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2022 Saudi Guidelines for the Management of Dyslipidemia

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

Department of Cardiology, King Faisal Cardiac Center, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, King Abdullah International Medical Research Center, King Saud Bin Abdulaziz University for Health Sciences, Dammam, Saudi Arabia
[1]Department of Cardiology, Saud AlBabtain Cardiac Center, Dammam, Saudi Arabia
[2]Department of Cardiology, Catheterization Laboratory, King Fahd Armed Forces Hospital, Jeddah, Saudi Arabia
[3]Medicine, Biochemistry and Molecular Genetics, Clinical Biochemistry Department, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[4]Department of Cardiology, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia
[5]Therapeutic Affairs Department, Ministry of Health, Riyadh, Saudi Arabia
[6]Department of Cardiology, Geneva University Hospital, Geneva
[7]Institute of Primary Healthcare (BIHAM), Bern University, Bern, Switzerland
[8]Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy [9]Cardiac Services Development, Ministry of Health, Riyadh, Saudi Arabia
[10]National Heart Center, Saudi Health Council, Riyadh, Saudi Arabia
Address for correspondence: Dr. Jamilah AlRahimi, King Abdullah International Medical Research Center, College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, P.O. Box 9515, Jeddah 21423, Saudi Arabia. E-mail: alrahimija@gmail.com

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 the quality of health-care 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 among the Saudi population.

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 has 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.[3,4,5] 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 and 64 years. The Saudi population is multiethnic, 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).[7,8,9,10] 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 (CVDs) collectively remained as the leading cause of disability-adjusted life years (DALYs quantifies the health loss due to specific diseases and injuries[150]) in Saudi Arabia from 1990 to 2017 [Figure 1].[12] The 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, smoking, obesity, physical inactivity, and diabetes in Saudi Arabia across different age groups. [7,8,13,14,15,16]

These Saudi clinical practice guidelines provide recommendations applicable to Saudi patients with or at risk of developing 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 cutoffs 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 given our population's biochemistry.

METHODS

Consensus approach

The 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.

Scope

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 health-care professionals to facilitate informed communication with individuals about their cardiovascular (CV) risk and the benefits of adopting and sustaining a healthy lifestyle and early modification of their lipid-related CV risk. This guideline has the potential to promote up-to-date management strategies and to translate them into locally delivered health-care services, in line with the recommendations of the World Health Organization (WHO).[6]

Literature review

A literature search was made in English language to identify published articles related to ASCVD and or lipids related to Saudi, Gulf, or Arab populations. Where local data or published material was found, it was always used. The designated steering committee also reviewed the previously published international guidelines and related statements deemed pertinent to these guidelines; thus, obviating the need to implement existing guideline recommendations of different regions.

Different authors had the responsibility to research specific sections of the guidelines and produce a draft that was discussed in a series of virtual meetings. During these meetings, different recommendations were considered and a consensus was reached, or voting was made on the adoption for each recommendation based on the strength of available evidence for that recommendation and its applicability to practice conditions within Saudi Arabia. The level of evidence and the strength of the recommendation are adapted from the 2019 European Society of Cardiology

(ESC)/European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidemia,[3] where management options were graded as per predefined scales [Table 1].

A third party 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.

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.

All experts involved in the development of these guidelines declared no real or potential sources of conflicts of interest.

CARDIOVASCULAR DISEASE RISK AND RISK GROUPS

Total cardiovascular risk estimation

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.[17,18,19,20,21,22,23,24,25,26] 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 nontraditional risk factors), is a gap that needs to be met to ensure all patients are adequately assessed and managed.

Recommendations for CVD risk estimation in Saudi Arabia are presented in Table 2.

In this context, it should be recalled that the mean age of presentation with 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].

Risk categories

The cutoff points used to define different risk categories in the 2019 ESC and 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), and 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.

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 CV 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 maximum compliance with 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.[37,38,39] 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 CVD risk categories are presented in Figure 2.

Patients with FH are at high CV 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.

Risk factors

The risk factors for ASCVD are age, gender, cholesterol and lipoprotein abnormalities, hypertension, DM, prediabetes, 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 4-6].

Age and gender

Age and gender are the 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 triglycerides (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] [Supplementary Table 1].

Low-density lipoprotein cholesterol

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 nonhigh-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 TGs 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]

Hypertension With regard 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]

Smoking Cigarette smoking prevalence in Saudi Arabia 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 and 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, among smokers surveyed in that study. Ibrahim Alasqah *et al*.[53] reported a prevalence of smoking ranging from 12.7% to 39.6% among adolescents regardless of their educational stage. The prevalence among female adolescents ranged between 1.6% and 11.1%.[54] Moreover, epidemiological data have shown alarming evidence of high water pipe usage among Saudi teenagers and college students.[55]

Overweight and obesity 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/m^2), 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]

Consumption of caffeinated or carbonated drinks 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 among the Saudi population are associated with an increased risk of dyslipidemia.[58] Moradi-Lakeh *et al*. conducted a household survey in 2013 of 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 [physical activities were assigned MET values based on the compendium of physical activity[151] and the compendium of physical activity for youth[152].])-min/week (=60 min per day × 7 days/week × 4 METs [moderate-intensity physical activity]) and more than 2520 METs-min/week (=60 min per day × 7 days/week × 6 METs [moderate-to-vigorous-intensity physical activity]) (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 places (especially for females), and lack of facilities and resources. Physical inactivity is significantly associated with obesity and waist circumference in adults, children, and adolescents.[60]

Air pollution 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 through 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] [Supplementary Table 1].

