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Saudi Health Council

Saudi Guidelines for Dyslipidemia Management

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The Task Force for Dyslipidemia Management Guideline

Jamilah AlRahimi[1,2,*], Shukri AlSaif[3], Mirvat Alasnag[4], Zuhier Awan[5], Fawaz Almutairi[6], Hajer Al Mudaiheem[7], Baris Gencer[8,9], Alberico L. Catapano[10], François Mach[8], Adel Tash[11,12]

[1]Cardiology Department, King Faisal Cardiac Center, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Jeddah, Saudi Arabia

[2] Cardiology Department, King Abdullah International Medical Research Center, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia

[3] Saud AlBabtain Cardiac Center, Dammam, Saudi Arabia

[4] Catheterization Laboratory, King Fahd Armed Forces Hospital, Jeddah, Saudi Arabia

[5] Medicine, Biochemistry and Molecular Genetics, Clinical Biochemistry Department, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

[6] Security Forces Hospital, Riyadh, Saudi Arabia

[7] Therapeutic Affairs Deputyship, Ministry of Health, Riyadh, Saudi Arabia

[8] Cardiology Department, Geneva University Hospital, Geneva, Switzerland

[9] Institute of Primary Healthcare (BIHAM), Bern University, Bern, Switzerland

[10] Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy

[11] Cardiac Services Development, Ministry of Health, Riyadh, Saudi Arabia

[12] National Heart Center, Saudi Health Council, Riyadh, Saudi Arabia

Corresponding Author*: Jamilah S. AlRahimi, Assistant Professor Medicine/Cardiology, Department of Cardiac Science, King AbdulAziz Medical City- Ministry of National Guard Health Affairs, King Abdullah International Medical Research Center, College of Medicine, King Saud bin AbdulAziz University for Health Sciences, Jeddah, Saudi Arabia. Address. P.O. Box 9515, 21423 Jeddah, Saudi Arabia. Tel. 00966505616454. Fax: 920008668 ext 25809. Email. alrahimija@gmail.com.

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Abbreviations and Acronyms

ACS	Acute coronary syndrome
Apo	Apolipoprotein
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft surgery
CAC	Coronary artery calcium
CAD	Coronary artery disease
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
CKD	Chronic kidney disease
COVID-19	Coronavirus disease 2019
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
CYP450	Cytochrome P450
DALYs	Disability-adjusted life-years
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
FH	Familial hypercholesterolemia
FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk
HbA1c	Glycated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HMG-CoA	Hydroxymethylglutaryl-coenzyme A
HTA	Health Technology assessment
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)

MACE	Major adverse cardiovascular events
MET	Metabolic equivalent
MI	Myocardial infarction
MOH	Ministry of Health
mRNA	Messenger RNA
ODYSSEY Outcomes	Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PHC	Primary healthcare
PURE	Prospective Urban Rural Epidemiology
RA	Rheumatoid arthritis
REDUCE-IT	Reduction of Cardiovascular Events with EPA-Intervention Trial
RR	Relative risk
SCORE	Systematic Coronary Risk Estimation
SFDA	Saudi Food and Drug Authority
SHC	Saudi Health Council
siRNA	Small interfering RNA
TC	Total cholesterol
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TGs	Triglycerides
TIA	TIA Transient ischemic attack
WHO	World Health Organization

1. Preamble

Since its establishment in 2014, the Saudi Health Council (SHC) has stepped up to embrace a core mission of "establishing regulations that ensure coordination and integration among health stakeholders to improve health care in Saudi Arabia, and to be an inspirational reference to a world-class Saudi health system". In light of this mission, SHC took over the responsibility to put forward efficient health care strategies, regulations, and policies in the Kingdom to ensure that hospitals run by the Ministry of Health (MOH) and other government agencies are operated in adherence to the principles of economic management as well as performance and quality standards.

In light of the alarming status of atherosclerotic cardiovascular disease (ASCVD) risk factors in Saudi Arabia and recent data about serious gaps in quality of healthcare delivery, specifically in areas of clinical effectiveness, patient-centered care, and patient safety [1,2], SHC has taken the worrying status of dyslipidemia in Saudi patients very seriously and assigned a task force to develop national guidelines for dyslipidemia management to be a cornerstone for the development of subsequent guidelines addressing other ASCVD risk factors amongst the Saudi population. This task force recruited Saudi experts and specialists from different regions of the Kingdom, including the Director-General of the National Heart Center and other members representing various health sectors, to typify professionals involved with managing patients with dyslipidemia. One member representing the Drug Policy and Regulation at the Saudi MOH ensured all recommendations are in line with the health economic considerations that consider both clinical- and cost-effectiveness perspectives. In addition to European experts who extensively reviewed the guidelines as well as the endorsement process. Members of the assigned Task force have volunteered their time and effort to produce these recommendations with the highest level of proficiency. The designated steering committee reviewed the previously published guidelines and related

statements deemed pertinent to these guidelines; thus, obviating the need to implement existing guideline recommendations of different regions. The overall aim of the present document is therefore to provide a nationwide, evidence-based policy and guidelines to implement a unified approach for the management of dyslipidemia in Saudi Arabia.

The level of evidence and the strength of the recommendation are adapted from the 2019 ESC/EAS Guidelines for the management of dyslipidemia [3], where management options were graded as per predefined scales ***(Table 1).*** A third party, RAY-Contract Research Organization (RAY-CRO), coordinated the preparation of these new guidelines and provided professional writing and editorial support. After appropriate revisions, the final document was approved by all Task Force members. All experts involved in the development of these guidelines declared no real or potential sources of conflicts of interest. These Saudi clinical practice guidelines provide recommendations applicable to Saudi patients with or at risk of developing cardiovascular disease (CVD). The guidelines summarize and evaluate available evidence with a focus on the Saudi published literature and the best-available up-to-date research evidence from other international research and guidelines. It is worth emphasizing that the European Society of Cardiology guideline recommendations, categorizations, targets, and cut-offs were the main guide while developing these Saudi dyslipidemia guidelines since it is strongly believed that the tighter control imposed by the European Society of Cardiology is the most appropriate to be implemented in Saudi Arabia.

Table 1. Classes of recommendations and levels of evidence

Classes of recommendations		Levels of evidence	
Class I	Evidence and/or general agreement that a given strategy is beneficial (wording to use "recommended").	**Level A**	Data derived from multiple randomized clinical trials or meta-analyses.
Class II	**Class IIa:** Conflicting evidence, but in favor of usefulness (wording; "should").	**Level B**	Data derived from a single randomized clinical trial or large non-randomized studies.
	Class IIb: Conflicting evidence, but usefulness is less well-established (wording; "may").		
Class III	Evidence or general agreement that the given strategy is not useful and may be harmful.	**Level C**	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Adapted from [3]

2. Introduction

The current recommendations state that adherence to lifestyle modifications and the use of lipid-lowering medications are the cornerstones for reducing the risk for ASCVD in patients with dyslipidemia. Nonetheless, the management of dyslipidemia undergone a number of significant changes over recent years, leading to revisions in both European and US guidelines [3,4]. Such revisions include new thresholds and goals, changes in primary and secondary preventive approaches, the new classification of the risk-enhancing factors, and new definitions for risk groups; these changes are also influenced by new equation values, recommendations, and actions [3–5]. However, the published international guideline cannot be directly applied to the Saudi population who differs in a number of aspects from European and American populations [6].

In Saudi Arabia, the mean age of the population is younger, with 72.5% aged between 15-64 years. The Saudi population is multi-ethnic, and disparities between groups are prevalent due also to geographical and cultural factors. The annual growth rate of the Saudi population is 2.3%, with a median life expectancy of 75 years. There is a high prevalence of obesity (24.7%), and approximately 25.2% of the total population have diabetes mellitus (DM). In addition, there is a lack of primary health care units (0.6 PHC per 10,000 population) [7–10]. In Saudi Arabia, over the past years, ischemic heart disease has persisted in ranking first as the top cause of death from 2000 to 2019, followed by stroke [11]. Furthermore, cardiovascular diseases collectively remained as the leading cause of disability-adjusted life-years (DALYs*) in Saudi Arabia from 1990 until 2017 ***(Figure 1)*** [12]. Prevalence of ASCVD risk factors has been consistently high over the past decades, and multiple surveys have shown the continued high prevalence of dyslipidemia, unhealthy diet, hypertension,

*disability-adjusted life-years quantifies the health loss due to specific diseases and injuries [150]

smoking, obesity, physical inactivity, and diabetes in Saudi Arabia across different age groups [7,8,13–16].

In this document, the Saudi experts have provided recommendations and guidance for detailed risk assessment, the position of newer cholesterol-lowering drugs within the management algorithm, and the need for special attention to patient subgroups. Besides, the experts recommended treatment algorithms using an evidence-based approach. The guideline updated the patient risk assessment and treatment options in primary and secondary prevention using the most up-to-date evidence to inform the clinicians during the process of shared decision-making, aiming to align these decisions with the recent recommendations of the international guidelines. This document has been developed for healthcare professionals to facilitate informed communication with individuals about their cardiovascular risk and the benefits of adopting and sustaining a healthy lifestyle, and of early modification of their lipid-related cardiovascular risk. This guideline has the potential to promote up-to-date management strategies and to translate them into locally delivered healthcare services, in line with the recommendations of the World Health Organization (WHO) [6].

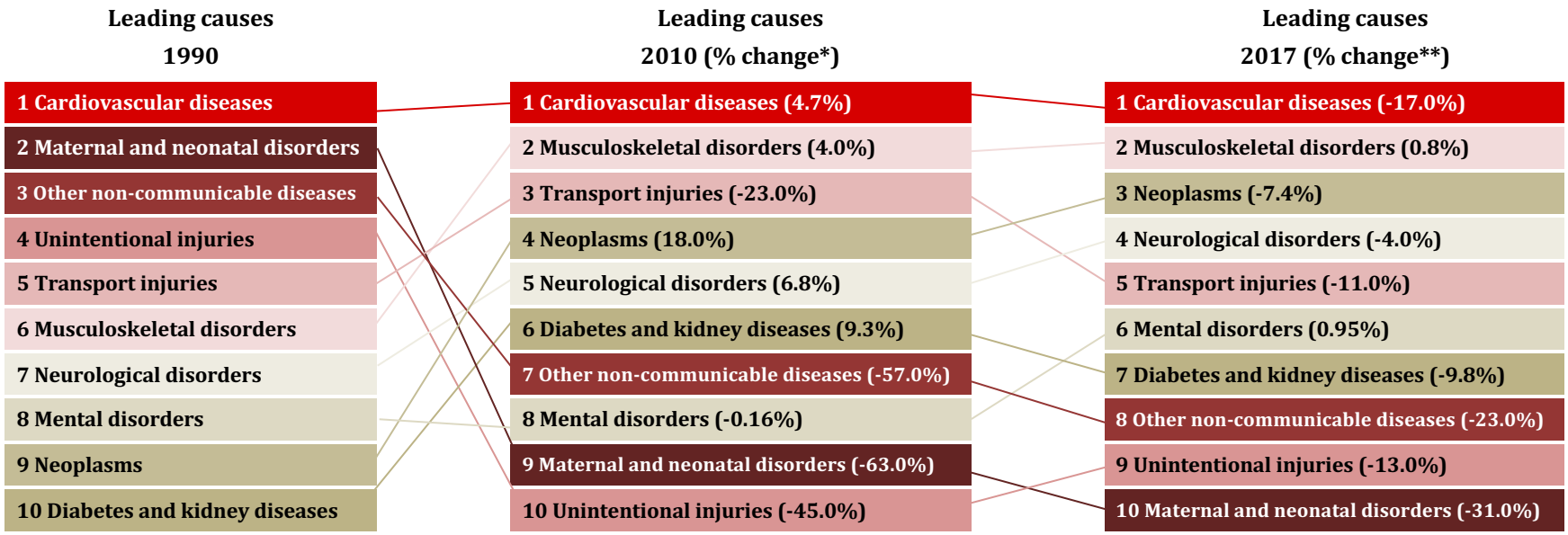

Figure 1. Top 10 causes of DALYs in Saudi Arabia for the periods 1990–2010 and 2010–2017, both sexes

Adapted from [12]
*Percentage change in the number of age-standardized DALYs, 1990–2007.
**Percentage change in the number of age-standardized DALYs, 2010–2017.

3. Cardiovascular Disease risk and risk groups

3.1. Total cardiovascular risk estimation

Cardiovascular (CV) risk is the likelihood of a person to develop an atherosclerotic CV event over a defined period of time, and the total risk of developing CVD, i.e., total CV risk estimation, is determined by the combined effect of multiple risk factors which commonly coexist and act multiplicatively [3]. Risk assessment systems are used to improve management decisions by way of providing a 10- year estimate of an individual's risk for ASCVD events, and therefore, many systems have been developed and comprehensively reviewed [17–26]. Ideally, risk charts should be based on country-specific cohort data since estimating risk based on cohorts that differ greatly from the target population could jeopardize the benefit of risk charts in practical terms. However, these are not available for most countries, including Saudi Arabia [27,28].

