manson, N.R. Cook, I.M. Lee, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer N Engl J Med,2019; 380:23-32.
391. Kalstad AA, P.L. Myhre, K. Laake, et al. Effects of n-3 fatty acid supplements in elderly patients after myocardial infarction: a randomized, controlled trial. Circulation,2021:143 : 528-539.
392. Shaya, F.T., Sing, K., Milam, R. et al. Lipid-Lowering Efficacy of Ezetimibe in Patients with Atherosclerotic Cardiovascular Disease: A Systematic Review and Meta-Analyses. Am J Cardiovasc Drugs 2020;20, 239-248.
393. Sando, K. R., & Knight, M. (2015). Nonstatin therapies for management of dyslipidemia: a review. Clinical therapeutics, 37(10), 2153-2179. https://doi.org/10.1016/j.clinthera.2015.09.001.
394. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. Am J Cardiol. 2005;95:120-122.
395. 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.
396. Jacobson, T. A., & Zimmerman, F. H. Fibrates in combination with statins in the management of dyslipidemia. J of Clin hypertension (Greenwich, Conn.), 2006: 8(1), 35-43.
397. Cano Cevallos, EJ, Shaikh, DH, Gonzalez, J, Sanchez, W, Patel, M. Tendon rupture associated with concomitant simvastatin and gemfibrozil use: Biological and pharmacokinetic implications. Clin Case Rep. 2019; 7: 1919-1922.
398. Guo J, Meng F, Ma N, Li C, Ding Z, Wang H, Hou R, Qin Y. Meta-analysis of safety of the coadministration of statin with fenofibrate in patients with combined hyperlipidemia. Am J Cardiol. 2012;110:1296-1301.
399. Taguchi I, Iimuro S, Iwata H, Takashima H, Abe M et al. High-Dose Versus Low-Dose Pitavastatin in Japanese Patients With Stable Coronary Artery Disease (REAL-CAD): A Randomized Superiority Trial. Circulation. 2018 May 8;137(19):1997-2009.
400. Pasceri V, Patti G, Nusca A, Pristipino C, Richichi G, Sciascio GD. Randomized Trial of Atorvastatin for Reduction of Myocardial Damage During Coronary Intervention. Circulation. 2004;110:674-678.
401. Briguori C, Visconti G, Focaccio A, Golia B, Chieffo A, Castelli A, Mussardo M, Montorfano M, Ricciardelli B, Colombo A. Novel Approaches for Preventing or Limiting Events (Naples) II Trial: Impact of a Single High Loading Dose of Atorvastatin on Periprocedural Myocardial Infarction. J Am Coll Cardiol. 2009;54:2157-2163.
402. Di Sciascio G, Patti G, Pasceri V, Gaspardone A, Colonna G, Montinaro A. Efficacy of Atorvastatin Reload in Patients on Chronic Statin Therapy Undergoing Percutaneous Coronary Intervention: Results of the ARMYDA-RE CAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial. J Am Coll Cardiol. 2009;54:558–565.
403. Tsimikas S. High-dose statins prior to percutaneous coronary intervention: a paradigm shift to influence clinical outcomes in the cardiac catheterization laboratory. J Am Coll Cardiol. 2009;54:2164-2166.
404. Kim JW, Yun KH, Kim EK, Kim YC, Joe D-Y, Ko JS, Rhee SJ, Lee EM, Yoo NJ, Kim N-H, Oh SK, Jeong J-W. Effect of High Dose Rosuvastatin Loading before Primary Percutaneous Coronary Intervention on Infarct Size in Patients with ST-Segment Elevation Myocardial Infarction. Korean Circ J. 2014;44:76-81.
405. Sardella G, Lucisano L, Mancone M, Conti G, Calcagno S, Stio RE, Pennacchi M, Biondi-Zoccai G, Canali E, Fedele F. Comparison of high reloading ROsuvastatin and Atorvastatin pretreatment in patients undergoing elective PCI to reduce the incidence of MyocArdial periprocedural necrosis. The ROMA II trial. Int J Cardiol. 2013;168:3715-3720.
406. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol. 2009;8:453-463.
407. Tsankof A, Tziomalos K. The Role of Lipid-Lowering Treatment in the Secondary Prevention of Ischemic Stroke. Diseases. 2021 Dec 27;10(1):3
408. Amarenco P, Kim JS, Labreuche J, Charles H, Abtan J et al for the Treat Stroke to Target Investigators. A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke. N Engl J Med 2020; 382:9-19.
409. Åivo J, Ruuskanen JO, Tornio A, Rautava P, Kytö V. Lack of Statin Therapy and Outcomes After Ischemic Stroke: A Population-Based Study. Stroke. 2023;54:781-790.
410. Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith SC, Goto S, Ohman EM, Elbez Y, Sritara P, Baumgartner I, Banerjee S, Creager MA, Bhatt DL; REACH Registry Investigators. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry.Eur Heart J. 2014; 35:2864-2872. doi: 10.1093/eurheartj/ehu080.CrossrefMedlineGoogle Scholar.
411. Arya S, Khakharia A, Binney ZO, DeMartino RR, Brewster LP, Goodney PP, Wilson PWF. Association of statin dose with amputation and survival in patients with peripheral artery disease.Circulation. 2018; 137:1435-1446.
412. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. Heart Protection Study Collaborative Group. J Vasc Surg. 2007 Apr;45(4):645-654
413. 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 Apr 4;285(13):1711-8.

