Review Article

Guidelines for dyslipidemia management in India: A review of the current scenario and gaps in research

Sanjana Misra [a], Tanica Lyngdoh [a, b], Rubina Mulchandani [a, *]

[a] *Indian Institute of Public Health-Delhi, Public Health Foundation of India, Gurgaon, India*
[b] *Epidemiology and Communicable Diseases Division, Indian Council of Medical Research, New Delhi, India*

ARTICLE INFO

ABSTRACT

Cardiovascular Diseases (CVD) have a high disease burden in India. Dyslipidemia, a major CVD risk factor, requires effective management.

Our review describes the appropriateness of the international dyslipidemia guidelines in the Indian context. A systematic search was performed in PubMed, Google Scholar, Cochrane Library and Science Direct to obtain relevant articles.

Dyslipidemia management guidelines by western medical associations are based on their studies, with ethnic minorities underrepresented and biological features of other racial groups inadequately incorporated. The Lipid Association of India (LAI) came up with a consensus statement guided by an expert panel to adapt the western guidelines to Indians. However, absence of Indian guidelines has led to physicians basing treatment on individual preference, contributing to heterogeneity. Our review underscores the need for formulating Indian dyslipidemia management guidelines and CV risk estimation algorithms, highlighting the scope for further research. This could supplement the clinical expertise of LAI and enhance patient experience.

1. Introduction

Dyslipidemia refers to either lipoprotein overproduction or deficiency, which is a consequence of abnormal lipoprotein metabolism. This leads to elevated total cholesterol, low-density lipoprotein (LDL-C) cholesterol and triglyceride (TG) concentrations, and a decrease in the high-density lipoprotein (HDL-C) cholesterol concentration in blood.[1] Dyslipidemia could be *Primary* (genetic defect in the lipid metabolism that causes abnormal lipid levels) and *Secondary* (caused due to modifiable lifestyle and environmental factors, diseases, and medications).[2] Dyslipidemia has been strongly associated with the pathophysiology of cardiovascular diseases (CVDs) and is a major independent risk factor for coronary artery disease (CAD), further leading to the development of atherosclerosis and associated cardiovascular events.[3] CVDs have become a growing burden across the globe and are highly prevalent, especially in the developing countries that alone account for 80% of the global CVD mortality.[4] India has seen a rapid increase in the prevalence of CVDs, accounting for around 24% of all deaths, aged 25—69 years. CVDs tend to occur at a younger age in Indians, with 10% of all heart attacks in people below 40 years and more than 50% of cardiovascular deaths in people below 70 years of age. The age-standardized estimates for disability-adjusted life-years (DALY's) lost due to CAD are three times higher in India than in the developed countries.[5,6]

To address the serious health effects of dyslipidemia, various developed countries have developed their own set of guidelines to manage the disease and provide clinical guidance for appropriate healthcare, especially in specific circumstances. Of all the available guidelines, the ACC/AHA and ESC/EAS are the most widely used so far. These guidelines have become a basis for other developing countries to follow, for the clinical management of abnormal lipids. However, these guidelines are restricted to the Western populations and do not cater to the geographical diversity, ethnicity, genetic and environmental variations as well as the cultural heterogeneity that exists in other populations, and the need for developing local guidelines that could cater to the Asian and Middle Eastern regions has been advocated in literature.[4] Studies have

* Corresponding author. Indian Institute of Public Health, Public Health Foundation of India, Plot 47, Sector 44, Gurugram, Haryana, India.
E-mail addresses: sanjanamisra7@gmail.com (S. Misra), lyngdoh.t@icmr.gov.in (T. Lyngdoh), rubinamulchandani19@gmail.com, rubina.mulchandani@iiphd.org (R. Mulchandani).

shown that Asians have a higher prevalence of lipid abnormalities as compared to non- Asians, owing to a difference in the pattern of dyslipidemia. It has been observed that dyslipidemia in Asians, especially Indians, is atherogenic, with a higher prevalence of low HDL cholesterol and high triglycerides and a lower prevalence of high serum cholesterol than their non-Asian counterparts.[3,7] While western studies and data from NHANES have highlighted the elevated LDL-C and TG levels in the development of CAD which confirms the pattern as seen in the west,[3,7,8] a study conducted among young CAD patients in India confirmed the Asian pattern of high TG, low HDL-C and a low level of LDL-C.[3,9] Studies conducted among Asian Indian immigrants in the USA have indicated the same pattern as well. The ICMR-INDIAB study, a cross-sectional survey conducted across India also confirmed a lipid abnormality pattern in the country with no rural-urban differentiation.[7,10]

The purpose of this narrative review is to summarize the various international dyslipidemia management guidelines in the Indian context, highlight the gaps that exist, and underline the need for country-specific guidelines for Indians.

2. Methodology

2.1. Types of studies

A literature search was performed to obtain relevant articles on dyslipidemia and its management, both from India and the west, along with original guidelines published by different countries. Both primary and secondary research articles were included in the review. Consensus statements and studies led by healthcare organizations were also included. The reference list of relevant articles was further searched for any additional literature.

2.2. Type of populations

Research studies involving young adults and the elderly were eligible for inclusion.

2.3. Information sources

A literature search was undertaken in PUBMED, Google Scholar, Cochrane Library and Science Direct using a combination of search terms like "dyslipidemia", "dyslipidemia management", "western guidelines", "Indian guidelines" and "cardiovascular disease", in different combinations, for obtaining relevant articles.

2.4. Study selection, data extraction, and synthesis

Only articles that catered specifically to dyslipidemia management and the associated guidelines were considered eligible. Our search was restricted to studies published in the English language. Further, no time filters were added for this search. After removing duplicates, articles that fit the eligibility criteria were first screened based on their titles, followed by a screening of their abstracts. Full texts of articles that were found eligible were then obtained and screened for their inclusion in the study. (The process of selection of studies is described in Fig. 1) Any disagreements were resolved by discussion within the study team. From the selected articles, information on the current guidelines of different countries, along with comparative data, was extracted for narrative synthesis.

3. Results

3.1. International guidelines at a glance

There are five major international guidelines currently referred to globally-the American College of Cardiology/American Heart Association (ACC/AHA), the Canadian Cardiovascular Society (CSS), the European Society for Cardiology/European Atherosclerosis Society (ECS/EAS), the Polish Lipid Association and the National Institute for Health and Care Excellence (NICE) guidelines.[11] Their main purpose is to assist clinicians in the optimal management of dyslipidemia in patients. All the guidelines have differences owing to differences in the existing literature and the medical principles of different countries, but they share some common features as well. All the guidelines agree on developing evidence-based recommendations, particularly from RCTs, as well as understanding the importance of shared decision making between the clinician and patient for better efficiency. They have all highlighted the role of statins as the first line of treatment. Every guideline has acknowledged the role of CV events and their association with dyslipidemia and hence developed a CV risk calculator for more precise diagnosis and treatment. However, in spite of the common themes, the guidelines differ in their risk calculator algorithms and treatment plans, depending on the country-specific evidence base. These have been further described in detail in Tables 1 and 2.[4,12−20] The lipid parameter goals also vary across the ACC/AHA, ESC/EAS and the LAI documents.[14,21,22] The LDL-C target goals for high risk and very high risk patients are <70 mg/dl and <50 mg/dl respectively, as per the Indian consensus document, which is similar to the conservative cut-offs of <70 mg/dl and <55 mg/dl as per the European recommendations. The ACC/AHA guidelines on the other hand set LDL-C thresholds combined with the use of therapeutics (statin and non-statin) for each threshold, instead of target goals. According to the American recommendations, if LDL-C remains above 70 mg/dl with maximally tolerated statins, additional ezetimibe is suggested in patients with ASCVD, and a PCSK9 inhibitor in ASCVD patients at very high risk. The cut off for adding a PCSK9 inhibitor is higher (more than or equal to 100 mg/dl) in patients of familial hypercholesterolemia.[14,22]

