Lipid Association of India 2023 update on cardiovascular risk assessment and lipid management in Indian patients: Consensus statement IV

Raman Puri MD, DM, FNLA, Chair ,
Manish Bansal MD, DM, Co-Chair ,
Vimal Mehta MD, DM, FACC, Co-Chair ,
P. Barton Duell MD, FAHA, FNLA, Co-Chair ,
Nathan D Wong PhD, FACC, FNLA , SS Iyengar MD, DM ,
Dinesh Kalra MD, FNLA , Devaki R. Nair MD , Navin C Nanda MD ,
Jagat Narula MD , P Deedwania MD , Jamal Yusuf MD, DM ,
Jamshed J Dalal MD, DM , Sadanand Shetty MD, DM ,
Vinod M Vijan MD, DM , Rajeev Agarwala MD, DM ,
Soumitra Kumar MD, DM , Kris Vijay MD, FNLA ,
Aziz Khan MD, DM , Gurpreet Singh Wander MD, DM ,
PC Manoria MD, DM , SK Wangnoo MD, DM ,
Viswanathan Mohan MD , Shashank R. Joshi MD, DM ,
Balbir Singh MD, DM , Prafulla Kerkar MD, DM ,
Rajesh Rajput MD, DM , D Prabhakar MD, DM ,
Abdul Hamid Zargar MD, DM , Banshi Saboo MD ,
Ravi R Kasliwal MD, DM , Saumitra Ray MD, DM ,
Sandeep Bansal MD, DM , MU Rabbani MD, DM ,
Shibba Takkar Chhabra MD, DM , Sarat Chandra MD, DM ,
Neil Bardoloi MD, DM , Narasaraju Kavalipati MD, DM ,
Immaneni Sathyamurthy MD, DM , Kunal Mahajan MD, DM ,
Akshya Pradhan MD, DM , NN Khanna MD, DM ,
Rajesh Khadgawat MD, DM , Preeti Gupta MD, DM ,
Milan C. Chag MD, DM , Ashu Gupta MD, DM ,
A Murugnathan MD , SN Narasingan MD ,
Sundeep Upadhyaya MD , Vinod Mittal MD ,
Rashida Patanwala Melinkeri MD , Madhur Yadav MD ,
M. Raseed Mubarak MD , KK Pareek MD ,
Pradeep Kumar Dabla MD , Rashmi Nanda MD ,
JC Mohan MD, DM

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Jamal Yusuf MD, DM , Jamshed J Dalal MD, DM , Sadanand Shetty MD, DM , Vinod M Vijan MD, DM , Rajeev Agarwala MD, DM , Soumitra Kumar MD, DM , Kris Vijay MD, FNLA , Aziz Khan MD, DM , Gurpreet Singh Wander MD, DM , PC Manoria MD, DM , SK Wangnoo MD, DM , Viswanathan Mohan MD , Shashank R. Joshi MD, DM , Balbir Singh MD, DM , Prafulla Kerkar MD, DM , Rajesh Rajput MD, DM , D Prabhakar MD, DM , Abdul Hamid Zargar MD, DM , Banshi Saboo MD , Ravi R Kasliwal MD, DM , Saumitra Ray MD, DM , Sandeep Bansal MD, DM , MU Rabbani MD, DM , Shibba Takkar Chhabra MD, DM , Sarat Chandra MD, DM , Neil Bardoloi MD, DM , Narasaraju Kavalipati MD, DM , Immaneni Sathyamurthy MD, DM , Kunal Mahajan MD, DM , Akshya Pradhan MD, DM , NN Khanna MD, DM , Rajesh Khadgawat MD, DM , Preeti Gupta MD, DM , Milan C. Chag MD, DM , Ashu Gupta MD, DM , A Murugnathan MD , SN Narasingan MD , Sundeep Upadhyaya MD , Vinod Mittal MD , Rashida Patanwala Melinkeri MD , Madhur Yadav MD , M. Raseed Mubarak MD , KK Pareek MD , Pradeep Kumar Dabla MD , Rashmi Nanda MD , JC Mohan MD, DM , Lipid Association of India 2023 update on cardiovascular risk assessment and lipid management in Indian patients: Consensus statement IV, *Journal of Clinical Lipidology* (2024), doi: https://doi.org/10.1016/j.jacl.2024.01.006

Highlights

- Indians develop ASCVD about a decade earlier than Western populations.
- Subclinical ASCVD reflects the susceptibility to develop adverse CV events.
- LAI recommends coronary artery calcium scoring to stratify ASCVD risk in selected patients.
- LDL-C goals recommended by the LAI are more aggressive than other guidelines.
- Extreme risk category C patients require the most intensive LDL-C lowering.

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Raman Puri[1], MD, DM, FNLA, **Chair**, Manish Bansal[2], MD, DM, **Co-Chair**, Vimal Mehta[3], MD, DM, FACC, **Co-Chair**, P. Barton Duell[4], MD, FAHA, FNLA, **Co-Chair**, Nathan D Wong[5], PhD, FACC, FNLA, S S Iyengar[6], MD, DM, Dinesh Kalra[7], MD, FNLA, Devaki R. Nair[8], MD, Navin C Nanda[9], MD, Jagat Narula[10], MD, P Deedwania[11], MD, Jamal Yusuf[12], MD, DM, Jamshed J Dalal[13], MD, DM, Sadanand Shetty[14], MD, DM, Vinod M Vijan[15], MD, DM, Rajeev Agarwala[16], MD, DM, Soumitra Kumar[17], MD, DM, Kris Vijay[18], MD, FNLA, Aziz Khan[19], MD, DM, Gurpreet Singh Wander[20], MD, DM, P C Manoria[21], MD, DM, S K Wangnoo[22], MD, DM, Viswanathan Mohan[23], MD, Shashank R. Joshi[24], MD, DM, Balbir Singh[25], MD, DM, Prafulla Kerkar[26], MD, DM, Rajesh Rajput[27], MD, DM, D Prabhakar[28], MD, DM, Abdul Hamid Zargar[29], MD, DM, Banshi Saboo[30], MD, Ravi R Kasliwal[31], MD, DM, Saumitra Ray[32], MD, DM, Sandeep Bansal[33], MD, DM, M U Rabbani[34], MD, DM, Shibba Takkar Chhabra[35], MD, DM, Sarat Chandra[36], MD, DM, Neil Bardoloi[37], MD, DM, Narasaraju Kavalipati[38], MD, DM, Immaneni Sathyamurthy[39], MD, DM, Kunal Mahajan[40], MD, DM, Akshya Pradhan[41], MD, DM, N N Khanna[42], MD, DM, Rajesh Khadgawat[43], MD, DM, Preeti Gupta[44], MD, DM, Milan C. Chag[45], MD, DM, Ashu Gupta[46], MD, DM, A Murugnathan[47], MD, S N Narasingan[48], MD, Sundeep Upadhyaya[49], MD, Vinod Mittal[50], MD, Rashida Patanwala Melinkeri[51], MD, Madhur Yadav[52], MD, M. Raseed Mubarak[53], MD, K K Pareek[54], MD, Pradeep Kumar Dabla[55], MD, Rashmi Nanda[56], MD, J C Mohan[57], MD, DM

1. **Chair,** FNLA, Sr. Consultant Cardiologist, Cardiac Care Centre, New Delhi.
2. **Co-Chair,** Senior Director, Department of Cardiology, Medanta- The Medicity, Gurugram, Haryana, India
3. **Co-Chair,** Director-Professor, Department of Cardiology, G. B. Pant Institute of Postgraduate Medical Education and Research, New Delhi. India
4. **Co-Chair,** FNLA, Professor of Medicine, Knight Cardiovascular Institute and Division of Endocrinology Diabetes and Clinical Nutrition, Oregon Health & Science University, Portland, OR, USA.
5. FNLA, Professor & Director Heart Disease Prevention program division of Cardiology, University of California, Irvine School of Medicine, USA.
6. Sr. Consultant and Head, Department of Cardiology, Manipal Hospital, Bangalore, Karnataka. India
7. FNLA, Professor of Medicine, University of Louisville School of Medicine, USA
8. Sr. Consultant Department of Lipidology and Chemical pathologist, Royal Free Hospital, London, UK.
9. Professor of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, KY, USA
10. Executive Vice President and Chief Academic Officer, UT Health, Houston, TX USA
11. Professor of Medicine, University of California San Francisco, San Francisco, CA, USA
12. Director-Professor and Head, Department of Cardiology, G. B. Pant Institute of Postgraduate Medical Education and Research, New Delhi. India

13. Sr. Consultant Cardiologist, Kokilaben Dhirubhai Ambani Hospital, Director–Centre for Cardiac Sciences, Mumbai, Maharashtra. India
14. Head, Department of Cardiology, K. J. Somaiya Super Specialty Institute, Sion (East), Mumbai, Maharashtra. India
15. Director, Vijan Hospital & Research Centre, Nashik, Uniqare Hospital, PCMC, Pune. India
16. Sr. Consultant Cardiologist, Jaswant Rai Specialty Hospital, Meerut, Uttar Pradesh. India
17. Professor and Head, Department of Cardiology, Vivekananda Institute of Medical Sciences, Kolkata. India
18. FNLA, Professor of Medicine, Arizona Heart Foundation, University of Arizona, Phoenix, USA
19. Sr. Consultant cardiologist, Crescent Hospital and Heart Centre, Nagpur, Maharashtra. India
20. Professor of Cardiology, Dayanand Medical College and Hospital, Ludhiana, Punjab. India
21. Director, Manoria Heart and critical Care Hospital, Bhopal, Madhya Pradesh. India
22. Sr. Consultant Endocrinology & Diabetologist, Indraprastha Apollo Hospitals, New Delhi. India
23. Director Madras Diabetic Research foundation and Chairman & chief Diabetology, Dr Mohan Diabetes Specialties Centre, Chennai. India
24. Sr. Consultant Endocrinologist, Lilavati Hospital, Mumbai, Maharashtra. India
25. Chairman - Cardiac Sciences, Max Hospital Saket, New Delhi. India
26. Sr. Consultant Cardiologist, Asian Heart Institute and Research Centre, Mumbai. India
27. Professor & Head, Department of Endocrinology, Post Graduate Institute of Medical Sciences, Rohtak, Haryana. India
28. Sr. Consultant, Department of Cardiology, Apollo Hospitals, Chennai, Tamil Nadu.
29. Medical Director, Centre for Diabetes and Endocrine Care, National Highway, Gulshan Nagar, Srinagar, J&K. India
30. Chairman-Diacare- Diabetes Care, and Hormone Clinic, Ahmedabad. India
31. Chairman, Division of Clinical & Preventive Cardiology, Medanta- The Medicity, Gurugram, Haryana. India
32. Director of Intervention Cardiology, AMRI (S), Kolkata. India
33. Professor and Head, Dept. of Cardiology, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi. India
34. Professor Dept. of Cardiology, J. N. Medical College, AMU, Aligarh. India
35. Professor Dept. of Cardiology, Dayanand Medical College and Hospital, Ludhiana. India
36. Chief Cardiologist, TX Group of Hospitals, Banjara Hills, Hyderabad. India
37. Managing Director and HOD, Cardiology, Excel Care Hospital, Guwahati, Assam. India
38. Director of Cardiology and Sr Interventional Cardiologist, Apollo Hospitals, Hyderabad. India
39. Sr. Consultant Cardiologist, Apollo Hospital, Chennai, Tamil Nadu. India
40. Director Dept. of Cardiology, Himachal Heart Institute, Mandi, Himachal Pradesh. India
41. Sr. Consultant, Department of Cardiology King George's Medical University, Lucknow, Uttar Pradesh. India
42. Sr. Consultant, Department of Cardiology, Indraprastha Apollo Hospitals, New Delhi. India
43. Professor, Department of Endocrinology and Metabolism, All India Institute of Medical Sciences (AIIMS), New Delhi. India
44. Associate Professor Dept. of Cardiology, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi. India