A recent Expert Opinion was published in 2018 by Alshamiri et al. [28], in which an expert panel had convened to review the commonly used international guidelines in Asia and the Middle East and to determine their applicability in the region. There was agreement that existing risk calculators may not be suitable for Asia and the Middle East, with many concerns about the validity of these calculators in local populations. However, despite disparities on which risk calculator to use across the countries represented, the panel advocated the value of using such tools to assess CV risk. In fact, the Systematic Coronary Risk Estimation (SCORE) system [29,30] is the most adopted in Saudi Arabia despite not being yet validated for the Saudi population. It provides a relatively straightforward method and allows for recalibration for use in different populations. However, it estimates the risk of fatal CVD events only and overlooks the total CVD events which occur at a higher frequency (approximately 3- to 4-fold greater) [28,31,32]. Thus, the development of a new risk calculator that is optimized for the Saudi population, and that includes important risk

factors in terms of relevance to the Saudi community (including non-traditional risk factors), is a gap that needs to be met to ensure all patients are adequately assessed and managed. Recommendations for cardiovascular disease risk estimation in Saudi Arabia are presented in ***Table 2.***

In this context, it should be recalled that the mean age of presentation with the acute coronary syndrome (ACS) in Saudi Arabia is almost 10 years younger than the average age in developed countries, and this is due to the high prevalence of poorly controlled ASCVD risk factors [33,34]. Thus, risk factor screening in Saudi Arabia, including the lipid profile, should be considered earlier than recommended in developed countries ***(Table 2)***.

Table 2. Recommendations for cardiovascular disease risk estimation in Saudi Arabia

Recommendations	COR[a]	LOE[b]
Total risk estimation using the SCORE system is recommended in Saudi Arabia despite not being yet validated for the Saudi population.	I	C [28–30]
The development of a new risk calculator that is optimized for the Saudi population is recommended.	I	C [28]
Routine assessment using the SCORE system of asymptomatic Saudi adults >40 years of age without evidence of CVD, DM, CKD, FH, or LDL-C >4.9 mmol/L (>190 mg/dL) is recommended to calculate the 10-year risk of ASCVD.	I	C [3]
For Saudi adults 20 to 39 years of age, traditional ASCVD risk factors should be assessed at least every 4 years.	IIa	B [24,35,36]

ASCVD= atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; SCORE = Systematic Coronary Risk Estimation.
[a]Class of recommendation
[b]Level of evidence

3.2. Risk categories

The cut-off points used to define different risk categories in the 2019 European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias [3] are recommended to be adopted in Saudi Arabia and are presented in ***Table 3.*** From a practical point, individuals with certain conditions (such as; patients with documented CVD, older individuals with long-standing DM, chronic kidney disease (CKD), familial hypercholesterolemia (FH), extreme Lipoprotein(a) (Lp(a)) elevation, coronary artery calcium (CAC) score >100, or carotid or femoral plaques) are at high or very high risk of CVD.

Table 3. Cardiovascular risk categories in the Saudi population

Very-high-risk	High-risk	Moderate-risk	Low-risk
Saudi individuals with any of the following: Documented ASCVD, either clinical[c] or unequivocal[d] on imaging. DM with target organ damage[e] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.	***Saudi individuals with any of the following:*** Markedly elevated single risk factors, in particular total cholesterol (TC) >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage[e] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 3059 mL/min/1.73 m2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.	***Saudi individuals with any of the following:*** Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.	***Saudi individuals with*** calculated SCORE <1% for 10-year risk of fatal CVD.

Adapted from [3]
ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM = type 2 DM; TC = total cholesterol; TIA = transient ischemic attack.
[a]Class of recommendation
[b]Level of evidence
[c]Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease.
[d]Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (a multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound.
[e]Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy.

3.3. Treatment goals across total cardiovascular disease risk categories

Treatment goals have been defined in accordance with an overall ASCVD risk score determining the 10-year risk of any cardiovascular event [3]. In general, it is accepted that the reduction in low-density lipoprotein cholesterol (LDL-C) levels should persist indefinitely as the reduction is associated with a parallel reduction of ASCVD events. The evidence has not identified a predetermined level of LDL-C below which benefit ceases, or harm supersedes. The purpose of defining targets is to attain the maximum compliance to lipid-lowering management on the part of both the patients and practitioners. As such, it is reasonable to target an LDL-C level that is as low as possible [37–39]. However, individual variations in response to therapy have been reported with ample evidence of residual risk. It is, therefore, imperative to individualize the treatment strategy [40]. Treatment goals across total cardiovascular disease risk categories are presented in ***Figure 2.***

Patients with FH are at high cardiovascular risk, and the treatment goal is LDL cholesterol <1.8 mmol/l or at least a 50 % reduction in LDL cholesterol. However, early detection and prevention of events are the real goals in the management of this high-risk population.

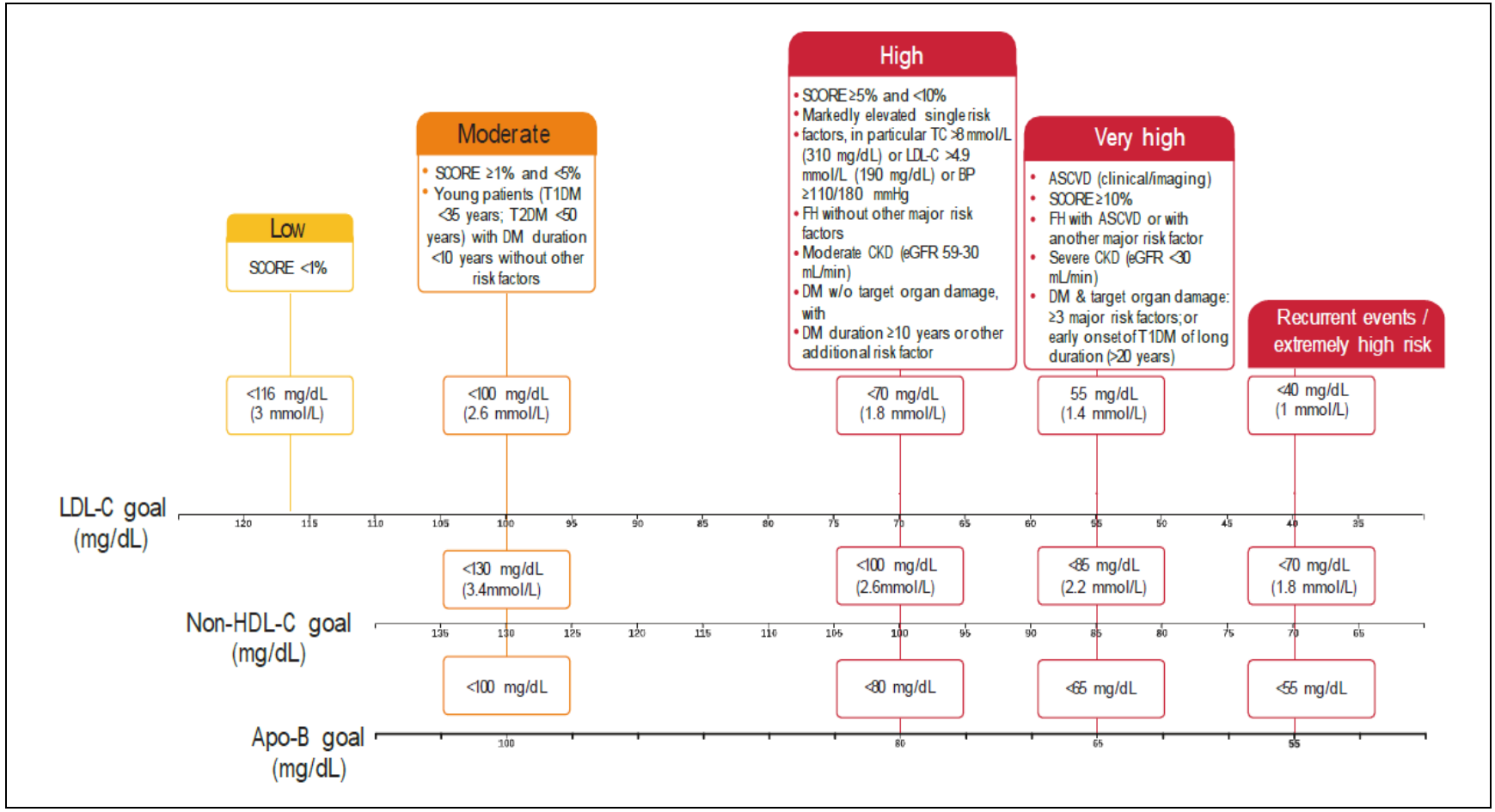

Figure 2. Treatment goals across total cardiovascular disease risk categories applied to the Saudi population

Apo-B = apolipoprotein B; ASCVD= atherosclerotic cardiovascular disease; BMI, body mass index; BP = blood pressure; CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TC = total cholesterol.

3.4. Risk factors

The risk factors for ASCVD are age, gender, cholesterol and lipoprotein abnormalities, hypertension, DM, pre-diabetes, insulin resistance, and lifestyle factors (including tobacco use, overweight and obesity, unhealthy diet, limited physical activity, and air pollution) ***(Figure 3)*** [4,35,41]. Continuing exposure to risk factors results in further ASCVD progression. Total CVD risk depends on the individual's overall risk-factor profile ***(Tables 4, 5&6)***.

Age and gender are main drivers of CVD risk. Women >75 and men >65 years of age are almost always at high 10-year CVD risk [41]. In Saudi Arabia, results from a cross-sectional community-based study covering the whole population from all the 20 health regions of the kingdom aged between 15 and 64 years revealed that TGs and the ratio of total cholesterol (TC)/ High-density lipoprotein cholesterol (HDL-C) were significantly higher in males, while HDL-C and TC were significantly higher in females. No significant differences in LDL-C concentration according to gender were observed (p = 0.341). Moreover, significantly higher dyslipidemia prevalence of TC and TG was found in older subjects [42] ***(See Supplementary Material; Supplementary Table 1)***.

LDL-C is highly atherogenic, and the cumulative LDL-C arterial burden is a central determinant for ASCVD initiation and progression. Lowering LDL-C reduces the risk of CV events, and both relative and absolute risk reductions are associated with the magnitude of LDL-C reduction [43]. Assessment of LDL-C is the mainstay component of the management of ASCVD risk [3,44]. Alike, the relationship between non-high-density lipoprotein cholesterol (non-HDL-C), which encompasses all atherogenic, i.e., Apo-B-containing, lipoproteins; and CV risk is at least as strong as the relationship with LDL-C [41]. Apo-B-containing lipoproteins have a central causal role in the initiation and progression of atherosclerosis, and quantitation of Apo-B directly estimates the number of atherogenic

particles in plasma [3]. In Saudi Arabia, dyslipidemia is the most prevalent ASCVD risk factor (68.6%) [45], and the prevalent pattern is low HDL-C and high triglycerides (TG) which is different from many other regions in the world. The high prevalence of metabolic syndrome, DM, FH, and consanguineous marriages is the main contributing factor behind this pattern in the kingdom [46,47].

With regards to hypertension, a national survey conducted in the kingdom including 10,735 participants found that 15.2% (17.8% for males and 12.5% for females) and 40.6% were hypertensive or borderline hypertensive, respectively [48]. DM is steadily increasing and rapidly becoming one of the main health issues in Saudi Arabia, with major fear about millions of undiagnosed cases [49]. More than one quarter (25.2%) of the Saudi adult population has diabetes, which is predicted to more than double by 2030. Moreover, the WHO ranks Saudi Arabia second in the prevalence of DM in the Middle East region and seventh in the world [50]. In fact, Saudi Arabia reached a point where DM is considered an epidemic [51]. Atherogenic dyslipidemia is one of the major risk factors for CVD in people with type 2 DM (of which about 50% have elevated TGs or low HDL-C levels) and in people with abdominal obesity and insulin resistance or impaired glucose tolerance [3].

Cigarette smoking prevalence in Saudi Arabia is has shown to be more prevalent in the Northern regions, relatively high in the male population at 32.5%, in particular among those aged between 25 - 44 years old, and 3.9% among females [52]. Heart disease, DM, and hypertension were already present and diagnosed in 5.2%, 12.5%, and 23.2%, respectively, amongst smokers surveyed in that study. Ibrahim Alasqah [53] reported a prevalence of smoking ranging from 12.7% to 39.6% among adolescents regardless of their educational stage. The prevalence amongst female adolescents ranged between 1.6% to 11.1% [54]. Moreover, epidemiological data have shown alarming evidence of high water pipe usage among Saudi teenagers and college students [55].

The prevalence of overweight and obesity in the Saudi population across different age groups is high, indicating ineffectiveness or lack of preventive measures ***(Figure 4)*** [8]. According to World Atlas data, Saudi Arabia is ranked 12 among obese countries [56]. The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration revealed that both overweight (body mass index (BMI) ≥25 to <30 kg/m^2) and obesity (BMI ≥30 kg/m^2) were associated with a significantly increased risk of coronary heart disease (CHD) and stroke, compared with normal weight (BMI ≥20 to <25 kg/m2), with 50% of the excess risk of overweight and 44% of the excess risk of obesity for CHD mediated by blood pressure (BP), cholesterol, and glucose [57].

Excessive consumption of caffeinated or carbonated drinks all sweetened with sugar, higher consumption of foods rich in fat, carbohydrates, and salt, and lower consumption of fruits and vegetables amongst the Saudi population are associated with increased risk of dyslipidemia [58]. Moradi-Lakeh et al. conducted a household survey in 2013 in 10,735 Saudi individuals aged ≥15 years. Dietary guideline recommendations were met by only 5.2% of individuals for fruits, 7.5 % for vegetables, 31.4 % for nuts and 44.7 % for fish [59]. The majority of Saudis are not active enough to meet the recommended guidelines for moderate to vigorous physical activity [60]. Females were significantly less active than males in terms of percentages spent more than 1680 metabolic equivalent values (METs[a])-min/week[b] and more than 2520 METs-min/week[c] (21.9% vs 55.5%, and 12.9% vs 43.5% for Saudi females and males, respectively, $p < 0.01$) [61]. The prevalence of physical inactivity appears to increase with advancing age. The most important barriers to physical inactivity are the lack of time, followed by lack of appropriate place (especially for females), and lack of facility and

[a] Physical activities were assigned metabolic equivalent (MET) values based on the compendium of physical activity [151] and the compendium of physical activity for youth [152].
[b] = 60 min per day × 7 days/week × 4 METs (moderate-intensity physical activity).
[c] = 60 min per day × 7 days/week × 6 METs (moderate- to vigorous-intensity physical activity)

resources. Physical inactivity is significantly associated with obesity and waist circumference in adults, children, and adolescents [60].