414. Saab FA, Eagle KA, Kline-Rogers E, et al. Comparison of outcomes in acute coronary syndrome in patients receiving statins within 24 hours of onset versus at later times. Am J Cardiol. 2004;94:1166-1168.
415. Fonarow GC, Wright RS, Spencer FA, Fredrick PD, Dong W, Every N, French WJ. Effect of Statin Use Within the First 24 Hours of Admission for Acute Myocardial Infarction on Early Morbidity and Mortality†. Am J Cardiol. 2005;96:611-616.
416. de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KAA, White HD, Rouleau J-L, Pedersen TR, Gardner LH, Mukherjee R, Ramsey KE, Palmisano J, Bilheimer DW, Pfeffer MA, Califf RM, Braunwald E, Investigators. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004;292:1307-1316.
417. Hulten E, Jackson JL, Douglas K et al. The Effect of Early, Intensive Statin Therapy on Acute Coronary Syndrome. A Meta-analysis of Randomized Controlled Trials. Arch Intern Med. 2006;166(17):1814-1821.
418. Koskinas KC, Mach F, Räber L. Lipid-lowering therapy and percutaneous coronary interventions. EuroIntervention. 2021 Apr 20;16(17):1389-1403.
419. Berwanger O, Santucci EV, de Barros E, Silva PGM, Jesuino IA et al. SECURE-PCI Investigators. Effect of Loading Dose of Atorvastatin Prior to Planned Percutaneous Coronary Intervention on Major Adverse Cardiovascular Events in Acute Coronary Syndrome: The SECURE-PCI Randomized Clinical Trial. JAMA. 2018;319:1331-40.
420. Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T et al. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. Circulation. 2004;110:1061-8.
421. Lee ZV, Lam H. Aggressive lipid-lowering therapy after percutaneous coronary intervention - for whom and how?: Aggressive lipid-lowering therapy after PCI. AsiaIntervention. 2022 Mar;8(1):24-31'
422. Victor Aboyans V, Criqui MH, Abraham P, Allison MA, Creage MA et al. on behalf of the American Heart Association Council on Peripheral Vascular Disease. Measurement and Interpretation of the Ankle-Brachial Index. A Scientific Statement From the American Heart Association. Circulation. 2012;126:2890-2909'
423. Leipsic J, Abbara S, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2014;8:342-58. 10.1016.
424. Nerlekar N, Ha FJ, Cheshire C, Rashid H, Cameron JD, Wong DT, Seneviratne S, Brown AJ. Computed tomographic coronary angiography-derived plaque characteristics predict major adverse cardiovascular events: a systematic review and meta-analysis.Circ Cardiovasc Imaging. 2018; 10:e006973.
425. SCOT-HEARTInvestigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial.Lancet. 2015; 385:2383-2391.
426. Ferencik M, Hoffmann U. High-Risk Coronary Plaque on Computed Tomography Angiography. Time to Recognize a New Imaging Risk Factor. Circulation: Cardiovascular Imaging. 2018;11:e007288
427. Kwon TG, Kim KW, Park HW, Jeong JH, Kim KY, Bae JH. Prevalence and significance of carotid plaques in patients with coronary atherosclerosis. Korean Circ J. 2009 Aug;39(8):317-21
428. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major Outcomes in Moderately Hypercholesterolemic, Hypertensive Patients Randomized to Pravastatin vs Usual Care. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002;288: 2998-3007.
429. Margolis, K.L.; Davis, B.R.; Baimbridge, C.; Ciocon, J.O.; Cuyjet, A.B.; Dart, R.A.; Einhorn, P.T.; Ford, C.E.; Gordon, D.; Hartney, T.J.; et al. Long-term follow-up of moderately hypercholesterolemic hypertensive patients following randomization to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). J. Clin. Hypertens. 2013, 15, 542-554.
430. Sever PS, Chang CL, Gupta AK, Whitehouse A, Poulter NR, ASCOT Investigators. The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the U.K. Eur Heart J. 2011;32:2525-2532.
431. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D et al.for the HOPE-3 Investigators. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. N Engl J Med 2016: 374: 2021-2031.
432. Yusuf S, Lonn E, Pais P, Bosch J, López-Jaramillo P et al. HOPE-3 Investigators. Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease. N Engl J Med. 2016;374(21):2032-43.
433. Messerli FH, Pinto L, Tang SSK, Thakker KM, Cappelleri JC, Sichrovsky T, Dubois RW. Impact of systemic hypertension on the cardiovascular benefits of statin therapy-a meta-analysis. Am J Cardiol. 2008;101:319-325.
434. Yusuf S, Joseph P, Dans A, Gao P, Teo K et al for the International Polycap Study 3 Investigators. Polypill with or without Aspirin in Persons without Cardiovascular Disease. N Engl J Med 2021; 384:216-228.
435. Muñoz D, Uzoije P, Reynolds C, Miller R, Walkley D et al. Polypill for Cardiovascular Disease Prevention in an Underserved Population. N Engl J Med 2019; 381:1114-1123.
436. Simon A, Dézsi CA. Treatment of Hypertensive and Hypercholesterolaemic Patients with the Triple Fixed Combination of Atorvastatin, Perindopril and Amlodipine: The Results of the CORAL Study. Adv Ther. 2019 Aug;36(8):2010-2020.
437. Borghi C, Fogacci F, Agnoletti D, Cicero AFG. Hypertension and Dyslipidemia Combined Therapeutic Approaches. High Blood Press Cardiovasc Prev. 2022 May;29(3):221-230.
438. Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. Diabetes Care. 1979;2:120-126.
439. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care. 1999;22:233-240.
440. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339:229-234.
441. Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med J Br Diabet Assoc. 2009;26:142-148.