45. Sr. Consultant Cardiologist, Marengo CIMS Hospital, Ahmadabad, Gujarat. India
46. Sr Consultant Cardiologist, Holy Heart Advanced Cardiac Care and Research Centre, Rohtak, Haryana. India
47. Sr. Consultant Internal Medicine, AG Hospital, Tirupur, Tamil Nadu. India
48. Former Adjunct Professor of Medicine, The Tamil Nadu Dr MGR Medical University & Managing Director, SNN Specialties Clinic, Chennai. India
49. Sr. Consultant, Department of Rheumatology, Indraprastha Apollo Hospitals, New Delhi. India
50. Sr. Consultant Diabetologist and Head, Centre for Diabetes & Metabolic disease Delhi Heart & Lung Institute, Delhi. India
51. Sr. Consultant, Department of Internal Medicine, KEM Hospital and Sahyadri Hospitals, Pune, Maharashtra. India
52. Director- Professor of Medicine, Lady Harding Medical College, New Delhi. India
53. Sr. Consultant Cardiologist, Lanka Hospital, Colombo, Sri Lanka
54. Head, Department of Medicine, S. N. Pareek Hospital, Dadabari, Kota, Rajasthan. India
55. Professor of Biochemistry, G. B. Pant Institute of Postgraduate Medical Education and Research, New Delhi. India
56. Managing Director, Ashakiran Family Wellness Clinic, Indrapuram, U. P. India
57. Sr. Consultant Cardiologist, Institute of Heart and Vascular Diseases, Jaipur Golden Hospital, New Delhi. India

Corresponding author:

Dr. Raman Puri

A-26, 2nd Floor, South Extension, Part-2, New Delhi-110049

Mob. +91- 9871071919

E-mail: lipidaoi@gmail.com

Abstract

Objective: In 2016, the Lipid Association of India (LAI) developed a cardiovascular risk assessment algorithm and defined low-density lipoprotein cholesterol (LDL-C) goals for prevention of atherosclerotic cardiovascular disease (ASCVD) in Indians. The recent refinements in the role of various risk factors and subclinical atherosclerosis in prediction of ASCVD risk necessitated updating the risk algorithm and treatment goals.

Methods: The LAI core committee held twenty-one meetings and webinars from June 2022 to July 2023 with experts across India and critically reviewed the latest evidence regarding the strategies for ASCVD risk prediction and the benefits and modalities for intensive lipid lowering. Based on the expert consensus and extensive review of published data, consensus statement IV was commissioned.

Results: The young age of onset and a more aggressive nature of ASCVD in Indians necessitates emphasis on lifetime ASCVD risk instead of the conventional 10-year risk. It also demands early institution of aggressive preventive measures to protect the young population prior to development of ASCVD events. Wide availability and low cost of statins in India enable implementation of effective LDL-C lowering therapy in individuals at high risk of ASCVD. Subjects with any evidence of subclinical atherosclerosis are likely to benefit the most from early aggressive interventions.

Conclusions: This document presents the updated risk stratification and treatment algorithm and describes the rationale for each modification. The intent of these updated recommendations is to modernize management of dyslipidemia in Indian patients with the goal of reducing the epidemic of ASCVD among Indians in Asia and worldwide.

Keywords

Atherosclerotic cardiovascular disease, high-intensity statin therapy, carotid plaque, femoral plaque, coronary calcium score, metabolic syndrome, non-conventional risk factors, guidelines, expert consensus

1. Key considerations underlying the revised Lipid Association of India recommendations

The epidemiology of atherosclerotic cardiovascular disease (ASCVD) in India differs considerably from the same in Western countries. It is well recognized that Indians develop ASCVD about a decade earlier than the Western populations,[1] despite having lower levels of low-density lipoprotein cholesterol (LDL-C). It has been reported that more than 50% of coronary artery disease (CAD)-associated deaths in India occur before the age of 50 years and 25% of myocardial infarctions (MIs) occur before the age of 40 years.[2] In the INTERHEART study, the median age of MI among Indians was 53.0 years compared to 58.1 years in other countries.[3] More recently, in a prospective multicenter study in India involving 2153 subjects with acute coronary syndrome (ACS), 720 (33.4%) were younger than 50 years.[4] Similar findings were repor2ted from a single-center large registry from Northern India, which recruited 4672 consecutive patients undergoing percutaneous coronary intervention. In this registry, 31% of subjects had premature or very premature CAD (defined as CAD in men <54 years and women <59 years of age).[5]

Early onset ASCVD in India has several important implications for disease prevention. First, the young age of onset renders conventional clinical ASCVD risk assessment tools less relevant because in all of them, age has an overriding influence on the estimated risk. It also raises questions about the relevance of 10-year estimated ASCVD risk and instead, emphasizes the importance of assessing lifetime ASCVD risk. Second, the high incidence of early onset ASCVD necessitates early institution of aggressive preventive measures to protect the young population prior to development of ASCVD events. Early treatment yields both short-term and long-term benefits. Results from Mendelian studies have clearly shown than even a small reduction in LDL-C achieved at an early age and maintained over decades leads

to several fold greater reductions in ASCVD risk compared to more aggressive LDL-C lowering initiated later in life.[6, 7] Third, lack of awareness among the general public in India of very high risk of early onset ASCVD necessitates development of strategies for improved detection and treatment of high-risk patients starting at a young age.

The socio-economic circumstances in India are also unique. Since many patients in India do not have health insurance, most of the expenditure on healthcare is paid by the patient out-of-pocket, highlighting the importance of prevention to avoid expensive hospitalizations and medical procedures. Treatment of cardiovascular complications in India is also associated with unique challenges. The healthcare infrastructure in government hospitals is affordable, but has limited capacity, whereas treatment at private hospitals is readily available, but expensive. The loss of productive life-years from ASCVD complications also puts an additional burden on patients and their families, as well as society. Conversely, implementation of LDL-C lowering therapy is a simple, efficacious and a relatively inexpensive means for ASCVD prevention. Statins are widely available and very affordable, and ezetimibe and bempedoic acid are only moderately more expensive, enabling the majority of patients to achieve recommended LDL-C lowering goals.

Over the last few years, our understanding of the relative contributions of various risk factors to ASCVD risk has expanded and the role of subclinical atherosclerosis in prediction of ASCVD events has become more refined. The further documentation of benefits of more intensive LDL-C lowering in select patient groups has reinforced recommendations for more intensive LDL-C and non-HDL-C treatment goals. In addition, new therapies have become available that facilitate achievement of lower lipid goals.[8] These developments necessitated updating the Lipid Association of India (LAI) risk algorithm and treatment goals. In 2020,

two new ASCVD risk categories- Extreme risk group, category A and B- were introduced by the LAI, but the overall treatment algorithm was not modified.[9]

In this document, the LAI risk assessment algorithm and corresponding recommendations for LDL-C lowering were critically reviewed and updated by the LAI expert panel in accordance with our current understanding of ASCVD risk in Indians and the above issues and concerns. Importantly, the recommendations focus on lifetime risk reduction necessitating early introduction of preventive measures. **Figure 1** shows the updated risk algorithm. Salient changes in the algorithm are described below.

2. The need for accurate ASCVD risk estimation

Estimation of the risk of future cardiovascular events is a necessity for guiding the intensity of lipid-lowering therapy and global ASCVD risk reduction. Commonly used tools for predicting ASCVD risk, such as the pooled cohort equations, have been documented to underestimate risk in South Asians; moreover, South Asians were not included in the derivation cohort. Therefore, they are not recommended for use in Indian subjects. Although the QRISK 3 score is better for risk assessment in Indians compared to the pooled cohort equations, a dedicated risk prediction score derived from the Indian population is needed.[10-13] Development of accurate risk assessment tools requires data from large-scale, population-specific, long-term prospective studies examining the strength of associations between various cardiovascular risk factors and incident ASCVD events in the population.[14-17] Unfortunately, no such data are currently available for Indians and hence, there is no validated ASCVD risk assessment tool for use in Indians. Recognizing this limitation, the LAI in 2016 developed an ASCVD risk algorithm to guide lipid management in day-to-day

clinical practice.[8] This algorithm was based on expert consensus, taking into consideration the high prevalence of ASCVD and its risk factors in India, early onset and complexity of ASCVD among Indians, and the unique sociodemographic circumstances in India. The previous LAI recommendations have found increasing acceptance among various national and international lipid experts and clinicians in India. The current recommendations provide updated guidance for ASCVD risk estimation in Indians based on expert opinion and the latest scientific data.

3. Important changes in the Lipid Association of India 2023 atherosclerotic cardiovascular disease risk assessment recommendations

3.1. Family history as a high-risk feature

Family history of premature ASCVD (defined as occurrence of an ASCVD event in a male first-degree relative <55 years of age and in a female first-degree relative <65 years of age or before menopause) identifies individuals at an elevated ASCVD risk. Unlike other risk factors, it uniquely reflects the net consequences of various known and unknown genetic factors as well as environmental and epigenetic risk factors that may be prevalent in a family. In addition, the occurrence of early ASCVD among family members implies heightened risk of early ASCVD in descendants, warranting early screening for ASCVD risk factors and implementation of aggressive risk factor modification. For these reasons, in the current algorithm, a family history of premature ASCVD has been designated as a high-risk feature for estimation of ASCVD risk. This modification is in line with the recommendations of the European Society of Cardiology/ European Atherosclerosis Society.[18] Clinicians should do an evaluation for premature family history of ASCVD in at least all first-degree relatives and optimally grandparents, aunts, and uncles documenting the event and age of occurrence in

each affected relative; the number of affected first-degree relatives is directly related to the patient's ASCVD risk conferred by the family history.

3.2. Subclinical atherosclerosis

A major limitation of clinical risk scoring algorithms is that they estimate the probability of developing ASCVD based on risk factors measured at a given point in time but cannot accurately identify specific individuals who will develop the disease. Variations in susceptibility to development of ASCVD can result in divergent risk in patients with identical risk factors. This lack of precision at the individual level results in overtreatment or undertreatment of individuals in high- or low-risk categories, respectively. In contrast, use of strategies to detect subclinical atherosclerosis provides a direct assessment of nascent or advanced plaque burden, which provides superior prediction of future ASCVD events compared to standard risk calculators. Assessment for subclinical ASCVD reflects the cumulative effects of all known and unknown ASCVD risk factors as well as the individual susceptibility to develop the disease, thereby providing a more robust prediction of future ASCVD risk than the traditional risk assessment models. However, for this strategy to be successful, it is essential that the modality used for assessment of subclinical atherosclerosis is accurate, reliable, widely available and affordable.

Many different tools are available for assessment of subclinical atherosclerosis, but quantification of the coronary artery calcium score (CACS) using computed tomography (CT) imaging and assessment of carotid and femoral arterial plaque using ultrasound have been the most studied and validated. Ankle brachial index (ABI) screening for detecting peripheral

arterial disease (PAD) is also a useful tool for assessing subclinical atherosclerosis, with a low ABI diagnostic of PAD.