The different strategies used in developing these guidelines highlight their limitations especially in terms of their restrictive nature. The ESC/EAS guidelines have endorsed the need for a systematic comparison of the current international recommendations in order to achieve a global consensus on dyslipidemia management. The NICE guidelines have also recognized the necessity for more data on effectiveness to utilize statin therapy to its fullest. As seen from Tables 1 and 2, the variations among all the guidelines indicate that recommendations are formulated based on the evidence from their population and its characteristics, with studies identifying patterns unique to the specific countries.

3.2. The Indian consensus statements

Owing to an increase in dyslipidemia and CVD-related morbidity and mortality in India, the Lipid Association of India (LAI) adopted the international guidelines for the Indian population. The European and American guidelines were decided as the guiding framework as their recommendations were based on changing global evidence. However, the LAI has provided flexibility by allowing the final decision for the patient to be taken by the physician based on the individual patient profile, owing to evolving medicine and prioritizing patient's wellbeing, even though, this has been prepared after an in-depth study by an expert panel. The LAI
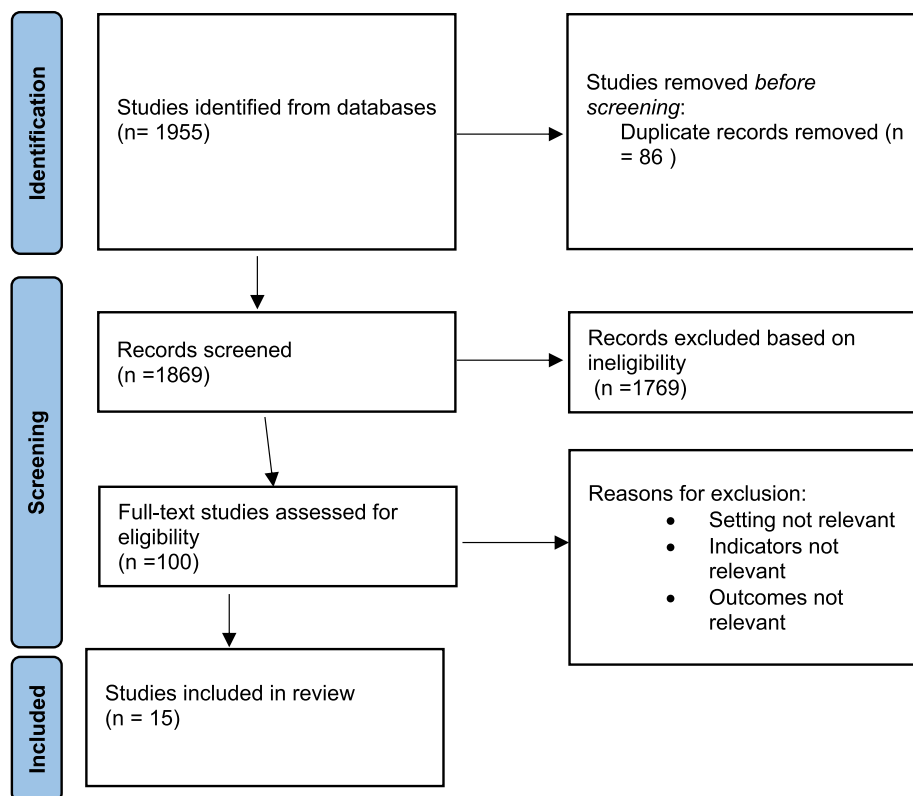
Fig. 1. A flowchart depicting the study selection flow

released a two-part consensus statement in the year 2016 followed by an updated third part in 2018.[21,23,24] The recommendations are based on cardiovascular risk factor assessment, treatment goals and targets, treatment recommendations, follow-up monitoring, and safety assessments.[25]

The first part of the statement consists of common concerns related to lipid management during clinical practice. It has highlighted and acknowledged the difference in patterns in the lipid profiling of Indians as compared to the west. It has also defined the criteria for identifying patients with a high risk of CVD and has considered risk estimation for patients below a 10-year risk of CVD, making them eligible for statin therapy too, if required.[23,24] Another highlight of the statement has been recommending the usage of non-HDL-C lipid levels as a co-primary target along with the primary LDL-C lowering by statins, thereby acknowledging the pattern of higher non-HDL-C in Indians. This could be attributed to the fact that non-HDL-C (total cholesterol − HDL-C), a surrogate marker for elevated TG levels, as well as an indicator of the levels of small, dense LDL, is a more accurate predictor of CVD risk in Indians, especially in people already on statins.[21,26] The statement has also defined the cut-offs for statin therapy depending on the extent of LDL-C reduction.

The second part deals with the management of dyslipidemia in special patient populations as well as in the elderly and women. It defines hypercholesterolemia in specific patient categories such as those with heart failure (HF), chronic kidney disease (CKD), non-alcoholic fatty liver disease (NAFLD), cerebrovascular disease, thyroid disorders, inflammatory joint diseases, familial hypercholesterolemia, human immunodeficiency virus (HIV) infection, heart and other organ transplants and recommends statin therapy accordingly.[21,26–28] It also has separate guidelines on the treatment of women under special circumstances like pregnancy, breast-feeding, and menopause.[23,28] The document has also provided a

rationale for formulating the recommendations based on an in-depth analysis. It has also covered dyslipidemia management strategies in HIV, organ transplant patients and recipients, and immune suppressant patients and provides a list of statins along with their effects on HIV patients for ease of analysis for the clinicians.[23,28] The detailed statements are presented in the Supplementary File.

The third part of the statement provides an overall updated version of the previously released statements highlighting the importance of shared decision and individual clinical judgement. It continues to endorse the earlier recommendations of Part I & II, i.e. proposing Apo B as the universally measured indicator to estimate the true CV risk, since LDL-C alone may underestimate the risk, especially in cases of atherogenic dyslipidemia. The cut-off for risk stratification has been mentioned in the earlier statement. It also continues to recommend triglyceride management in patients with hypertriglyceridemia as well as implement lifestyle modifications as a preventive measure. Lastly, it recommends the use of non-HDL-C as co-primary targets for lowering lipids as its monitoring is simple, practical for treatment decisions, and takes care of both LDL-C and triglycerides targets.[24] However, LAI has now proposed lower LDL-C goals for Indians based on a recent randomized trial that had shown to further reduce CV risk by non-statin drugs.[24]

The advantage of the consensus statement is that it eliminates to some extent, the confusion of clinicians to choose from the many international guidelines that can otherwise cause confusion and complicate the decision-making process. However, the statement has been developed using data from the western guidelines that are specific to their populations, which in turn affects the accuracy of implementation in other populations. Table 3 summarizes the contrast between the Indian guidelines and the corresponding LAI recommendations, to highlight issues with applicability.[11,21]

Table 1
Similarities and differences among the various international dyslipidemia management guidelines.