442. Rana JS, Liu JY, Moffet HH, Jaffe M, Karter AJ. Diabetes and Prior Coronary Heart Disease are Not Necessarily Risk Equivalent for Future Coronary Heart Disease Events. J Gen Intern Med. 2016;31:387-393.
443. Hero C, Rawshani A, Svensson A-M, Franzén S, Eliasson B, Eeg-Olofsson K, Gudbjörnsdottir S. Association Between Use of Lipid-Lowering Therapy and Cardiovascular Diseases and Death in Individuals With Type 1 Diabetes. Diabetes Care. 2016;39:996-1003.
444. Ministry of Health Malaysia. 2021. National Diabetes Registry Report 2020.
445. American Diabetes Association. Management of Dyslipidemia in Children and Adolescents With Diabetes. Diabetes Care. 2003;26:2194-2197.
446. National Heart Lung and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. 2012: NIH Publication No. 12-7486A.
447. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Paediatrics 2011;128(Suppl 5):S213-S256.
448. Bays HE, Jones PH, Orringer CE, Brown WV, Jacobson TA. National Lipid Association Annual Summary of Clinical Lipidology 2016. J Clin Lipidol. 2016;10(1):S1-S43.
449. Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371(9607):117-125.
450. Giugliano RP, Cannon CP, Blazing MA, et al. Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus: Results From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). Circulation. 2018;137(15):1571-1582.
451. Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. Lancet Diabetes Endocrinol. 2017;5(12):941-950.
452. Harris WS, Miller M, Tighe AP, Davidson MH, Schaefer EJ. Omega-3 fatty acids and coronary heart disease risk: clinical and mechanistic perspectives. Atherosclerosis. 2008;197:12-24.
453. Elam MB, Ginsberg HN, Lovato LC, et al. Association of Fenofibrate Therapy With Longterm Cardiovascular Risk in Statin-Treated Patients With Type 2 Diabetes. JAMA Cardiol. 2017;2(4):370-380.
454. Scott R, O'Brien R, Fulcher G, et al. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetes Care. 2009;32(3):493-498.
455. Saha SA, Arora RR. Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus-a pooled meta-analysis of randomized placebo-controlled clinical trials. Int J Cardiol. 2010;141(2):157-166.
456. Keech AC, Mitchell P, Summanen PA, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet. 2007;370(9600):1687-1697.
457. Chew EY, Ambrosius WT, Davis MD, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med. 2010;363(3):233-244.
458. Elam MB, Hunninghake DB, Davis KB, et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: A randomized trial. Arterial Disease Multiple Intervention Trial. JAMA. 2000;284(10):1263-1270.
459. Grundy SM, Vega GL, McGovern ME, et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. Arch Intern Med. 2002;162(14):1568-1576.
460. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365(24):2255-2267.
461. Lee MMY, Sattar N, McMurray JJV, Packard CJ. Statins in the Prevention and Treatment of Heart Failure: a Review of the Evidence. Curr Atheroscler Rep. 2019 Jul 27;21(10):41
462. Bielecka-Dabrowa, A., Bytyçi, I., Von Haehling, S. et al. Association of statin use and clinical outcomes in heart failure patients: a systematic review and meta-analysis. Lipids Health Dis 2019; 18, 188.
463. Preiss D, Campbell RT, Murray HM, Ford I, Packard CJ et al. The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data from major randomized trials. Eur Heart J. 2015 Jun 21;36(24):1536-46.
464. Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JGF et al for the CORONA Group. Rosuvastatin in older patients with systolic heart failure. N Engl J Med. 2007;357:2248-2261.
465. Rogers JK, Jhund PS, Perez AC, Böhm M, Cleland JG et al. Effect of rosuvastatin on repeat heart failure hospitalizations: the CORONA Trial (Controlled Rosuvastatin Multinational Trial in Heart Failure). JACC Heart Fail. 2014 Jun;2(3):289-97.
466. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G; Gissi-HF Investigators. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Oct 4;372(9645):1231-9.
467. Greene SJ, Vaduganathan M, Lupi L, et al. Lipid levels influence the prognosis of heart failure patients. Am J Cardiol. 2013;111:574-81.
468. Rauchhaus M, Clark AL, Doehner W, Davos C, Bolger A et al. The relationship between cholesterol and survival in patients with chronic heart failure. J Am Coll Cardiol 2003: 42 (11): 1933-1940.
469. Niessner A, Drexel H. PCSK9 inhibition in patients with heart failure: neutral or harmful intervention?, Eur Heart J 2022: 43:1566-1568.
470. White HD, Schwartz GG, Szarek M, Bhatt DL,Bittner VA et al. Alirocumab after Acute Coronary syndrome in patients with a history of Heart Failure. Eur Heart J 2022: 43:1554-1565.
471. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW. Kidney Disease as a Risk Factor for Development of Cardiovascular Disease. Circulation. 2003;108:2154-2169.

472. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJL, Mann JF, Matsushita K, Wen CP. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet. 2013;382:339-352.
473. van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey AS, Paul Jong D, Gansevoort R, Prognosis CKD. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int. 2011;79:1341-1352.
474. Foley R. N., Parfrey P. S., Sarnak M. J. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32:S112-119.
475. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney International 2021: 99, S1-S87.
476. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 2020;98:S1-S115
477. Lee S, Kang S, Joo YS, Lee C, Nam KH, Yun HR, Park JT, Chang TI, Yoo TH, Kim SW, Oh KH, Kim YH, Park SK, Kang SW, Choi KH, Ahn C, Han SH. Smoking, Smoking Cessation, and Progression of Chronic Kidney Disease: Results From KNOW-CKD Study. Nicotine Tob Res. 2021 Jan 7;23(1):92-98
478. Weiner DE, Sarnak MJ. Managing Dyslipidemia in Chronic Kidney Disease. J Gen Intern Med. 2004;19:1045–1052.
479. Trevisan R, Dodesini AR, Lepore G. Lipids and renal disease. J Am Soc Nephrol. 2006 Apr;17(4 Suppl 2):S145-7.
480. Chu M., Wang A. Y., Chan I. H., Chui S. H., Lam C. W. Serum small-dense LDL abnormalities in chronic renal disease patients. British journal of biomedical science. 2012;69:99-102.
481. Tonelli M, Muntner P, Lloyd A, Manns B, Klarenbach S et al. Alberta Kidney Disease Network. Association between LDL-C and risk of myocardial infarction in CKD. J Am Soc Nephrol. 2013 May;24(6):979-86.
482. Kuznik A., Mardekian J., Tarasenko L. Evaluation of cardiovascular disease burden and therapeutic goal attainment in US adults with chronic kidney disease: an analysis of national health and nutritional examination survey data, 2001-2010. BMC nephrology. 2013;14:132.
483. Lo JC, Go AS, Chandra M, Fan D, Kaysen GA. GFR, body mass index, and low high-density lipoprotein concentration in adults with and without CKD. Am J Kidney Dis. 2007;50:552-558.
484. Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Hegbrant J, Strippoli GFM. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database Syst Rev. 2014;CD007784.
485. Barylski M, Nikfar S, Mikhailidis DP, Toth PP, Salari P, Ray KK, Pencina MJ, Rizzo M, Rysz J, Abdollahi M, Nicholls SJ, Banach M, Lipid and Blood Pressure Meta-Analysis Collaboration Group. Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy-a meta-analysis of 11 randomized controlled trials involving 21,295 participants. Pharmacol Res. 2013;72:35-44.
486. Stanifer JW, Charytan DM, White J, Lokhnygina Y, Cannon CP, Roe MT, Blazing MA. Benefit of Ezetimibe Added to Simvastatin in Reduced Kidney Function. J Am Soc Nephrol. 2017 Oct;28(10):3034-3043
487. KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. Kidney International Suppl 2013;volume 3. 259-305.
488. Wanner C, Tonelli M. Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO Clinical Practice Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient. Kidney Int 2014;85:1303-9.
489. Rosenstein K, Tannock LR. Dyslipidemia in Chronic Kidney Disease. [Updated 2022 Feb 10]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK305899/
490. Toto R. D., Grundy S. M., Vega G. L. Pravastatin treatment of very low density, intermediate density and low density lipoproteins in hypercholesterolemia and combined hyperlipidemia secondary to the nephrotic syndrome. Am J Nephrol. 2000;20:12-17.
491. Matzkies F. K., Bahner U., Teschner M., Hohage H., Heidland A., Schaefer R. M. Efficiency of 1-year treatment with fluvastatin in hyperlipidemic patients with nephrotic syndrome. Am J Nephrol. 1999;19:492-494.
492. de Zeeuw D, Anzalone DA, Cain VA, Cressman MD, Heerspink HJL, Molitoris BA, Monyak JT, Parving H-H, Remuzzi G, Sowers JR, Vidt DG. Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial. Lancet Diabetes Endocrinol. 2015;3:181-190.
493. Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. Kidney Int. 2001;59:260-269.
494. 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.
495. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae D-W, Chevaile A, Cobbe SM, Grönhagen-Riska C, De Lima JJ, 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.
496. Holdaas H., Fellstrom B., Jardine A. G., Holme I., Nyberg G., Fauchald P., Gronhagen-Riska C., Madsen S., Neumayer H. H., Cole E., Maes B., Ambuhl P., Olsson A. G., Hartmann A., Solbu D. O., Pedersen T. R. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Lancet. 2003;361:2024-2031.
497. Holdaas H, Fellström B, Cole E, Nyberg G, Olsson AG, Pedersen TR, et al. Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators. Longterm cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. Am J Transplant 2005;5:2929-36.