3.2.1. Coronary artery calcium score

With the exception of a few conditions associated with dystrophic calcification such as chronic kidney disease and hyperparathyroidism, calcification in the coronary arteries occurs almost exclusively due to atherosclerosis. Thus, the presence of calcium in the coronary arteries virtually confirms the presence of coronary atherosclerosis, although the absence of it cannot exclude atherosclerosis. Autopsy studies have shown that total amount of coronary calcium assessed by CT imaging correlates very well with the total coronary atherosclerotic burden.[19]

CACS quantification can be performed using any commercially available multidetector CT, provided the required software is available. The Agatston method is used for this purpose, which quantifies calcified lesions within four major coronary arteries that have radiodensity exceeding 130 Hounsfield units (indicative of calcification).[20, 21] The test is simple to perform and is relatively inexpensive in India. No specific patient preparation is required for this test, other than avoidance of factors that may elevate the heart rate, such as caffeine or exercise before the procedure, and there is usually no need for heart rate control. There are no renal safety issues as no contrast is required. The test can be performed very rapidly, with actual scan time of only a few seconds and the total room time of <15 minutes. The total radiation exposure with current digital imaging devices is <1 millisievert, roughly equivalent to a mammogram.[22]

3.2.1.1. Evidence-base for atherosclerotic cardiovascular disease prediction with coronary artery calcium score

Results from many studies have consistently shown that CACS is an excellent predictor of incident ASCVD events, and the predictive power is incremental to any conventional risk factors and risk algorithms for primary prevention.[23-29] Nasir et al[29] analyzed data from 44,052 consecutive asymptomatic individuals who were free of known coronary heart disease (CHD) and were referred for CACS imaging. Within each risk category defined by the number of conventional ASCVD risk factors, increasing CACS was associated with progressively higher all-cause mortality after 5.6±2.6 years of follow-up. Importantly, patients with CACS >100 but no conventional risk factors had higher event rates than those with 3 or more risk factors but no coronary artery calcification (i.e., zero CACS).

There is a dose-response relationship between CACS and the risk of incident ASCVD events.[30, 31] Patients with CACS values ≥100 have 10-year ASCVD event rates in the range of 10-15%[32, 33], which is greater than the 7.5% threshold recommended by the American College of Cardiology/ American Heart Association for initiation of statin therapy.[34] The adverse prognostic implication of CACS ≥100 is greater in young individuals. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, 3043 subjects underwent CACS measurement at a mean age of 40.3±3.6 years.[27] Among 58 individuals (1.9%) with CACS ≥100, the absolute all-cause mortality rate was 22.4% over a follow-up of 12.5 years, a strikingly high mortality rate for young participants. In contrast, zero CACS is associated with a very low risk of events over the subsequent 5-10 years, except in individuals who have multiple ASCVD risk factors with high ASCVD risk as determined by the clinical risk scores.[29, 35-37] The negative predictive value of zero CACS is famously known as the 'power of zero',[38, 39] but a CACS of zero should not be

misinterpreted as an indication of low risk in a patient deemed to be at high risk because of multiple ASCVD risk factors. In addition, more than 50% of coronary artery plaque is not calcified, particularly in young individuals, so consideration of coronary CT angiography may be appropriate in otherwise high-risk patients with a CACS of zero. On the basis of the above evidence, it has been proposed that thresholds of zero CACS and CACS ≥100 may be used for refining ASCVD risk in appropriately selected patients and this information may be used for guiding decisions regarding statin or aspirin therapy.[40-42] The interpretation of CACS 1-99 is more challenging. The values in this range are mostly associated with low to intermediate risk over 10 years, especially in older persons where mild CAC is quite common, but a CACS >0 is associated with a much higher risk of incident ASCVD events compared to CACS =0. Moreover, among younger persons with CACS between 1 and 99, if the value is higher than the 75th percentile for age, gender and ethnicity, or the individual is younger than 45 years, the presence of mild coronary artery calcification is indicative of substantially increased ASCVD 10-year risk relative to the general population, which translates into high lifetime risk.[41] Thus, CACS values between 1-99 and >75th percentile are indicative of increased risk for ASCVD events and a need for appropriate risk reduction measures. In the CARDIA study, 10.2% individuals had CACS >0 despite a young mean age of 40.3 years.[27] The mean CACS in this population was 21.6. After adjustment for demographics, risk factors, and treatments, CACS values 1-19 and 20-99 vs CACS =0 were associated with CHD event rates of 4.8 per 1000 person-years (hazard ratio 2.6, 95% confidence interval 1.0-5.7) and 10.6 per 1000 person-years (hazard ratio 5.8, 95% confidence interval 2.6-12.1), respectively.

The Multi-Ethnic Study of Atherosclerosis (MESA) provided age- and sex-specific 75th percentile CACS values for four different ethnic groups down to an age of 45 years in the United

States (**Table 1**).[43] Since South Asians tend to have a CACS distribution similar to that of Whites[44], the reference values described for Whites may be extrapolated for use in Indians. A recent publication based on pooled data from 3 studies (including CARDIA) provided similar reference values for younger individuals <45 years of age (**Table 2**).[45] Below 45 years of age, any CACS value >0 corresponds to >75th percentile, except in white men aged 43-45 years. However, in the context of very low CACS values, it should be recognized that recent studies have reported variability in CACS obtained with different CT scanners. Approaches to estimate vendor neutral CACS are being evaluated.[46] Since non-cardiac vascular calcification is a marker for ASCVD risk, which is sometimes detected as incidental finding, we encourage initiation or intensification risk factor modification including lipid lowering in patients with this finding. Caution should also be exercised when interpreting CACS values in patients already on statin therapy as statins tend to convert soft, non-calcified plaque to calcified plaque, which can result in modest short-term increases in CACS.[47] Thus, repeat CAC screening for the purposes of assessing the effects of statin or other preventive therapies can be difficult to interpret and is generally discouraged. In addition to lipid-lowering therapy, other evidence-based therapies for cardiovascular risk reduction (e.g. low dose aspirin) are recommended in patients with CACS ≥100.

3.2.2. Carotid and femoral artery imaging

Several studies have demonstrated that the presence of lumen encroaching, but hemodynamically non-obstructive carotid or femoral plaques is associated with a high risk of cardiovascular events. The Carotid And FEmoral ultrasound morphology Screening and CArdioVascular Events in low-risk subjects study (CAFES-CAVE) recruited 14,300 healthy, asymptomatic individuals from Italy.[48] All subjects underwent an initial evaluation that included carotid and femoral

ultrasonography and were followed for at least 10 years or until the development of a cardiovascular event. The study was concluded when at least 10,000 patients had completed 10-years of follow-up or had suffered a cardiovascular event. Among subjects with non-obstructive carotid or femoral plaque [defined as wall thickening ≥1 mm in association with irregular, increased echogenicity involving all the ultrasonic layers], the 10-year event rate was 39.1%.

In another study, 391 subjects with mean age 58 years and no known cardiovascular disease underwent ultrasound imaging of both internal carotid arteries and the right femoral artery.[49] The presence of plaque in any of the studied arteries was associated with significantly increased risk of cardiovascular events over 10-years of follow-up. There was a linear increase in event rates in proportion to the number of arteries affected (5.7% in subjects with no plaque, 12-13% with involvement of one or two arteries and 22-23% with involvement of all the three arteries). In multivariate analyses, only the presence of arterial plaque predicted events and not clinical risk factors.

The relative contribution of carotid versus femoral plaque in prediction of ASCVD events is uncertain. In the CAFÉS-CAVE study described above, both carotid and femoral arteries had comparable predictive value, but their combination was associated with an almost 15% higher rate of events.[48] In comparison, the Aragon Workers' Health Study suggested that detection of plaque on femoral ultrasound was more informative than identification of carotid plaque.[50] In this study, 1423 middle-aged (age 40-59 years) men in Spain were evaluated with carotid and femoral ultrasound as well as CACS determination. Subclinical atherosclerosis was identified in 72% of subjects and was most prevalent in femoral arteries (54%) followed by coronary artery calcification (38%) and carotid arterial plaque (34%). Femoral plaque was associated with a higher odds ratio for CACS ≥1 compared to carotid plaque (2.6 vs 1.8).

Plaque assessment has also been shown to be more informative than the measurement of carotid intima-media thickness. Nambi and colleagues showed in the Atherosclerosis Risk in Communities (ARIC) study that the addition of information on carotid plaque identified higher CVD event risks within each quartile of carotid intimal media thickness with subsequent reclassification of risk in 23% of the 13,145 included subjects.[51]

While the above studies prove the prognostic value of carotid and femoral artery plaque assessment, the results of other studies have shown that clinical risk algorithms are not sufficiently sensitive to detect subclinical atherosclerosis. In a study of 1,464 asymptomatic adults in the United States aged 23 to 87 years without previous evidence of ASCVD, 37.4% of the subjects had either carotid or femoral plaques. The 10-year Framingham risk score identified only 9% of the men with arterial plaque as high-risk. In comparison, the 30-year and lifetime risk assessment identified 45% and 59% subjects, respectively.[52] These results further highlight the insensitivity of global cardiovascular risk assessment algorithms for identifying patients at risk for ASCVD events.

Thus, the available evidence suggests that assessment of carotid and femoral arterial plaque burden may be a useful tool for ASCVD risk prediction, but this has not been well studied in South Asian populations. Compared with CACS, carotid and femoral ultrasonography have the advantages of being less expensive, more widely available and radiation-free. However, the accuracy of CACS for prediction of ASCVD events is comparatively higher and better standardized.[40] Assessment of arterial plaque with ultrasonography is also much more user dependent and suffers from the lack of standardized imaging protocols. Lumen-encroaching plaques are relatively easy to identify but some ultrasound technicians may have difficulty

recognizing minimal to mild plaque. Various definitions have been proposed for characterizing arterial plaque[53], which may include a focal structure that-

- protrudes into the arterial lumen by ≥0.5 mm, or
- is ≥50% thicker than the adjacent unaffected intima-media thickness, or
- has increased overall intima-media thickness ≥1.5 mm.

The plaque burden can also be characterized by measuring [53]-

- Plaque score, consisting of the number of carotid and femoral segments with plaque
- Maximum plaque height
- Total plaque area
- Total plaque volume

Compared with qualitative imaging interpretation (i.e., plaque present or absent), quantitative assessment of arterial plaque is more sensitive and accurate for discriminating ASCVD risk.[40, 54] More recently, newer techniques have been developed for characterization of arterial plaques that include assessment for plaque ulceration, neovascularization, percent atheroma volume, and other clinically relevant features.[53] Magnetic resonance imaging (MRI) is another useful modality for plaque characterization in superficial arteries that allows assessment of the lipid core, calcium content and remodeling index, all of which are prognostically relevant.[55] However, its availability and utility for doing these assessments, as well as evidence for improving risk prediction remains limited. The high cost and need for high magnetic field strength further restrict access to this imaging modality.

3.2.3. Ankle-brachial index

Measurement of the ABI, particularly in older persons in whom asymptomatic PAD is more common, can be helpful in risk stratification. Measured with a relatively simple Doppler instrument or standard blood pressure cuff, an ABI in either leg <0.9 is diagnostic of PAD and is recognized in the United States guidelines as a risk enhancing factor.[34] However, since a low ABI indicates obstructive PAD, which carries at least as poor a prognosis as those with established CAD, the 2016 LAI recommendations designated ABI <0.9 as evidence of established ASCVD, with LDL-C targets similar those for patients with ASCVD.[8]

The ABI collaboration comprising over 45,000 subjects among 16 cohort studies showed nearly two-fold increased mortality in association with borderline ABI levels of 0.9-<1.0 and greater risks below 0.9. Importantly, it demonstrated that the estimated ASCVD risk would be reclassified in 36% of women and 19% of men when ABI was added to the Framingham risk score.[56] While data on ABI are limited in Asian populations, the increased prevalence of cardiometabolic risk factors in Indian populations and the relatively low cost of ABI measurement warrants its consideration for further ASCVD risk assessment, particularly when CACS or carotid/femoral plaque assessment is not available and/or in situations where PAD may be suspected.