Themes	Similarities	Differences
Evidence-base for guidelines	All the guidelines have developed based on evidence from various sources.	Each guideline differs in the source of evidence: • ACC/AHA- RCTs, systematic reviews & meta-analysis. • ESC/EAS & CCS- No restriction on the type of studies but analysed the published data and recommendations. • PoLA- Data from research done on random selection of participants and patients in primary care. • NICE- RCTs and systematic reviews.
Diagnosis	All have advised for a 10-year risk estimation for atherosclerotic cardiovascular disease (ASCVD) events important for proper diagnosis. All the estimators are evaluating absolute risk.	The risk estimation calculator differs in each guideline. They have been developed suiting the characteristics found in their population as well as endpoints selected for accurate calculation an development of treatment plan which has been further described in Table 2: • ACC/AHA- Pooled Cohort Risk Equation (PCRE) • CCS- Framingham Risk Score (FRS) • ESC/EAS- Systematic Coronary Risk Evaluation (SCORE) • PoLA- Pol SCORE. • NICE- QRISK2
	Parameters for developing the CV risk estimator include sex, age, HDL-C, TC and systolic blood pressure.	Diabetes, ethnicity, and treatment for hypertension have not been included in parameters in most of the guidelines and therefore there will be a difference in the way the risk may be calculated and may not cover all the ethnic groups. This may also lead to poor predictivity.
Categorisation of statins	Most of the guidelines have classified statins as low, medium and high intensity depending on their ability to reduce pre-treatment concentrations of LDL-C levels by <30%, 30 to 40–50% & >40–50% respectively.	PoLA guidelines however have classified the statins as low intensity ranging <50%, medium being minimum 50% and high intensity being 50 –60% reduction in LDL-C levels.
Usage of statins	All the guidelines recommend statins as the first line of medication for treatment.	There is difference in the utilisation and prescription due to the difference sources involved in developing these guidelines: • CCS & ESC/EAS- does not focus on statin intensity but more on targeted reduction in plasma LDL-C levels. • ACC/AHA & NICE- recommend statin dose or intensity based on patient's clinical profile and characteristics.
	All the guidelines also agree on analysing the 10-year CV risk calculation for recommending the dosage and intensity of statins in primary prevention.	The recommended dosage and intensity differ due to the different calculators recommended by different guidelines: • ACC/AHA- recommend high or moderate-intensity statin therapy for patients with ≥7.5% 10-year ASCVD risk • ESC/EAS & CCS- selection and dosing of statins depends on the treatment goals defined by the CV risk calculator.
Monitoring recommendations	All guidelines recommend monitoring of transaminases and particularly, the creatine kinase (CK) biomarker in each patient before starting treatment with statins.	There is difference in the patient profile for requirement of monitoring the CK biomarker in some guidelines: • ESC/EAS &PoLA- recommend monitoring in all patients. • ACC/AHA- recommend for only those patients with muscular symptoms, risk for myopathy (family or personal burden of muscle disease or statin intolerance or drug therapy which can increase the risk for myopathy). • NICE- To be monitored only after assessing smoking status, blood pressure, alcohol consumption, body mass index (BMI), TC, non-HDL-C, HDL-C and TG, HbA1c, renal function and estimated glomerular filtration rate, transaminase level (alanine aminotransferase or aspartate aminotransferase), and thyroid stimulating hormone (TSH). There is also a difference in how transaminase should be monitored: • ACC/AHA- To be checked 8 weeks after starting statin therapy and once a year if the level is three times lower than normal. • NICE- To be always measured at the beginning of treatment and then subsequently after 3rd and 12th month of statin therapy.
	All guidelines also recommend periodic monitoring and analysis of lipid profiles after starting statin therapy.	The duration of monitoring differs in guidelines: • ACC/AHA- Recommend monitoring after 4–12 weeks of statin therapy and then every 3–12 months. • ESC/EAS- Recommend after 1–12 weeks of statin therapy, 3–4 weeks after changing medication and then once a year after reaching the treatment endpoint. • NICE- recommend 3 months after starting treatment and then once a year.

Another gap recognized during the development of the consensus statement is the inadequate number of large epidemiological studies from India that define normal lipid values and their association with CVD, somewhat affecting the accuracy of the current Indian recommendations.[21] It has also been observed that there is frequent use of non-standardized laboratories by physicians across the country which not only makes management of the disease difficult but also creates discrepancies while reporting their experiences. Although, the LAI recommendations are based on the clinical experience of the expert consensus group, this is not the most ideal approach because adapting western strategies to suit the Indian subjects has its own drawbacks in terms of applicability.[5,7]

Indians have atherogenic dyslipidemia-high TG and low HDL-C which predisposes them to a higher risk of diabetes, insulin resistance, metabolic disorders and CVDs.[7,26] The prevalence of type 2 diabetes mellitus is found to be almost 2 times higher in South Asians, when compared to non-hispanic whites.[29] The INTERHEART study showed that the levels of apolipoprotein were elevated

Table 2
Characteristics of CV calculators.

Guideline	Calculator	Development factors	Inclusion	CV risk & LDL evaluation	Statin Treatment
ACC/AHA	PCRE	Seven major National Heart, Lung and Blood Institute- funded cohort studies for US population	Non-fatal myocardial infarction, fatal coronary heart disease and non-fatal or fatal stroke.	Low <5% Moderate 5 −7.5% High ≥7.5% LDL ≥190 mg/dl	Risk ≥7.5%: moderate or high intensity Risk >5% but <7.5%: moderate intensity
ESC/EAS	SCORE	Prospective cohort studies in Europe	First fatal atherosclerotic event: myocardial infarction, stroke, other occlusive arterial disease or sudden cardiac death	Low <5% Moderate 5 −7.5% High ≥7.5% LDL-C ≥ 70 mg/dl	Maximally tolerated statin dose to achieve target treatment goal
NICE	QRISK2	Electronic health records of general practice in UK	Includes all atherosclerotic events	Low 5% Moderate 10% High 15% Very High ≥20% LDL-C	Moderate risk can begin with statins
CCS	FRS	Framingham Heart Study and Cardiovascular Life Expectancy Model	Coronary heart disease, cerebrovascular events, peripheral artery disease and heart failure	Low <1% Moderate 1−4% High ≥ 5−10% Very High >10% LDL-C ≥ 193 mg/dl	Target ≥50% reduction or LDL-C < 77

Table 3
Applicability of International guidelines versus the LAI recommendations in the Indian population.