498. Newman CB, Blaha MJ, Boord JB, Cariou B, Chait A et al. Lipid Management in Patients with Endocrine Disorders: An Endocrine Society Clinical Practice Guideline, The Journal of Clinical Endocrinology & Metabolism,2020:105(12) :3613-3682.
499. Jung KY, Ahn HY, Han SK, Park YJ, Cho BY, Moon MK. Association between thyroid function and lipid profiles, apolipoproteins, and high-density lipoprotein function. J Clin Lipidol. 2017;11(6):1347-1353.
500. Duntas LH, Brenta G. The effect of thyroid disorders on lipid levels and metabolism. Med Clin North Am. 2012;96(2):269-281.
501. Tauchmanovà L, Rossi R, Biondi B, Pulcrano M, Nuzzo V et al. Patients with Subclinical Cushing's Syndrome due to Adrenal Adenoma Have Increased Cardiovascular Risk, The Journal of Clinical Endocrinology & Metabolism, 2002: 87(11): 4872-4878.
502. Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BM, Colao A. Complications of Cushing's syndrome: state of the art. Lancet Diabetes Endocrinol 2016: 4(7):611-29.
503. Arnaldi G, Scandali VM, Trementino L, Cardinaletti M, Appolloni G, Boscaro M. Pathophysiology of dyslipidemia in Cushing's syndrome. Neuroendocrinology. 2010;92(Suppl):186-190.
504. Giordano R, Picu A, Marinazzo E, et al. Metabolic and cardiovascular outcomes in patients with Cushing's syndrome of different aetiologies during active disease and 1 year after re- mission. Clin Endocrinol (Oxf). 2011;75(3):354-360.
505. Colao A, Pivonello R, Spiezia S, et al. Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. J Clin Endocrinol Metab. 1999;84(8):2664-2672.
506. Hescot S, Seck A, Guerin M, et al. Lipoprotein-free mitotane exerts high cytotoxic activity in adrenocortical carcinoma. J Clin Endocrinol Metab. 2015;100(8):2890-2898.
507. Feinstein MJ, Bahiru E, Achenbach C, Longenecker CT, Hsue P, So-Armah K, Freiberg MS, Lloyd-Jones DM. Patterns of cardiovascular mortality for HIV-infected adults in the United States: 1999 to 2013. Am J Cardiol. 2016;117:214-220.
508. Wang, S. C., Kaur, G., Schulman-Marcus, J., Purga, S., Mookherjee, S., Miller, C., Sidhu, M. S., & Rosenson, R. S. Implementation of Cholesterol-Lowering Therapy to Reduce Cardiovascular Risk in Persons Living with HIV. Cardiovascular drugs and therapy,2022: 36(1), 173-186.
509. Feinstein, M. J., Hsue, P. Y., Benjamin, L. A., Bloomfield, G. S., Currier, J. S., Freiberg, M. S., Grinspoon, S. K., Levin, J., Longenecker, C. T., & Post, W. S. (2019). Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV: A Scientific Statement From the American Heart Association. Circulation, 140(2), e98-e124.
510. Vigny, N. N., Bonsu, K. O., & Kadirvelu, A. Effectiveness and safety of statins on outcomes in patients with HIV infection: a systematic review and meta-analysis. Scientific reports 2022;, 12(1), 18121.
511. Li, Y., Wang, Z., Xia, H., & Zhang, J. Influence of Statin Therapy on the Incidence of Cardiovascular Events, Cancer, and All-Cause Mortality in People Living With HIV: A Meta-Analysis. Frontiers in medicine,2021: 8, 769740.
512. Coll B, Aragonés G, Parra S, Alonso-Villaverde C, Masana L. Ezetimibe effectively decreases LDL-cholesterol in HIV-infected patients. AIDS. 2006;20:1675-1677.
513. Shulman M, Miller A, Misher J, Tentler A. Managing cardiovascular disease risk in patients treated with antipsychotics: a multidisciplinary approach. J Multidiscip Healthc. 2014 Oct 31;7:489-501.
514. Osborn, D.P.; Nazareth, I.; King, M.B. Physical activity, dietary habits and Coronary Heart Disease risk factor knowledge amongst people with severe mental illness. Soc. Psychiatry Psychiatr. Epidemiol. 2007, 42, 787-793.
515. Nasrallah H , Meyer JM , Goff DC , et al.: Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: data from the CATIE schizophrenia trial sample at baseline. Schizophrenia Research 86:15-22, 2006
516. Avan R, Sahebnasagh A, Hashemi J, Monajati M, Faramarzi F, Henney NC, Montecucco F, Jamialahmadi T, Sahebkar A. Update on Statin Treatment in Patients with Neuropsychiatric Disorders. Life. 2021; 11(12):1365.
517. Ventriglio, A. Gentile, E. Stella, et al. Metabolic issues in patients affected by schizophrenia: clinical characteristics and medical management. Front. Neurosci., 9 (2015), p. 297.
518. Kanagasundaram P, Lee J, Prasad F, Costa-Dookhan KA, Hamel L, Gordon M, Remington G, Hahn MK and Agarwal SM (2021) Pharmacological Interventions to Treat Antipsychotic-Induced Dyslipidemia in Schizophrenia Patients: A Systematic Review and Meta Analysis. Front. Psychiatry 12:642403. doi: 10.3389/fpsyt.2021.642403.
519. Ojala K, Repo-Tiihonen E, Tiihonen J, Niskanen L. Statins are effective in treating dyslipidemia among psychiatric patients using second-generation antipsychotic agents. J Psychopharmacol. 2008 Jan;22(1):33-8. doi: 10.1177/ 0269881107077815.
520. Li, R., Zhang, Y., Zhu, W. et al. Effects of olanzapine treatment on lipid profiles in patients with schizophrenia: a systematic review and meta-analysis. Sci Rep 10, 17028 (2020). https://doi.org/10.1038/s41598-020-73983-4.
521. McEvoy GK, editor. AHFS Drug Information®. 56th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2014.
522. Meltzer HY, Cola PA, Parsa M. Marked elevations of serum creatine kinase activity associated with antipsychotic drug treatment. Neuropsychopharmacology. 1996;15(4):395-405.
523. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, Goldberg AC, Howard WJ, Jacobson MS, Kris-Etherton PM, Lennie TA, Levi M, Mazzone T, Pennathur S, on behalf of the American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular N. Triglycerides and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2011;123:2292-2333.
524. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw K-T, Gudnason V. Triglycerides and the Risk of Coronary Heart Disease. Circulation. 2007;115:450-458.
525. Nordestgaard BG, Benn M, Schnohr P, Tybjærg-Hansen A. Nonfasting Triglycerides and Risk of Myocardial Infarction, Ischemic Heart Disease, and Death in Men and Women. JAMA. 2007;298:299-308.

526. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting Compared With Nonfasting Triglycerides and Risk of Cardiovascular Events in Women. JAMA. 2007;298:309-316.
527. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, et al for the Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302:1993-2000.
528. Ference BA, Kastelein JJP, Ray KK, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. JAMA. 2019;321: 364-373
529. Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, Di Angelantonio E, Boekholdt SM, Ouwehand W, Watkins H, Samani NJ, Saleheen D, Lawlor D, Reilly MP, Hingorani AD, Talmud PJ, Danesh J. Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration,Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. Lancet. 2010;375:1634-1639.
530. Stalenhoef AFH, de Graaf J. Association of fasting and nonfasting serum triglycerides with cardiovascular disease and the role of remnant-like lipoproteins and small dense LDL. Curr Opin Lipidol. 2008;19:355-361.
531. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. JAMA. 2008;300:2142-2152.
532. Ridker PM. Fasting versus nonfasting triglycerides and the prediction of cardiovascular risk: do we need to revisit the oral triglyceride tolerance test? Clin Chem. 2008;54:11-13.
533. Kathiresan S, Otvos JD, Sullivan LM, Keyes MJ, Schaefer EJ, Wilson PWF, D'Agostino RB, Vasan RS, Robins SJ. Increased small low-density lipoprotein particle number: a prominent feature of the metabolic syndrome in the Framingham Heart Study. Circulation. 2006;113:20-29.
534. Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Averna M, Borén J, Bruckert E, Catapano AL, Descamps OS, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AFH, Stroes E, Taskinen M-R, Tybjærg-Hansen A, Watts GF, Wiklund O. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. Lancet Diabetes Endocrinol. 2014;2:655-666.
535. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, Witztum JL. Lipoprotein Management in Patients With Cardiometabolic Risk. Diabetes Care. 2008;31:811-822.
536. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER, Conlin PR, Erlinger TP, Rosner BA, Laranjo NM, Charleston J, McCarron P, Bishop LM, OmniHeart Collaborative Research Group. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. JAMA. 2005;294:2455-2464.
537. Johnson RK, Appel LJ, Brands M, Howard BV, Lefevre M, Lustig RH, Sacks F, Steffen LM, Wylie-Rosett J, American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism and the Council on Epidemiology and Prevention. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. Circulation. 2009;120:1011-1020.
538. Laimer MW, Engl J, Tschoner A, Kaser S, Ritsch A, Tatarczyk T, Rauchenzauner M, Weiss H, Aigner F, Patsch JR, Ebenbichler CF. Effects of weight loss on lipid transfer proteins in morbidly obese women. Lipids. 2009;44:1125-1130.
539. Stoedefalke K. Effects of Exercise Training on Blood Lipids and Lipoproteins in Children and Adolescents. J Sports Sci Med. 2007;6:313-318.
540. Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, Bales CW, Henes S, Samsa GP, Otvos JD, Kulkarni KR, Slentz CA. Effects of the amount and intensity of exercise on plasma lipoproteins. N Engl J Med. 2002;347:1483-1492.
541. Ginsberg H, Olefsky J, Farquhar JW, Reaven GM. Moderate ethanol ingestion and plasma triglyceride levels. A study in normal and hypertriglyceridemic persons. Ann Intern Med. 1974;80:143-149.
542. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, Stalenhoef AFH, Endocrine society. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97:2969-2989.
543. Eckel RH, Jakicic JM, Ard JD, et al. 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.
544. Stein EA, Lane M, Laskarzewski P. Comparison of statins in hypertriglyceridemia. Am J Cardiol. 1998;81:66B-69B.
545. Van JT, Pan J, Wasty T, Chan E, Wu X, Charles MA. Comparison of extended-release niacin and atorvastatin monotherapies and combination treatment of the atherogenic lipid profile in diabetes mellitus. Am J Cardiol. 2002;89:1306-1308.
546. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, Dowdy AA, Marino EK, Bolson EL, Alaupovic P, Frohlich J, Albers JJ. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med. 2001;345:1583-1592.
547. Nerbrand C, Nyberg P, Nordstrom L, Samsioe G. Effects of a lipid lowering fibrate and hormone replacement therapy on serum lipids and lipoproteins in overweight postmenopausal women with elevated triglycerides. Maturitas. 2002;42:55-62.
548. L. Bowman, M. Mafham, K. Wallendszus, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. N Engl J Med,2018: 379: 1540-1550.
549. Curfman G. Omega-3 Fatty Acids and Atrial Fibrillation. JAMA. 2021;325(11):1063.
550. NICE Clinical Guidelines CG181. Lipid modification. Cardiovascular risk assessment and modification of blood lipids for the primary and secondary prevention of cardiovascular diseases [Internet]. [cited 2015 Oct 24]. Available from: http://www.nice.org.uk/guidelines/cg181/evidence/lipid-modification-update-full-guideline-243786637.
551. 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.