3.2.4. Implications for the Lipid Association of India recommendations

As discussed above, the assessment of subclinical atherosclerosis is a useful method for prediction of future ASCVD risk and the available evidence supports its role for ASCVD risk stratification in South Asians.[57] This may be particularly useful for the Indian population because no validated clinical risk score is currently available for Indians. In view of this

limitation, the LAI has designated the following abnormalities as indicative of very high ASCVD risk, warranting intensive LDL-C lowering to <50 mg/dL:

- CACS ≥100
- CACS 1-99 and >75th percentile for age, sex, and race
- Non-stenotic coronary, carotid or femoral arterial plaque

Stenotic (>50%) coronary, carotid or femoral arterial plaques and low ABI (<0.9) represent ASCVD and are already considered to indicate very-high risk as per the 2016 LAI recommendations.[8]

A lower CACS value (1-99 and <75th percentile for age, sex, and race) is designated as a high-risk feature with target LDL-C <70 mg/dL, whereas a CACS value ≥300 is included in the extreme risk group, category A with an LDL-C target <50 mg/dL and optional target ≤30 mg/dL [**Figure 1, 2**]. Some experts in the consensus group suggested including patients with any CACS in the very high-risk group, particularly young patients in whom the presence of arterial calcification is highly abnormal, with an LDL-C target <50 mg/dL because the presence of coronary calcium indicates increased risk for progressive atherosclerosis. However, this is a matter of personal opinion without scientific validation and warrants clinical judgment and shared decision-making.

Assessment for subclinical atherosclerosis is recommended for persons aged 30 years and over for whom treatment decisions may be uncertain after consideration of risk scoring and additional risk factors and high-risk features, especially in the following scenarios-

- Individuals considered to be in the moderate risk and high risk group as per the LAI risk algorithm
- Family history of premature ASCVD or uncertain family history
- Suspected or diagnosed familial hypercholesterolemia (FH)
- Individuals with multiple ASCVD risk factors
- Individuals with reluctance for or intolerance to statin therapy

The above recommendations are necessarily more aggressive compared to Western guidelines because of the high baseline risk of ASCVD among Indians, as described below. Recently, the American College of Cardiology recommended moderate to high intensity statin therapy with ezetimibe if needed to lower LDL-C <70 mg/dL in those with CACS $\geq$100 or $\geq$75th percentile for age, sex, and race, with further consideration for a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor in those with CACS $\geq$1000.[58]

While carotid or femoral arterial plaque assessments are not included in the current United States guidelines for ASCVD risk assessment, the European Society of Cardiology does indicate carotid plaque assessment may be reasonable (class IIa-B recommendation) if CACS is not available or feasible.[59]

A more intensified approach is recommended for the Indian population for several reasons.[41, 58, 60] Indians tend to develop ASCVD at a younger age and hence, most of the individuals who require primary prevention are young or middle-aged.[61] In these age groups, atherosclerosis is relatively less abundant, but the mere presence of atherosclerosis indicates high lifetime risk of ASCVD events. Thus, the thresholds recommended for Western populations, which are mostly applicable to older individuals, are less applicable for Indians. For example, a recent

study from North India, correlated CACS with coronary artery plaque in 380 subjects who were free of clinical ASCVD.[62] The mean age of the subjects was 52.8±10 years, 35.5% had diabetes, 45% had hypertension and 15.7% had history of current or previous smoking. More than one-third (34.2%) had coronary artery plaque, but mostly non-obstructive (74.6% of all subjects with plaques). One-third of all subjects also had non-zero CACS but only 7.1% had CACS between 100 and 299 and only 2.4% had CACS ≥300. Among those with coronary plaque, 72.3% had CACS <100. These findings suggest that CACS thresholds of ≥100 or ≥300 are infrequently encountered in Indian subjects seeking primary prevention of ASCVD, despite very high risk of early onset ASCVD in India. Hence, inclusion of only the higher CACS in the risk stratification algorithm is likely to miss significant proportions of high-risk subjects who may qualify for risk reduction strategies. However, it is of interest to note that South Asian women in the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study had CACS progression similar to other ethnic groups in MESA and findings for South Asian men were similar to white men in MESA.[63] Furthermore, aggressive risk reduction in young individuals with early atherosclerosis is expected to be much more effective in preventing ASCVD events than allowing the atherosclerosis to progress and then intervening at a later stage. Our expert consensus group advocates implementing aggressive measures to reverse atherosclerosis or at least halt its progression once it has been detected, especially in the Indian population. There is ample evidence from Mendelian randomization studies, as discussed above, showing that early intervention is several times more effective in preventing ASCVD events than delayed intervention at a late stage of plaque accumulation.[6, 7] An LDL-C target <50 mg/dL is reasonable for these subjects because LDL-C lowering to this level provides the greatest opportunity for achieving plaque regression and stabilization,

whereas less intensive LDL-C lowering may lead to plaque stabilization only.[64] Also, other evidence-based therapies like antiplatelets and guideline directed medical therapy for comorbidities are to be instituted in patients with CACS ≥100.

Lastly, the efficacy of statins in reducing ASCVD is well-established. Statins are widely available and inexpensive in India. They also have an excellent safety profile safe, with a very low risk of serious side-effects and most of the common side-effects being reversible on discontinuing statin therapy.[65-67]

3.3. Other high-risk features

3.3.1. Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD), also referred to as metabolic dysfunction-associated steatotic liver disease (MASLD) as described below, is a widely prevalent but underrecognized clinical condition. It is estimated that worldwide 25% of the adult population suffers from NAFLD and the proportion is more than 50% among those with diabetes mellitus.[68] In India, the prevalence of NAFLD is reported to vary from 9% to 35%.[69] Published reports also suggest that Indian NAFLD cases are relatively younger and less commonly associated with type 2 diabetes mellitus compared to Western counterparts, despite having similar or higher hepatic necro-inflammatory activity and hepatic fibrosis.[70] South Asians also have a higher degree of visceral adiposity and adverse body fat distribution and dyslipidemia compared to Western patients, typically at lower body-mass index levels.[71, 72]

NAFLD is intricately associated with obesity, insulin resistance, metabolic syndrome and diabetes and this association appears to be bidirectional. The increased prevalence of these metabolic abnormalities and other cardiovascular risk factors leads to an increased risk of

ASCVD in these patients. In addition, NAFLD has also been demonstrated to be an independent risk factor for ASCVD. Patients with NAFLD have increased ASCVD risk as compared to those who have same risk factors without NAFLD. ASCVD is the commonest cause of death in patients with NAFLD.[73, 74]

Considering the pathophysiological associations with NAFLD, a new nomenclature has recently been proposed by a consortium of hepatologists.[75] Steatotic liver disease (SLD) is proposed as the main term since this is more specific and less pejorative than NAFLD. Metabolic dysfunction-associated steatotic liver disease (MASLD) has been suggested to replace NAFLD. When no known cause is apparent, it is designated as cryptogenic SLD. MetALD is used to describe those with MASLD who consume excess amounts of alcohol per week (140 to 350 g/week and 210 to 420 g/week for females and males, respectively). However, these terminologies are new and yet to find wider acceptance.

The diagnostic evaluation of NAFLD remains challenging.[69] There is no single modality that is sufficiently accurate, widely available and inexpensive. Risk prediction tools such as the NAFLD fibrosis score (receiver-operating characteristic curve for predicting advanced fibrosis is 0.85) or fibrosis-4 index score are available as screening tools, but sensitivity and specificity are suboptimal.[62] A high index of suspicion is appropriate in patients who have clinical phenotypes associated with NAFLD (e.g., obesity, metabolic syndrome, diabetes, elevated aminotransferase levels).[62] If NAFLD is suspected, the initial goals are to confirm the diagnosis and then assess the severity of the liver disease. Ultrasonography is the most commonly used modality for initial assessment and has a sensitivity of 84.8% and a specificity of 93.6% for detecting ≥20–30% steatosis.[76] Fibroscan elastography can be considered next to assess and quantify the degree of liver fibrosis. MRI is more sensitive and accurate in detecting and quantifying hepatic steatosis

and fibrosis, but it is expensive and not readily available. Liver biopsy is the gold standard, but is invasive and hence, reserved for selected individuals. All patients with suspected NAFLD also require a thorough clinical and biochemical evaluation to assess for other associated co-morbid conditions and causes of hepatic steatosis.[69]

The safety of statin therapy in patients with NAFLD with or without raised liver enzymes has been studied. Many clinicians have been hesitant to use statins in patients with NAFLD and elevated liver enzymes because of concerns about possible aggravation of liver enzyme elevation. Although statins are not a treatment for NAFLD, the results of several studies have demonstrated that statins are safe in patients with NAFLD with mild elevation of liver enzymes (aminotransferase) (up to 3 times the upper limit of normal).[77-79] More importantly, statins substantially reduce the ASCVD risk in NAFLD and the benefit is much greater than that seen in patients without NAFLD.[80-82]

In view of the close association between NAFLD and ASCVD risk factors, and recognition that ASCVD is the leading cause of death in patients with NAFLD, the LAI designates NAFLD with fibrosis grade 2 or 3 as a high-risk feature. The presence of NAFLD would require an LDL-C goal <50-70 mg/dL, depending on the overall risk profile of the patient.

3.3.2. Metabolic syndrome

There is a high prevalence of insulin resistance and metabolic syndrome in South Asians, including Indians.[83] The age-adjusted estimated prevalence of metabolic syndrome in urban Indian populations was approximately 25% (around 31% in women and 18.5% in men) prior to 2021. Both men and women experience age-related escalating prevalence of metabolic syndrome.[84] The current prevalence is much greater than a previous international study's estimate

that about 13–15% of adults in India have metabolic syndrome, with females being more affected (18–19% of adult females vs 8%–9% of adult males).[85]

Although the incremental value of a diagnosis of metabolic syndrome compared to its individual components for prediction of ASCVD risk remains debated, it is well-recognized that metabolic syndrome is associated with increased ASCVD risk in proportion to the number of features of the metabolic syndrome that are present.[86-91] The risk is particularly elevated in long-term follow-up, compared to a shorter period of 5-10 years.[92, 93] The metabolic syndrome is associated with two- to three-fold increased risk of cardiovascular events. The risk of type 2 diabetes mellitus is also increased about five-fold.[94] There are also increases in cardiovascular and all-cause mortality with metabolic syndrome, even in the absence of diabetes, with mortality rates successively higher for those with diabetes, and highest when both diabetes and cardiovascular disease are present, emphasizing the very high ASCVD risk in this condition.[79] Moreover, those with metabolic syndrome and diabetes have a greater extent, incidence, and progression of CACS that is subsequently associated with greater risk for ASCVD events.[95, 96] In a ten-year follow-up study, the hazard ratio for cardiovascular events jumped from 1.84 (1.40-2.42) in the presence of one component to 7.08 (3.63-13.80) in patients with five components as compared to those with no features of metabolic syndrome.[97] Based on this evidence, the LAI proposes designation of the metabolic syndrome as a high-risk feature with risk proportional to the number and severity of the metabolic syndrome factors present. The presence of metabolic syndrome would require an LDL-C goal <50-70 mg/dL, depending on the patient's overall risk profile.

3.4. Risk modifiers

There are a number of clinical, biochemical or genetic markers that may be associated with increased ASCVD risk. However, the strength of their association with ASCVD, their

incremental value over other risk factors or their applicability in the Indian population are less well established. Hence, these risk factors are currently recognized as "risk modifiers" instead of major risk factors or high-risk features. Their incorporation into the overall risk algorithm is depicted in **Figure 1**. The presence of one or more of these risk modifiers in low- or moderate-risk patients would reclassify them into a higher risk group.

3.4.1. Female-specific risk enhancing factors

Several female specific ASCVD risk enhancing factors have been identified. Premature menopause is one condition that is associated with increased risk of ASCVD. A meta-analysis was performed which included 32 studies with 310,329 nonoverlapping women. It showed that premature menopause before the age of 45 years was associated with a 50% increase in the risk of coronary heart disease (CHD), 23% increased risk of stroke, 19% higher cardiovascular mortality and 12% increase in all-cause mortality.[98] Late menarche is also associated with increased risk of ASCVD.