Risk enhancers

Risk-enhancing factors are independent of other risks 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 years and females, age <60 years) is a risk-enhancing factor that should be considered for clinician–patient risk discussion [Table 8; 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]

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]

COVID-19 and cardiovascular disease

The CV complications of acute coronavirus disease 2019 (COVID-19) are well reported in several studies.[90,91,92,93,94] A recent study by Xie *et al*.[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 nonischemic 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.

MANAGEMENT OF DYSLIPIDEMIA IN DIFFERENT CLINICAL SETTINGS

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

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 the benefit with early initiation of treatment, that is, in-hospital and continued long-term.[96,97,98,99] 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 24 h.[100] Assays before

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 proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies is recommended. For extremely high-risk (extremely high risk = post-ACS + history of other vascular event/peripheral artery disease/polyvascular disease/multivessel coronary artery disease/familial hypercholesterolemia) patients, initiation of triple combination therapy should be considered 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.

Diabetes mellitus

DM is often referred to as an ASCVD equivalent. It confers an independent risk for multiple CV 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 CV events. Additional risk factors render diabetics at an even higher risk of CV 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 CV events, suggest intensive therapy should be encouraged and outweighs any potential risk of new-onset diabetes.[104,105,106]

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 meta-analysis, de Carvalho *et al*. 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 subanalysis of the landmark Odyssey trial did not observe

conversion to diabetes with these agents.[77,107]

Chronic kidney disease

CKD stage 3 is considered high, and stage 4–5 is considered very high risk. An estimated glomerular filtration rate of <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 CV events in patients with CKD.[108] In addition, in patients with CKD presenting with ACSs, PCSK9 monoclonal antibodies were associated with a lower incidence of ASCVD events and all-cause death across all ranges of dysfunction. In fact, the absolute reduction in the major adverse CV events (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.[109,110,111]

Women

Women have historically been underrepresented in prevention trials. However, meta-analyses and pooled data for both statin and nonstatin 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, preeclampsia, eclampsia, and a miscarriage, are at higher overall CV risk.[113,114] Therefore, risk assessment and lipid-lowering measures should be appropriately timed in women after delivery.

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 [Supplementary Table 2].[3,116,117]

FH is an autosomal codominant 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 the diagnosis of high levels of LDL-C, and even after documented CV 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 the 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. PCSK9 inhibitors have been approved for their management. Recommendations for FH management in Saudi Arabia are presented in Table 10.

REGIMEN SELECTION

Pharmacological interventions

Pharmacological interventions and approved indications

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) [Tables 11 and 12].

Regimen selection for different clinical settings Individuals who have developed ASCVD, 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% and 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 135 mg/dL or higher up to 500 mg/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 CV 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]

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 and 14]. Monitoring strategies for Statin therapy [Figure 5].

HEALTH TECHNOLOGY ASSESSMENT TRENDS ON DYSLIPIDEMIA TREATMENTS

Health-care system and access to care in Saudi Arabia

Saudi Arabia is one of the largest Arab nations 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 health care. Just like many other countries, Saudi Arabia is struggling to provide quality health-care 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 health-care 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 and comprehensive and equitable geographical distribution.[140]

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 5 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 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 the 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.

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 CV outcomes, and assess the response of local populations to preventive measures. Second, 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 health-care practitioners.[145,146,147] Finally, an important impediment to a unified policy has been the fragmented health-care system in Saudi Arabia. With multiple parallel public systems, there are multiple prioritization matrices, redundant care plans, and disjointed medical records. Ultimately, health-care 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 health-care workers. [Figure 6] Strategies to encourage the adoption of these guidelines include the following:

Comprehensive solutions

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 through social media that counteract the misinformation.

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 and physical activities in safe, dedicated outdoor areas.

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. Nonfasting/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 nonfasting 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 CV 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, a 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 <1 mmol/L in the 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.

EVIDENCE-BASED "TO DO" AND "NOT TO DO"

The recommended evidence based "to do" and "not to do" in dyslipidemia management are summarized [Table 16].