Air pollution is a major contributor to the global burden of disease, and accounted for 12% and 20% of all deaths and CVD deaths, respectively in 2019. Further, air pollution was the 4th highest-ranking risk factor for mortality, with more attributable deaths than high LDL-C, high BMI, physical inactivity, or alcohol use [62]. Air pollution is a complex and dynamic mixture of numerous compounds in gaseous and particle form, originating from diverse sources. Particulate matter is responsible for the vast majority of the disease burden via its impact on ischemic heart disease and stroke [63,64]. In Saudi Arabia, several studies have emphasized the association between air pollutants and CVD, as well as the detrimental induction of genes involved in inflammation, lipid metabolism, and atherosclerosis [65,66] ***(See Supplementary Material; Supplementary Table 1)***.

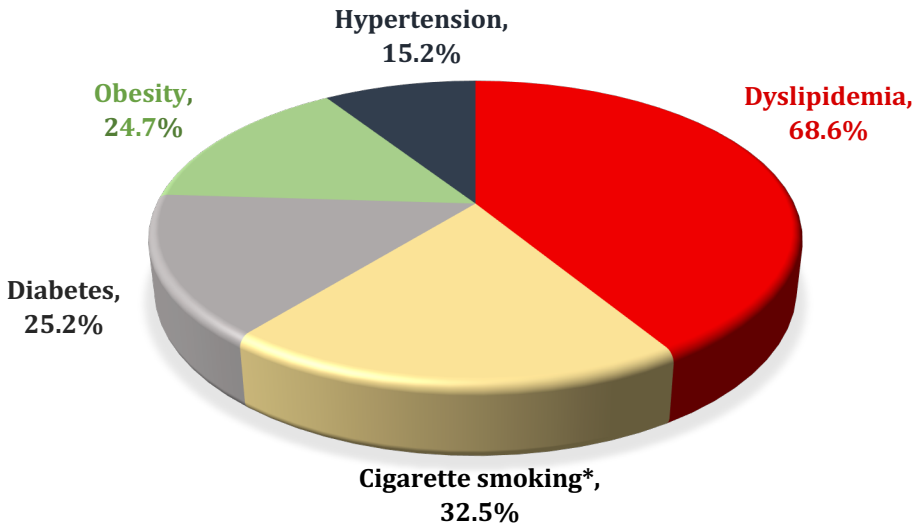

Figure 3. **Prevalence of cardiovascular risk factors in Saudi Arabia**

*Males.

Adapted from [4,35,41].

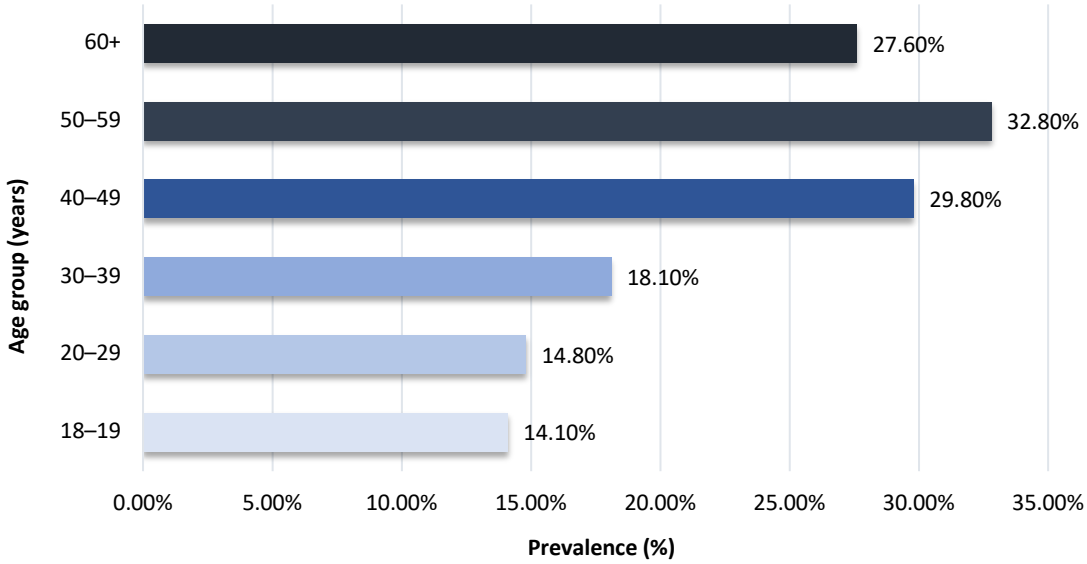

Figure 4. **Prevalence of obesity in Saudi Arabia stratified by age group**

Adapted from [7].

Table 4. Recommendations for lipid analyses in Saudi Arabia

Recommendations	COR[a]	LOE[b]
TC, TG, HDL-C, LDL-C, and non-HDL-C are recommended as the primary lipid panel to estimate the risk of ASCVD and to guide therapeutic decision-making.	**I**	**C** [67]
LDL-C analysis is recommended as the mainstay component for screening, diagnosis, and management of ASCVD, and LDL-C is recommended as the primary target of lipid-lowering therapies.	**I**	**C** [43,68–70]
Apo-B can be measured directly and accurately and better predicts risk under all circumstances than LDL-C or non-HDL-C. If available, Apo-B analysis may be used as an alternative to LDL-C as the primary measurement for screening, diagnosis, and management.	**IIb**	**C** [71]
Apo-B analysis should be considered over LDL-C or non-HDL-C for risk assessment in patients with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels.	**IIa**	**C** [71]
Lp(a) should be considered for ASCVD risk estimation at least once in each adult person's lifetime, especially in patients with premature ASCVD[c], family history of premature ASCVD, and/or elevated Lp(a), FH, recurrent ASCVD despite optimal lipid-lowering treatment.	**IIa**	**C** [72]
Non-fasting/random lipid sampling may be used for screening purposes. An alternative approach is to measure the random non-HDL-C for convenience and better prediction.	**IIb**	**B** [73]
Fasting lipid profile is recommended to confirm the diagnosis and for further monitoring.	**I**	**B** [73]

ASCVD= atherosclerotic cardiovascular disease; DM = diabetes mellitus; FH = familial hypercholesterolaemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides.

[a]Class of recommendation

[b]Level of evidence

[c]Men <55 years, women <60 years

Table 5. Recommendations for treatment goals for LDL-C in Saudi Arabia

Recommendations	COR[a]	LOE[b]
In secondary prevention for patients at very-high risk, an LDL-C reduction of >_50% from baseline[c] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended	I	A [68,74–77]
In primary prevention for individuals at very-high risk but without FH, an LDL-C reduction of >_50% from baselined and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended	I	C [68,75,78]
In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of >_50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended.	I	C [3]
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy are considered at extremely high risk, and an LDL-C goal of <1.0 mmol/L (<40 mg/dL) is recommended.	I	B [5,76,77]
In patients at high risk, an LDL-C reduction of >_50% from baselined and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.	I	A [68,75]
In individuals at moderate risk, an LDL-C goal of <2.6 mmol/L (<100 mg/dL) is recommended.	I	A [75]
In individuals at low risk, an LDL-C goal <3.0 mmol/L (<116 mg/dL) should be considered.	IIa	A [78]

ASCVD= atherosclerotic cardiovascular disease; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.
[a]Class of recommendation
[b]Level of evidence
[c]The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C-lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.

Table 6. Goals for cardiovascular disease prevention in Saudi Arabia

Parameter	Goal
LDL-C	• Recurrent events (extremely high-risk); an LDL-C goal of <1 mmol/L (<40 mg/dL). • Very-high-risk in primary or secondary prevention; an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended. • High-risk; a therapeutic regimen that achieves ≥50% LDL-C reduction from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL). • Moderate-risk; an LDL-C goal of <2.6 mmol/L (<100 mg/dL). • Low-risk; an LDL-C goal of <3.0 mmol/L (<116 mg/dL).
Non-HDL-C	• Recurrent events (extremely high-risk); a non-HDL-C goal of <1.8 mmol/L (<70 mg/dL). • Very-high-risk in primary or secondary prevention; a non-HDL-C goal of <2.2 mmol/L (<85 mg/dL) are recommended. • High-risk; a non-HDL-C goal of <2.6 mmol/L (<100 mg/dL). • Moderate-risk; a non-HDL-C goal of <3.4 mmol/L (<130 mg/dL).
Apo-B	• Recurrent events (extremely high-risk); an Apo-B goal of <55 mg/dL. • Very-high risk in primary or secondary prevention; an Apo-B goal of <65 mg/dL. • High-risk; an Apo-B goal of <80 mg/dL. • Moderate-risk; an Apo-B goal of <100 mg/dL.
TG	• No goal, but <1.7 mmol/L (<150 mg/dL) indicates lower risk, and higher levels indicate a need to look for other risk factors.
Blood pressure	• <140/90 mmHg.
DM	• HbA1c <7% (<53 mmol/mol).
Tobacco use[a]	• No exposure to tobacco in any form
Body weight	• BMI 20-25 kg/m^2, waist circumference <94 cm (men) and <80 cm (women).
Diet	• A healthy diet low in saturated fat with a focus on wholegrain products, nuts, vegetables, lean vegetable or animal protein, and fish, and minimizes the intake of trans fats, red meat and processed red meats, refined carbohydrates, and sweetened beverages.

Physical activity	• 3.5-7 h moderately vigorous physical activity per week or 30-60 min most days.

Adapted from [3,35]

[a]This includes all types of tobacco products such as cigarettes, cigars, shisha, electronic cigarettes, etc., as well as smokeless tobacco use (e.g., chewing tobacco) and secondhand smoke.
BMI, body mass index; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol; TG = triglycerides.

3.5. Risk enhancers

Risk enhancing factors are independent of other risk associated with ASCVD. Assessing for risk-enhancing factors can help guide decisions about preventive interventions in adults at borderline or intermediate risk and to adjust the intensity of LDL-lowering therapy ***(Table 7)*** [4,35]. Family history of premature ASCVD (males, age <55 y; females, age <60 y) is a risk-enhancing factor that should be considered for clinician-patient risk discussion ***(See Table 10; Recommendations for FH management in Saudi Arabia).*** Metabolic syndrome, another risk enhancer, is characterized by the clustering of central obesity, dyslipidemia, elevated BP, and hyperglycemia [35]. A large cross-sectional study that included 12,126 Saudi subjects reported a high prevalence of metabolic syndrome in Saudi Arabia that equals 39.8% (34.4% in men and 29.2% in women). The most frequently observed component of metabolic syndrome was low levels of HDL-C, followed by abdominal obesity [79]. Despite patients with metabolic syndrome being classified as high-risk, precise figures about its prevalence and response to treatment in Saudi Arabia are still lacking [80].

CKD is an important disorder worldwide that affects more than 10% of adults and increases the risk of many adverse outcomes; among them, CVD is particularly important. As CKD progresses, kidney-specific risk factors for CV events and disease come into play and ultimately increase the risk for CVD. Moreover, raised concentrations of albumin in urine and impaired kidney function increase the risk of CVD by 2 to 4 times. CVD is the leading cause of death in persons with CKD [81,82]. In Saudi Arabia, adequate epidemiological data about CKD is lacking. However, figures from a pilot community-based screening program in 2010 concluded that the prevalence of CKD is around 5.7% in Riyadh city [83].

Table 7. **ASCVD risk-enhancing factors, cut-off values/conditions, and recommendations in Saudi Arabia**

Risk-enhancing factors and the corresponding cut-off values/conditions	Cut-off values/conditions	Recommendations	COR[a]	LOE[b]
Metabolic syndrome*	Increased waist circumference Elevated TG >150 mg/dL, non-fasting Elevated BP (≥130/85 mm Hg) Elevated fasting glucose (≥110 mg/dL) Low HDL-C <40 mg/dL in men; <50 mg/dL in women	Counseling and comprehensive lifestyle interventions, including calorie restriction and adjunctive therapies, are recommended to reduce waist circumference and improve the cardio-metabolic risk profiles.	**I**	**B** [35,84,85]
CKD	eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation	Patients with Kidney Disease Outcomes Quality Initiative stage 3-5[c] CKD are recommended to be managed as the high or very-high risk of ASCVD.	**I**	**A** [3]
Elevated high-sensitivity C-reactive protein	≥2.0 mg/L	The high-sensitivity C-reactive protein diagnostic test is recommended to detect very low levels of C-reactive protein and thereby enable a more accurate and precise measure of chronic inflammation compared with standard C-reactive protein.	**I**	**A** [86]
		In adults 40 to 75 years of age without DM and at intermediate risk, high-sensitivity C-reactive protein ≥2.0 mg/L is associated with increased ASCVD risk and should favor initiation of lipid-lowering therapy.	**IIa**	**A** [4]

History of premature menopause	Age <40 y	Clinicians should consider conditions specific to women when discussing lifestyle intervention and the potential for the benefit of therapy	**IIa**	**B** [4]
History of pregnancy-associated conditions that increase later ASCVD risk	Such as hypertension, preeclampsia, gestational DM			
Persistently elevated* primary hypertriglyceridemia	≥175 mg/dL, non-fasting	Clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (ex. DM, chronic liver disease or CKD, hypothyroidism), or medications that increase triglycerides.	**IIa**	**B** [4]
Primary hypercholesterolemia*	LDL-C, 160–189 mg/dL (4.1–4.8 mmol/L) Non–HDL-C 190–219 mg/dL (4.9–5.6 mmol/L)	In intermediate-risk patients; LDL-C levels should be reduced by 30% or more. In high-risk patients; levels should be reduced by 50% or more.	**IIa**	**B** [4]
Chronic inflammatory conditions	Such as RA, lupus, psoriasis, or HIV/AIDS	In patients with chronic inflammatory disorders or HIV, a fasting lipid profile and assessment of ASCVD risk factors before and 4 - 12 weeks after starting inflammatory disease-modifying therapy or antiretroviral therapy may be useful as a guide to benefit and for monitoring lipid-lowering drug therapy.	**IIb**	**B** [4]
		In adults with RA, it may be useful to recheck lipid values and other major ASCVD risk factors 2 - 4 months after	**IIb**	**B** [4]

		controlling the patient's inflammatory disease.		

