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Improvement initiative in LDL-C management in Saudi Arabia: A call to action ☆

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ABSTRACT

Purpose: Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in the Saudi Arabia (KSA). Over the last decade dyslipidemia has been the predominant risk factor in KSA. The linear relationship between low density lipoprotein cholesterol (LDL-C) levels, a marker for dyslipidemia, and progression of ASCVD is well established. The objective of this paper is to to provide an overview of the burden of disease, outline current clinical practice guidelines (CPG), examine gaps in care, and provide actionable recommendations to prevent, diagnose, and treat dyslipidemia in KSA.

Results: Saudi Arabia has the highest prevalence of ASCVD in the Gulf region. Several gaps in the implementation of CPGs, including the underdiagnosis and undertreatment of dyslipidemia, inadequate primary and secondary prevention efforts, complicated by a fragmented health system have been identified. Compelling evidence indicates that target LDL-C levels are not achieved throughout the Middle East region. In addition, high-risk patients are often left unidentified with adequate treatment.

Conclusion: This statement recommends specific multilevel interventions to optimize the prevention, diagnosis, and treatment of ASCVD. These recommendations focus on strengthening primary and secondary prevention through education initiatives, establishment of specialized prevention and treatment centers, and development of local and regional CPGs.

Contents

Abbreviations: LDL-C, low density lipoprotein cholesterol; PURE, Prospective Urban Rural Epidemiology study; MOH, Ministry of Health; CEPHUS, Centralized Pan-Middle East Survey on the Under-treatment of Hypercholesterolemia; DYSIS, Dyslipidemia International Study.

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1. Introduction

Cardiovascular mortality is the leading cause of death in the Kingdom of Saudi Arabia (KSA) with atherosclerotic cardiovascular disease (ASCVD) accounting for the majority of these deaths. Multiple ASCVD risk factors have been identified, with dyslipidemia being the predominant risk factor in the Kingdom. Despite established guidelines on lipid management, to date, primary and secondary prevention efforts have been inadequate in reducing cardiovascular mortality.

As such, it is imperative to intensify and streamline clinical pathways and healthcare expenditures to address a growing and changing Saudi population. The purpose of this paper is to provide an overview of the burden of disease in the Kingdom, outline current guidelines for lipid management, examine the gaps in care, and provide actionable recommendations to prevent, diagnose, and treat dyslipidemia in the Kingdom.

2. Methodology

To address the above issues, the Americas Health Foundation (AHF) identified clinicians and scientists with expertise in the field and who have published in the CVD arena since 2013. As a result of this effort, AHF convened a five-member panel of clinical and scientific experts from KSA. The panel consists of a diverse group representing various disciplines related to cardiovascular disease and prevention.

To better focus on the discussion, AHF staff independently developed specific questions, addressing the salient issues on the subject for the panel to address. A written response to each question was initially drafted by a different member of the panel. During the multi-day meeting of the Panel, each narrative was discussed and edited by the entire group, through numerous drafts and rounds of discussion until complete consensus was obtained. The objective of this article is to create a practical document with standardized guidelines for screening and diagnosing CVD in KSA.

3. Landscape of ASCVD in Saudi Arabia

The Global Burden of Disease Study for the Middle East revealed that cardiovascular mortality from ASCVD is the leading cause of death in the entire region in all adults and both sexes [1]. Amongst the six Gulf Council Countries (GCC), KSA has the highest death rate from cardiovascular disease [2]. Coronary artery disease (CAD), cerebrovascular disease and peripheral arterial disease (PAD) are all recognized manifestations of ASCVD that remain under-reported in KSA, given that the International Classification of Disease coding system is not compulsory.

ASCVD is associated with conventional risk factors that include dyslipidemia, diabetes mellitus (DM), hypertension, smoking, age, and sex. Unique to the Middle Eastern population is the early onset of ASCVD when compared to Western countries. The INTERHEART study, a case-control cohort conducted in 52 countries, found that the Middle East has the lowest average age to first myocardial infarction (MI) at 51 years of age [3]. More recently, other factors that contribute to atherosclerosis have been identified such as impaired glucose tolerance, chronic kidney disease (CKD), and chronic inflammatory conditions [4]. Dyslipidemia is the most prevalent risk factor for ASCVD, its relationship with other risk factors is intertwined, making a comprehensive management strategy imperative to successfully reduce overall mortality and morbidity.