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Conflicts of interest

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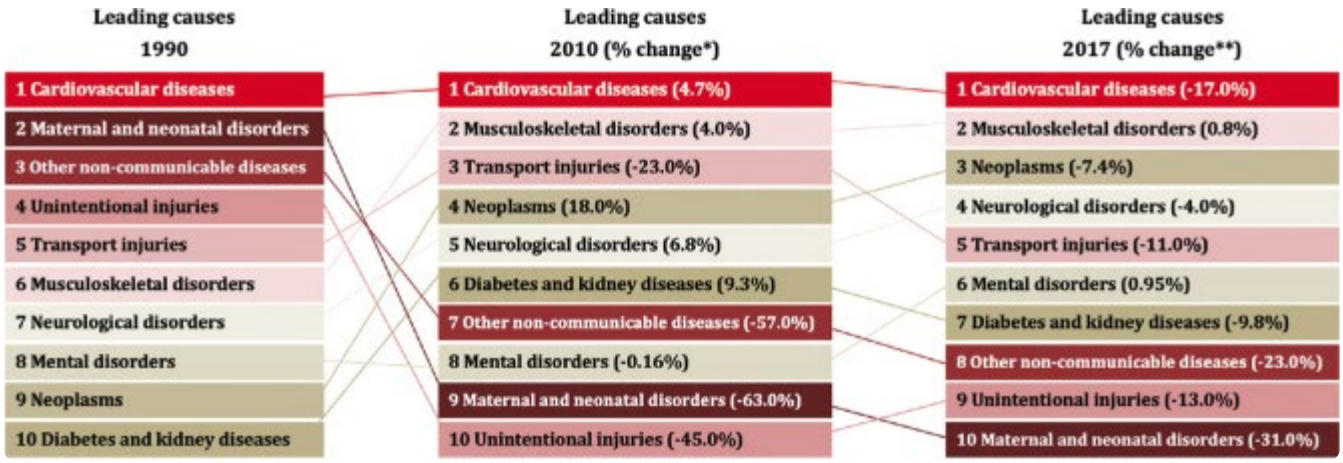
Figures and Tables

Figure 1



Top 10 causes of DALYs in Saudi Arabia for the periods 1990–2010 and 2010–2017, both sexes. Adapted from Tyrovolas *et al*.[12] *Percentage change in the number of age-standardized DALYs, 1990–2007, **Percentage change in the number of age-standardized DALYs, 2010–2017. DALYs: Disability-adjusted life-years

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	Level C	Consensus of opinion of the experts and/or small studies, retrospective

	harmful.		studies, registries.

Adapted from[3]

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[28,29,30]
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

Table 3

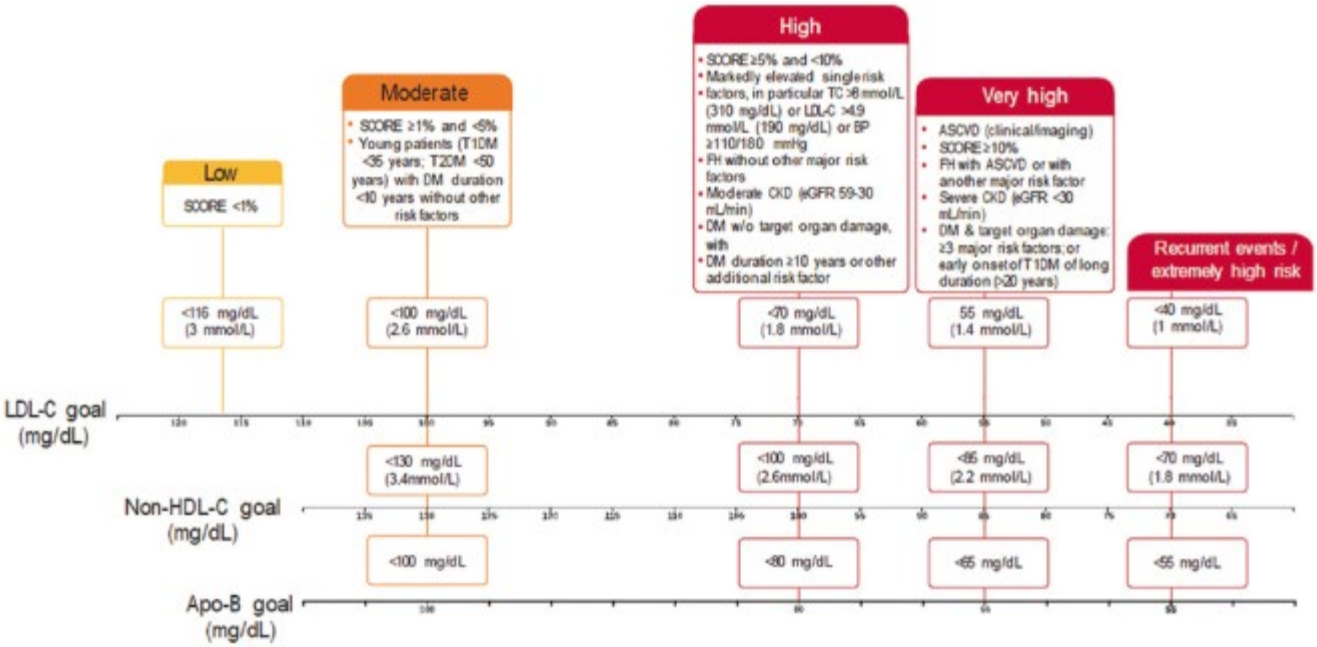
Cardiovascular risk categories in the Saudi population.