AIDS = acquired immunodeficiency syndrome; Apo-B = apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BP = blood pressure; CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); non-HDL-C = non-high-density lipoprotein cholesterol; RA = rheumatoid arthritis, TG = triglycerides.

*Optimally, 3 determinations

[a]Class of recommendation

[b]Level of evidence

[c]Defined as eGFR < 60ml/min/1.73m^2 on two measurements more than 3 months apart.

3.6. Risk modifiers

Risk modifiers are additional risk factors or individual information that can modify the calculated risk. Assessment of risk modifiers is particularly relevant if the individual's risk is close to a decision threshold (i.e., in low-risk or very-high-risk situations, additional information is less likely to alter management decisions) ***(Table 8)*** [41].

Table 8. ASCVD risk modifiers, cut-off values/conditions, and recommendations in Saudi Arabia

Risk Modifier	Cut-off values/conditions	Recommendations	COR[a]	LOE[b]
Coronary artery calcium (CAC) scoring*	In asymptomatic individuals with low or moderate risk, the presence of a CAC score >100 Agatston, and carotid or femoral plaque burden on ultrasonography may reclassify them to a higher risk category.	CAC score assessment with CT should be considered in individuals at low or moderate risk in whom the respective LDL-C goal is not achieved with lifestyle intervention alone.	**IIa**	**B** [3]
Arterial (carotid and/or femoral) plaque burden on arterial ultrasonography	Assessment of carotid or femoral plaque burden with ultrasound is predictive of CV events.	Arterial (carotid and/or femoral) plaque burden on arterial ultrasonography should be considered as a risk modifier in individuals at low or moderate risk.	**IIa**	**B** [87]
Psychosocial stress	Stress symptoms and psychosocial stressors modify CVD risk and are associated in a dose-response pattern with the development and progression of ASCVD.	Physicians should be equally attentive to somatic as to emotional causes of symptoms. Assessment of psychosocial stressors should be considered (RRs are commonly between 1.2 and 2.0).	**IIa**	**B** [65,66]
Socioeconomic determinants	Socioeconomic inequalities are strong determinants of CVD risk. Low socioeconomic status and work stress are independently associated with ASCVD development and prognosis in both sexes.	Clinicians should tailor advice to a patient's socioeconomic and educational status, as well as cultural, work, and home environments	**IIa**	**A** [35,41,88,89]

Ethnicity	Considerable variability in ASCVD risk factors exists between different ethnic groups.	No single CVD risk score performs adequately in all groups. Thus, the use of a multiplying factor may be helpful to take account of CVD risk imposed by ethnicity independent of other risk factors.	**IIb**	**A** [41]

ASCVD= atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CT = computed tomography; CV = cardiovascular; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; RR = relative risk.
*CAC score is increased following statin treatment; therefore, the CAC scores of statin-treated patients should be interpreted with caution.

3.7. COVID-19 and cardiovascular disease

The CV complications of acute coronavirus disease 2019 (COVID-19) are well reported in several studies [90–94]. A recent study by Xie and colleagues [95] used databases of 153,760 individuals with COVID-19 infection, 5,637,647 individuals as contemporary controls, and 5,859,411 individuals as historical controls to estimate risks and 1-year burdens of CV outcomes. The results revealed that individuals with COVID-19 are at increased risk of incident CV disease categories including ischemic and non-ischemic heart disease, myocarditis, pericarditis, dysrhythmias, heart failure, thromboembolic disease, and cerebrovascular disorders beyond the first 30 days after infection. These risks were evident among all individuals, whether hospitalized or not during the acute phase of the COVID-19 infection. These results flagged the evidence that CV disease risk and 1-year burden in survivors of acute COVID-19 are substantial, and care of those survivors should include attention to CV disease.

4. Management of Dyslipidemia in different clinical settings

Aggressive lipid management has been demonstrated to improve cardiovascular outcomes in specific clinical settings such as ACS and other very high-risk entities, namely diabetes, CKD, and FH ***(Table 9).***

4.1. Acute coronary syndromes

With respect to ACS, intensive statin therapy early after a clinical event can reduce future events permitting a significant early pleiotropic effect. Randomized evidence has unequivocally demonstrated benefit with early initiation of treatment, that is, in-hospital and continued long-term [96–99]. Furthermore, high-intensity statin therapy in all patients with ACS is recommended irrespective of the baseline LDL-C values. Immediately after an ACS, it is well known that LDL levels will drop; therefore, ideally, assays should be drawn within the first twenty-four hours [100]. Assays prior to the event are more reliable. The recommended target for LDL-C is a 50% reduction and a level of <1.4 mmol/L (<55 mg/dL). For individuals suffering recurrent events (even in a different territory) within 2 years, a goal of <1.0 mmol/L (<40 mg/dL) for LDL-C is recommended. For very high-risk patients, the first-line treatment strategy is recommended to include high-intensity statin in combination with ezetimibe. If the target is not reached, the addition of PCSK9 monoclonal antibodies is recommended. For the extremely*high-risk patients, initiation of triple combination therapy should be considered as the first-line approach [5,74,77,101]. These agents achieve a sustained reduction in all subgroups and permit a reduction in all events, including cerebrovascular, rehospitalizations, and all-cause death.

*Extremely high risk = post ACS + history of other vascular event/peripheral artery disease/ polyvascular disease/ multivessel coronary artery disease/familial hypercholesterolemia

4.2. Diabetes mellitus

DM is often referred to as an ASCVD equivalent. It confers an independent risk for multiple cardiovascular disorders that is double other factors [102]. Fasting blood glucose has a log-linear correlation with the risk of vascular disease at all concentrations, including below 7 mmol/L, i.e., below the threshold for diabetes. Those with end-organ damage, such as retinopathy and nephropathy, and microvascular dysfunction have a higher risk of cardiovascular events. Additional risk factors render diabetics at even higher risk of cardiovascular events. Diabetics with concomitant coronary artery disease have a significantly worse prognosis and survival after an ACS [103]. Optimal dosing, escalation, and lipid management are critical. Although data suggests a higher risk of development of new-onset diabetes with statin therapy, the majority occur in the subset with prediabetes. The magnitude of the absolute reduction of LDL-C levels and, consequently cardiovascular events, suggest intensive therapy should be encouraged and outweighs any potential risk of new-onset diabetes [104–106].

Of note, data extracted from the Odyssey and Fourier studies revealed no increase in the risk of new-onset diabetes with the use of PCSK9 monoclonal antibodies [76,77]. In their metanalysis, de Carvalho and colleagues reported an increase in fasting blood glucose and glycated hemoglobin (HbA1c) levels in 68,123 patients who were taking concomitant statins and PCSK9 monoclonal antibodies; however, this did not result in a higher incidence of type 2 diabetes. Furthermore, the analysis only included short-term follow-up. The sub-analysis of the landmark Odyssey trial did not observe conversion to diabetes with these agents [77,107].

4.3. Chronic kidney disease

CKD stage 3 is considered high, and stage 4-5 is considered a very-high risk. An estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 and an albumin creatinine ration of 1.1 mg/mmol (10 mg/g) or more are independent predictors of mortality. Therefore, a high-intensity statin is recommended in those with adjunctive risk, established ASCVD, or presenting with an ACS to achieve the maximum reduction [82]. Although adverse events with statin therapy require monitoring, appropriate intensity is advisable as this population has an overall higher risk of cardiovascular events in patients with CKD [108]. In addition, in patients with CKD presenting with acute coronary syndromes, PCSK9 monoclonal antibodies were associated with lower incidence of ASCVD events and all-cause death across all ranges of dysfunction. In fact, the absolute reduction in the MACE* with PCSK9 monoclonal antibodies is greater with more advanced CKD. This further supports the need to intensify lipid-lowering therapy and consider combination regimens early [109–111].

4.4. Women

Women have historically been under-represented in prevention trials. However, metanalyses and pooled data for both statin and non-statin therapy showed an equivalent benefit of women and men in preventive therapies [68,101,112]. Lipid-lowering agents are not recommended during pregnancy or lactation due to the absence of evidence suggesting benefit or harm. However, women with pregnancy-related complications, including gestational diabetes, pre-eclampsia, eclampsia, and a miscarriage, are at higher overall cardiovascular risk [113,114]. Therefore, risk assessment and lipid-lowering measures should be appropriately timed in women after delivery.

* Major adverse cardiovascular events

Table 9. Recommendations for dyslipidemia management in different clinical settings in Saudi Arabia

Recommendations	COR[a]	LOE[b]
Acute coronary syndrome		
Intensive statin therapy early after an ACS clinical event is recommended.	**I**	**A** [96–99]
A statin therapy that includes high-intensity agents in combination with ezetimibe or PCSK9 monoclonal antibodies in all patients with ACS is recommended irrespective of the baseline LDL-C values. The recommended target for LDL-C is a 50% reduction and a level of <1.4 mmol/L (<55 mg/dL).	**I**	**A** [74,76,77]
For secondary prevention in patients at very-high risk not achieving their goal on a maximum tolerated dose of a statin and ezetimibe, a combination with PCSK9 monoclonal antibodies is recommended.	**I**	**C** [3]
For the extremely[c] high-risk patients, initiation of triple combination therapy should be considered as the first-line approach	**IIa**	**C** [5]
Diabetes		
With respect to patients with diabetes and prediabetes, intensive therapy should be encouraged and outweighs any potential risk of new-onset diabetes.	**IIa**	**A** [104–106]
DM with target organ damage or ≥3 major risk factors or early onset of type 1 diabetes mellitus of long duration patients are at very high-risk and a statin therapy that includes high-intensity agents in combination with ezetimibe is recommended, and if target level is not achieved, addition of PCSK9 monoclonal antibodies is recommended.	**I**	**C** [5]
Chronic kidney disease		
High-intensity statin is recommended in patients with CKD stage 3 or higher with adjunctive risk, established ASCVD, or presenting with an ACS to achieve the maximum reduction.	**I**	**A** [3]
Severe CKD (eGFR <30 mL/min/1.73 m^2) patients are at very high-risk and a statin therapy that includes high-intensity agents in combination with ezetimibe is recommended, and if target level is not achieved, addition of PCSK9 monoclonal antibodies is recommended	**I**	**C** [5]

Women		
Lipid-lowering agents are not recommended during pregnancy or lactation due to the absence of evidence suggesting benefit or harm.	**III**	**A** [115]
Risk assessment and lipid-lowering measures should be appropriately timed in women after delivery.	**IIa**	**A** [115]

ASCVD= atherosclerotic cardiovascular disease; CHD = coronary heart disease; CVD = cardiovascular disease; DM = diabetes mellitus; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a).

[a]Class of recommendation

[b]Level of evidence

[c]Extremely high risk = post ACS + history of other vascular event/peripheral artery disease/ polyvascular disease/ multivessel coronary artery disease/familial hypercholesterolemia

4.5. Familial hypercholesterolemia

Dyslipidemia has long been recognized to have a strong genetic basis, which is explicitly related to abnormal lipoproteins levels. When this becomes in its more extreme forms, it can be manifested as familial dyslipidemias. There are different types of familial lipid disorders; among these, FH is the prototypical form of genetic dyslipidemia ***(See Supplementary Material; Supplementary Table 2)*** [3,116,117].

FH is an autosomal co-dominant genetic disorder where both homozygous and heterozygous forms are characterized by elevations in LDL-C > 95th percentile for age and sex. This disorder represents a high-risk population where adequate research on the prevalence and response to treatment in Saudi Arabia is lacking. Nevertheless, it remains underdiagnosed and undertreated in the region, with an estimated prevalence of 1/232 based on the Gulf FH registry. In addition to elevated LDL-C, patients with FH often present with premature ASCVD. Despite diagnosis of high levels of LDL-C, and even after documented cardiovascular events, FH frequently remains undetected and underdiagnosed in the entire Gulf region [118]. Early diagnosis and aggressive therapy are necessary to delay ASCVD complications and reduce future events.