4. Epidemiology of dyslipidemia in KSA

Overall, a wide range of prevalence rates for dyslipidemia are reported in the Gulf countries (Table 1) [5–9]. In 2013, the Saudi Ministry of Health (MOH) conducted a survey of 10,735 participants which revealed that 8.5% of Saudis had dyslipidemia and 19.6% had borderline dyslipidemia. Among dyslipidemic Saudis, 65.1% were undiagnosed or unaware, 2.3% were treated but uncontrolled, 28.3% were treated and controlled, and 4.3% were untreated [6]. The prevalence reported in this survey is likely underestimated as the threshold value in 2013 was higher than the value established in more recent guidelines, under which the borderline group would be captured as diseased participants. The Africa Middle East Cardiovascular Epidemiological Study (ACE) is a large study published in 2017 evaluating risk factors in the general population which reported that 68.6% of outpatients had dyslipidemia. Of these, only 16% were receiving lipid-lowering medications and 13.3% were not achieving LDL-C goals recommended in international guidelines [8–9]. Two other large prospective registries of inpatients with Acute Coronary Syndrome (ACS) conducted in Gulf countries (GULF RACE and GULF RACE-2) estimated the prevalence of dyslipidemia to be 31–32%, despite statin therapy [5–6].

Table 1
Prevalence of Dyslipidemia in Regional Studies.

Study	Date	Location	Population	Dyslipedemia Prevalence
GULF RACE [5]	2008	GULF	ACS	31.0%
GULF RACE 2 [6]	2012	GULF	ACS	32.0%
MOH Survey [7]	2013	KSA	GENERAL POPULATION	8.5%
ACE STUDY [8–9]	2017	MIDDLE EAST AFRICA	STABLE OUTPATIENT	70.0%

Abbreviations: ACS: acute coronary syndrome; MOH: Ministry of Health; KSA: Kingdom of Saudi Arabia

The inconsistent prevalence rates in these trials may be explained by factors inherent to the design of each study including the different populations, use of different cutoff values, and lack of adjudication of results. More importantly, the results may be representative of the differing specific time periods during which they were conducted.

4.1. Familial hypercholesterolemia

Familial hypercholesterolemia (FH) and metabolic syndrome are two disorders that represent high risk patients where adequate research on the prevalence and response to treatment in the region is lacking. FH, in particular, remains largely underdiagnosed and undertreated in the Middle East region, with an estimated prevalence of 1/232 based on the Gulf FH registry [7]. It is an autosomal co-dominant genetic disorder (homozygous or heterozygous) characterized by elevations in LDL-C > 95th percentile for age and sex. Individuals with FH often present with premature CAD. Despite very high levels of LDL-C, and even after documented cardiovascular events, FH frequently remains undetected and underinvestigated [10]. Timely diagnosis and aggressive treatment of FH is necessary to mitigate its ASCVD complications and reduce future events.

4.2. Low density lipoprotein cholesterol: The lower the better

Dyslipidemia is a heterogeneous disorder consisting of high LDL-C, low HDL-C, and high TG, among others, of which LDL-C is the predominant marker. Evidence derived from epidemiological studies has consistently demonstrated a linear relationship between LDL-C and the development of atherosclerotic disease. In particular, a direct association between LDL-C and risk for CAD has been established [11]. Since LDL-C is a modifiable risk factor, all international guidelines recommend lowering plasma LDL-C concentrations in those with dyslipidemia or at risk for ASCVD [4,12–13]. The latest European guidelines set strict target levels for primary and secondary prevention as well as recurrent ASCVD events within two years. Briefly, a target of < 55 mg/dl (1.4 mmol/L) is recommended for secondary prevention of very high risk individuals and primary prevention of those with familial hyperlipidemia who are at high risk. Those with a recurrent ASCVD event (even if it is of a different type) the target is < 40 mg/dl (1.0 mmol/L).

Risk stratification models and calculators are widely available. These aim to provide healthcare professionals with a 10- year estimate of an individual's risk for an ASCVD event, allowing them to decide on the appropriate lipid lowering strategy. Generally, individuals are stratified into low, borderline, intermediate, high, and very high categories. Additionally, risk enhancers have been recognized in the most recent guidelines and include chronic inflammatory diseases, CKD, pregnancy-associated conditions such as preeclampsia, family history of premature CAD, etc. Individuals requiring intensive LDL-C level reduction are those with multiple major risk factors for ASCVD, DM, severe and poorly controlled risk factors, metabolic syndrome, and patients with established ASCVD (4). However, gaps between guideline recommendations and practice continue to exist.