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).	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	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.

Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.	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 30-59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.		

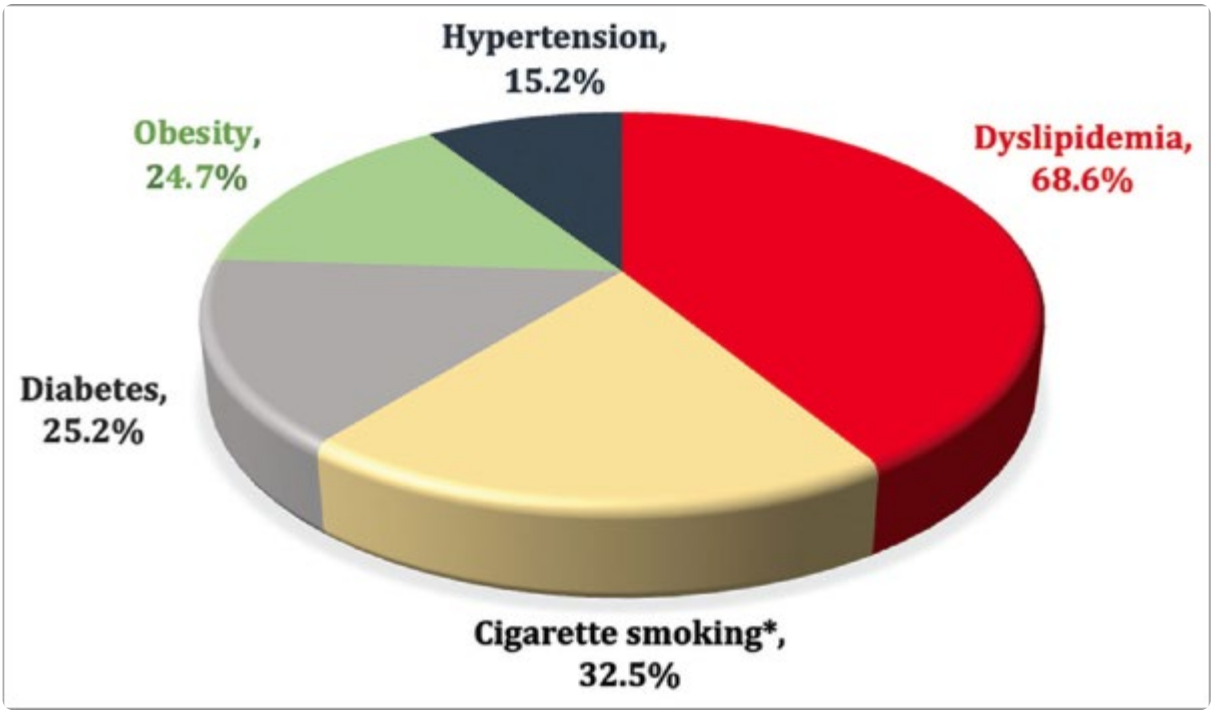
Adapted from[3]. ASCVD=atherosclerotic cardiovascular disease; ACS=acute coronary syndrome; BP=blood pressure; CABG=coronary artery bypass graft surgery; CKD=chronic kidney disease; CT=computed tomography; CVD=cardiovascular disease; DM=diabetes mellitus; eGFR=estimated glomerular filtration rate; FH=familial 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. eTarget organ damage is defined as microalbuminuria, retinopathy, or neuropathy.

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: Nonhigh-density lipoprotein cholesterol, SCORE: Systematic Coronary Risk Estimation, T1DM: Type 1 diabetes mellitus, T2DM: Type 2 diabetes mellitus, TC: Total cholesterol

Figure 3



Prevalence of cardiovascular risk factors in Saudi Arabia. *Males. Adapted from Althumiri *et al*., Alhabib *et*

al., Ahmed *et al*., Ahmed *et al*.[7,8,45,52]

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[43,68,69,70]
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[68,74,75,76,77]
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.

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.