Limited data are available worldwide about FH prevalence, and various studies revealed that FH is underdiagnosed, with only 1% are identified in most countries [119]. In 2021, the results of a multicenter, multinational Gulf FH registry [118] included adults (≥18 years old; 3713 patients had suspected FH and 306 patients had definite or probable FH) recruited from five Arabian Gulf countries over a 5-year period revealed a higher prevalence of FH in the Arabian Gulf region (0.9%; 1:112) compared to the global figures (about 3-fold). Consanguinity, first-cousin marriage, and endogamy rates in Arabian countries are among the highest in the world and are believed to be the major factors contributing to high prevalence of FH [120]. These worrying figures impose a “call-to-action” for further

confirmation studies in Saudi Arabia, in addition to the urgent need for implementation of a nationwide screening program, raising FH awareness, and improving FH management strategies [118,121]. Patients require intensive treatment with statins and ezetimibe and/or colesevelam. Proprotein convertase subtilisin/kexin type 9 inhibitors have been approved for their management. Recommendations for FH management in Saudi Arabia are presented in ***Table 10.***

Table 10. Recommendations for FH management in Saudi Arabia

Recommendations	COR[a]	LOE[b]
Establishing national programs and policies (i.e., national Saudi FH registry, supporting genetic analyses, setting up of specialized lipid clinics, and raising physician awareness) is recommended for early detection of FH in Saudi Arabia, which is particularly important among high-risk populations.	**I**	**A** [118,120]
Diagnosis of FH is recommended to be considered in patients with CHD aged <55 years for men and <60 years for women, in people with relatives with premature fatal or non-fatal CVD, in people with relatives who have tendon xanthomas, in people with severely elevated LDL-C (in adults >5 mmol/L or >190 mg/Dl; in children >4 mmol/L or >150 mg/dL), and in first-degree relatives of patients with FH.	**I**	**A** [3,35]
Patients with FH and no prior ASCVD or other risk factors are recommended to be treated as high-risk patients, and patients with FH and ASCVD or another major risk factor are recommended to be treated as very-high-risk.	**I**	**A** [3]
A one-off measurement of Lp(a) should be considered in further risk stratification of patients with a family history of premature CVD and to identify people with very high inherited Lp(a) levels.	**IIa**	**A** [3]
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor or inclisiran is recommended.	**I**	**C** [3]

ASCVD= atherosclerotic cardiovascular disease; CHD = coronary heart disease; CVD = cardiovascular disease; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a).
[a]Class of recommendation
[b]Level of evidence

5. Regimen Selection

5.1. Pharmacological interventions

When lifestyle interventions are insufficient to attenuate the risk of atherosclerotic vascular disease, drug treatment becomes an essential part of the overall management. Lipid modifying drugs, in addition to continuing lifestyle interventions, should be considered for individualized patient regimen selection. The treatment goals include serum LDL-C, serum TGs or non-HDL-C and Lp(a).

5.1.1. Pharmacological interventions and approved indications (Tables 11&12)

5.1.2. Regimen Selection for different clinical settings

Individuals who have developed ASCVD, have DM or CKD do not require any further risk estimation. These individuals are at very high risk, and pharmacological intervention is recommended to reduce their risk to the lowest possible in addition to appropriate lifestyle interventions. Others require an assessment of overall ASCVD risk. Therapy is recommended for subjects with FH or those that have an elevated 10-year atherosclerotic vascular risk.

Statins are the initial drugs of choice for all patients being considered for pharmacological interventions. The selection of the individual statin must be based on the level of risk and the level of baseline LDL-C. Moderate intensity statins are expected to lower LDL-C between 30 to 50%, while high-intensity statins could reduce this by more than 50%. Patients who do not achieve the desired target should have combination therapy. Patients with FH are likely to require combination therapy with a high intensity statin, a cholesterol absorption inhibitor ezetimibe, and either PCSK9 monoclonal antibody or inclisiran. Patients that have TGs 135mg/dL or higher up to 500mg/dL despite initial therapy with statins should be considered for combination therapy with Eicosapentaenoic Acid Ethyl

Ester, which has been shown to reduce the risk of ischemic events, including cardiovascular death [122]. Patients admitted with ACS are at particularly high risk for recurrent events and justify in-hospital initiation of lipid-lowering therapy starting with high-intensity statin upon admission [123]. Patients with DM must be treated in the same way as patients with established ASCVD. Many of these patients also have elevated TGs that may be related to poor diabetic control. Therefore, these patients require optimization of diabetic control in addition to lifestyle interventions. When these are insufficient to achieve the desired LDL targets or the TGs remain elevated beyond 150 mg/dL then the addition of Eicosapentaenoic Acid Ethyl Ester or fenofibrate should be considered [3].

Table 11. Pharmacological interventions and approved indications

Pharmacological intervention	Lipid reduction (%)	Drugs used in Saudi Arabia	Therapeutic indications approved by the SFDA[a]
Moderate or high-intensity HMG-CoA reductase inhibitors (statins)	Reduce LDL-C by approx. 30-50% [4].	*Moderate-intensity statins:* Simvastatin	1. Hypercholesterolemia • Treatment of primary hypercholesterolemia or mixed dyslipidemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g., exercise, weight reduction) is inadequate. • Treatment of homozygous FH as an adjunct to diet and other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are not appropriate. 2. Cardiovascular prevention • Reduction of CV mortality and morbidity in patients with manifest ASCVD or DM, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy.
		Pitavastatin	• It is indicated for the reduction of elevated TC and LDL-C, in adult patients with primary hypercholesterolemia, including heterozygous FH, and combined (mixed) dyslipidemia, when response to diet and other non-pharmacological measures is inadequate.

		Fluvastatin	1. Dyslipidemia • Treatment of adults with primary hypercholesterolemia or mixed dyslipidemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g., exercise, weight reduction) is inadequate. 2. Secondary prevention in CHD • Secondary prevention of major adverse cardiac events in adults with CHD after percutaneous coronary interventions.
	Reduce LDL-C by greater than 50% [4].	*High-intensity statins:* Atorvastatin (40 to 80 mg)	1. Hypercholesterolemia • It is indicated as an adjunct to diet for reduction of elevated TC, LDL-C, apo-B, and TGs in adults, adolescents and children aged 10 years or older with primary hypercholesterolemia including FH (heterozygous variant) or combined (mixed) hyperlipidemia (corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate. • It is also indicated to reduce TC and LDL-C in adults with homozygous FH as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

			2. Prevention of CVD • Prevention of CV events in adult patients estimated to have a high risk for a first CV event, as an adjunct to correction of other risk factors.
		Rosuvastatin (20 to 40 mg)	• Rosuvastatin is approved to treat primary hypercholesterolemia and mixed dyslipidemia, as an adjunct to diet and other non-pharmacological treatments, and for homozygous FH. It is also approved for prevention of CV events in adult patients estimated to have a high risk for a first CV event, as an adjunct to correction of other risk factors.
Cholesterol Absorption Inhibitors	Reduce LDL-C by 10–18% and Apo-B by 11–16% [74].	Ezetimibe	1. Primary Hypercholesterolemia • Ezetimibe, co-administered with an HMG-CoA reductase inhibitor (statin) is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolemia who are not appropriately controlled with a statin alone. • Ezetimibe monotherapy is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolemia in whom a statin is considered inappropriate or is not tolerated.

			2. Homozygous FH • Ezetimibe co-administered with a statin, is indicated as adjunctive therapy to diet for use in patients with homozygous FH. • Patients may also receive adjunctive treatments (e.g., LDL apheresis). 3. Homozygous Sitosterolemia (phytosterolemia) • Ezetimibe is indicated as adjunctive therapy to diet for use in patients with homozygous familial sitosterolemia. 4. Prevention of CV events • Ezetimibe is indicated to reduce the risk of CV events in patients with CHD and a history of ACS when added to ongoing statin therapy or initiated concomitantly with a statin.
Fibrates	Reduce serum LDL-C, TC, TGs, and Apo-B. Increase HDL-C [124,125].	Fenofibrate	Fenofibrate 200mg is indicated as an adjunct to diet and other non-pharmacological treatment (e.g., exercise, weight reduction) for the following: 1. Treatment of severe hypertriglyceridemia with or without low HDL-C. 2. Mixed hyperlipidemia when a statin is contraindicated or not tolerated. 3. Mixed hyperlipidemia in patients at high CV risk in addition to a statin when TGs and HDL-C are not adequately controlled.

		Gemfibrozil	Gemfibrozil is indicated as an adjunct to diet and other non-pharmacological treatment (e.g., exercise, weight reduction) for the following: 1. Treatment of severe hypertriglyceridemia with or without low HDL-C. 2. Mixed hyperlipidemia when a statin is contraindicated or not tolerated. 3. Primary hypercholesterolemia when a statin is contraindicated or not tolerated. 4. Primary prevention • Reduction of CV morbidity in males with increased non-HDL-C and at high risk for a first CV event when a statin is contraindicated or not tolerated.
PCSK9 Monoclonal antibodies	Reduce LDL-C by 45-70%, Apo-B by 40-50%, Lp(a) by 30-35%, and TGs by 8-10%. Increase HDL-C by 8-10% and apoprotein A1 by 4-5% [76,77].	Alirocumab	1. Primary hypercholesterolemia and mixed dyslipidemia • It is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet. • In combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, • Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. 2. Established ASCVD

			• It is indicated in adults with established ASCVD to reduce CV risk by lowering LDL-C levels, as an adjunct to correction of other risk factors. • In combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or, • Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.
		Evolocumab	1. Hypercholesterolemia and mixed dyslipidemia • It is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet. • In combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, • Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. 2. Homozygous FH • It is indicated in adults and adolescents aged 12 years and over with homozygous FH in combination with other lipid-lowering therapies. 3. Established ASCVD • It is indicated in adults with established ASCVD (myocardial infarction, stroke or peripheral

			arterial disease) to reduce CV risk by lowering LDL-C levels, as an adjunct to correction of other risk factors. • In combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or, • Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.
Eicosapentaenoic Acid Ethyl	At 4 g/day, reduces LDL-C by 6.2%, Apo-B by 9.3%, TC by 12.0%, very-LDL-C by 24.4% [122].	Icosapent ethyl	• It is indicated as an adjunct to diet to reduce TG levels in adult patients over 18 years of age with severe (≥ 500 mg/dL) hypertriglyceridemia.
Small interfering RNA molecule; Inclisiran	Reduces LDL-C by approximately 50% at day 180 after administration of two 300-mg doses on days 1 and 90, Lp(a) by approximately 25%, and significant reductions in other atherogenic lipoproteins, including Apo-B, non–HDL-C, and very-LDL-C [126].	Inclisiran	• It is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet. • In combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or • Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Microsomal triglyceride transfer protein inhibitor; Lomitapide	Reduce LDL-C levels by 50.9% and Apo-B levels by 55.6% from baseline at a dose of 1mg per kilogram per day [127]	Lomitapide	• It is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low LDL apheresis in adult patients with homozygous FH. Genetic confirmation of homozygous FH should be obtained whenever possible. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded.

Apo-B = apolipoprotein B; ACS= acute coronary syndrome; ASCVD= atherosclerotic cardiovascular disease; CHD= coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; HMG-CoA= hydroxymethylglutaryl-coenzyme A; LDL-C = low-density lipoprotein cholesterol; Lp(a)= lipoprotein(a); non-HDL-C = non-high-density lipoprotein cholesterol; PCSK9= Proprotein convertase subtilisin/kexin type 9; TC = total cholesterol; TG = triglycerides.
[a]Saudi Food and Drug Authority

Table 12. New therapies that are being developed

Bempedoic acid	Reduces LDL-C by 15–25% in clinical trials and up to 38% when combined with ezetimibe [128]. In a recent phase 2 study, patients were randomized to triple therapy (bempedoic acid, ezetimibe, and atorvastatin) or placebo for 6 weeks. Results revealed LDL-C reduction by 63.6% [129].
Olpasiran	It is a GalNAc-conjugated siRNA therapy that was shown to reduce Lp(a) by >90% [130]. A phase 2 study that was designed to end in 2023 is now assessing the efficacy and safety of olpasiran in patients with elevated Lp(a) (>60 mg/dL, >150 nmol/L) [131].

LDL-C = low-density lipoprotein cholesterol; Lp(a)= lipoprotein(a); siRNA= small interfering RNA.

5.2. Monitoring of lipids and enzymes for patients on lipid-lowering therapy

Lipid-lowering increases the risk of side effects from pharmacological treatment, and the question of how to monitor safety during treatment has become more important ***(Tables 13&14).***

Table 13. Monitoring strategies for different lipid-lowering therapies

Drug	Monitoring strategy
Statins	***See Figure 5***
Ezetimibe	No special monitoring is required or recommended for safety while on ezetimibe therapy [132].
Fibrates	Myopathy has been reported more frequently with fibrates than with statins alone. Serum levels of statins are increased when combined with gemfibrozil thereby increasing the risk of muscle toxicity [133].
Eicosapentaenoic Acid Ethyl Ester	In ANCHOR 10 study, no significant effects were reported with regard to the liver enzymes or kidney function evaluations as evidenced by alanine aminotransferase, aspartate aminotransferase, or creatine kinase. No special monitoring is required or recommended for safety while on Eicosapentaenoic Acid Ethyl Ester therapy [134]. In REDUCE-IT study, the rate of atrial fibrillation was significantly higher in the icosapent ethyl group than in the placebo group (5.3% vs. 3.9%) [122,135].
PCSK9 monoclonal antibodies	The safety profile was the same for individuals with preserved kidney function and for those with mild or moderate kidney impairment. The analysis included 27,554 randomized patients in the FOURIER trial confirmed the excellent safety profile of this medication. No special monitoring is required or recommended for safety while on PCSK9 monoclonal antibodies [76].
Inclisiran	Inclisiran prevents translation of PCSK9 mRNA through RNA interference in liver cells. No effect on major CYP450 isoforms or transporters; therefore, it is not expected to cause drug-drug interactions or to be affected by inhibitors or inducers of CYP450 enzymes or transporters. Studies have shown that inclisiran, when combined with atorvastatin, did not result in exacerbated toxicities compared to atorvastatin alone. No special monitoring is required or recommended for safety while on

	inclisiran, but because it is generally combined with statin therapy, the required monitoring is similar to statin therapy [126].

