CONSENSUS STATEMENT

Navigating Cardiovascular Risk and Lipid Management in Indian Patients: Key Messages from the Lipid Association of India 2024 Consensus Statement IV

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Received: 30 May 2024; *Accepted:* 22 June 2024

Abstract

Effective lipid management is crucial for preventing atherosclerotic cardiovascular disease (ASCVD). The Western lipid guidelines may not apply to Indian subjects because of the vast differences in cardiovascular (CV) disease epidemiology. To overcome this challenge, the Lipid Association of India (LAI) in 2016 proposed an ASCVD risk stratification algorithm. The appropriate low-density lipoprotein cholesterol (LDL-C) goals for various risk groups were proposed, with an LDL-C target of <50 mg/dL recommended for the first time globally for patients in the very high-risk group. Subsequently, in 2020, an extreme risk group was added because of observations that patients with more severe or extensive ASCVD, along with multiple risk factors and comorbidities, had increased rates of adverse CV events and could benefit from more intensive LDL-C lowering. The extreme risk group was subdivided into categories A and B, with LDL-C targets as low as 30 mg/dL or lower.

The availability of further evidence regarding the significance of novel risk factors and the availability of new LDL-C lowering therapies necessitated refining the ASCVD risk assessment algorithm, defining LDL-C targets for subjects with these risk factors, and incorporating recommendations for attaining very low LDL-C levels in a defined, select group of patients. Accordingly, the LAI expert group recently published the Consensus Statement IV, which is a comprehensive document addressing several key issues about risk stratification and dyslipidemia management in Indian subjects. LDL-C and nonhigh-density lipoprotein cholesterol (non-HDL-C) are not only primary and co-primary targets for lipid-lowering therapy but also risk factors for ASCVD risk stratification. Apolipoprotein B is a secondary target. The risk assessment algorithm has been updated to incorporate several nonconventional yet relevant CV risk factors. Additionally, the role of subclinical atherosclerosis has been highlighted. The CV risk due to subclinical atherosclerosis has been considered equivalent to that of established ASCVD, and hence, similar LDL-C targets have been recommended. Furthermore, a new risk category—extreme risk group category C has been added for the small subgroup of patients who continue to experience ASCVD sequelae despite achieving LDL-C levels of 30 mg/dL or lower. An ultralow LDL-C target (10–15 mg/dL) has been recommended along with optimal control of risk factors and guideline-directed management of comorbidities. Dyslipidemia management should be effective with sustained LDL-C lowering. In high-risk situations (e.g., acute coronary syndrome), the LDL-C target should be achieved as early as possible, preferably within the first 2 weeks. The present document summarizes the key messages from the LAI Consensus Statement IV.

Journal of The Association of Physicians of India (2024): 10.59556/japi.72.0614

The Lipid Association of India (LAI) in 2016 proposed an atherosclerotic cardiovascular disease (ASCVD) risk assessment algorithm and defined low-density lipoprotein cholesterol (LDL-C) goals based on risk stratification.[1] An LDL-C goal of <50 mg/dL was proposed for the first time globally for patients in the very high-risk group, which included those with established ASCVD, diabetes with two or more major ASCVD risk factors or target organ damage, and homozygous familial hypercholesterolemia (HoFH).[1] These goals were more stringent than the LDL-C targets recommended by other major societies at that time. Even in 2019, the European Society of Cardiology guidelines recommended an LDL-C goal of <55 mg/dL for ASCVD patients.[2] The American College of Cardiology expert consensus statement in 2022 recommended an LDL-C level of <55 mg/dL for individuals with multiple ASCVD events or one major ASCVD event associated with one or more high-risk conditions.[3] Subsequently, the LAI recommendations were revised in 2020, and an extreme risk group was added to the risk stratification algorithm.[4,5] This was done to suitably address the lipid-associated risk of individuals who were at markedly increased risk of experiencing future cardiovascular (CV) events due to severe or extensive ASCVD along with multiple CV risk factors or comorbidities. It was also important to incorporate new evidence generated with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor monoclonal antibodies, showing that achieving even lower LDL-C levels beyond those achieved with statin therapy was associated with further reduction of CV risk.[6,7] In fact, ultralow LDL-C levels achieved with treatment were associated with incremental benefits without any safety concerns.[8] Several subgroup analyzes from PCSK9 inhibitor trials showed that patients at the highest risk achieved the greatest benefit. In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) study, high-risk subgroups such as those with diabetes mellitus, recent myocardial infarction, multivessel coronary artery disease

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How to cite this article: Puri R, Mehta V, Bansal M, *et al.* Navigating Cardiovascular Risk and Lipid Management in Indian Patients: Key Messages from the Lipid Association of India 2024 Consensus Statement IV. J Assoc Physicians India 2024;72(8):80–82.

(CAD), or peripheral arterial disease had increased event rates and accordingly obtained more reduction in adverse CV events with even lower LDL-C levels achieved by the PCSK9 inhibitor monoclonal antibody evolocumab in addition to statins, thus supporting the highest risk, highest benefit strategy.[9–11]

The extreme risk group defined by LAI was further subdivided into category A and category B. In category A, an LDL-C goal of <50 mg/dL was recommended, with an optional LDL-C goal of 30 mg/dL or lower, while in category B, an LDL-C goal of 30 mg/dL or lower was recommended. A comprehensive risk-benefit conversation between the physician and the patient was recommended before embarking on such intensive lipid-lowering therapy.[4,5]

The LAI guidelines categorically state that the first priority for lipid management is the achievement of the LDL-C goal, followed by nonhigh-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (apo-B) goals.[1,4,5,12,13] Lifestyle management and control of all modifiable risk factors, comorbidities, and secondary causes of dyslipidemia, if any, are recommended for all subjects, along with suitable lipid-lowering therapy as needed. To achieve recommended LDL-C goals, statins remain the drug of choice, followed by ezetimibe and bempedoic acid.[4,5,14] PCSK9 inhibitors may be required only in a minority of patients who do not attain recommended LDL-C goals with the above therapies.[5] If the LDL-C goal is achieved but non-HDL-C remains above the goal, omega-3 fatty acids, preferably icosapent ethyl, are recommended, and fenofibrate can also be considered in addition to maximally tolerated LDL-C lowering therapy.[12,15] To maximally lower the lipid-associated CV risk, it is important to target apo-B as well after reaching LDL-C and non-HDL-C goals. This can be achieved by further intensifying the lipid-lowering therapy.