Several pregnancy-associated complications are also associated with increased risk of ASCVD during later life.[99-101] In a study of 146,748 first time pregnant women followed for a median duration of 4.7 years, the occurrence of hypertensive disorders during the pregnancy was associated with a 2.2-fold higher risk of subsequent ASCVD.[99] Preeclampsia was associated with a 4-fold increase in the risk of incident heart failure and a 2-fold increased risk of CHD, stroke, and cardiovascular mortality.[100] In another study of 8,127 parous women aged >20 years, a history of gestational diabetes mellitus was associated with 63% higher odds of ASCVD.[101]

Polycystic ovary syndrome (PCOS) affects 4–22% of reproductive age Indian women and is associated with insulin resistance and visceral adiposity.[102, 103] Women with PCOS have

increased risk for metabolic syndrome, diabetes mellitus and complications of pregnancy, as well as endometrial cancer.[104, 105] Women with PCOS, regardless of adiposity, have insulin resistance and dyslipidemia. Compared with findings in insulin-sensitive women, PCOS is associated with higher triglycerides, higher total cholesterol and lower HDL-C.[106]

Therefore, clinical evaluation of ASCVD risk in female patients needs to include a complete assessment of their reproductive history.

3.4.2. Inflammatory diseases

Rheumatoid arthritis (RA) and spondyloarthropathies (e.g., ankylosing spondylitis and psoriatic arthritis) are associated with significantly increased ASCVD risk. The risk in other inflammatory disorders such as systemic lupus erythematosus and systemic sclerosis is also higher compared to the general population, but the magnitude of the increase is less than that associated with RA.[107]

In a large longitudinal study of 4,311,022 Danish individuals followed from 1 January 1997 until 31 December 2006, 10,477 individuals developed RA and 130,215 developed diabetes mellitus. The development of RA or diabetes was associated with the same risk of incident MI that was comparable to the risk in subjects without RA who were 10 years older.[108] A large meta-analysis of twenty-four studies involving 111,758 patients and 22,927 cardiovascular events reported a 50% increase in risk of cardiovascular mortality, 59% increase in ischemic heart disease (IHD), and 52% increase in cerebrovascular accidents in patients with RA.[109] Based on the overall evidence, a calibration factor of 1.5 has been recommended for estimating true ASCVD risk in patients with RA when using the ASCVD risk prediction algorithms.[110] Some risk algorithms such as QRISK II and QRISK III incorporate systemic inflammatory disorders in the risk equation.

Several mechanisms have been postulated to explain increased ASCVD risk in patients with chronic inflammatory conditions. These include systemic inflammation, concomitant presence of general ASCVD risk factors (e.g., lack of physical activity, stress, smoking, hypertension) and the long-term use of steroids and non-steroidal anti-inflammatory drugs.[107]

Lipid profile testing in patients with inflammatory diseases can be misleading because total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglycerides may decrease during active inflammation, whereas lipoprotein(a) levels may increase. Hence, lipid parameters should be reassessed 2-4 months after starting anti-inflammatory therapy. Furthermore, the TC/HDL-C ratio may be preferred over other lipid parameters for ASCVD risk assessment,[34, 107, 111-114] but LDL-C and non-HDL-C measurements still have predictive value.

Recent clinical trials involving treatment with canakinumab as well as low dose colchicine have now proven the concept that some anti-inflammatory treatments reduce cardiovascular events[115-118], but methotrexate did not.[119] While canakinumab is not approved for cardiovascular event reduction in part due to its association with increased risk of fatal infections, low dose colchicine 0.5 mg daily was recently approved by the United States Food and Drug Administration for the purpose of cardiovascular event reduction for both secondary prevention and primary prevention in individuals with multiple risk factors, now providing a means for addressing residual inflammatory risk.

3.4.3. Plasma triglycerides versus non-high density lipoprotein cholesterol

Elevated levels of plasma triglycerides are associated with increased ASCVD risk. An old meta-analysis including 17 population-based prospective studies showed that each 1 mmol/L increase in the triglyceride concentration was associated with a 32% increased risk for incident ASCVD

in men and 76% increased risk in women. The risk attenuated after adjustment for HDL-C and other risk factors but remained statistically significant.[120] More recently, the prospective Copenhagen City Heart study demonstrated that elevated non-fasting triglycerides were associated with increased risk for MI, overall ischemic heart disease, stroke and death in both men and women. The increased risk persisted even after adjustment for other important ASCVD risk factors.[121, 122]

The mechanism underlying the association between hypertriglyceridemia and ASCVD risk is complex, multifactorial, and varies between individuals. Hypertriglyceridemia rarely occurs in isolation and is a marker of increased risk of insulin resistance, glucose intolerance and diabetes, visceral adiposity, increased inflammation, and other factors known to increase ASCVD risk. In patients with moderate hypertriglyceridemia (triglycerides <500 mg/dL), very-low density lipoprotein (VLDL) and its remnants are the major carriers of triglycerides whereas both VLDL and chylomicrons can be elevated in individuals with severe hypertriglyceridemia (triglycerides ≥500 mg/dL), particularly >1000 mg/dl.[34] VLDL and remnant lipoproteins are atherogenic apolipoprotein-B (Apo-B) containing particles. The excess ASCVD risk associated with elevated triglycerides is predominantly mediated by atherogenic effects of cholesterol present in Apo-B containing triglyceride rich lipoproteins. Since non-HDL-C encompasses the cholesterol content of all atherogenic particles, including LDL, VLDL, lipoprotein (a), and remnant lipoproteins, the risk imparted by elevated triglycerides is reflected by the non-HDL-C concentration. Indeed, the ASCVD risk associated with hypertriglyceridemia is nullified after adjustment for non-HDL-C.[123] The Apo-B concentration is somewhat more predictive of ASCVD risk compared to non-HDL-C and may be helpful for predicting ASCVD risk in patients with hypertriglyceridemia.[124, 125]

A recent analysis of the Copenhagen General Population study also assessed the association of LDL triglycerides with ASCVD risk.[126] The concentration of LDL triglycerides was robustly associated with increased risk of ASCVD, and this finding was validated by a metanalysis of data from eight previous studies. During hypertriglyceridemia, the cholesteryl ester transfer protein transfers cholesteryl esters from LDL in exchange for triglycerides from triglyceride-rich remnant lipoproteins, thus leading to elevated levels of LDL triglycerides. The elevated ASCVD risk is possibly due to the hydrolysis of LDL-triglycerides releasing toxic free fatty acids in the arterial wall. The study also showed in a discordance analysis that the association between LDL triglycerides and risk of ASCVD persisted after adjusting for Apo-B. However, an accompanying editorial importantly clarified and summed up the issue for the clinicians that "targets of lipid-lowering therapy will continue to be LDL-C, non-HDL-C, and Apo-B, [and potentially lipoprotein(a) when specific therapies become available], with the awareness that hypertriglyceridemia is a marker for persistent ASCVD risk"[127] at all levels of LDL-C.

In the updated LAI risk algorithm, both LDL-C and non-HDL-C are included as risk factors [**Figure 1**]. In addition, non-HDL-C is also designated as the coprimary target for treatment. In view of this, it may be argued that inclusion of plasma triglycerides in the risk algorithm may not have incremental value beyond measurements of non-HDL-C (or Apo-B). However, it is noteworthy that despite strong evidence supporting the prognostic value of non-HDL-C (as well as its practical utility allowing measurement in the nonfasting state), it has still not been widely adopted in clinical practice. Both clinicians and patients often focus on triglyceride levels to guide treatment decisions.

Placebo-controlled interventions to lower plasma triglycerides have yielded inconsistent and conflicting results, with recent clinical trials showing no ASCVD benefit from triglyceride

lowering. In contrast, a recent landmark study, the Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT), recruited high risk patients with either ASCVD (71%) or diabetes and multiple risk factors with moderately elevated triglyceride levels 135-499 mg/dL and showed a significant reduction in the composite primary endpoint and most secondary endpoints, including cardiovascular mortality in response to treatment with icosapent ethyl 4 grams daily.[128] In the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trial in patients with type 2 diabetes having mild-to-moderate hypertriglyceridemia with low HDL-C, pemafibrate significantly lowered triglycerides, VLDL cholesterol, remnant cholesterol, and apolipoprotein C-III levels, but did not reduce the incidence of cardiovascular events, possibly because Apo-B and LDL-C levels did not decrease.[129] However, the findings of this trial cannot be generalized to other fibrates.

In light of these considerations, the expert panel has designated plasma triglycerides ≥150 mg/dL fasting or ≥175 mg/dL non-fasting as a risk modifier in the treatment algorithm. This will help remind providers that persistent hypertriglyceridemia is a marker for persistent ASCVD risk, although the optimal intervention for hypertriglyceridemia has not been determined. However, the overall treatment approach remains focused on LDL-C, non-HDL-C and Apo-B goals to reduce ASCVD risk.

3.4.4. Polygenic risk score

Genetic predisposition for development of ASCVD is an important modulator of interindividual ASCVD risk, as well as the atherogenic response to individual risk factors. Recent advances in genetic testing have allowed the development of genome-wide polygenic risk score (PRS) assessment that integrates information from over 6 million sites across the genome.[130] Although

it is logical and appealing to consider assessing an individual's polygenic risk for ASCVD, there is ongoing uncertainty about which genes and genetic variants should be included in the polygenic risk score. There is also inconsistency between labs in the gene panels analyzed, and techniques for genotyping, which makes it difficult to compare data from various laboratories. Moreover, the optimal intervention for a particular polygenic risk profile remains undefined. Accordingly, many organizations have not advocated current use of polygenic risk scores in assessment of ASCVD risk in individual patients for clinical care.[131]

Studies have shown that PRS may help refine risk estimates within each risk stratum based on clinical risk scores (e.g., the pooled cohort equations).[132, 133] It has also been shown that the individuals with high PRS (overall score in the top 5 percentile) have >3-fold increased odds of early-onset MI, a risk which is equivalent to that seen in individuals with genetically confirmed familial hypercholesterolemia (FH). Since a high PRS has a much higher prevalence (10-20% higher) than FH mutations, the former may have a much greater relevance for ASCVD risk assessment in the general population.[134] However, the incremental value of PRS over clinical risk scores remains under investigation.[135, 136]

A major advantage of PRS is that it can be applied at any time after birth and allows identification of 'at-risk' individuals at a young age, even before the development of traditional ASCVD risk factors. This may offer an opportunity to intervene early which could potentially lead to a more profound risk reduction. In this context, it is noteworthy that the risk imparted by a high PRS may be modifiable through lifestyle intervention. In fact, the individuals with high PRS seem to derive a greater absolute benefit from lifestyle interventions and statin therapy.[137, 138]

PRS may have greater relevance for Indians because of higher incidence of premature ASCVD as compared to Western populations. The PRS developed initially was not directly applicable to the Indians because it was derived from the individuals of European ancestry.[133] However, recently, a framework has been created to develop and validate ancestry specific PRS for ASCVD in South Asians, including Indians.[139] This may enable a wider use of PRS for ASCVD risk estimation and management in Indians, but more studies are needed to guide proper interpretation of results and identification of optimal interventions.

3.4.5. Human immunodeficiency virus infection

Infection with human immunodeficiency virus (HIV) increases ASCVD risk through several mechanisms.[34, 107, 140, 141] Active inflammation and prolonged activation of the immune system can directly accelerate atherosclerosis. Various major ASCVD risk factors (esp. smoking) are also more common in patients with HIV. The long-term use of anti-retroviral therapy itself is associated with increased ASCVD risk, which may be mediated by its unfavorable metabolic effects such as insulin resistance, abnormalities of lipid metabolism, central obesity, and lipodystrophy.[142] Endothelial dysfunction may also occur, either as a consequence of inflammation or the effects of anti-retroviral therapy. Lastly, associated conditions such as concomitant infection with hepatitis C also increase ASCVD risk in patients with HIV.[143] The results of a recent large, randomized study of 7769 patients who had HIV infection and were deemed to be at low to moderate ASCVD risk showed that pitavastatin significantly reduced the risk of major adverse cardiovascular events by 35% over a mean follow-up of 5.1 years (95% confidence interval 0.48 to 0.90; P=0.002).[144, 145] Hence, statin therapy is a proven intervention to reduce risk of ASCVD events in patients with HIV.