CK= Creatine kinase; CYP450= cytochrome P450; FOURIER= Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; mRNA= Messenger RNA; PCSK9= Proprotein convertase subtilisin/kexin type 9; REDUCE-IT= Reduction of Cardiovascular Events with EPA Intervention Trial.

Table 14. Recommendations for monitoring safety in patients with ASCVD during the pharmacological intervention

Recommendations	COR[a]	LOE[b]
If the CK is elevated more than 5 times the upper limit of normal, it is recommended to stop the statin and monitor both the CK and renal function to ensure recovery.	**I**	**C** [133]
Hepatic transaminases should be tested before starting therapy, 12 weeks after initiating therapy, after a dose increase, and periodically thereafter.	**IIa**	**A** [136]
The clinician should be alert to patient reports of jaundice, malaise, fatigue, lethargy, and related symptoms in patients taking statin therapy as a signal of potential hepatotoxicity.	**IIa**	**A** [136]
Regular monitoring of liver and muscle enzymes is therefore recommended when statins are combined with fibrate therapy.	**I**	**C** [133]

ASCVD= atherosclerotic cardiovascular disease; CK = creatine kinase.
[a]Class of recommendation
[b]Level of evidence

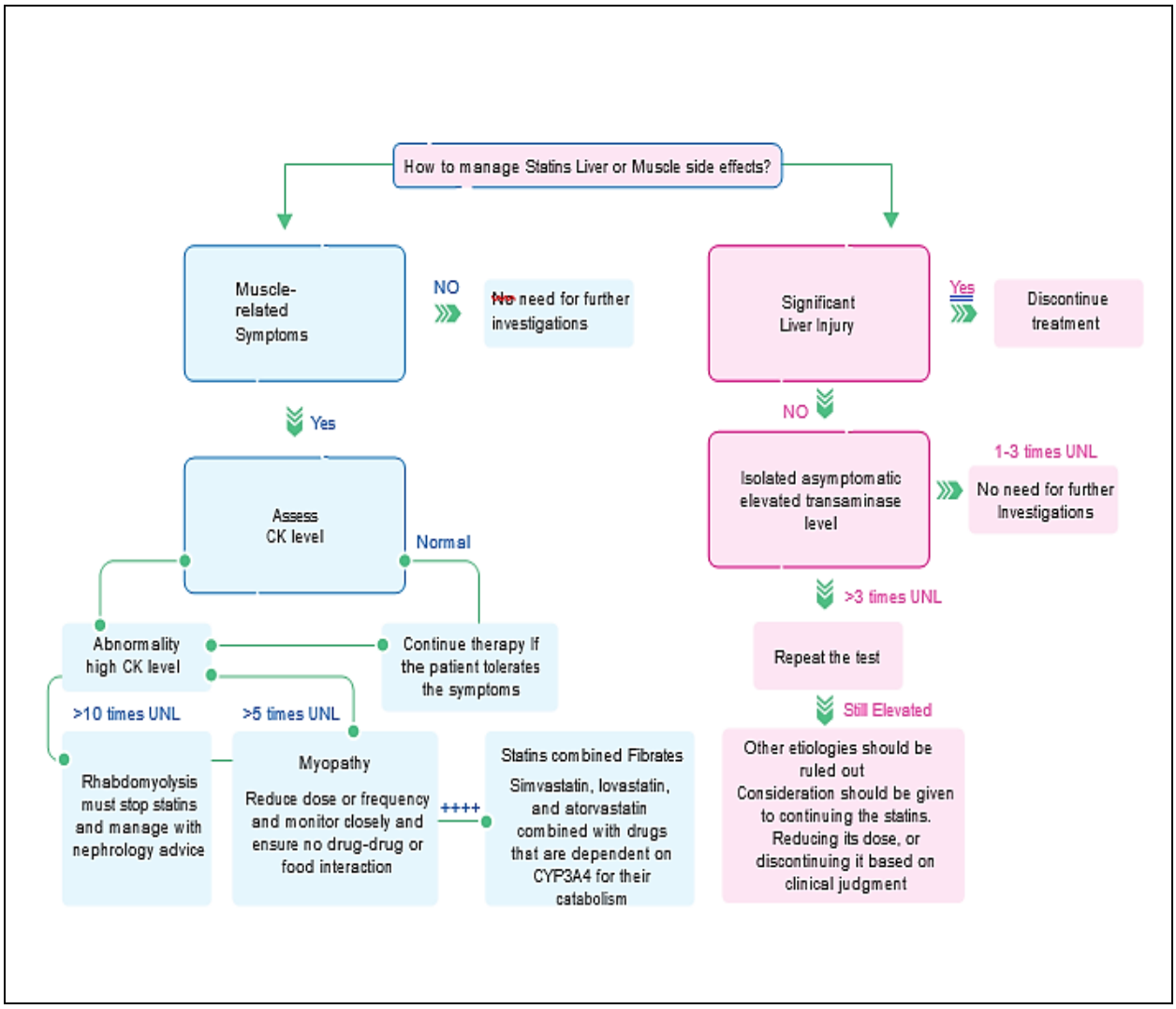

Figure 5. Monitoring statins safety

(Note: the risk of myopathy increases in patients with previously high CK, women, elderly and patients with reduced renal or liver function)

6. Health Technology Assessment Trends on Dyslipidemia Treatments

6.1. Healthcare system and access to care in Saudi Arabia

Saudi Arabia is the largest Arab nation in the Middle East region with a population that has been rapidly growing over years, as established by the Saudi census. This rise is the main reason for increasing demands on all aspects of healthcare. Just like many other countries, Saudi Arabia is struggling to provide quality healthcare services to its citizens, and this imposes big efforts to be devoted to controlling their costs while at the same time ensuring the quality of care. Healthcare spending in the kingdom is led mainly by governmental expenditure through the MOH and augmented by other governmental organizations (ex. the military health services), together with a reasonable contribution from the private sector which is consistently increasing [137,138]. Notwithstanding that there are several methodical and structured healthcare institutions, this also hinders efficient coordination and engenders inefficient allocation of resources [139].

In line with this Saudi landscape, the released Health Sector Transformation Program-Vision 2030 advocates the principle of value-based care and has assigned definite initiatives that focus on including health economics to improve access to all health services through optimal coverage, comprehensive, and equitable geographical distribution [140].

6.2. Economic burden of cardiovascular diseases in Saudi Arabia and health technology assessment overview

In Saudi Arabia, CVD imposes a massive economic burden along with enormous resource utilization. For each patient with CVD, the direct medical costs per event were estimated to be $US10,710 in 2011 [15]. Moreover, CVD accounts for 41,000 deaths (45.7% of all deaths) every year in Saudi Arabia [141]. A budget impact analysis for the use of PCSK9 monoclonal

antibodies in combination with statins for the treatment of uncontrolled LDL-C in CHD or hypercholesterolemia patients in Saudi Arabia was published in 2020. The aim was to evaluate the budgetary impact of introducing PCSK9 monoclonal antibodies as an add-on to statin therapy for the management of uncontrolled LDL-C levels among patients with CHD in the Saudi MOH over five years. The introduction of PCSK9 monoclonal antibodies resulted in an increased cost of SAR 91.16 million (6.1%), where the cost of the drug itself was the major contributor to the total cost. The use of PCSK9 monoclonal antibodies was associated with a gradual decrease in the annual number of CV events (ranging from 0.3% in year 1 to 1.5% in year 5) compared to other PCSK9 monoclonal antibodies -lacking measures. The CV event cost was reduced by 13.55 million (4.5%) with the addition of PCSK9 monoclonal antibodies compared to no PCSK9 monoclonal antibodies over 5 years [142]. Seven published cost-effectiveness analysis studies were conducted based on Saudi settings between 2015 and 2020, which reflect the need to develop a set of social utility values in Saudi Arabia [143].

As per the WHO definition, health technology assessment (HTA) is "the systematic evaluation of properties, effects, and/or impacts of health technology. It is a multidisciplinary process to evaluate the social, economic, organizational, and ethical issues of a health intervention or health technology. The main purpose of conducting an assessment is to inform a policy decision making" [144]. In Saudi Arabia's pursuit to adopt and deploy the HTA in decision-making processes, especially in those related to reimbursement decision making on the national level, MOH has started focusing on capacity building and establishing proper infrastructures to bring more efficiency to it and optimize the reimbursement review timelines. Saudi MOH has already initiated two critical projects, which will be a cornerstone for the HTA, including valuation of the Saudi utilities and establishing a cost-effectiveness threshold.

Given the multiple HTA agencies worldwide and the fact that the decision-making process differs between countries whose decision-making is determined only by clinical inputs, those that are more dependent on economic ones, and those who adopt a hybrid model, it is critical to assess the countries/HTA agencies which could be used as a proper benchmark for Saudi Arabia. For PCSK9 monoclonal antibodies drugs, HTA reviews gained positive recommendations in many countries such as Australia, Poland, Netherlands, Spain, Croatia, and others, or positive recommendations with restrictions in England, China, Scotland, and others. Similarly, inclisiran gained positive recommendations in England or positive recommendations with restrictions in the Netherlands. Recommendations for proper HTA implementation regarding dyslipidemia treatments in Saudi Arabia are presented in ***Table 15.***

Table 15. Recommendations for proper HTA implementation regarding dyslipidemia treatments in Saudi Arabia

Recommendations	COR[a]	LOE[b]
The valuation of the Saudi utilities and establishing a cost-effectiveness threshold is recommended since they are for any future assessments and, consequently, proper decision-making within the Saudi MOH.	I	C
Conduction of economic analysis studies that are based on the Saudi setting is recommended for proper decision-making. It is recommended to investigate health benefits related not only to dyslipidemia treatments but also to the adoption of preventive measures (such as screening programs including genetic testing, the establishment of lipid clinics, etc.) in those analyses.	I	C

MOH= Ministry of Health
[a]Class of recommendation
[b]Level of evidence

7. Gaps in care and strategies to encourage adoption of preventive measures

In addressing hypercholesterolemia, it is critical to identify the challenges facing practitioners in Saudi Arabia. First and foremost, there are no regional data that provide a basis for predictive risk scores, capture population-level cardiovascular outcomes, and assess the response of local populations to preventive measures. Secondly, there is a lack of insight into the burden of ASCVD as well as the application of international guidelines regionally. This is registered both at the level of individual patients and healthcare practitioners [145–147]. Finally, an important impediment to a unified policy has been the fragmented healthcare system in Saudi Arabia. With multiple parallel public systems, there are multiple prioritization matrices, redundant care plans, and disjointed medical records. Ultimately, healthcare expenditure and comprehensive oversight are difficult to streamline across these systems [80,140,148,149].

Solutions for this complex challenge require multilevel interventions. Elaboration of national guidelines rises to the forefront by emphasizing the importance of prevention pathways and defining targets for both individual patients and treating healthcare workers. Strategies to encourage the adoption of these guidelines include the following:

A. *Comprehensive solutions* ***(Figure 6)***

1. Establishment of standardized clinical pathways that are shared across all specialties and endorsed by policymakers ***(Figure 7).***
2. Establishment of primary prevention and advanced lipidology clinics that screen and optimize treatment plans.
3. Establishment of a unified medical record that facilitates consistent adoption of preventive therapies.
4. Increase public awareness through national campaigns.
5. Provide infographics via social media that counteract the misinformation.

B. Long-term solutions

1. Generate national data to guide future practices and tailor recommendations to the local population.
2. Invest in lipid training programs to create experts in the field.
3. Design national-level programs to monitor the impact of preventive measures on long-term outcomes and cost-efficiency.
4. Engage government agencies such as the Saudi Food and Drug Authority (SFDA) to provide food labeling, and City planning /municipalities to improve parks/sidewalks to enable accessible activities that encourage lifestyle modification and permit exercise & physical activities in safe, dedicated outdoor areas.