International guidelines	LAI recommendations
ASCVD risk identification is straightforward as the population is mostly homogenous and the onset of risk factors is at a late age. All the guidelines recommend assessment of a 10-year ASCVD risk as the population mostly has a high-risk tendency owing to a late age onset.	ASCVD risk identification requires stratification owing to a heterogeneous population and the development of the disease at a relatively younger age. Considering Indians are prone to ASCVD at a younger age and have a relatively low 10- year ASCVD risk, they tend to have an elevated lifetime scare. Hence, LAI recommends lifetime ACVD risk estimation for all individuals who are presently free from ASCVD and have a low 10-year ASCVD risk.
The risk estimators identified in each guideline have been developed based on large studies done in their population and calibrated through computer tools and algorithms.	Due to the limitation of availability of large data and access to such tools and the internet in many parts of the country, LAI has proposed a risk algorithm that helps in risk categorization based on the presence and absence of risk factors. LAI has also recommended the use of JBS and FRS risk scores (FRS x calibration factor). However, due to a lack of consensus and no prospective validation of these estimators in the Indian context, these have major limitations. For example, The International Atherosclerotic Society (IAS) has proposed a 1.81 calibration factor for urban Asian men. However, using this factor with FRS calculations will lead to an overestimation of ASCVD risk in urban Indian men. This is because one risk factor imparts 25% lifetime ASCVD risk in the FRS calculation which when multiplied by 1.8 becomes 45% risk for ASCVD which is defined as high risk.
International guidelines recommend the highest or tolerated dose (on the higher side) to reach lipid level goals owing to lesser secondary issues. Only in the case of high-risk patients, the LDL goal of ≤ 50 mg/dl can be considered in correlation to the clinical profile and clinical trial data as per EAS/ESC guidelines.	In India, there is a risk of using high-dose statins even in high-risk patients because of the greater predisposition to adverse effects owing to high plasma levels of statins. Also, Indians are prone to diabetes and other metabolic disorders at a young age which further adds to the risk. Therefore, LAI has recommended low levels of high-dose intensity statins and low and moderate levels of statin for lipid therapy initiation.
International guidelines recommend two rounds of measurements: at the beginning and after a certain time duration to initiate lipid-lowering treatment.	LAI recommends the use of one lipid assessment to initiate treatment with statin due to the cost involved and the low probability of patients returning with secondary measurements. Lipid assessment, clinical history, and CV risk evaluation should guide the treatment plan.

among South Asians with a history of myocardial infarction, compared to similar subjects from other nations.[30–32] The dietary patterns of South Asians are also different from other ethnic groups, with a predominance of saturated fats and carbohydrates. Knowledge about the importance of physical activity and levels of daily exercise have also been found to be lower among South Asians as compared to other populations. A 2009 KAP study had reported that the level of understanding of coronary heart disease, effects of physical exercise and role of various risk factors was sub-optimal.[30]

Additionally, it has been noted that various health-related aspects and behaviours like education, socio-economic conditions, awareness levels, healthcare access and insurance could vary between native South Asians and South Asians abroad (in the US and UK), with the latter representing this ethnic group in various dyslipidemia and CVD epidemiological studies.[30] This calls attention to the need for greater representation of native racial and cultural groups in such research as well as the importance of indigenous studies and guidelines.

4. Discussion

Dyslipidemia is a condition characterized by an elevation in plasma cholesterol, triglycerides, or both or low high-density lipoprotein (HDL) or high low-density lipoprotein (LDL) levels that lead to the development of atherosclerosis which in turn is known to cause CVDs. It is an independent preventable risk factor for coronary heart disease and has been shown to significantly increase the risk of cardiovascular mortality.[33,34]

CVDs are the most prevalent cause of death and disability in both developed and developing countries, especially in India. Managing dyslipidemia among patients for both primary and secondary prevention of cardiovascular disease is thus of prime importance.[8,35,36] Various international organizations have come up with guidelines to address this issue, out of which the ESC/EAS and ACC/AHA are the two most prominent ones.[37,38] They aim to facilitate improvement in patient care and reduce costs. However, these guidelines vary in their emphasis on pharmacotherapy, stratification of patient groups, lifestyle modification, and use of fixed target or percentage reduction in LDL-C.[39] Moreover, none of the guidelines are in complete alliance and have data associated with the Caucasian subjects only. The 2013 clinical practice guidelines of the ACC/AHA on the treatment of blood cholesterol to reduce cardiovascular risk recommend high-intensity statin therapy to prevent cardiovascular events.[27] They distinctly advocate for high-intensity statin treatment for high-risk patients, but have dropped the use of LDL-C target levels and non-statin lipid-lowering drugs. The updated 2016 guidelines by the ESC/EAS, on the other hand, have underscored the seriousness of implementing a healthy lifestyle and introduced specific LDL-C goals for different risk groups. This is more in line with the needs of Asians and Middle Eastern populations who may require less intensive statin therapy to achieve LDL-C targets despite high CV risk status at screening.

Although the European guidelines do cater to some aspects of the Indian population, the pattern of dyslipidemia in this group is different from that of the west. Unlike the western populations where LDL levels are high, Indians have been shown to have lower HDL, an increase in triglycerides, and a high proportion of small dense LDL. It has also been seen that Indians develop CVD at a younger age owing to lifestyle changes due to urbanization, as well as the various nutritional and epidemiological modifications brought about by economic development.

Keeping all these constraints in mind, the LAI in 2016 and recently in 2018 came up with recommendations in line with the ACC/EAS guidelines that considered all aspects of treatment, utilization of available Indian data, and practical applicability of the recommendations.[40] However, these are still, just recommendations, like a guidance document, that have led to differences in treatment modalities owing to an absence of a formal set of population specific guidelines.

4.1. Need for India specific guidelines and associated challenges

The genetic, phenotypic, cultural, and socio-economic variability among Indians as compared to the west, along with a few other factors that emphasize the need for country specific recommendations,[25] are discussed below.

4.1.1. Heterogeneous treatment strategies

The absence of dyslipidemia management guidelines from India has led to Indian physicians resorting to western guidelines, which in turn results in non-uniformity in treatment. This was shown in a survey where the participating physicians were found to be choosing different methods of lipid management.[41] Most clinicians chose to set LDL-C targets in their patients, however, they chose to continue with the existing therapy in patients with elevated non-HDL-C but controlled LDL-C levels. The latest ACC/AHA guidelines have abandoned the old NCEP ATP III guidelines of LDL-C and non-HDL-C goals because of a lack of data from randomized controlled trials (RCTs) to support their continued use. The NLA guidelines, however, consider treatment goals beneficial for ensuring aggressiveness of therapy and maximizing long-term adherence to medication, and follow the NCEP ATP III approach of recommending non-HDL-C and LDL-C goals in dyslipidemic patients. These guidelines have proposed non-HDL-C as a better primary target for modification rather than LDL-C due to the stronger predictability of atherosclerotic cardiovascular disease (ASCVD) morbidity and mortality. The Indian consensus statement recommends LDL-C as the primary target for lipid-lowering therapy in patients with serum TG < 500 mg/dl. It further suggests that LDL-C target goals be based on the available western guidelines due to a paucity of evidence from India. It also prescribes non-HDL-C as the co-primary treatment target where the accurate estimation of LDL-C is unavailable, and a secondary target in patients with LDL-C at goal and TG > 200 mg/dL.[41]

Most of the participants from the physician's survey who set LDL-C targets in their patients reported using a combination approach based on baseline lipid levels along with ASCVD risk assessment, concordant with the NLA guidelines. The Indian consensus statement also recommends setting targets for patients as per the estimated global cardiovascular (CV) risk for proper management. However, many clinicians felt that the lipid targets for Indians should be lower than those recommended by the NCEP ATP III guidelines for the west. This indicated their perception of a higher CVD risk among South Asians in contrast to the west, leading them to recommend more aggressive targets.[42—44] But a dearth of literature on optimal LDL-C levels and treatment thresholds for Asian Indians has led to clinicians basing their recommendations on the different available western guidelines as per their individual assessment.