Supplementary Table 1

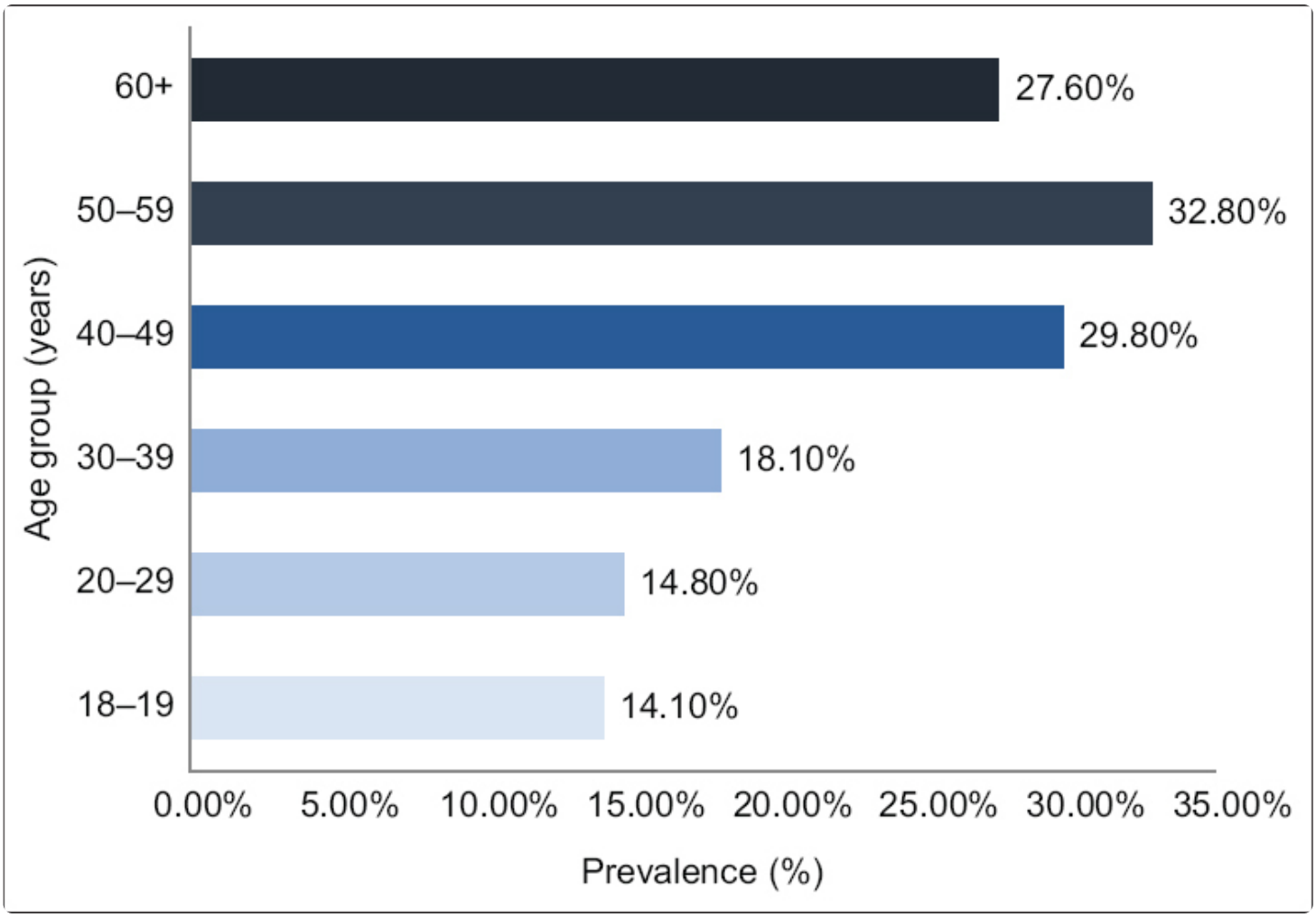
Recommendations for atherosclerotic cardiovascular disease risk factors; age and air pollution and their corresponding interventions in Saudi Arabia

Risk factor	**Recommended intervention/goal**	**COR**	**LOE**

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[1,2,3]
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[1,2,3]
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[1,2,3]
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 encouraged to avoid long-term exposure to high air pollution	IIb	C[1]
	In regions where people have long-term	IIb	C[1]

CV: Cardiovascular, CVD: CV disease, ASCVD: Atherosclerotic CVD, PM: Particulate matter, SCORE: Systematic Coronary Risk Estimation, COR: Class of recommendation, LOE: Level of evidence

Figure 4



Prevalence of obesity in Saudi Arabia stratified by age group. Adapted from Althumiri *et al.*[7]

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-	Counseling and comprehensive lifestyle interventions, including calorie restriction and adjunctive therapies, are recommended to reduce waist circumference and	I	B [35,84,85]

	C <40 mg/dL in men; <50 mg/dL in women	improve the cardio-metabolic risk profiles.		
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	I	A[86]

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/1.73 m^2 on two measurements more than 3 months apart.

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	CAC score assessment with CT should be considered in individuals at low or moderate risk in whom the respective	IIa	B [3]

	carotid or femoral plaque burden on ultrasonography may reclassify them to a higher risk category.	LDL-C goal is not achieved with lifestyle intervention alone.		
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 [41]
Socioeconomic	Socioeconomic	Clinicians should tailor	IIa	A[35,41,88,89]

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.

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[96,97,98,99]
A statin therapy that includes high-intensity agents in combination with	I	A [74,76,77]

ezetimibe or PCSK9 monoclonal antibodies in all patients with ACS not achieving the goal 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).		
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	A [3]
For the extremelyc 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[104,105,106]
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	I	A[3]

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

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 155-500 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	*APO-E*	↑↑ IDL and	In severe cases	Very high risk of

Apo-B: Apolipoprotein-B, CAD: Coronary artery disease, CV: Cardiovascular, FCH: Familial combined hyperlipidemia, FH: Familial hypercholesterolemia, HeFH: Heterozygous FH, HoFH: Homozygous FH, IDL: Intermediate-density lipoprotein, LDL-C: Low-density lipoprotein cholesterol, VLDL: Very LDL-C, CVD: CV disease, TC: Total cholesterol, TGs: Triglycerides

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

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	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. 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

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. aSaudi Food and Drug Authority

Table 12

New therapies that are being developed.