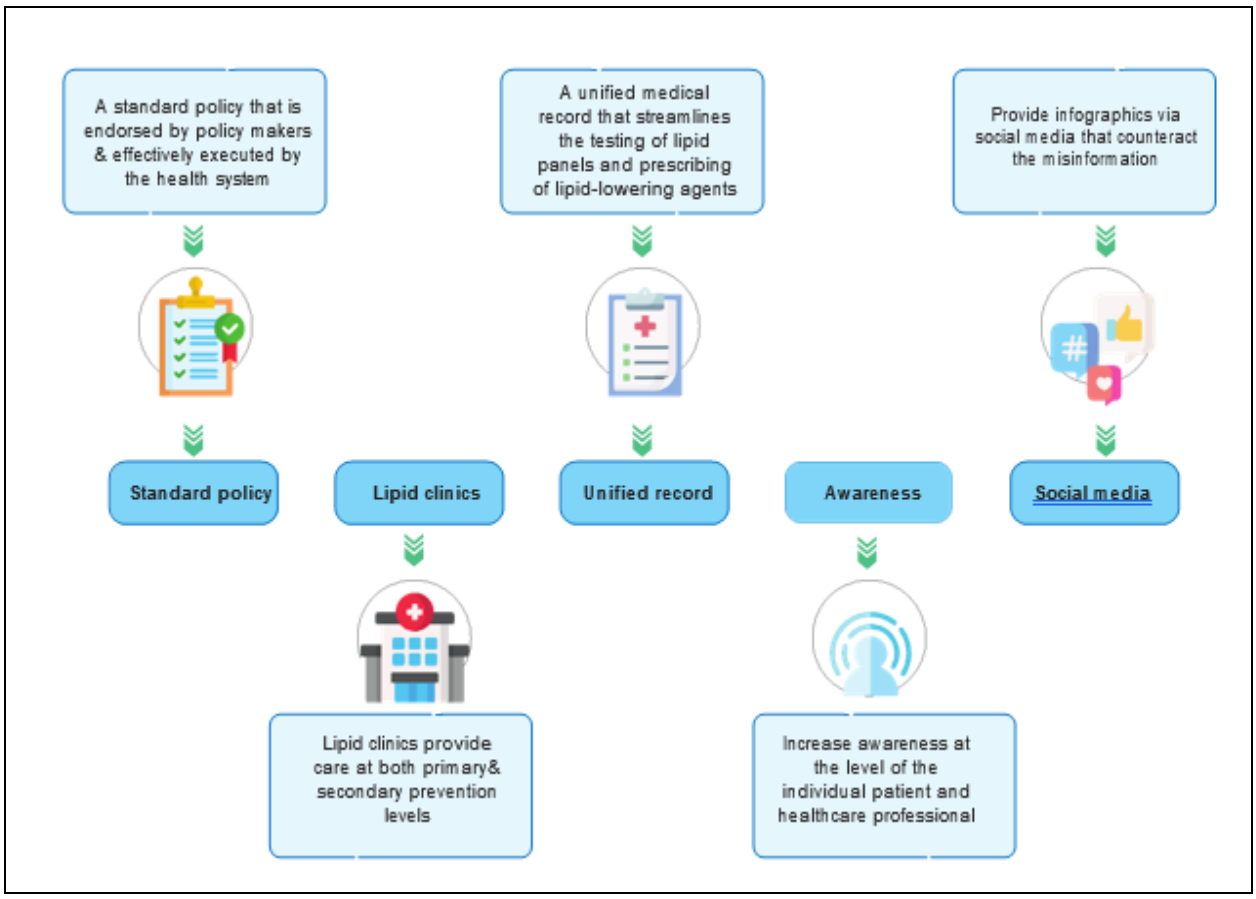

Figure 6. Comprehensive solutions to encourage adoption of preventive measures in Saudi Arabia

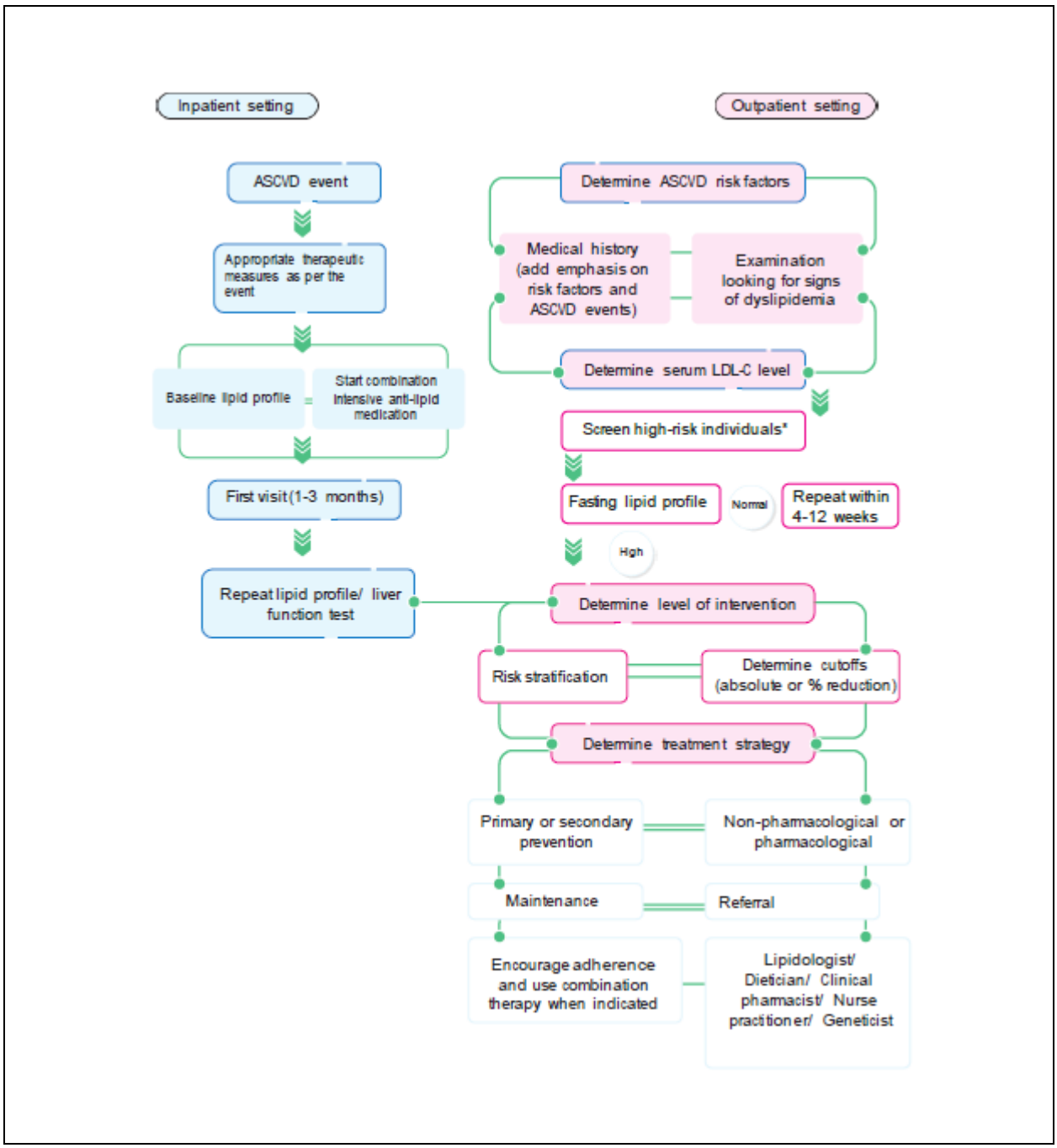

Figure 7. Clinical pathway (patient journey) of ASCVD patient in Saudi Arabia

*If the non-fasting lipid profile is available with normal levels, no further intervention is needed.

8. Key Messages

1) Several studies have shed light on the alarming status of premature ASCVD risk factors in Saudi Arabia. Counseling and comprehensive interventions, including lifestyle interventions, are recommended to reduce the ASCVD risk profiles. The development of a new risk calculator that is optimized for the Saudi population and that includes all important factors underlying CVD is a current gap that needs to be met.
2) Non-fasting/random lipid sampling can be used for screening purposes. If it is positive, the test should be repeated using fasting sampling to confirm the diagnosis, and the fasting lipid profile should be continued for further monitoring. An alternative approach is to measure the non-HDL-C with the non-fasting sampling since this strategy is a more immediate resource and has a better predictor. Apo-B can be measured directly and accurately and better predicts risk than LDL-C or non-HDL-C. If available, Apo-B analysis can be used as an alternative to LDL-C as the primary measurement for screening, diagnosis, and management.
3) Risk modifiers are additional risk factors or individual information that can modify the calculated risk in ASCVD, particularly if the individual's risk is close to a decision threshold. Risk enhancers are several other factors associated with ASCVD. Assessing for risk-enhancing factors can help guide decisions about preventive interventions in adults at borderline or intermediate risk and to adjust the intensity of LDL-lowering therapy.
4) CAC score assessment with CT should be considered in individuals at low or moderate risk in whom the respective LDL-C goal is not achieved with lifestyle intervention alone.

5) Aggressive lipid management has been demonstrated to improve cardiovascular outcomes in different clinical settings such as ACS and other very high-risk entities, namely FH, diabetes, and CKD.
6) Establishing national programs and policies (i.e., national Saudi FH registry, supporting genetic analyses, setting up of specialized lipid clinics, and raising physician awareness) is recommended for early detection of FH in Saudi Arabia, which is particularly important among high-risk populations.
7) Statins are the first-line drugs for dyslipidemia. If the treatment goal is not achieved with statins, combination with the other treatment options is recommended. Myopathy has been reported more frequently with fibrates than with statins alone.
8) PCSK9 monoclonal antibodies have shown a further reduction in ASCVD risk in patients who are in high or very high CVD risk groups. Furthermore, PCSK9 monoclonal antibodies have proven to significantly reduce LDL-C levels in the aforementioned groups when combined with statins and/or ezetimibe.
9) Strengthening the treatment goals is important to ensure that treatment of the highest-risk patients achieves the largest LDL-C reduction possible by setting both a minimum percentage LDL-C reduction (50%) and an absolute LDL-C treatment goal of <1.4 mmol/L (<55 mg/ dL) for very-high-risk patients and of <1mmol/L in extremely high-risk group (recurrence).
10) To appropriately manage hypercholesterolemia in the Saudi population, it is critical to adopt a multidisciplinary approach that involves the patient, physician, medical societies, and government agencies. Strategies to encourage the adoption of these guidelines include comprehensive and long-term solutions.

9. Evidence-based 'to do' and 'not to do'

Recommendations	COR[a]	LOE[b]
Cardiovascular disease risk estimation in Saudi Arabia		
Total risk estimation using the SCORE system is recommended in Saudi Arabia despite not being yet validated for the Saudi population.	**I**	**C** [28–30]
The development of a new risk calculator that is optimized for the Saudi population is recommended.	**I**	**C** [28]
Routine assessment using the SCORE system of asymptomatic Saudi adults >40 years of age without evidence of CVD, DM, CKD, FH, or LDL-C >4.9 mmol/L (>190 mg/dL) is recommended to calculate the 10-year risk of ASCVD.	**I**	**C** [3]
For Saudi adults 20 to 39 years of age, traditional ASCVD risk factors should be assessed at least every 4 years.	**IIa**	**B** [24,35,36]
Lipid analyses in Saudi Arabia		
TC, TG, HDL-C, LDL-C, and non-HDL-C are recommended as the primary lipid panel to estimate the risk of ASCVD and to guide therapeutic decision-making.	**I**	**C** [67]
LDL-C analysis is recommended as the mainstay component for screening, diagnosis, and management of ASCVD, and LDL-C is recommended as the primary target of lipid-lowering therapies.	**I**	**A** [43,68–70]
Apo-B can be measured directly and accurately and better predicts risk under all circumstances than LDL-C or non-HDL-C. If available, Apo-B analysis may be used as an alternative to LDL-C as the primary measurement for screening, diagnosis, and management.	**IIb**	**C** [71]
Apo-B analysis should be considered over LDL-C or non-HDL-C for risk assessment in patients with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels.	**IIa**	**C** [71]
Lp(a) should be considered for ASCVD risk estimation at least once in each adult person's lifetime, especially in patients with premature ASCVD[c], family history of premature ASCVD, and/or elevated Lp(a), FH, recurrent ASCVD despite optimal lipid-lowering treatment.	**IIa**	**C** [72]

Non-fasting/random lipid sampling may be used for screening purposes. An alternative approach is to measure the random non-HDL-C for convenience and better prediction.	**IIb**	**B** [73]
Fasting lipid profile is recommended to confirm the diagnosis and for further monitoring.	**I**	**B** [73]
Treatment goals for LDL-C in Saudi Arabia		
In secondary prevention for patients at very-high risk, an LDL-C reduction of >_50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended	**I**	**A** [68,74–77]
In primary prevention for individuals at very-high risk but without FH, an LDL-C reduction of >_50% from baselined and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended	**I**	**C** [68,75,78]
In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of >_50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended.	**I**	**C** [3]
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy are considered at extremely high risk, and an LDL-C goal of <1.0 mmol/L (<40 mg/dL) is recommended.	**I**	**B** [5,76,77]
In patients at high risk, an LDL-C reduction of >_50% from baselined and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.	**I**	**A** [68,75]
In individuals at moderate risk, an LDL-C goal of <2.6 mmol/L (<100 mg/dL) is recommended.	**I**	**A** [75]
In individuals at low risk, an LDL-C goal <3.0 mmol/L (<116 mg/dL) should be considered.	**IIa**	**A** [78]
Risk-enhancing factors;		
Metabolic syndrome[e]		
Counseling and comprehensive lifestyle interventions, including calorie restriction and adjunctive therapies, are recommended to reduce waist circumference and improve the cardio-metabolic risk profiles.	**I**	**B** [35,84,85]
CKD		
Patients with Kidney Disease Outcomes Quality Initiative stage 3-5[f] CKD are recommended to be managed as high or very-high risk of ASCVD.	**I**	**A** [3]