4.1.2. Variation in CV risk calculation and prediction

According to the survey respondents, various methods were applied for CV risk stratification by the clinicians. Interestingly, most of them continued with the NCEP ATP III recommended Framingham Risk Score that has been replaced by the pooled cohort equation, in the recently published ACC/AHA cholesterol-lowering guidelines. It is crucial to note that many ethnic groups, mainly Asian Indians, have not been factored into this equation, since these RCTs are conducted in the west and have an inadequate representation of minority groups. This could be due to the inclusion of Asian patients in the 'Whites' or 'Others' category, owing to the absence of a specific 'Asian Indian' category in the race section of pooled cohort risk calculator.[4,5,41,43] A proportion of clinicians reported depending on their clinical judgment for CV risk stratification.

The CV risk prediction models are vital in the prevention and management of CV diseases. Indian populations are characterized by an early onset of cardiovascular conditions with a higher frequency of emerging risk factors. Hence, the performance of the current risk calculators may not be equal and accurate[5] . Various studies have been conducted to see which risk model works best for Indians. One such study showed that the Framingham Risk Score (FRS) (old version) could identify only a small percentage (5%) of the population to be at a high risk whereas another retrospective study found that the British Society risk calculator 3 (JBS 3) showed best results.[45—47] Another study comparing the various risk prediction scores and statin eligibility depending on their respective scores showed that the FRS global CVD risk assessment model could categorize most of the patients into high risk for

cardiovascular events. QRISK2 and JBS3 performed intermediately while ACC/AHA-ASCVD risk score and WHO risk score could identify the least number of high-risk patients. ACC/AHA tool underestimates the risks in Asians and does not take into account the family history or the emerging risk factors.[45] A study by Chia et al validated the same by showing that the calculator over predicted the risk if the patients received treatment for risk factors.[48] It is important to note that the FRS-CVD estimates the risk for a large combination of CVD outcomes, whereas the other tools estimate it mainly for myocardial infarction and stroke. Hence, if outcomes are to be measured uniformly across all the risk estimators, the FRS-CVD wouldn't be the best for Indians since it cannot be appropriately compared to the other tools. Considering all parameters, QRISK2 and JBS3 seem to suit Indians the most as they also count South Asian ethnicity as an additional risk factor and median scores for South Asians are higher than the other tools. However, they provide lower 10-year risk estimates for diabetic patients.[30,45]

One reason why these risk calculators somewhat underestimate the risk of CVD among South Asians could be the fact that age is a major factor that drives the risk estimation algorithms and the younger age group of this population leads to an overall lower risk score. However, this doesn't take into account the presence of a large number of risk factors present in such groups at a young age.[47,49] Also, the prevalence of diabetes is significantly higher in India as compared to a majority of high and middle-income countries; tobacco smoking is lower in South Asian men as compared to other ethnic groups.[5,46] Additionally, none of this data has come from prospective CV epidemiological studies identifying risk factors at a national level, rather has come from regional studies, targeting special groups which by design do not represent the whole population.[15] Some researchers have suggested multiplying the CVD risk score for South Asians by a factor of 1.5, to accommodate these ethnic variations and the subsequent greater risk for cardiovascular conditions.[50] Hence, adopting a prediction model for clinical assessment of a patient to determine treatment options has its risks since it is dependent on local applicability and the degree of modifiability of the risk model.[46] An exclusive CV risk stratification protocol for Indians or South Asians needs to be developed that includes the heterogeneity and lifestyle of the Indian population for accurate assessment.

4.1.3. Unique pattern of dyslipidemia among indians and inadequacies in literature

Literature on the epidemiology of dyslipidemia in Asians, specifically Indians, has continued to grow and expand at a rapid pace in the last few decades.[2,3,9,31,36,51,52] However, while the current evidence is significant in augmenting our understanding of this disease in the Indian population over time, there is still scope for further research in the area. LAI has also highlighted in the consensus statement, a lack of large-scale epidemiological studies having national representation. The limited studies taken into account have highlighted not only a higher prevalence of dyslipidemia among Indians, especially the younger population, but also variations in patterns among the population itself.[5]

Variations have been observed within cities with Tier-3 city patients having higher lipid values, possibly due to diet and comorbidities like diabetes; the elderly patients mostly belonged to Tier-1 cities suggesting better health facilities and higher life expectancy in major cities.[53]

Reviews of Indian epidemiological studies in the past have underlined the need for more such epidemiological studies with larger sample sizes, multi-site studies, prospective cohorts with outcomes focused on the cardiovascular benefit offered by various combinations of treatment strategies in dyslipidemic patients and epigenetic studies on lipid biomarkers. Moreover, a majority of the existing studies are not nationally representative, thus affecting the overall generalizability of the findings. The limited usability of heterogeneous data owing to varied study methodologies has also been pointed out. Further, inadequate literature on the prevalence of the various types of lipid abnormalities in both rural and urban Indians, details of Indian dyslipidemia patterns and their prognostic implications, and the relevance of different cholesterol lipoproteins in India, need greater attention.[36]

4.1.4. Statin metabolism and adverse effects

Pharmacokinetic studies have shown that Asians respond more strongly to statins as compared to the western populations while reporting a significant difference in the pharmacokinetics of lipid-lowering drugs like statins among different racial/ethnic groups. Non-Hispanic whites or Caucasians require a higher dosage of statins when compared to Asians, for the same pharmacological action. It has been shown that the maximum prescribed dosage of Atorvastatin in Japan is about half of what is prescribed to patients in the United States (40 mg/day vs 80 mg/day). Also, a 10 mg dosage of Rosuvastatin is found to be lesser effective in lowering LDL-C in western populations than it is in Chinese patients. This can be explained by the fact that the plasma levels of the same dose of statins are seen to be almost 1.5 to 2.3 times higher in different Asian ethnic groups, as compared to Caucasians/whites. According to a study conducted in Singapore, upon administration of a single dose of Rosuvastatin 40 mg, Asian Indians achieved 1.7 times the plasma levels of the drug when compared to Caucasians.[54] Further, a meta-analysis reported that Asians required statin administration for a much shorter duration (almost 50%), when compared to the western populations, to achieve the same level of lipid lowering.[55-59]

Multiple reasons have been cited for this difference, including a lower body mass index (BMI), and a slower statin metabolism owing to genetic variability among Asian and western populations.[5] Cholesterol uptake and synthesis and statin metabolism are driven by single nucleotide polymorphisms (SNPs) in ABCG2, SLCO1B1, LDLR, HMGCR and CYP2D6 genes. Studies have shown polymorphisms on chromosome 12 of the SLCO1B1 gene in Asians, which is responsible for a reduced hepatic uptake and thus an increased blood plasma concentration of the lipid lowering drug. This in turn makes Asians more susceptible to the adverse effects of statins too. South-Asian ethnicity has also been reported as one of the determinants of elevated homocysteine which increases the risk of atherosclerosis.[3,30,55,57,60]