552. Jialal I, Amess W, Kaur M. Management of hypertriglyceridemia in the diabetic patient. Curr Diab Rep. 2010 Aug;10(4):316-20.
553. Newman CB, Blaha MJ, Boord JB, Cariou B, Chait A et al. Lipid Management in Patients with Endocrine Disorders: An Endocrine Society Clinical Practice Guideline, The Journal of Clinical Endocrinology & Metabolism, 2020: 105 (12): 3613-3682,
554. Maki KC, Bays HE, Dicklin MR. Treatment options for the management of hypertriglyceridemia: strategies based on the best-available evidence. J Clin Lipidol. 2012;6:413-426.
555. Wolbrink DRJ, Grundsell JR, Witteman B, van de Poll M, van Santvoort HC et al for the Dutch Pancreatitis Study Group. Are omega-3 fatty acids safe and effective in acute pancreatitis or sepsis? A systematic review and meta-analysis. Clin Nutrition 2020:39 (9): 2686-2694.
556. Briel M, Ferreira-Gonzalez I, You JJ, Karanicolas PJ, Akl EA, Wu P, Blechacz B, Bassler D, Wei X, Sharman A, Whitt I, Alves da Silva S, Khalid Z, Nordmann AJ, Zhou Q, Walter SD, Vale N, Bhatnagar N, O'Regan C, Mills EJ, Bucher HC, Montori VM, Guyatt GH. Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis. BMJ. 2009;338:b92.
557. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 1999; 341:410.
558. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987; 317:1237.
559. Bezafibrate Infarction Prevention (BIP) study. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. Circulation 2000; 102:21.
560. Rabkin SW. Effect of cigarette smoking cessation on risk factors for coronary atherosclerosis. A control
561. Shaw LJ, Bugiardini R, Merz CNB. Women and ischemic heart disease: evolving knowledge. J Am Coll Cardiol. 2009;54:1561-1575.
562. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, Keltai M, Diaz R, Rangarajan S, Yusuf S, INTERHEART Investigators. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur Heart J. 2008;29:932-940.
563. Kappert K, Böhm M, Schmieder R, Schumacher H, Teo K, Yusuf S, Sleight P, Unger T, ONTARGET/TRANSCEND Investigators. Impact of sex on cardiovascular outcome in patients at high cardiovascular risk: analysis of the Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects With Cardiovascular Disease (TRANSCEND) and the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET). Circulation. 2012;126:934-941.
564. Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. Diabetes Care. 2000;23:962-968.
565. Orchard TJ. The Impact of Gender and General Risk Factors on the Occurrence of Atherosclerotic Vascular Disease in Non-insulin-dependent Diabetes Mellitus. Ann Med. 1996;28:323-333.
566. Laing SP, Swerdlow AJ, Slater SD, Botha JL, Burden AC, Waugh NR, Smith AWM, Hill RD, Bingley PJ, Patterson CC, Qiao Z, Keen H. The British Diabetic Association Cohort Study, II: cause-specific mortality in patients with insulin-treated diabetes mellitus. Diabet Med. 1999;16:466-471.
567. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ. 2006;332:73-78.
568. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer later in life: a systematic review and meta-analysis. BMJ 2007;335:974.
569. Smith GN, Pudwell J, Roddy M. The maternal health clinic: a new window of opportunity for early heart disease screening and intervention for women with pregnancy complications. J Obstet Gynaecol Can 2013;35:831-9.
570. Bateman BT, Hernandez-Diaz S, Fischer MA, et al. Statins and congenital malformations: cohort study. BMJ 2015;350:h1035.
571. Pollack PS, Shields KE, Burnett DM, et al. Pregnancy outcomes after maternal exposure to simvastatin and lovastatin. Birth Defects Res AClin Mol Teratol 2005;73:888–96.
572. Edison RJ, Muenke M. Central nervous system and limb anomalies in case reports of first-trimester statin exposure. N Engl J Med 2004;350:1579-82.
573. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med. 1998 Jun 4;338(23):1650-6.
574. Schienkiewitz, A., Truthmann, J., Ernert, A. et al. Age, maturation and serum lipid parameters: findings from the German Health Survey for Children and Adolescents. BMC Public Health 2019: 19: 1627
575. Chin C, Gamberg P, Miller J, Luikart H, Bernstein D. Efficacy and safety of atorvastatin after pediatric heart transplantation. J Heart Lung Transplant. 2002; 21: 1213-1217.
576. Catapano, A.L.; Graham, I.; De Backer, G.;Wiklund, O.; Chapman, M.Jet al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis 2016, 253, 281-344.
577. Cholesterol Clinical Practice Guidelines. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive summary. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1046-e108.