Elevated high-sensitivity C-reactive protein		
The high-sensitivity C-reactive protein diagnostic test is recommended to detect very low levels of C-reactive protein and thereby enable a more accurate and precise measure of chronic inflammation compared with standard C-reactive protein.	**I**	**A** [86]
In adults 40 to 75 years of age without DM and at intermediate risk, high-sensitivity C-reactive protein ≥2.0 mg/L is associated with increased ASCVD risk and should favor initiation of lipid-lowering therapy.	**IIa**	**A** [4]
History of premature menopause or pregnancy-associated conditions that increase later ASCVD risk		
Clinicians should consider conditions specific to women when discussing lifestyle intervention and the potential for the benefit of therapy	**IIa**	**B** [4]
Persistently elevated[e] primary hypertriglyceridemia		
Clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (ex. DM, chronic liver disease or CKD, hypothyroidism), or medications that increase triglycerides.	**IIa**	**B** [4]
Primary hypercholesterolemia[e]		
In intermediate-risk patients, LDL-C levels should be reduced by 30% or more. In high-risk patients, levels should be reduced by 50% or more.	**IIa**	**B** [4]
Chronic inflammatory conditions		
In patients with chronic inflammatory disorders or HIV, a fasting lipid profile and assessment of ASCVD risk factors before and 4 - 12 weeks after starting inflammatory disease-modifying therapy or antiretroviral therapy may be useful as a guide to benefit and for monitoring lipid-lowering drug therapy.	**IIb**	**B** [4]
In adults with RA, it may be useful to recheck lipid values and other major ASCVD risk factors 2 - 4 months after controlling the patient's inflammatory disease.	**IIb**	**B** [4]
Risk modifiers;		
Coronary artery calcium scoring[g]		
CAC score assessment with CT should be considered in individuals at low or moderate risk in whom the respective LDL-C goal is not achieved with lifestyle intervention alone.	**IIa**	**B** [3]
Arterial (carotid and/or femoral) plaque burden on arterial ultrasonography		

Arterial (carotid and/or femoral) plaque burden on arterial ultrasonography should be considered as a risk modifier in individuals at low or moderate risk.	**IIa**	**B** [87]
Psychosocial stress		
Physicians should be equally attentive to somatic as to emotional causes of symptoms. Assessment of psychosocial stressors should be considered (RRs are commonly between 1.2 and 2.0).	**IIa**	**B** [65,66]
Socioeconomic determinants		
Clinicians should tailor advice to a patient's socioeconomic and educational status, as well as cultural, work, and home environments	**IIa**	**A** [35,41,88,89]
Ethnicity		
No single CVD risk score performs adequately in all groups. Thus, the use of a multiplying factor may be helpful to take account of CVD risk imposed by ethnicity independent of other risk factors.	**IIb**	**A** [41]
Dyslipidemia management in different clinical settings;		
Acute coronary syndrome		
Intensive statin therapy early after an ACS clinical event is recommended.	**I**	**A** [96–99]
A statin therapy that includes high-intensity agents in combination with ezetimibe or PCSK9 monoclonal antibodies in all patients with ACS is recommended irrespective of the baseline LDL-C values. The recommended target for LDL-C is a 50% reduction and a level of <1.4 mmol/L (<55 mg/dL).	**I**	**A** [74,76,77]
For secondary prevention in patients at very-high risk not achieving their goal on a maximum tolerated dose of a statin and ezetimibe, a combination with PCSK9 monoclonal antibodies is recommended.	**I**	**C** [3]
For the extremely[h] high-risk patients, initiation of triple combination therapy should be considered as the first-line approach	**IIa**	**C** [5]
Diabetes		
With respect to patients with diabetes and prediabetes, intensive therapy should be encouraged and outweighs any potential risk of new-onset diabetes.	**IIa**	**A** [104–106]
DM with target organ damage or ≥3 major risk factors or early onset of type 1 diabetes mellitus of long duration patients are at very high-risk and a statin therapy that includes high-intensity agents in combination with ezetimibe is	**I**	**C** [5]

recommended, and if target level is not achieved, addition of PCSK9 monoclonal antibodies is recommended.		
Chronic kidney disease		
High-intensity statin is recommended in patients with CKD stage 3 or higher with adjunctive risk, established ASCVD, or presenting with an ACS to achieve the maximum reduction.	**I**	**A** [3]
Severe CKD (eGFR <30 mL/min/1.73 m^2) patients are at very high-risk and a statin therapy that includes high-intensity agents in combination with ezetimibe is recommended, and if target level is not achieved, addition of PCSK9 monoclonal antibodies is recommended	**I**	**C** [5]
Women		
Lipid-lowering agents are not recommended during pregnancy or lactation due to the absence of evidence suggesting benefit or harm.	**III**	**A** [115]
Risk assessment and lipid-lowering measures should be appropriately timed in women after delivery.	**IIa**	**A** [115]
FH		
Establishing national programs and policies (i.e., national Saudi FH registry, supporting genetic analyses, setting up of specialized lipid clinics, and raising physician awareness) is recommended for early detection of FH in Saudi Arabia, which is particularly important among high-risk populations.	**I**	**A** [118,120]
Diagnosis of FH is recommended to be considered in patients with CHD aged <55 years for men and <60 years for women, in people with relatives with premature fatal or non-fatal CVD, in people with relatives who have tendon xanthomas, in people with severely elevated LDL-C (in adults >5 mmol/L or >190 mg/Dl; in children >4 mmol/L or >150 mg/dL), and in first-degree relatives of FH patients.	**I**	**A** [3,35]
FH patients with no prior ASCVD or other risk factors are recommended to be treated as high-risk patients, and FH patients with ASCVD or another major risk factor are recommended to be treated as very-high-risk.	**I**	**A** [3]
A one-off measurement of Lp(a) should be considered in further risk stratification of patients with a family history of premature CVD and to identify people with very high inherited Lp(a) levels.	**IIa**	**A** [3]
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal on a maximum tolerated dose of a	**I**	**C** [3]

statin and ezetimibe, a combination with a PCSK9 inhibitor or inclisiran is recommended.		
Monitoring safety in ASCVD patients during the pharmacological intervention		
If the CK is elevated more than 5 times the upper limit of normal, it is recommended to stop the statin and monitor both the CK and renal function to ensure recovery.	**I**	**C** [133]
Hepatic transaminases should be tested before starting therapy, 12 weeks after initiating therapy, after a dose increase, and periodically thereafter.	**IIa**	**A** [136]
The clinician should be alert to patient reports of jaundice, malaise, fatigue, lethargy, and related symptoms in patients taking statin therapy as a signal of potential hepatotoxicity.	**IIa**	**A** [136]
Regular monitoring of liver and muscle enzymes is therefore recommended when statins are combined with fibrate therapy.	**I**	**C** [133]
Proper HTA implementation regarding dyslipidemia treatments in Saudi Arabia		
The valuation of the Saudi utilities and establishing a cost-effectiveness threshold is recommended since they are for any future assessments and, consequently, proper decision-making within the Saudi MOH.	**I**	**C**
Conduction of economic analysis studies that are based on the Saudi setting is recommended for proper decision-making. It is recommended to investigate health benefits related not only to dyslipidemia treatments but also to the adoption of preventive measures (such as screening programs including genetic testing, the establishment of lipid clinics, etc.) in those analyses.	**I**	**C**

Dark green color indicates new recommendations for the Saudi population.

AIDS = acquired immunodeficiency syndrome; Apo-B = apolipoprotein B; ASCVD= atherosclerotic cardiovascular disease; BP = blood pressure; CAC = coronary artery calcium; CT = computed tomography; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; HTA = Health Technology Assessment; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); MOH= Ministry of Health; non-HDL-C = non-high-density lipoprotein cholesterol; RA = rheumatoid arthritis; RR = relative risk; SCORE = Systematic Coronary Risk Estimation; TC = total cholesterol; TG = triglycerides.

[a]Class of recommendation

[b]Level of evidence

[c]The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C-lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.

[d]Men <55 years, women <60 years

[e]Optimally, 3 measurements.

[f]Defined as eGFR < 60ml/min/1.73m^2 on two measurements more than 3 months apart.

[g]CAC score is increased following statin treatment; therefore, the CAC scores of statin-treated patients should be interpreted with caution

[h]Extremely high risk = post ACS + history of other vascular event/peripheral artery disease/ polyvascular disease/ multivessel coronary artery disease/familial hypercholesterolemia

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المركز الوطني للقلب
National Heart Center

المجلس الصحي السعودي
Saudi Health Council

Supplementary Material

Saudi Guidelines for Dyslipidemia Management

The Task Force for Dyslipidemia Management Guideline

Jamilah AlRahimi[1,2,*], Shukri AlSaif[3], Mirvat Alasnag[4], Zuhier Awan[5], Fawaz Almutairi[6], Hajer Al Mudaiheem[7], Baris Gencer[8,9], Alberico L. Catapano[10], Francois Mach[8], Adel Tash[11,12]

[1]Cardiology Department, King Faisal Cardiac Center, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Jeddah, Saudi Arabia

[2] Cardiology Department, King Abdullah International Medical Research Center, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia

[3] Saud AlBabtain Cardiac Center, Dammam, Saudi Arabia

[4] Catheterization Laboratory, King Fahd Armed Forces Hospital, Jeddah, Saudi Arabia

[5] Medicine, Biochemistry and Molecular Genetics, Clinical Biochemistry Department, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

[6] Security Forces Hospital, Riyadh, Saudi Arabia

[7] Therapeutic Affairs Deputyship, Ministry of Health, Riyadh, Saudi Arabia

[8] Cardiology Department, Geneva University Hospital, Geneva, Switzerland

[9] Institute of Primary Healthcare (BIHAM), Bern University, Bern, Switzerland

[10] Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy

[11] Cardiac Services Development, Ministry of Health, Riyadh, Saudi Arabia

[12] National Heart Center, Saudi Health Council, Riyadh, Saudi Arabia

Corresponding Author*: Jamilah S. AlRahimi, Assistant Professor Medicine/Cardiology, Department of Cardiac Science, King AbdulAziz Medical City- Ministry of National Guard Health Affairs, King Abdullah International Medical Research Center, College of Medicine, King Saud bin AbdulAziz University for Health Sciences, Jeddah, Saudi Arabia. Address. P.O. Box 9515, 21423 Jeddah, Saudi Arabia. Tel. 00966505616454. Fax: 920008668 ext 25809. Email. alrahimija@gmail.com.

Supplementary Table 1. Recommendations for ASCVD risk factors; Age and Air pollution and their corresponding interventions in Saudi Arabia

Risk Factor	Recommended Intervention/goal	COR[a]	LOE[b]
Age			
In apparently healthy people with low-to-moderate CVD risk; SCORE <2.5% in people <50 years of age; SCORE <5% in people 50-69 years of age; SCORE <7.5% in people ≥70 years of age	Risk factor treatment is not recommended	III	**A** [1–3]
In apparently healthy people with high CVD risk; SCORE 2.5 to <7.5% in people <50 years of age; SCORE 5 to <10% in people 50-69 years of age; SCORE 7.5 to <15% in people ≥70 years of age	Risk factor treatment should be considered	IIa	**A** [1–3]
In apparently healthy people with very-high CVD risk; SCORE ≥7.5% in people <50 years of age; SCORE ≥10% in people 50-69 years of age; SCORE ≥15% in people ≥70 years of age	Risk factor treatment is recommended	I	**A** [1–3]
Air pollution	Implementation of in place measures to reduce air pollution (i.e., reducing PM emission and gaseous pollutants, reducing the use of fossil fuels, and limiting carbon dioxide emissions) is recommended to reduce CVD mortality and morbidity	I	**A** [1]
	Patients at very/high risk for CVD may be	IIb	**C** [1]

	encouraged to avoid long-term exposure to high air pollution		
	In regions where people have long-term exposure to high levels of air pollution, screening programs for CVD risk may be considered	IIb	**C** [1]

ASCVD= atherosclerotic cardiovascular disease; CVD = cardiovascular disease; PM = particulate matter; SCORE = Systematic Coronary Risk Estimation.
[a]Class of recommendation
[b]Level of evidence

Supplementary Table 2. **Familial dyslipidemia disorders**

Disorder	Gene(s)	Effect on lipoproteins	Other manifestations or criteria	If untreated
FH [4,5]	*LDLR* *APO-B* *PCSK9*	↑ LDL-C	Xanthomas	Increase CV risk
HeFH [4,5]	*LDLR* *APO-B* *PCSK9*	↑↑ LDL-C (in the range of 155 to 500 mg/dL)	Tendon/skin xanthomas	Develop early CAD before the age of 55 years (men) and 60 years (women)
HoFH [4,5]	*LDLR* *APO-B* *PCSK9*	↑↑ LDL-C (can reach > 600 mg/dL)	Planar and tendinous xanthomas, valvar and supravalvar atheroma	Rarely survive beyond the age of 30 years
FCH [4]	*USF1* + modifying genes	↑ LDL-C and/or high TGs ↑ VLDL-C ↑ Apo-B	The combination of Apo-B >120 mg/dL and TGs >1.5 mmol/L (>133 mg/dL) with a family history of premature CVD can be used to identify people who most probably have FCH.	Develop premature CAD
Familial dysbetalipoproteinemia [4]	*APO-E*	↑↑ IDL and chylomicron remnants (βVLDL) ↑ TC and ↑ TGs (usually both in the range of 7-10 mmol/L)	In severe cases, patients develop tuberoeruptive xanthomas (particularly over the elbows and knees), and palmar	Very high risk of CAD and accelerated atherosclerosis of the femoral and tibial arteries

			xanthomata (in the skin of the hands and wrists)	
Hypertriglyceridaemia [4]	*LPL* *APO-C2* *APO-A5* *LMF1* *GPIHBP1* *GPD1*	Profound defect in the catabolism of chylomicrons and VLDL leading to chylomicronemia and ↑ TG levels >11.2 mmol/L (>1000 mg/dL)	Turbid and milky serum	Chylomicronemia, pancreatitis, and lipid deposits.

Apo = apolipoprotein; CAD = coronary artery disease; CV = cardiovascular; FCH = familial combined hyperlipidemia; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; IDL = intermediate-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; VLDL = very low-density lipoprotein cholesterol. ASCVD= atherosclerotic cardiovascular disease; TC = total cholesterol; TGs = triglycerides.

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