The heightened response among Asians thus raises possible concerns regarding a greater risk of statin-associated adverse effects too, mainly myalgia, neuropathy, increased blood glucose and cognitive changes.[61] However, there are limited studies regarding the safety of statins for Asians, especially Indians, and the results for some of them are rather inconclusive. Some studies showed an increased risk of haemorrhagic strokes and cancer on achieving very low serum cholesterol levels due to exaggerated responses from statins.[5,62,63] On the other hand, one study conducted among participants of South Asian origins in the USA and Canada showed no significant side effects following a high dose of statins.[54] Most statins show dose-related side effects which further aggravates the risk of increased sensitivity to statins.[59] One large-scale trial done in Japan from 1994 to 2004 showed a reduction in cardiovascular events with a lower dosage of statins, however, no large-scale studies have been done to compare the same exclusively in Indians.[5] Even though LAI recommends statins as the first line of defence for dyslipidemia management and CV events, and Indians have a 1.5—2 fold ASCVD risk compared to Caucasians, the use of statin therapy among South Asians with ASCVD is low.[26] This could be because of a lack of understanding of the history of ASCVD,

efficacy, and cost of statins, and the complexity associated with multiple guidelines.[24,64] On the contrary, there is also some literature to suggest a possibility of statins being overprescribed in the Indian population. The pharmaceutical market share of statins in India has significantly increased from 2008 to 2018.[65] The physician survey on lipid management showed that more than 60% of the doctors preferred prescribing statins in patients with no risk of coronary heart disease, solely based on normal triglycerides and slightly high LDL-C levels.[40] Research has shown that while statins offer significant benefit in CVD patients, the benefit of its use in primary prevention in healthier patients may not be that pronounced and could even do more harm than good.[66] A 2018 paper published in the BMJ reported that the 10 year CVD risk cut-off at which statin initiation is recommended is much lower than the cut-off value at which statin benefits significantly outweigh their risks in primary prevention.[67] Our use of statins, its metabolism and biological effects are therefore significantly different as compared to the westerners, further limiting the use of their guidelines in India. It becomes paramount to have more information on not just the efficacy but also the safety of statins in different sub-groups and incorporate that data into India specific recommendations.

4.1.5. Pricing issues

It has also been observed that there is a price variation between statin generic brands, and high dose statin therapy adds to increased health expenditure which becomes a crucial factor for Indian patients with limited finances.[5,54] This highlights another aspect of the need for India-specific guidelines, which is to achieve economic effectiveness. Medicines constitute a majority of the treatment costs, and hence affordability is largely determined by the cost of medications. Medication in India is expensive, and regular and consistent use of drugs for CVDs makes it unaffordable, which can push the population into poverty. This was observed in a study where only 2.6% of CVD patients took regular medications among low-income countries including India. This directly impacts the periodic health check-ups, negatively affecting the management of Dyslipidemia.[5,68,69] Thus, the economic constraints with regards to healthcare expenditure demand different treatment perspectives as well.[25]

As the popular adage goes, 'prevention is better than cure'. This holds true for cardiovascular disease as well. There is ample research to show the importance of lifestyle changes including dietary modifications and some form of physical activity in the delay of the onset of risk factors and thus, reduced risk of cardiovascular disease.[70–73] Such approaches can also aid in better management of disease in secondary prevention cases, and lower the recurrence of cardiac events, as well as morbidity and mortality numbers in populations.

This is of immense value in resource-limited countries like India, where access to healthcare is a challenge, and individuals from lower socio-economic backgrounds often do not receive optimal treatment due to financial constraints and associated barriers.[74] Emphasis on prevention and the effectiveness of lifestyle modifications can be useful in these settings. Studies recommend that clinicians include such advice as part of their routine counselling, especially in cases where medication is not well tolerated or is cost prohibitive.[75]

Considering these intricacies, an individualized treatment schedule and a targeted therapeutic approach providing optimal management of risk factors is warranted.[23,39] This would also help physicians in early screening and identification of disease patterns, leading to better management which could be more cost-effective.[23]

4.2. Recommendations

A guideline tailor-made for dyslipidemia management in Indians is cardinal, as the current statement by the LAI is based on international guidelines and involves recommendations by clinical experts, which could be driven by varied schools of thought regarding different treatment strategies adopted in the west. The Indian Consensus Statement can therefore be strengthened by supplementing the rich expertise of the clinical group with population-specific evidence, for greater robustness and homogeneity. This would require.

i) Development of indigenous calculators to obtain more accurate estimates of cardiovascular disease risk among Indians.
ii) Design and conduct of large scale prospective Indian studies with long-term follow-ups. Community-based epidemiological studies may provide insights into the ethnic variations in the lipid patterns, statin dosing, and cardiac risk profile of Indian patients, which in-turn would help ascertain optimal treatment targets among various population sub-groups.

5. Conclusion

Management of dyslipidemia has become a grave concern owing to the rise in CVDs among Indians. Management guidelines aim to provide evidence-based recommendations from studies conducted in the west. A dearth of studies among Indian populations to address the depth of the issue has added to the challenge in formulating strategies for management. Despite these hurdles, LAI in 2016 and 2018 came up with recommendations based on the western guidelines. The statement also highlighted possible alternatives if there were gaps in improving management strategies. However, the unavailability of a uniform set of country-specific guidelines makes it difficult for clinicians to chalk out the diagnosis which leads to varied treatment approaches and personal choice of treatment, especially in terms of CV risk estimation and statin dose recommendations. The current western guidelines also do not consider the Indian phenotype pattern of lipids or the different socio-economic, cultural, lifestyle, and genetic factors that make it harder to treat dyslipidemia in Asian Indians. Statin metabolism and adverse effect profile also differ between Asians and Caucasians. Also, unlike the western counterparts, periodic check-ups and treatment rates are borne out of pockets in India, which further adds to the challenges in management and treatment. Our review attempts to summarize the available evidence in this regard, underlining the need for dyslipidemia management guidelines for the Indian population.

This would require more population specific research to fill some of the lacunae pertaining to data on dyslipidemia prevalence, statin dosage, epigenetics of lipid biomarkers and varied lipid patterns among sub-groups, along with the development of CV risk estimation algorithms for Indians. An indigenous set of recommendations for lipid management that complement the clinical expertise of the LAI would help augment treatment decision making.

Funding

Author contributions

All authors contributed to the manuscript. RM and TL conceptualized the manuscript and SM prepared the first draft. RM and TL

reviewed the draft and provided inputs. SM and RM contributed to the subsequent drafts.

Declaration of competing interest

The authors have no competing interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2022.07.009.