Therapy	Mechanism of Action
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.

Table 13

Monitoring strategies for different lipid-lowering therapies

Drug	**Monitoring strategy**
Statins	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

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

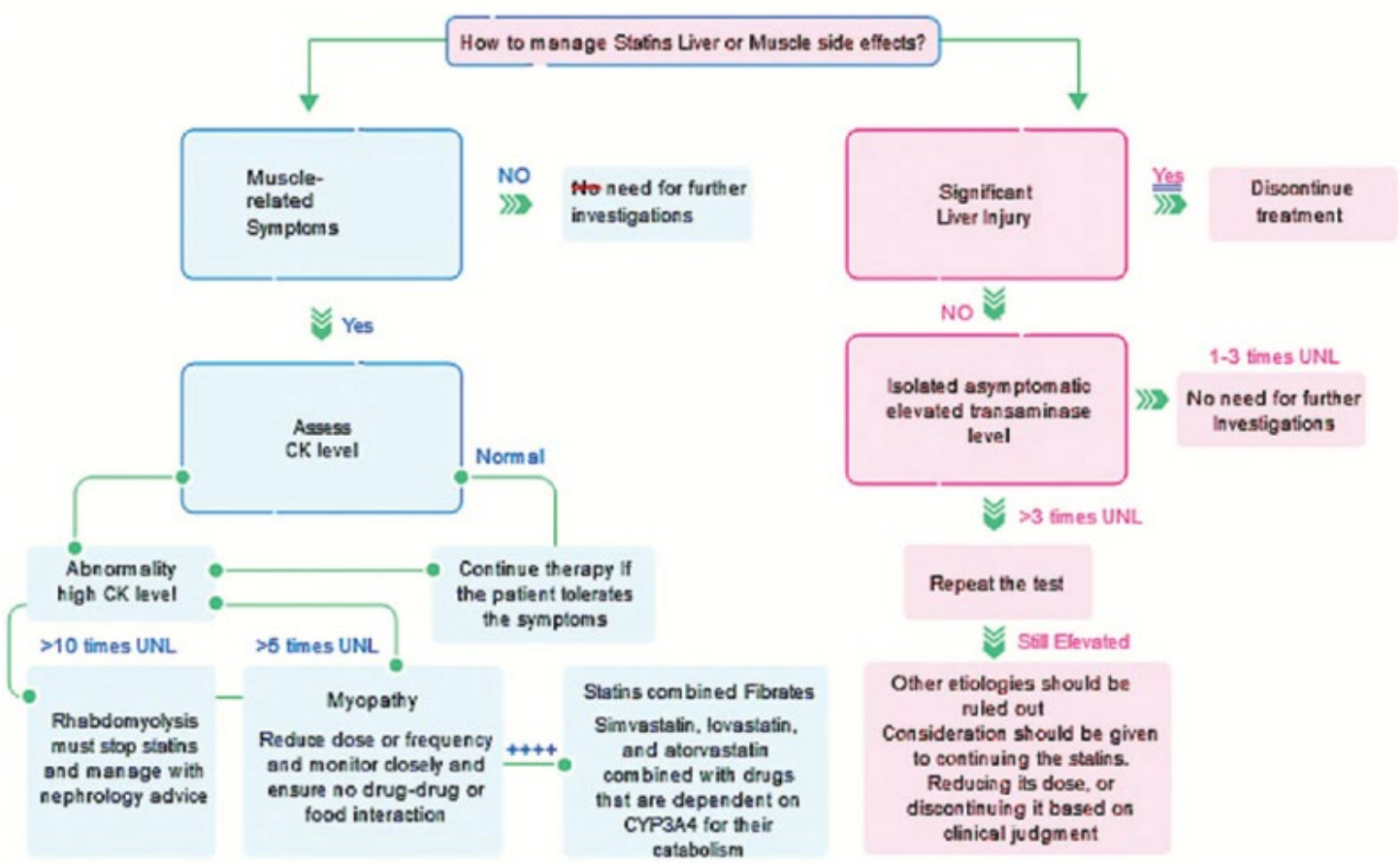
Table 14

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. CK: Creatine kinase

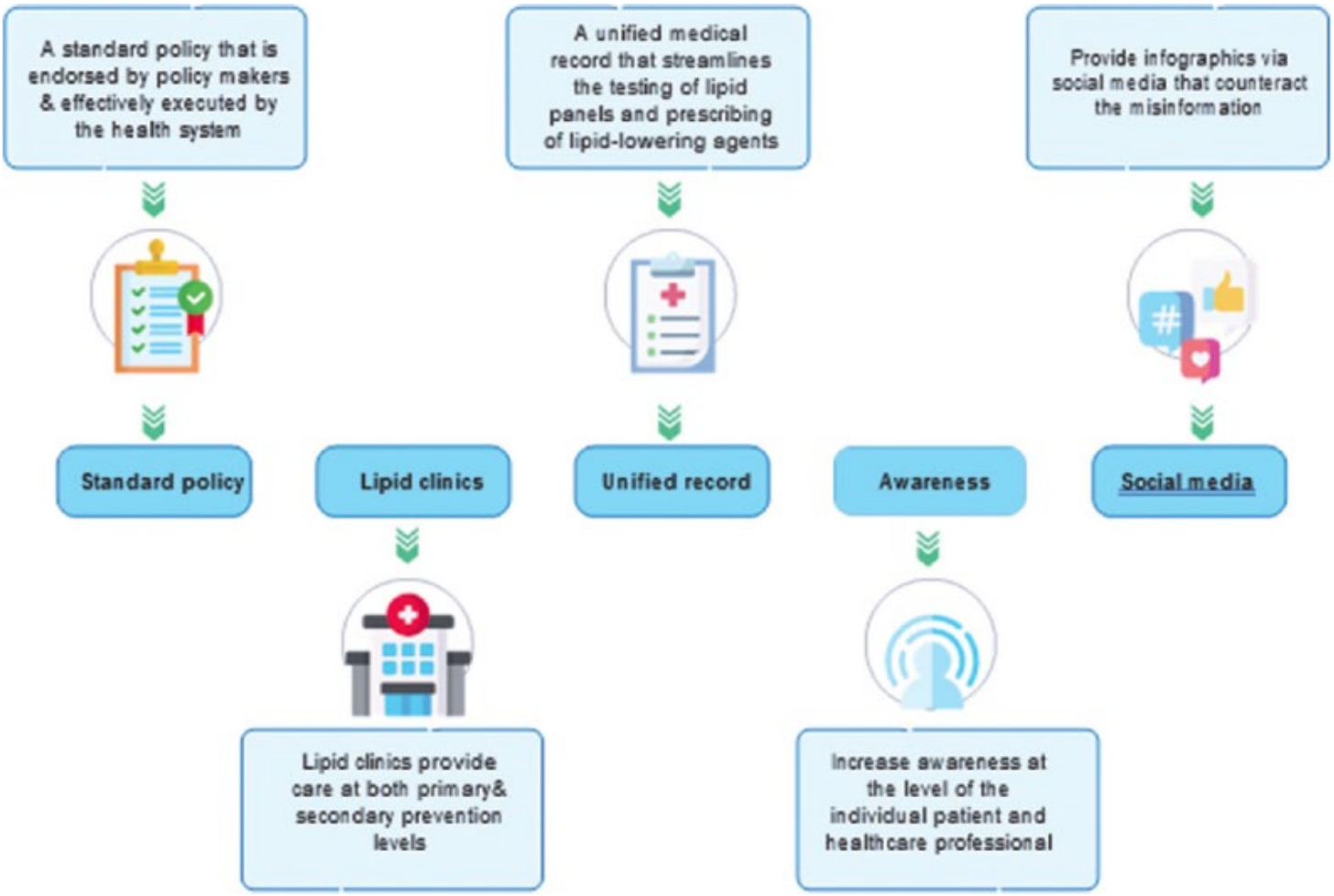
Table 15

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

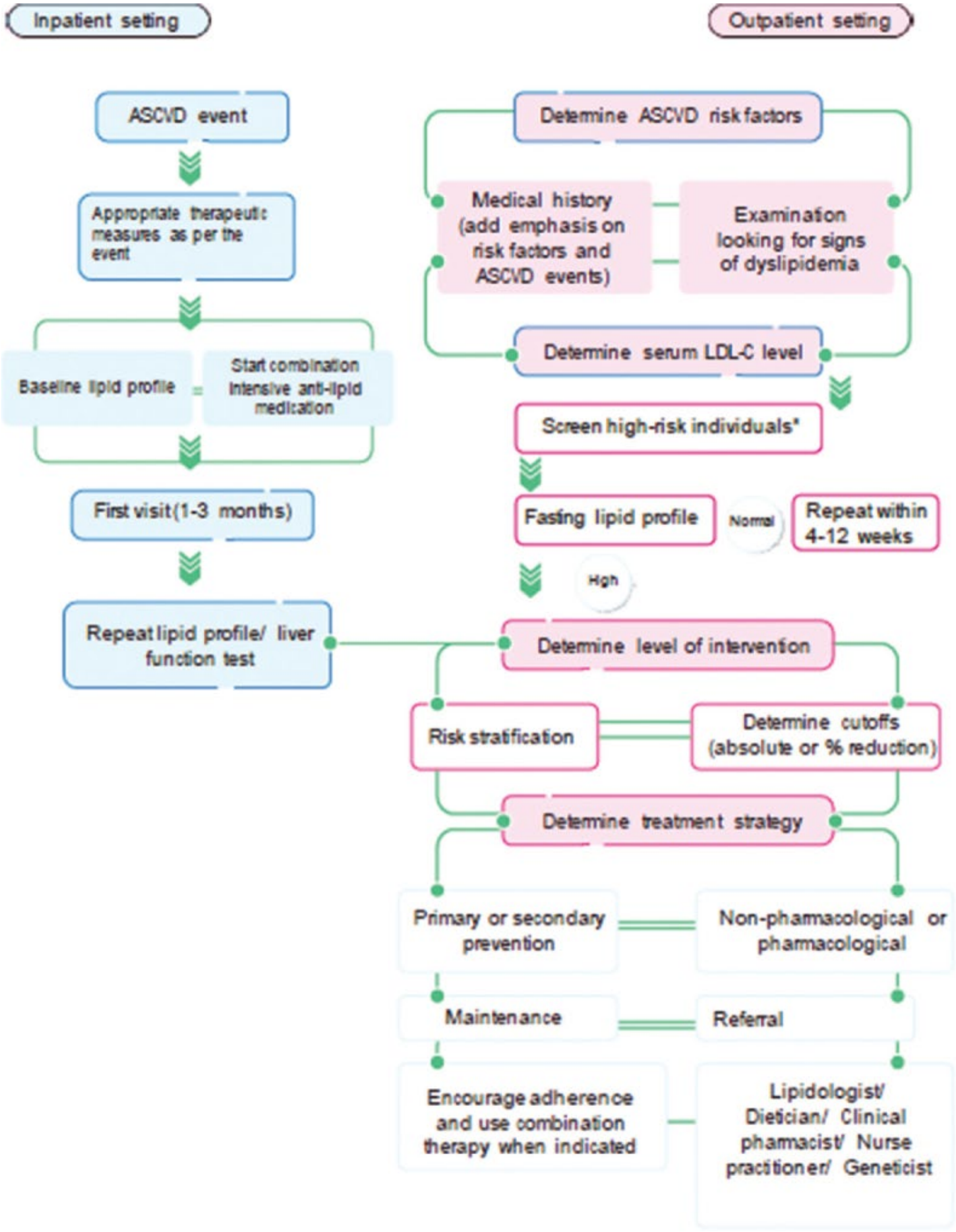
MOH=Ministry of Health. [a]Class of recommendation, [b]Level of evidence

Figure 6



Comprehensive solutions to encourage the adoption of preventive measures in Saudi Arabia

Figure 7


Inpatient setting
Outpatient setting
ASCVD event
Appropriate therapeutic measures as per the event
Baseline lipid profile
Start combination intensive anti-lipid medication
First visit (1-3 months)
Repeat lipid profile/ liver function test
Determine ASCVD risk factors
Medical history (add emphasis on risk factors and ASCVD events)
Examination looking for signs of dyslipidemia
Determine serum LDL-C level