5. Management options

In line with The World Heart Federation's Cholesterol Roadmap of reducing ASCVD by 25% by 2025, aggressive lipid management should be encouraged and implemented. Recent international guidelines for lipid management emphasize the role of lifestyle modification as well as intensive medical therapy with the escalation of doses or addition of other agents to lower LDL-C [4,12–13]. The most commonly used groups of lipid lowering drugs in the treatment of LDL-C are statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9i).

5.1. Statins

Pharmacological management largely consists of statin therapy which has invariably demonstrated a reduction in major adverse cardiovascular events (MACE) in both primary and secondary prevention [14]. Since the 4S trial in 1994, many other landmark trials have unequivocally demonstrated that statins, as first line lipid lowering agents, reduce MACE [14–15].

International guidelines have incorporated statin therapy into their recommendations and identified groups of patients who benefit from intensive statin therapy [4,12–13]. A meta analysis of individual data from 26 randomized controlled trials of statins reported a 10% proportional reduction in all cause mortality and a 20% proportional reduction in CV death for every 40 mg/dL of LDL C reduction. The risk of major coronary events was reduced by 23%, and the risk of stroke was reduced by 17% for every 40 mg/dL of LDL C reduction [11].

It is important to acknowledge that residual risk occurs in a substantial population of those on statin therapy. These individuals remain at high risk of a subsequent event one year after initiation of lipid lowering therapies. Residual risk can be categorized into three groups: those who fail to achieve LDL-C targets despite optimal statin therapy, those who reach LDL-C goals on optimal statin therapy but continue to suffer ASCVD events, and those who do not reach optimal statin doses. Failure to achieve targets on optimal statin doses in the first group is attributed to FH, secondary causes of dyslipidemia, elevated lipoprotein A, and individual result variability. The second group consists of those with poorly controlled non-lipid related risk factors such as DM and CKD, who continue to present with clinical events despite optimal statin doses and target LDL-C levels. In the third group, there is intolerance to statins, defined as muscle pain and/or liver dysfunction, or poor adherence which results in an inability to reach LDL-C targets [16–19].

5.2. Ezetimibe

When LDL-C targets are not met with statins even after escalation of doses, other options should be added as second line therapies, such as combination therapy with ezetimibe and PCSK9i. The IMPROVE-IT trial demonstrated that the combination of ezetimibe and simvastatin reduced LDL-C by up to 50 mg/dL and showed a significant reduction in MACE after an ACS. Its safety is well established and there is no increase in the risk of muscle or liver toxicity, gallbladder lithiasis, or cancer [20].

5.3. PCSK9i

The reported LDL-C reduction with PCSK9i reaches 57% in different populations including homozygous or heterozygous FH [25]. Two trials providing cardiovascular outcome data are now published. In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER), a total of 27,564 ASCVD patients on statin therapy and evolocumab were enrolled, achieving LDL-C reductions up to 30 mg/dL. In addition, on follow-up of 2.2 years, there was a significant decrease in the composite primary endpoint of cardiovascular death, MI, stroke, hospitalization due to unstable angina, and coronary artery revascularization by 15% [21–22]. Similarly, alirocumab was examined in the ODYSSEY OUTCOMES trials that demonstrated LDL reductions reaching 47% in high risk patients. The ODYSSEY trial also revealed a reduction in cardiovascular outcomes and all-cause

Table 2
LDL-C Target Level Achievement in Regional Studies.

Study	Date	Sample Size	Statin use	LDL-C target Achieved*	Region
PURE [32]	2011	13,5335	YES	14.6%	Global
MOH Survey [7]	2013	10,735	YES	28.3%	Saudi Arabia
CEPHEUS [34]	2014	527	YES	32.0%	Arabian Gulf Countries
DYSIS MIDDLE EAST [35]	2014	2,182	YES	38.2%	Middle East

*Percentage studied population that achieved target LDL-C level

mortality by 15% in a group of high-risk presenting with ACS [23]. At this time, PCSK9i are beneficial in three subsets: patients who are at very high risk for ASCVD on maximally tolerated statins alone or in combination with ezetimibe therapy and fail to reduce their LDL levels, patients who are at very high risk for ASCVD and are intolerant to statins, and those with FH without clinically diagnosed ASCVD [24]. In a recent publication by Santos et al, examined the role of PCSK9i in FH (both homozygous and heterozygous). The primary endpoint was the incidence of adverse and the secondary endpoints were changes in LDL-C and other lipids. A total of 300 patients were evaluated and evolocumab was well tolerated and effectively reduced plasma LDL-C levels in patients with homozygous and heterozygous FH during the follow up period of 4.1 years [25].