References

1. Basak RC, Chatterjee M, Sarma PSA. AN OVERVIEW ON MANAGEMENT OF DIABETIC DYSLIPIDEMIA. :10.
2. Misra A, Luthra K, Vikram NK. Dyslipidemia in Asian Indians: determinants and significance. *Japi*. 2004;52:137–142.
3. Mahalle N, Garg MK, Naik SS, Kulkarni MV. Study of pattern of dyslipidemia and its correlation with cardiovascular risk factors in patients with proven coronary artery disease. *Indian J Endocrinol Metab*. 2014;18(1):48.
4. Alshamiri M, Ghanaim MMA, Barter P, et al. Expert opinion on the applicability of dyslipidemia guidelines in Asia and the Middle East. *Int J Gen Med*. 2018;11: 313.
5. Chandra KS, Bansal M, Nair T, et al. Consensus statement on management of dyslipidemia in Indian subjects. *Indian Heart J*. 2014;66(Suppl 3):S1.
6. Prabhakaran D, Jeemon P, Sharma M, et al. The changing patterns of cardiovascular diseases and their risk factors in the states of India: the Global Burden of Disease Study 1990–2016. *Lancet Global Health*. 2018;6(12):e1339–e1351.
7. Frank AT, Zhao B, Jose PO, Azar KM, Fortmann SP, Palaniappan LP. Racial/ethnic differences in dyslipidemia patterns. *Circulation*. 2014;129(5):570–579.
8. Ariyanti R, Besral B. Dyslipidemia associated with hypertension increases the risks for coronary heart disease: a case-control study in Harapan Kita Hospital, National Cardiovascular Center, Jakarta. *J Lipids*. 2019;2019.
9. Bilen O, Kamal A, Virani SS. Lipoprotein abnormalities in South Asians and its association with cardiovascular disease: current state and future directions. *World J Cardiol*. 2016;8(3):247–257. https://doi.org/10.4330/wjc.v8.i3.247.
10. Joshi SR, Anjana RM, Deepa M, et al. Prevalence of dyslipidemia in urban and rural India: the ICMR–INDIAB study. *PLoS One*. 2014;9(5), e96808.
11. Bartlomiejczyk MA, Penson P, Banach M. Worldwide dyslipidemia guidelines. *Curr Cardiovasc Risk Rep*. 2019;13(2):1–7.
12. Gerritsen S, Renker-Darby A, Harre S, et al. Improving low fruit and vegetable intake in children: findings from a system dynamics, community group model building study. *PLoS One*. 2019;14(8). https://doi.org/10.1371/journal.pone.0221107.
13. Baigent C. Cholesterol Treatment Trialists'(CTT) Collaborators: efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366: 1267–1278.
14. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur Heart J*. 2020;41(1):111–188. https://doi.org/10.1093/eurheartj/ehz455.
15. Lokanath DA, Chandrashekariah SA. Study on prevalence and patterns of dyslipidemia among kodavas. *J Med Sci Clinial Res*. 2014;2(6):1416–1427.
16. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: Part 1—full report. *J Clin Lipidol*. 2015;9(2):129–169. https://doi.org/10.1016/j.jacl.2015.02.003.
17. Anderson TJ, Mancini GJ, Genest Jr J, Grégoire J, Lonn EM, Hegele RA. The new dyslipidemia guidelines: what is the debate? *Can J Cardiol*. 2015;31(5): 605–612.
18. Magalhães MEC. *New Cholesterol Targets of SBC Guidelines on Dyslipidemia*. vol. 30. SciELO Brasil; 2017:466–468.
19. Esteban MD, López-Gutiérrez JS, Negro V. *Offshore Wind Farms*. Multidisciplinary Digital Publishing Institute; 2020.
20. Giner-Galvañ V, Esteban-Giner MJ, Pallares-Carratala V. Overview of guidelines for the management of dyslipidemia: EU perspectives. *Vasc Health Risk Manag*. 2016;12:357.
21. Iyengar SS, Puri R, Narasingan SN. Lipid association of India expert consensus statement on management of dyslipidemia in Indians 2016: Part 1-executive summary. *J Clin Prev Cardiol*. 2016;5(2):51.
22. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;73(24):e285–e350.
23. Iyengar SS, Puri R, Narasingan SN, et al. Lipid Association of India (LAI) expert consensus statement on management of dyslipidaemia in Indians 2017: part 2. *Clin Lipidol*. 2017;12(1):56–109.
24. Puri R, Mehta V, Duell PB, et al. Proposed low-density lipoprotein cholesterol goals for secondary prevention and familial hypercholesterolemia in India with focus on PCSK9 inhibitor monoclonal antibodies: expert consensus statement from Lipid Association of India. *J Clin Lipidol*. 2020;14(2):e1–e13.
25. Ray S, Sawhney JPS, Das MK, et al. Adaptation of 2016 European Society of Cardiology/European Atherosclerosis Society guideline for lipid management to Indian patients–A consensus document. *Indian Heart J*. 2018;70(5): 736–744.
26. Enas EA, Dharmarajan TS. The lipid association of India expert consensus statement 2016: a sea change for management of dyslipidemia in Indians. *J Clin Prev Cardiol*. 2016;5(2):62.
27. Narasingan S. Newer Lipid Guidelines: Interpretation and Applications for Indians.
28. Athyros VG, Katsiki N, Doumas M. Lipid association of India (LAI) expert consensus statement: part 2, specific patient categories. *Clin Lipidol*. 2018;13(1):1–3.
29. Misra A, Shrivastava U. Obesity and dyslipidemia in South Asians. *Nutrients*. 2013;5(7):2708–2733. https://doi.org/10.3390/nu5072708.
30. Volgman AS, Palaniappan LS, Aggarwal NT, et al. Atherosclerotic cardiovascular disease in South Asians in the United States: epidemiology, risk factors, and treatments: a scientific statement from the American Heart Association. *Circulation*. 2018;138(1):e1–e34.
31. Joshi P, Islam S, Pais P, et al. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. *JAMA*. 2007;297(3): 286–294. https://doi.org/10.1001/jama.297.3.286.
32. Yusuf S, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364(9438):937–952. https://doi.org/10.1016/S0140-6736(04)17018-9.
33. Jupaneant O, Hegyi G, Tudor A, Dragan S. Comparative study on complementary and alternative medicine (cam) use by physicians in Romania and Hungary. *J Pediatrului*. 2014;17(67–68):71–77.
34. Martin-Breen P, Anderies JM. *Resilience: A Literature Review*. 2011. Published online.
35. Hendrani AD, Adesiyun T, Quispe R, et al. Dyslipidemia management in primary prevention of cardiovascular disease: current guidelines and strategies. *World J Cardiol*. 2016;8(2):201.
36. Gupta R, Rao RS, Misra A, Sharma SK. Recent trends in epidemiology of dyslipidemias in India. *Indian Heart J*. 2017;69(3):382–392.
37. Wengrofsky P, Lee J, Makaryus AN. Dyslipidemia and its role in the pathogenesis of atherosclerotic cardiovascular disease: implications for evaluation and targets for treatment of dyslipidemia based on recent guidelines. In: *Dyslipidemia*. IntechOpen; 2019.
38. Morris PB, Ballantyne CM, Birtcher KK, Dunn SP, Urbina EM. Review of clinical practice guidelines for the management of LDL-related risk. *J Am Coll Cardiol*. 2014;64(2):196–206.
39. Guha S, Chatterjee S. Management of dyslipidaemia in India: what should be our approach in View of the Differing Guidelines. *API Update Med Update*. 2017;2:726–730.
40. Cram F. *Improving Māori Access to Health Care: Research Report*. Wellingt Minist Health; 2014. Published online.
41. Wander GS, Jadhav UM, Chemburkar A, Lopez M, Gogtay J. Lipid management in India: a nationwide, cross-sectional physician survey. *Lipids Health Dis*. 2017;16(1):1–9.
42. Nair M, Prabhakaran D. Why do South Asians have high risk for CAD? *Glob Heart*. 2012;7(4):307–314.
43. Levy D, Kannel WB. Cardiovascular risks: new insights from Framingham. *Am Heart J*. 1988;116(1):266–272.
44. Patel V, Chatterji S, Chisholm D, et al. Chronic diseases and injuries in India. *Lancet*. 2011;377(9763):413–428.
45. Garg N, Muduli SK, Kapoor A, et al. Comparison of different cardiovascular risk score calculators for cardiovascular risk prediction and guideline recommended statin uses. *Indian Heart J*. 2017;69(4):458–463.
46. Kanjilal S, Rao VS, Mukherjee M, et al. Application of cardiovascular disease risk prediction models and the relevance of novel biomarkers to risk stratification in Asian Indians. *Vasc Health Risk Manag*. 2008;4(1):199.
47. Bansal M, Kasliwal RR, Trehan N. Comparative accuracy of different risk scores in assessing cardiovascular risk in Indians: a study in patients with first myocardial infarction. *Indian Heart J*. 2014;66(6):580–586.
48. Chia YC, Lim HM, Ching SM. Validation of the pooled cohort risk score in an Asian population–a retrospective cohort study. *BMC Cardiovasc Disord*. 2014;14(1):1–7.
49. Aarabi M, Jackson PR. Predicting coronary risk in UK South Asians: an adjustment method for Framingham-based tools. *Eur J Cardiovasc Prev Rehabil Off J Eur Soc Cardiol Work Groups Epidemiol Prev Card Rehabil Exerc Physiol*. 2005;12(1):46–51.
50. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ*. 2008;336(7659):1475–1482. https://doi.org/10.1136/bmj.39609.449676.25.
51. Nirwan R, Singh D. Distribution of lipids and prevalence of dyslipidemia among Indian expatriates in Qatar. *J Lipids*. 2021;2021, e8866784. https://doi.org/10.1155/2021/8866784.
52. Rani RAJ, Deepa P, Shanthi R. Prevalence of atherogenic dyslipidemia in young asymptomatic medical professionals of a Tertiary Care Hospital in South India:

a cross-sectional study. *Int J Clin Biochem Res*. 2020;7(3):403–407. https://doi.org/10.18231/j.ijcbr.2020.086.

53. Bharadwaj SP, Patel AT, Rana DA, Malhotra SD, Patel TM. Linking of different ethnicities, races and religions to lipid profile patterns and hypolipidaemic drug usage patterns in coronary artery disease patients. *Int J Basic Clin Pharmacol*. 2019;8(8):1707.

54. Menon AS, Kotwal N, Singh Y, Girish R. Statins: cholesterol guidelines and Indian perspective. *Indian J Endocrinol Metab*. 2015;19(5):546.

55. Naito R, Miyauchi K, Daida H. Racial differences in the cholesterol-lowering effect of statin. *J Atherosclerosis Thromb*. 2017;24(1):19–25. https://doi.org/10.5551/jat.RV16004.

56. Li YF, Feng QZ, Gao WQ, Zhang XJ, Huang Y, Chen YD. The difference between Asian and Western in the effect of LDL-C lowering therapy on coronary atherosclerotic plaque: a meta-analysis report. *BMC Cardiovasc Disord*. 2015;15:6. https://doi.org/10.1186/1471-2261-15-6.

57. Wang P. Statin dose in Asians: is pharmacogenetics relevant? *Pharmacogenomics*. 2011;12(11):1605–1615. https://doi.org/10.2217/pgs.11.98.

58. Birmingham BK, Bujac SR, Elsby R, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in Caucasian and Asian subjects residing in the United States. *Eur J Clin Pharmacol*. 2015;71(3):329–340.

59. Liao JK. Safety and efficacy of statins in Asians. *Am J Cardiol*. 2007;99(3):410–414.

60. Mahadevan L, Yesudas A, Sajesh PK, et al. Prevalence of genetic variants associated with cardiovascular disease risk and drug response in the Southern Indian population of Kerala. *Indian J Hum Genet*. 2014;20(2):175–184. https://doi.org/10.4103/0971-6866.142896.

61. Mulchandani R, Lyngdoh T, Kakkar AK. Statin use and safety concerns: an overview of the past, present, and the future. *Expet Opin Drug Saf*. 2020;19(8):1011–1024.

62. Cullen P, Schulte H, Assmann G. The Munster Heart Study (PROCAM) Total Mortality in Middle-Aged Men is increased at low total and LDL cholesterol concentrations in smokers but not in nonsmokers. *Circulation*. 1997;96(7):2128–2136.

63. Ward NC, Watts GF, Eckel RH. Statin toxicity: mechanistic insights and clinical implications. *Circ Res*. 2019;124(2):328–350.

64. Enas EA, Varkey B, Gupta R. *Expanding Statin Use for Prevention of ASCVD in Indians: Reasoned and Simplified Proposals*. vol. 72. Elsevier; 2020:65–69.

65. Blais JE, Wei Y, Yap KK, et al. Trends in lipid-modifying agent use in 83 countries. *Atherosclerosis*. 2021;328:44–51.

66. For most healthy people, benefits of statins "may be marginal at best" | BMJ. https://www.bmj.com/company/newsroom/for-most-healthy-people-benefits-of-statins-may-be-marginal-at-best/. Accessed April 30, 2022.

67. Torjesen I. Statins are overprescribed for primary prevention, study suggests. *BMJ*. 2018;363:k5110. https://doi.org/10.1136/bmj.k5110.

68. Pandey KR, Meltzer DO. Financial burden and impoverishment due to cardiovascular medications in low and middle income countries: an illustration from India. *PLoS One*. 2016;11(5), e0155293.

69. Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. *Lancet*. 2011;378(9798):1231–1243.

70. Lüscher TF. Prevention is better than cure: the new ESC Guidelines. *Eur Heart J*. 2016;37(29):2291–2293. https://doi.org/10.1093/eurheartj/ehw321.

71. Chiuve SE, McCullough ML, Sacks FM, Rimm EB. Healthy lifestyle factors in the primary prevention of coronary heart disease among men. *Circulation*. 2006;114(2):160–167. https://doi.org/10.1161/CIRCULATIONAHA.106.621417.

72. Broers ER, Gavidia G, Wetzels M, et al. Usefulness of a lifestyle intervention in patients with cardiovascular disease. *Am J Cardiol*. 2020;125(3):370–375. https://doi.org/10.1016/j.amjcard.2019.10.041.

73. Chu P, Pandya A, Salomon JA, Goldie SJ, Hunink MGM. Comparative effectiveness of personalized lifestyle management strategies for cardiovascular disease risk reduction. J Am Heart Assoc. 5(3):e002737. doi:10.1161/JAHA.115.002737.

74. Prabhakaran D, Jeemon P, Roy A. Cardiovascular diseases in India. *Circulation*. 2016;133(16):1605–1620. https://doi.org/10.1161/CIRCULATIONAHA.114.008729.

75. Brinks J, Fowler A, Franklin BA, Dulai J. Lifestyle modification in secondary prevention. *Am J Lifestyle Med*. 2016;11(2):137–152. https://doi.org/10.1177/1559827616651402.