578. McCrindle BW, Uubian EM, Dennsion BA, Jacobson MS, Steinberger J, Rocchini AP: Drug therapy of high-risk lipid abnormalities in children and adolescents. A scientific statement of from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Diseases in the Young with the Council on Cardiovascular Nursing. Circulation. 2007, 115: 1948-1967.
579. Van der Graaf, A.; Cuffie-Jackson, C.; Vissers, M.N.; Trip, M.D.; Gagné, C.; Shi, G.; Veltri, E.; Avis, H.J.; Kastelein, J.J. Efficacy and safety of coadministration of ezetimibe and simvastatin in adolescents with heterozygous familial hypercholesterolemia. J. Am. Coll. Cardiol. 2008, 52, 1421-1429.
580. Shepherd J , Blauw GJ , Murphy MB , et al . Pravastatin in elderly individuals at risk of vascular disease (prosper): a randomised controlled trial. Lancet 2002;360:1623-30.
581. Williams MA, Fleg JL, Ades PA, Chaitman BR, Miller NH, Mohiuddin SM, Ockene IS, Taylor CB, Wenger NK. Secondary Prevention of Coronary Heart Disease in the Elderly (With Emphasis on Patients ≥75 Years of Age). Circulation. 2002;105:1735-1743.
582. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet 2019;393:407-15.
583. Savarese G, Gotto Jr. AM, Paolillo S, D'Amore C, Losco T, Musella F, Scala O, Marciano C, Ruggiero D, Marsico F, De Luca G, Trimarco B, Perrone-Filardi P. Benefits of Statins in Elderly Subjects Without Established Cardiovascular Disease: A Meta-Analysis. J Am Coll Cardiol. 2013;62:2090-2099.
584. Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RGJ, Craen AJM de, Knopp RH, Nakamura H, Ridker P, Domburg R van, 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.
585. Mortensen MB & Nordestgaard BG. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70-100 years: a contemporary primary prevention cohort. Lancet. 2020 Nov 21;396(10263):1644-1652
586. Ramos R, Comas-Cufí M, Martí-Lluch R, Balló E, Ponjoan A, Alves-Cabratosa L, Blanch J, Marrugat J, Elosua R, Grau M, Elosua-Bayes M, García-Ortiz L, Garcia-Gil M. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. BMJ. 2018 Sep 5;362:k3359.
587. Marcellaud E, Jost J, Tchalla A, Magne J, Aboyans V. Statins in Primary Prevention in People Over 80 Years. Am J Cardiol. 2023 Jan 15;187:62-73.
588. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. Am J Med. 2012; 125(9):882-887.
589. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, Johnson JA. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ. 2006;333:15.
590. World Health Organization. Adherence to long term therapies. Evidence for Action [Internet]. 2003. Available from: http://www.who.int/chp/knowledge/publications/adherence_report/en/
591. Mukhtar O, Weinman J, Jackson SHD. Intentional Non-Adherence to Medications by Older Adults. Drugs Aging. 2014;31:149-157.
592. Bailey SC, Oramasionwu CU, Wolf MS. Rethinking Adherence: A Health Literacy-Informed Model of Medication Self-Management. J Health Commun. 2013;18:20-30.
593. Maningat P, Gordon BR, Breslow JL. How do we improve patient compliance and adherence to long-term statin therapy? Curr Atheroscle Rep. 2013;15(1):291.
594. Wouters H, Van Dijk L, Geers HCJ, Winters NA, Van Geffen ECG, Stiggelbout AM, et al. (2016) Understanding Statin Non-Adherence: Knowing Which Perceptions and Experiences Matter to Different Patients. PLoS ONE 11(1): e0146272. doi:10.1371/journal.pone.0146272.
595. Kini V, Ho PM. Interventions to Improve Medication Adherence: A Review. JAMA. 2018;320(23):2461-2473.
596. Flowers N, Hartley L, Todkill D, Stranges S, Rees K. Co-enzyme Q10 supplementation for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2014;CD010405.
597. 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 [Internet]. London: National Institute for Health and Care Excellence (UK); 2014 [cited 2017 Feb 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK248067/
598. Natural Medicines Comprehensive Database; Therapeutic Research Center. Natural medicines in the clinical management of hyperlipidemia [Internet]. 2013;Available from: http://naturaldatabase.therapeuticre search.com/ce/ceCourse
599. Grant SJ, Bin YS, Kiat H, Chang DH-T. The use of complementary and alternative medicine by people with cardiovascular disease: a systematic review. BMC Public Health. 2012;12:299.
600. Voon PT, Ng TK, Lee VK, Nesaretnam K. Diets high in palmitic acid (16:0), lauric and myristic acids (12:0 1 14:0), or oleic acid (18:1) do not alter postprandial or fasting plasma homocysteine and inflammatory markers in healthy Malaysian adults. Am J Clin Nutr. 2011;94:1451-1457.
601. U.S. Department of Agriculture, Agricultural Research Service.USDA National Nutrient Database for Standard Reference, Release September 2015, slightly revised May 2016.Available at: https://ndb.nal.usda.gov/ndb/ Accessed March 7th 2023.

Acknowledgements

The committee of this guideline would like to express their gratitude and appreciation to the following for their contribution:

- Technical Advisory Committee, Clinical Practice Guidelines, Ministry of Health for their valuable input and feedback.
- Panel of external reviewers who reviewed the draft.

Disclosure Statement

The panel members have no potential conflict of interest to disclose.

Sources of Funding

The development of the CPG was funded by the National Heart Association of Malaysia. The views and interests of the funding body did not influence the content of the guideline.

e ISBN 978-967-11794-7-5