Importantly, the concept of 'lower is better' has been clearly demonstrated in the PCSK9i trials in which very low levels of LDL–C were achieved with a linear reduction in cardiovascular risk. No safety concerns were detected with very low LDL-C levels, especially with respect to neurocognitive dysfunction [26]. Unlike statins, there is no evidence that PCSK9i increase the incidence of new-onset diabetes [27–28]. As such, regional health authorities should adopt a policy of lower is better reflecting the growing body of evidence.

6. The gap between clinical practice guidelines and practice

Clinical practice guidelines (CPG) are commonly developed by specialized organizations to provide practitioners with evidence-based recommendations. There are currently no regional or local guidelines in KSA or the Middle East on the management of dyslipidemia with the exception of a consensus statement that was published in 2016 for the region. Most healthcare professionals in Saudi Arabia refer to international CPGs, namely the ACC/AHA or the European guidelines. However, adherence to and implementation of these guidelines has been inadequate in KSA and the Middle East region [29–32].

Several international and regional cohorts highlight this gap [33–37] (Table 2). In the Prospective Urban Rural Epidemiology (PURE) study, of the 5,650 participants with a prior CAD event, only 14.6% remained on statins after 4–5 years. In this study, use of statins was significantly different between urban and rural areas (19.9% vs. 11.6%, respectively), suggesting unequal distribution of resources and poor adherence to CPGs by the physicians [33]. A similar observation was noted in the INTERHEART trial. In this cohort, urban populations exhibited more ASCVD risk factors compared to rural areas; however, cardiovascular outcomes were worse in the rural population. This paradox may be explained by the early detection and treatment of risk factors in urban areas. Such interventions are known to modify disease progression and improve outcomes. These findings warrant a more uniform distribution of resources and implementation of prevention programs [34].

The Saudi MOH survey conducted in 2013 revealed that 65.1% of participants were unaware of their dyslipidemia or their LDL-C levels (7). This demonstrates the need for an effective and broad prevention policy focused on improving awareness. The Centralized Pan-Middle East Survey on the under-treatment of hypercholesterolemia (CEPHEUS) study, conducted in six GCC countries, further exemplified the suboptimal management of dyslipidemia throughout the region. In this study, the National Cholesterol Education Program LDL-C goals were referenced and attained in 91.1% of low-risk, 52.7% of high-risk, and 32% of very high-risk patients. Contrary to the recommendations, the higher risk individuals were less aggressively controlled [35].

Yet another study, the Dyslipidemia International Study (DYSIS)-Middle East, evaluated patients from Jordan, Lebanon, KSA, and the Emirates who had been on statin therapy for $\geq$ 3 months. Of the 2,182 patients enrolled, 52.3% had established ASCVD and 82.6% were at very high risk of CV events. Notably, 61.8% of all patients did not achieve target LDL-C levels [36].

As such, LDL-C should be used as a metric that is recorded and tracked. This may incentivize healthcare professionals in the region to routinely screen at risk individuals. It may also serve as a tool to educate patients with emphasis on programs such as the "Know Your Number" campaign. These campaigns have been effective in other regions and will allow the health authorities to measure progress of prevention programs.

7. Healthcare system structure and challenges

Although CPGs developed by global healthcare organizations have improved patient outcomes in their populations, there are limitations that affect their implementation and uptake by many clinicians and payers at the local level. Many reasons could explain this such as differing definitions of quality of care by clinicians, lack of patient and physician education or motivation, and misinformation on side effects. A study reported the physician awareness of the recommended LDL-C targets in patients with CAD and PAD to be 40% and 36% respectively. This ultimately creates a gap between scientific evidence-based knowledge and actual practice and decision making [37].

In line with global trends, the Saudi healthcare system has experienced growing expenditures. However, a challenge unique to KSA is the fragmentation of the health care system which includes multiple sectors - MOH, ministry of defense, ministry of higher education, among others - each with its own mandate, administration, and funding. This results in a disjointed system that creates gaps due to the absence of a unified medical records system and standardized clinical pathways and policies. Ultimately, there is duplication in treatments and unnecessary expenditure. As a result, the system is undergoing a massive transformation defined by the national "Vision 2030" program. One of the main initiatives of this program is the establishment of a national center for health technology assessment as an independent entity to help maximize the efficient use of resources. This can be achieved by streamlining services and creating a unified system with standardized targets and incentives for physicians to adhere to guidelines.