3.4.6. Air pollution

Air pollution is currently a major, yet underappreciated risk factor for cardiovascular and all-cause mortality. The Global Burden of Disease (GBD) 2019 study reported that air pollution was the fourth-largest cause of disease and death worldwide, accounting for 6.7 million deaths in 2019.[146, 147] It is likely this is an underestimation of disease burden because of the difficulties in quantifying air pollution exposure and its contribution to adverse health.

Air pollution refers to the presence of harmful contents in air, which include particulate matter (PM), gaseous primary pollutants, secondary pollutants (which form within the air itself) and additional components such as volatile and semi-volatile organic chemicals. Of these, the health effects of PM have been studied the most. PM can be categorized as coarse particles (PM_{10}, mean diameter 2.5-10 μm), fine particles ($PM_{2.5}$, mean diameter 0.1-2.5 μm) and ultrafine particles ($PM_{0.1}$, mean diameter <0.1 μm). Air pollution can also be categorized as ambient air pollution and household air pollution. The contribution of ambient air pollution has increased significantly over time, whereas that of household air pollution has declined.[148, 149]

Air pollution due to $PM_{2.5}$ primarily results from combustion of fossil-fuel and biomass and is the most relevant for health hazards. The World Health Organization (WHO) recommends that the annual daily mean $PM_{2.5}$ exposure should be <10 $\mu g/m^3$ and 24-h mean exposure <25 $\mu g/m^3$. However, the Indian standards are relatively less stringent with the acceptable limits recommended as annual daily mean exposure <40 $\mu g/m^3$ and 24-h mean exposure <60 $\mu g/m^3$, respectively.[148-150] It is estimated that over 90% of the global population live in areas with $PM_{2.5}$ exposure exceeding the recommended WHO thresholds.[148, 149]

Unfortunately, India is among the worst affected countries with typical $PM_{2.5}$ exposure several times higher than current recommendations.[147-149, 151] In 2017, annual population-weighted mean exposure to ambient particulate matter $PM_{2.5}$ in India was 89.9 $\mu g/m^3$.[151] In 2019, 1.67 million deaths in India were attributable to air pollution, which accounted for 17.8% of the total deaths. Ambient air pollution exposure accounted for about 60% more deaths than household air pollution (0.98 million versus 0.61 million deaths).[151]

Cardiovascular disease is the major cause of morbidity and mortality resulting from air pollution worldwide, and accounts for more than half of all air pollution related deaths. This proportion is even greater in low- and middle-income countries where 70-80% of the deaths due to air pollution are estimated to result from cardiovascular causes.[148]

Several mechanisms contribute to air pollution-related adverse cardiovascular effects,[148, 149, 152] many of which are comparable to the effects of cigarette smoking. Oxidative stress, inflammatory responses and activation of various signaling pathways are the initial events, which lead to endothelial dysfunction, vascular inflammation, increased vascular tone, thrombosis risk due to platelet activation, and other factors. When sustained for long duration, these effects may result in systemic hypertension, diabetes mellitus, left ventricular hypertrophy, renal injury and initiation and progression of atherosclerosis. Clinically these deleterious effects manifest as ASCVD, heart failure, arrhythmias such as atrial fibrillation and ventricular tachyarrhythmia, and thromboembolism.

Several studies have evaluated the impact of $PM_{2.5}$ exposure on various cardiovascular endpoints. Even short-term exposure to $PM_{2.5}$ is associated with increased risk of MI, stroke and cardiovascular death, with a 0.1-1.0% increase in risk associated with each increment of

10 μg/m^3 in the $PM_{2.5}$ level.[152, 153] A meta-analysis of data 34 studies showed that each 10 μg/m^3 increment in $PM_{2.5}$ exposure (same day levels or lag of 0 days) was associated with a 2.5% relative increase in the risk of MI.[154] Acute exposure leads to more deaths from cardiovascular causes than the respiratory diseases (69% versus 28%).[155]

Similarly, the effect of longer-term exposure to $PM_{2.5}$ has also been studied extensively. An approximately 16%-31% increase in IHD mortality has been reported with each 10 μg/m^3 increment in annual mean $PM_{2.5}$ exposure over 1 to 5 years.[156, 157] In a large prospective study, an annual increase of 5 μg/mm^3 in $PM_{2.5}$ was associated with a 13% increased risk of MI.[158] The results of some studies have suggested that exposure to high levels of $PM_{2.5}$ may impart a risk of ASCVD that is comparable to smoking 1 pack of cigarettes daily.[159]

The effect of air pollution on other adverse cardiovascular outcomes has also been studied. A meta-analysis of data from 35 studies showed that each 10 μg/mm^3 increment in the $PM_{2.5}$ level was associated with a 2.12% increase in the risk of hospitalization or death from heart failure, with the strongest association seen on the day of exposure.[160] Similarly, increased risk of venous thromboembolism, stroke, atrial fibrillation and ventricular tachyarrhythmia is also associated with $PM_{2.5}$ exposure.[161-165] An association between air pollution exposure and carotid atherosclerosis as well as coronary calcification has also been reported.[166, 167]

However, despite extensive evidence strongly linking air pollution exposure with increased cardiovascular risk, the lack of robust methods to quantify individual exposure to air pollution is a challenge in incorporating it into clinical decision-making. Nevertheless, given the strong association between air pollution and cardiovascular risk, and the high prevalence of $PM_{2.5}$ air pollution in many large urban areas in India, it is important to recognize its contribution to

ASCVD risk. Hence, exposure to air pollution should at least be considered a risk modifier in the clinician-patient discussion about ASCVD risk assessment and identification of optimum LDL-C targets.

3.5. Recurrent cardiovascular events despite very low levels of low-density lipoprotein cholesterol

Some patients experience recurrent ASCVD events despite achieving an LDL-C concentration around 30 mg/dL. These patients appear to have excessively high risk, and it may be reasonable to categorize them as "extreme risk group C" in our LAI classification scheme. The elevated ASCVD risk in these individuals is likely to be multifactorial and therefore requires a multifaceted approach tailored to the specific patient profile [**Figure 3**]. Thus, although the optimal intervention in such patients is unknown, they may benefit from a variety of pharmacological therapies that may include icosapent ethyl for those with elevated triglycerides,[128] sodium-glucose cotransporter-2 inhibitors or glucagon-like peptide-1 receptor agonists for reduction of metabolic residual risk,[168, 169] colchicine for inflammatory residual risk,[116, 118] and dual antiplatelet therapy or a combination of aspirin with low-dose rivaroxaban for residual thrombotic risk.[170, 171] In the recently published Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity Trial (SELECT), treatment with semaglutide, a glucagon-like peptide-1 receptor agonist, at a dose of 2.4 mg subcutaneously weekly compared to placebo resulted in a 20% decrease ($P < 0.001$) in MACE (cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke) in patients with preexisting cardiovascular disease and overweight or obesity but without diabetes over a mean follow-up of 39.8 months. Modest placebo-corrected LDL-C and triglyceride lowering occurred (-2.18% and -15.64%, respectively) with semaglutide, but these changes were insufficient to account

for the substantial reduction in MACE.[172] Although the focus of this LAI guideline document is on management of hyperlipidemia, the findings from the SELECT study underscore the importance of overweight and obesity as modifiable cardiometabolic risk factors and the potential of newer therapies such as semaglutide to reduce their associated ASCVD risks.

Among individuals who continue to suffer recurrent vascular events despite aggressive risk reduction including lifestyle modification, effective control of all modifiable risk factors and implementation of relevant evidence-based pharmacotherapies described above, despite already having LDL-C reduced to 30 mg/dL, further lowering of LDL-C to around 10-15 mg/dL may be considered in highly select group of patients with shared decision making with the patient. Although there are no randomized trial data to support such a recommendation, there is evidence that ultralow LDL-C levels are associated with the lowest risk of ASCVD events without a safety signal during short-term follow-up. The post-hoc analysis of data from the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) and ODYSSEY OUTCOMES trials showed that LDL-C lowering to levels as below 10 mg/dL was safe and associated with incremental cardiovascular event reduction.[173, 174] A similarly low ASCVD risk was observed in individuals with PCSK9 null mutations resulting in LDL-C levels around 14–15 mg/dL.[175]

It must however be noted that not every patient with recurrent cardiovascular events will require LDL-C reduction to ultra-low levels. Instead, the overall risk profile of the patient needs to be carefully assessed and the focus should always be on multifactorial risk reduction which should be implemented based on the patient-specific considerations. Shared decision-making is essential, with thorough discussion with the patient about the existing evidence-base as well as pros and cons of each therapy.

4. Lipid targets and treatment approaches

Table 3 summarizes the lipid targets recommended by the LAI for various ASCVD risk groups. As mentioned above, LDL-C is the primary therapeutic target and non-HDL-C is the co-primary target with Apo-B as the secondary target. Non-HDL-C in particular is obtainable from a non-fasting state and should be used together with LDL-C to guide lipid management.

LDL-C reflects the cholesterol content of LDL particles in plasma, whereas non-HDL-C is a measurement of the cholesterol content of all atherogenic lipoprotein particles. Since one molecule of Apo-B is present in each atherogenic lipoprotein particle including LDL, triglyceride-rich remnant particles, intermediate density lipoprotein and lipoprotein (a), the Apo-B concentration reflects the number of atherogenic particles in circulation. Several studies have shown that Apo-B is a better analytic tool for ASCVD prediction than LDL-C or non-HDL-C at the population level,[176] but it is important to note that measurements of LDL-C, non-HDL-C, and Apo-B may yield concordant results in many patients, particularly individuals with normal triglyceride levels. Therefore, the LAI recommends Apo-B as a secondary target for lipid lowering therapy.

Figures 4 presents an overall approach to LDL-C lowering therapy. **Figures 5 and 6** describe the approach to lipid lowering therapy in patients with elevated triglycerides and those with diabetes, respectively. **Figure 7** depicts the lipid management approaches in patients presenting with acute coronary syndrome. These management algorithms were developed from previously published recommendations of the LAI, with necessary modifications and updates to reflect current knowledge and perspectives.[8, 9, 177-179]

5. Conclusions

Effective lipid lowering through non-pharmacological and pharmacological means is one of the most important strategies for ASCVD prevention. The selection of modality and intensity of lipid lowering therapy and identification of treatment targets depend on the patient's future risk of developing ASCVD. Hence, an accurate assessment of ASCVD risk is an essential first step to guide the intensity of treatment, including lipid management. The updated risk assessment algorithm presented in this document is intended to help clinicians select appropriate lipid lowering treatment regimens, optimal lipid goals, and comprehensive risk reduction in their patients, thereby improving cardiovascular outcomes. Although these recommendations provide solid guidance for cardiovascular risk assessment and lipid management in Indian patients, clinical judgement and shared decision making remain important at every step in applying these recommendations in clinical practice.

Author Contributions

Raman Puri, Manish Bansal, Vimal Mehta, and P Barton Duell conceived and designed the paper, acquired, analyzed, and interpreted the information/data used in the paper and drafted the article. Nathan Wong, S S Iyengar, Dinesh Kalra, Devaki R. Nair , Navin C Nanda, Jagat Narula, P Deedwania, Jamal Yusuf, Jamshed J Dalal, Sadanand Shetty, Vinod M Vijan, Rajeev Agarwala , Soumitra Kumar , Kris Vijay , Aziz Khan , Gurpreet Singh Wander , P C Manoria , S K Wangnoo, Viswanathan Mohan, Shashank R. Joshi, Balbir Singh, Prafulla Kerkar, Rajesh Rajput, D Prabhakar, Abdul Hamid Zargar, Banshi Saboo, Ravi R Kasliwal, Saumitra Ray, Sandeep Bansal, M U Rabbani, Shibba Takkar Chhabra, Sarat Chandra, Neil Bardoloi, Narasaraju Kavalipati, Immaneni Sathyamurthy, Akshya Pradhan, N N Khanna, Rajesh Khadgawat, Preeti Gupta, Milan C. Chag, Ashu Gupta, A Murugnathan, S N Narasingan, Sundeep Upadhyaya, Vinod Mittal, Rashida Patanwala Melinkeri, Madhur Yadav, Raseed Mubarak, K K Pareek, Pradeep Kumar Dabla, Rashmi Nanda, and J C Mohan revised it critically for important intellectual content and gave final approval for the version to be submitted.