Screen high-risk individuals*
Fasting lipid profile
Normal
Repeat within 4-12 weeks
High
Determine level of intervention
Risk stratification
Determine cutoffs (absolute or % reduction)
Determine treatment strategy
Primary or secondary prevention
Non-pharmacological or pharmacological
Maintenance
Referral
Encourage adherence and use combination therapy when indicated
Lipidologist/ Dietician/ Clinical pharmacist/ Nurse practitioner/ Geneticist

Clinical pathway (patient journey) of ASCVD patients in Saudi Arabia. *If the nonfasting lipid profile is available with normal levels, no further intervention is needed. ASCVD: Atherosclerotic cardiovascular disease

Table 16

Evidence-Based "to do" and "Not to do"

Recommendations	COR	LOE
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[28,29,30]
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 years risk of ASCVD	I	C[3]
For Saudi adults 20-39 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[43,68,69,70]
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]

Green color indicates new recommendations for the Saudi population. [a]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, [b]Men <55 years, women <60 years, [c]Optimally, 3 measurements, [d]Defined as eGFR <60 mL/min/1.73 m2 on two measurements >3 months apart, [e]CAC score is increased following statin treatment; therefore, the CAC scores of statin-treated patients should be interpreted with caution, [f]Extremely high risk = Post ACS + history of other vascular event/peripheral artery disease/polyvascular disease/multivessel CAD/FH. Apo-B: Apolipoprotein B, CVD: CV disease, ASCVD: Atherosclerotic CVD, CAC: Coronary artery calcium, CT: Computed tomography, CKD: Chronic kidney disease, DM: Diabetes mellitus, eGFR: Estimated glomerular filtration rate, FH: Familial hypercholesterolemia, 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-HDL-C, RA: Rheumatoid arthritis, RRs: Relative risks, SCORE: Systematic Coronary Risk Estimation, TC: Total cholesterol, CAD: Coronary artery disease, TGs: Triglycerides, ACS: Acute coronary syndrome, PCSK9: Proprotein convertase subtilisin/kexin type 9, CHD: Coronary heart disease, CK: Creatine kinase, COR: Class of recommendation, LOE: Level of evidence, AIDS: Acquired immunodeficiency syndrome, BP: Blood pressure, CV: Cardiovascular, HDL-C: High-density lipoprotein cholesterol