8. Economic perspectives in dyslipidemia

In recent years, there has been a growing interest in the concept of value in healthcare and its potential role in clinical practice. The

term value can be simply defined as the health outcomes achieved per dollar or cost spent to achieve those outcomes. The rising concern about the value of healthcare services is mainly related to the rapid increase in healthcare spending in KSA that increased from 27 billion USD in 2005 to 45.9 billion USD in 2019 [38].

Although local data is not available, in most developed countries 85–90% of healthcare expenditure is allocated to secondary prevention, whereas health expenditures for primary care interventions accounts for only 5%. As such, primary prevention programs for the control of dyslipidemia would benefit from reevaluation of the budget allocation [39–41]. Public spending on prevention generally entails regulatory mechanisms for the intial authorization of drugs or preventive measures and subsequent post-marketing surveillance. It also involves the cost of public awareness projects. Parallel to public efforts and expenditure, individual and industry driven projects often supplement prevention particularly in the areas of research and health education (Supplementary Figure 1).

In general, economic considerations have been excluded from CPGs. A recent exception is the cost-effectiveness analysis conducted for PCSK9i which was included in the ACC/AHA 2018 guidelines and provided an understanding of the expected value of adopting expensive drugs with regard to lifetime costs, savings, and quality of life [4]. The price of PCSK9i was substantially reduced in the United States and the Kingdom. Most new technologies for ASCVD that are clinically effective lack robust economic evaluation. It is important to bare in mind the cost of prevention and drugs is generally lower than invasive procedures and hospitalizations that result from the complications of atherosclerosis. However, quality of life and prevention of morbidity and mortality is the primary goal of early interventions irrespective of cost.

9. Recommendations

KSA has the highest prevalence of ASCVD in the Gulf Region, highlighting the need for an intervention in the prevention, diagnosis, and treatment of this disease. This paper has addressed particular issues related to the need for appropriate treatment of elevated LDL-C levels in Saudi Arabia. Despite clear recommendations for primary and secondary prevention at all levels of care, there are several barriers that currently impede a positive impact of cardiovascular outcomes in the country. This gap between guideline recommendations and clinical practice emphasizes the need for a call to action to achieve a comprehensive approach to the management of LDL-C. Several levels of intervention are necessary and may be beneficial for many countries regionally confronting the same challenges.

9.1. Government/Medical Societies:

- Prioritize primary prevention in terms of dyslipidemia
- Create wide reaching primary prevention programs that raise awareness among the general population of the risks of ASCVD and the importance of its prevention and control
- Devise continuous medical education programs, accredited and endorsed by the Saudi Commission for Health Specialties (SCHS) and scientific societies, to improve awareness of dyslipidemia prevention, diagnosis, and treatment
- Develop and incentivize a dedicated training in SCHS certification
- Generate local data through research that defines the current healthcare landscape for ASCVD and dyslipidemia
- Develop dyslipidemia and atherosclerosis guidelines for the country
- Develop collaborative efforts endorsed by medical societies in partnership with public entities (eg tertiary cardiac centers) to curtail further events in the most vulnerable population that is High and Very High Risk patients, ie secondary prevention.

9.2. Healthcare Professionals:

- Recognize the importance of LDL-C in the genesis and progression of atherosclerosis
- Address the gaps in medical education regarding ASCVD
- Identifying patients with high LDL-C, performing adequate risk stratification, and delivering appropriate treatment and follow up, in concordance with international clinical practice guidelines
- Dispel myths associated with dangers of achieving very low LDL-C levels

9.3. Healthcare System:

- Establish sufficient primary care clinics that are evenly distributed throughout the Kingdom to facilitate access to screening and management
- Create specialized lipid referral centers to offer comprehensive care that involves a multidisciplinary team including a dietician, educator, nurse practitioner, clinical pharmacist and lipidologist
- Optimize and standardize clinical pathways to streamline care for dyslipidemia (Supplementary Figure 2)
- Create a unified electronic medical records system, avoiding redundancy in care and ultimately reducing costs

10. Novel concepts

- Provide incentives at the individual and institutional level. For example, both individual physician bonuses and hospital allowances can be determined by a value-based payment (Pay for Performance)
- Conduct post-marketing surveys and cost-effectiveness analyses based on which healthcare initiatives can be launched and aligned with the Vision 2030 project
- Design Quality rating systems that ranks specialized primary care and lipid centers to help improve the diagnosis, treatment and adherence as well as reduce discrepancies in the level of LDL-c care across a jurisdictions.

Many regions worldwide are facing the gaps discussed in this paper. Hence, the recommendations stated here may be adapted as a framework for other countries seeking to develop dyslipidemia prevention programs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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