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Conflict of interest

Raman Puri: Boehringer Ingelheim, Novartis

Manish Bansal: Sun Pharmaceuticals, USV, Dr Reddy's Labs, Cipla, Eris Lifesciences, Intas Pharmaceuticals, AstraZeneca Pharma India, Novartis

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V Mohan: Servier, MSD, Novo Nordisk, Novartis, Eli Lilly, USV, Lifescan J & J, Sanofi Aventis, Merck, Boehringer Ingelheim, Abbott, Several Indian Pharmaceutical companies

Shashank Joshi: Biocon, Cadilla, Twin Health, Glenmark, Torrent, Marico, MSD, Novo Nordisk, Sanofi, Boehringer Ingelheim, Abbott, AstraZeneca, USV, Alkem, Serdia

Saumitra Ray: Merck, Novartis, Boehringer Ingelheim, Astra Zeneca, Novartis

Sandeep Bansal: Novo Nordisk, Vascular Innovations Co. Ltd, Bayer, Portico India, ICMR

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Figure legends:

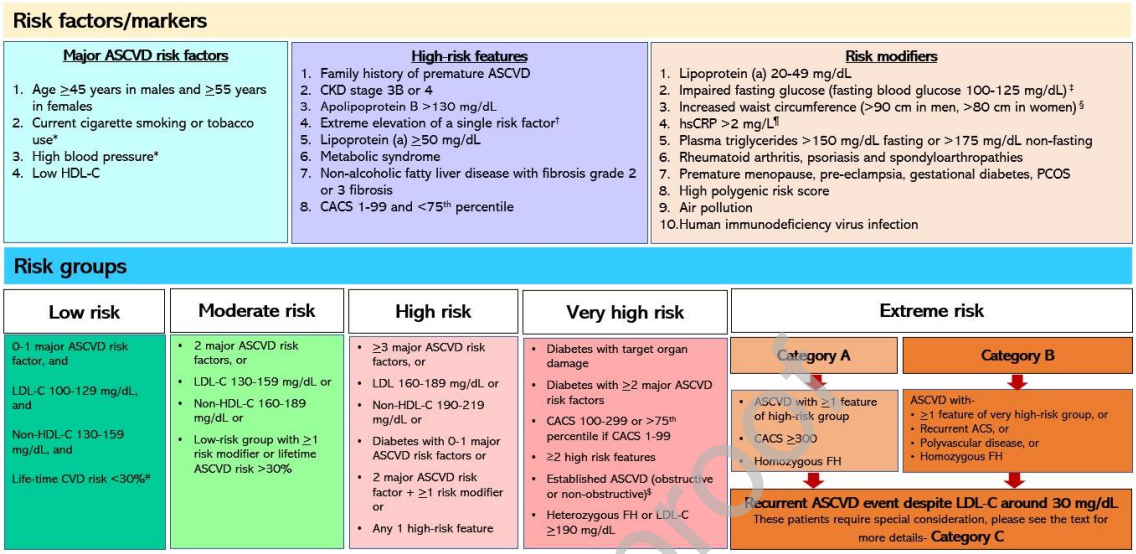

Figure 1: Updated 2023 risk stratification approach recommended by the Lipid Association of India.

* High blood pressure has been defined as office blood pressure ≥140/90 mm Hg or on anti-hypertensive treatment. Tobacco use includes cultural tobacco such as bidis, paan, gutka, etc.;†Extreme of a single risk factor defined as regular smoking >1 pack of cigarettes per day or blood pressure >180/110 mmHg; ‡Should be confirmed by repeat testing; §Waist circumference is to be measured at the superior border of the iliac crest just after expiration. If increased waist circumference is the only risk factor, it should be measured again 6 months after initiating heart healthy lifestyle measures; ¶On two occasions at least 2 weeks apart; #Estimated using the QRISK3-lifetime cardiovascular risk calculator (https://qrisk.org/lifetime/); $Includes stenotic or non-stenotic carotid, femoral or coronary arterial plaques as well as an ankle-brachial index <0.9 in either leg.

ACS- acute coronary syndrome, ASCVD- atherosclerotic cardiovascular disease, CACS- coronary artery calcium score, FH- familial hypercholesterolemia, HDL-C- high-density lipoprotein cholesterol, hsCRP- high sensitivity C-reactive protein, LDL-C- low-density lipoprotein cholesterol, non-HDL-C- non-high-density lipoprotein cholesterol, PCOS- polycystic ovary syndrome.

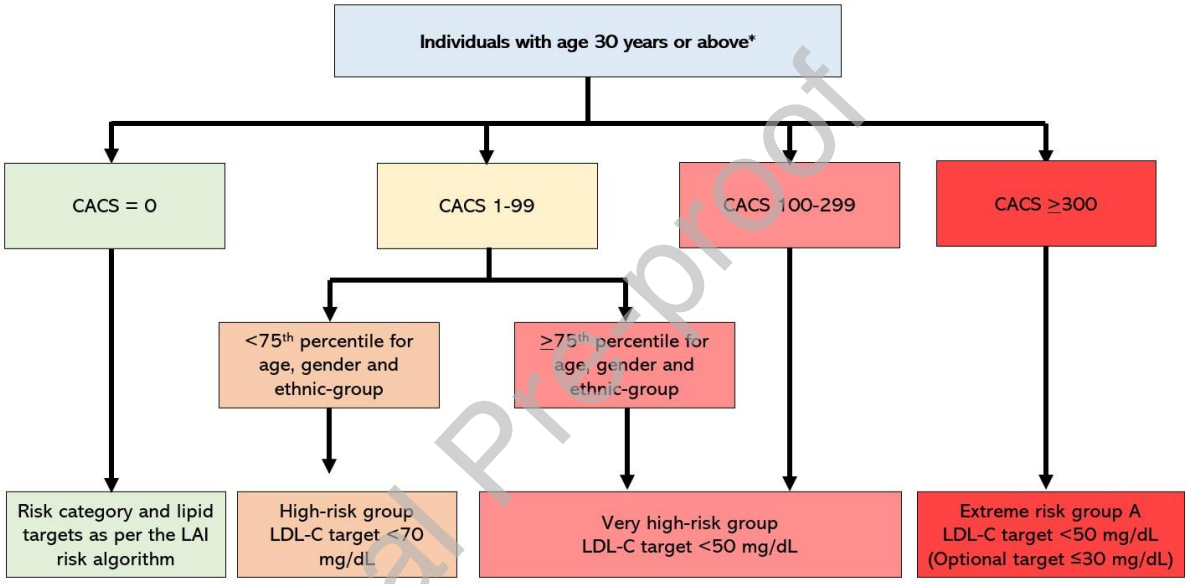

Figure 2: Risk categories and lipid targets according to the coronary artery calcium score.

*Please see text for indications for subclinical atherosclerosis assessment.

CACS- coronary artery calcium score, LAI- Lipid Association of India, LDL-C- low-density lipoprotein cholesterol.

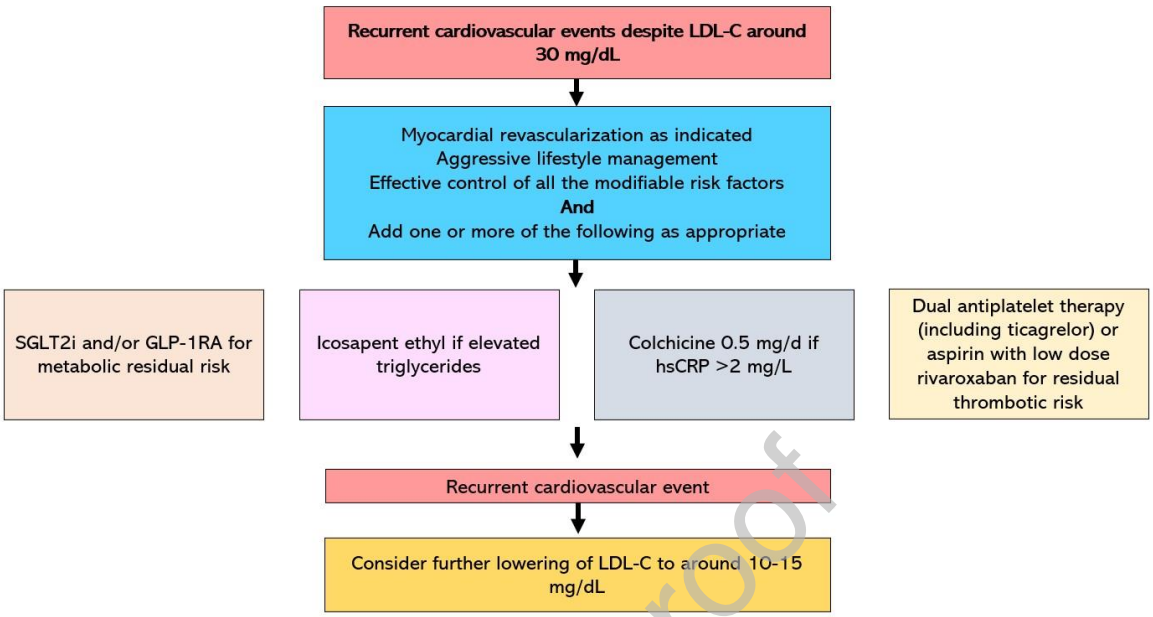

Figure 3: Management strategy for patients suffering recurrent cardiovascular events despite achieving a very low level of low-density lipoprotein cholesterol.

Recurrent cardiovascular events include new acute coronary syndrome or peripheral arterial disease or stroke. The physician or other health care provider must ensure that LDL-C levels were around 30 mg/dL and all appropriate non-lipid measures as listed are undertaken before aiming for extremely low LDL-C levels. A detailed informed discussion with the patient is a must regarding the above.

GLP-1RA- glucagon-like peptide-1 receptor agonists, hsCRP- high sensitivity C-reactive protein, LDL-C- low-density lipoprotein cholesterol, SGLT2i- sodium-glucose cotransporter-2 inhibitors.

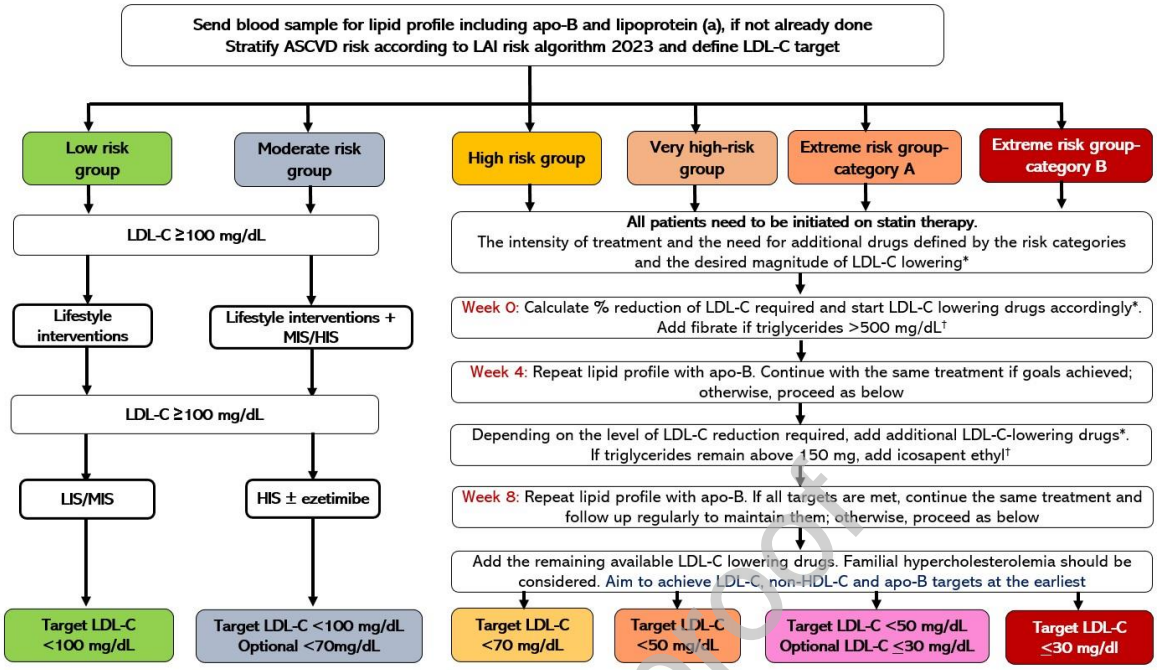

Figure 4: Low-density lipoprotein cholesterol targets in various atherosclerotic cardiovascular disease risk groups and the overall management approach.

*To reduce low-density lipoprotein cholesterol (LDL-C) by 30%, start with moderate intensity statin (MIS); to reduce it by 50%, start with high intensity statin (HIS); and to reduce it by 65%, start with HIS + ezetimibe. Add bile acid sequestrant or bempedoic acid if an additional LDL-C reduction of 20% is required; if the additional LDL-C reduction is >20%, consider proprotein convertase subtilisin/kexin type 9 inhibitors (this will require shared decision-making). †Look for and treat secondary causes of hypertriglyceridemia.

ASCVD- atherosclerotic cardiovascular disease, LAI- Lipid Association of India, LIS- low-intensity statin.

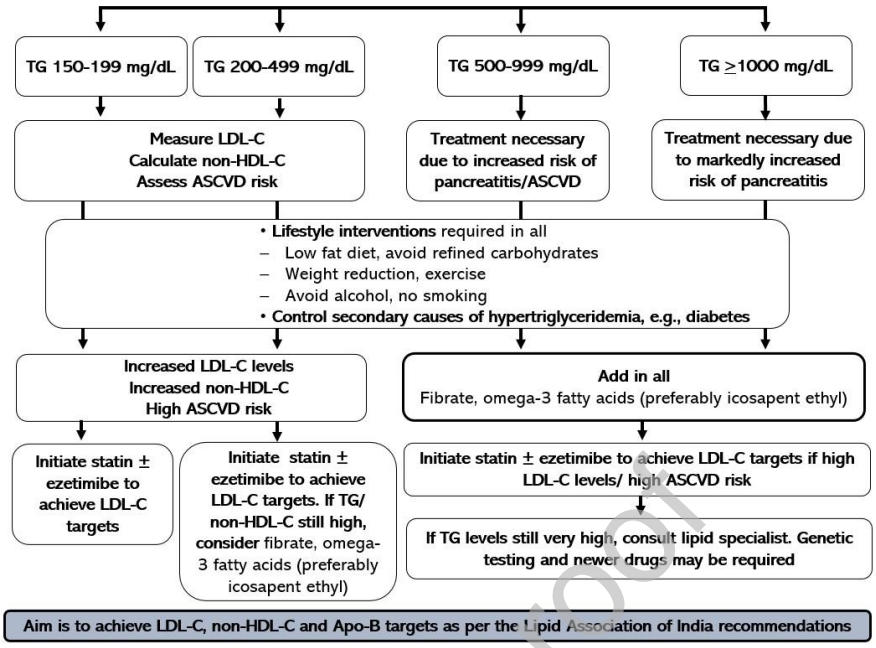

Figure 5: Algorithm for managing hypertriglyceridemia based on atherosclerotic cardiovascular disease risk and the baseline triglyceride levels.

Apo-B- apolipoprotein B, ASCVD- atherosclerotic cardiovascular disease, LDL-C- low-density lipoprotein cholesterol, non-HDL-C- non-high-density lipoprotein cholesterol, TG- triglycerides.

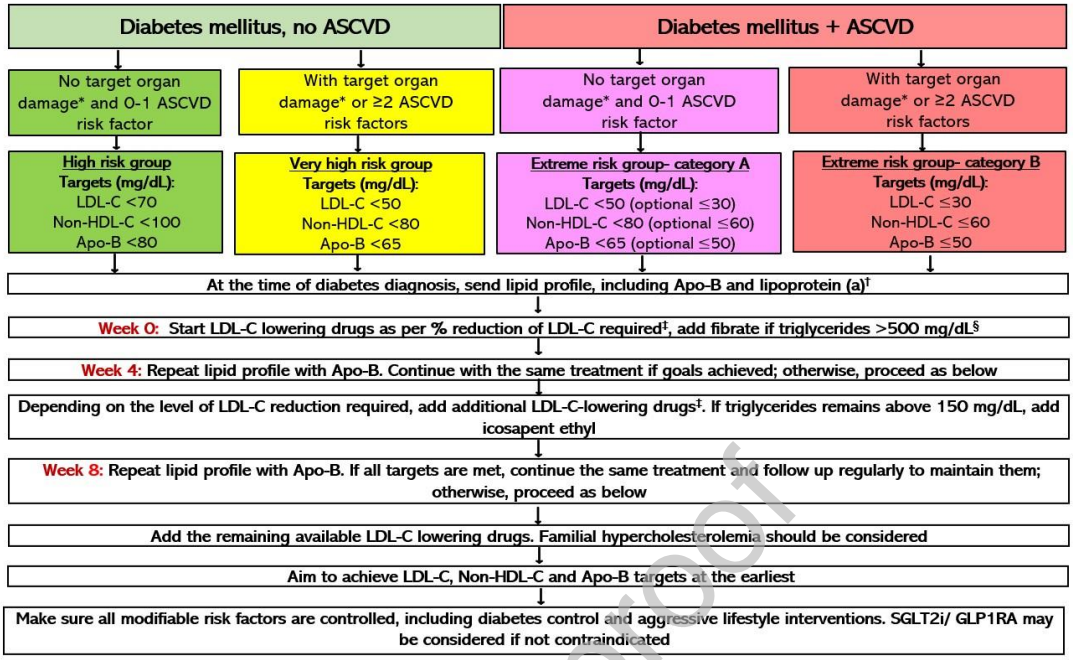

Figure 6: The Lipid Association of India recommendations for the management of diabetic dyslipidemia.

*Refers to microvascular complications of diabetes mellitus. †Consider proprotein convertase subtilisin/kexin type 9 inhibitors if lipoprotein (a) >50 mg/dL (this will require shared decision-making). ‡To reduce low-density lipoprotein cholesterol (LDL-C) by 30%, start with moderate intensity statin; to reduce it by 50%, start with high intensity statin; and to reduce it by 65%, start with high intensity statin + ezetimibe. Add bile acid sequestrant or bempedoic acid if an additional LDL-C reduction of 20% is required; if the additional LDL-C reduction is >20%, consider proprotein convertase subtilisin/kexin type 9 inhibitors (this will require shared decision-making). §Look for and treat secondary causes of hypertriglyceridemia, if present.

Apo-B- apolipoprotein B, ASCVD- atherosclerotic cardiovascular disease, non-HDL-C- non-high-density lipoprotein cholesterol, GLP-1RA- glucagon-like peptide-1 receptor agonists, SGLT2i- sodium-glucose cotransporter-2 inhibitors.

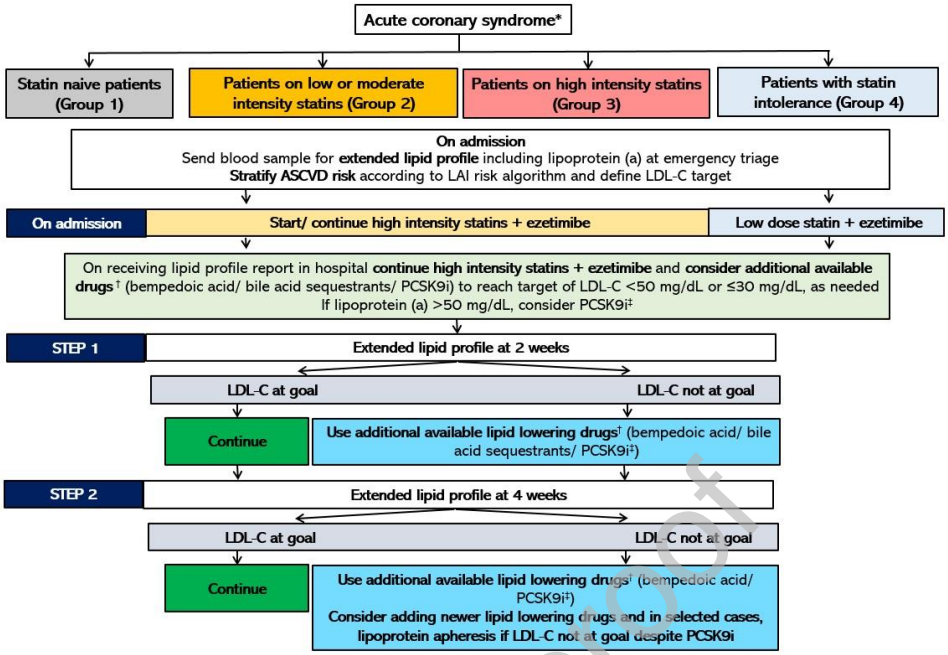

Figure 7: Approach to lipid management in patients presenting with acute coronary syndrome.

*Guideline directed medical treatment for acute coronary syndrome to be continued. Emphasis on aggressive risk factor modification is essential; †For low-density lipoprotein cholesterol (LDL-C) reduction of ≤20%, add bempedoic acid or bile acid sequestrants depending upon availability. If >20% LDL-C reduction needed, add proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i); ‡shared decision; §For more details, refer to the Lipid Association of India (LAI) recommendations for lipid management in acute coronary syndrome (J Clin Lipidol 2022;16(3):261-271).

ASCVD- atherosclerotic cardiovascular disease.

Table 1: Data from the Multi-Ethnic Study of Atherosclerosis providing 75th percentile values of coronary artery calcium score for different age, gender and ethnic groups. The values for Whites may be extrapolated for use in Indians.

Ethnic group	Men				Women			
	45-54 years	55-64 years	65-74 years	75-84 years	45-54 years	55-64 years	65-74 years	75-84 years
White	22	155	540	1200	0	16	119	370
Chinese	14	67	174	305	0	18	70	146
Black	2	40	191	516	0	5	77	214
Hispanic	9	75	247	494	0	2	51	205

Based on data presented in- McClelland RL, et al. Circulation. 2006;113:30-37.

Table 2: The 75th percentile reference values of coronary artery calcium score in White men and women ≤45 years of age

	Age (years)					
	30-40	**41**	**42**	**43**	**44**	**45**
Men	0	0	0	1	3	5
Women	0	0	0	0	0	0

Based on data presented in- Javaid A, et al. J Am Coll Cardiol. 2022;79:1873-1886.

Table 3: Treatment targets for lipid lowering therapy for various atherosclerotic cardiovascular disease risk groups

Risk group	Treatment targets		
	LDL-C, mg/dL (primary target)	**Non-HDL-C, mg/dL (co-primary target)**	**Apo-B, mg/dL (secondary target)**
Low risk group	<100	<130	<90
Moderate risk group	<100 (optional <70)	<130 (optional <100)	<90
High risk group	<70	<100	<80
Very high-risk group	<50	<80	<65
Extreme risk group-category A	<50 (optional ≤30)	<80 (optional ≤60)	<65
Extreme risk group-category B	≤30	≤60	<50
Extreme risk group-category C	10-15	40-45	-