The major strength of the LAI guidelines, since their inception, has been their recognition of the epidemiological characteristics of ASCVD and prevailing socioeconomic circumstances in India, and their adaptation to these realities. The following are the key concepts underlying the LAI recommendations:

- Several studies have shown that Indians have LDL-C values about 10 mg/dL lower than their Western counterparts. At the same time, Indian subjects also tend to have a higher incidence, prevalence, and severity of ASCVD, associated with higher case fatality rates. Hence, the LDL-C goals proposed by the European and American guidelines cannot be directly applied to Indians, who may require more intensive LDL-C lowering. LAI has consistently proposed more stringent LDL-C goals for Indian subjects.
- Indian subjects tend to have higher non-HDL-C and apo-B levels, with high discordance between LDL-C and non-HDL-C levels.[16] Therefore, more intensive lipid-lowering is needed to achieve the non-HDL-C and apo-B targets, providing yet another rationale for lowering LDL-C targets.
- ASCVD manifests in Indian subjects at a younger age than in Western populations. Hence, any risk stratification tool based on age is not applicable to Indians. To overcome this challenge, LAI developed a unique CV risk assessment algorithm that relies less on age.
- The presence of atherosclerosis in any form (including nonobstructive plaques) identifies individuals who are at increased risk of developing clinically manifest atherosclerotic disease and deserve intensive risk factor modification to halt the progression of the atherosclerotic process. Denying them the advantage of early, aggressive LDL-C lowering due to otherwise perceived low risk (e.g., because of young age) misses the opportunity to curb atherosclerosis in its nascent phase. Recognizing this, the LAI has clearly emphasized the role of subclinical atherosclerosis in triggering intensive LDL-C lowering, regardless of other ASCVD risk factors. Such an approach seems ideal for a population with a high burden of premature ASCVD.

The latest "LAI 2023 Update on CV Risk Assessment and Lipid Management in Indian Patients: Consensus statement IV," incorporates these fundamental principles along with the latest evidence regarding ASCVD prevention and, more specifically, lipid management.[17] The salient points of the consensus statement are summarized below.

- As discussed above, these recommendations are based on the following key considerations—(1) ASCVD occurs at a younger age in Indian subjects despite lower baseline LDL-C, in contrast to other populations, and is associated with higher mortality; (2) early and sustained LDL-C lowering leads to more benefits; and (3) the higher the baseline risk, the greater the benefit from intensive LDL-C lowering.
- In view of the early onset of ASCVD, early detection and initiation of dyslipidemia treatment at a younger age in high-risk patients is very important. Even a minor decrease in LDL-C achieved earlier results in several-fold greater CV event reduction than starting treatment at a later age.
- Low-density lipoprotein cholesterol and non-HDL-C levels are not only treatment targets but also risk factors, as higher baseline levels result in progressively increasing CV risk.
- Low-density lipoprotein cholesterol is the primary target, non-HDL-C is the co-primary target, and apo-B is the secondary target.
- The lipoprotein(a) screening should be done at age 18 or earlier to assess the risk of premature ASCVD.
- Family history replicates numerous genetic, epigenetic, and environmental risk factors. Hence, a family history of premature CAD is considered a high-risk feature, independently warranting an LDL-C target of <70 mg/dL.
- Nonalcoholic fatty liver disease with fibrosis grades II and III, metabolic syndrome, chronic kidney disease stage 3B/4, apo-B greater than 130 mg/dL, lipoprotein(a) 50 mg/dL or higher, coronary artery calcium (CAC) score 1–99 but <75th percentile for age, gender, and ethnic group, and extreme elevation of a single risk factor are other high-risk features that place the individual in the high-risk group with an LDL-C target of <70 mg/dL.
- Elevated triglyceride levels (fasting >150 mg/dL or nonfasting >175 mg/dL), lipoprotein(a) level 20–49 mg/dL, increased waist circumference (>90 cm in men and >80 cm in women), impaired fasting glucose (fasting blood glucose 100–125 mg/dL), high sensitivity C-reactive protein >2 mg/L, air pollution, inflammatory joint diseases, premature menopause, preeclampsia, gestational diabetes, or polycystic ovary syndrome, high polygenic risk score, and human immunodeficiency virus infection are considered risk modifiers. Their presence in patients with low/moderate risk may place them in a higher risk group, thereby necessitating lower LDL-C targets.
- All patients with diabetes mellitus should be initiated on dyslipidemia treatment on day 1 of diagnosis. The recommended LDL-C goal is <70 mg/dL, with a lower target of <50 mg/dL if there is target organ damage or two or more major ASCVD risk factors. In those with diabetes and ASCVD (extreme risk group A), more intensive LDL-C lowering to an optional target of 30 mg/dL or lower may be preferable, whereas in patients with ASCVD and diabetes with target organ damage or

two or more major ASCVD risk factors, the LDL-C target is 30 mg/dL or lower. The above LDL-C targets need to be attained by week 12.

- All ASCVD patients must achieve LDL-C <50 mg/dL. If there is a history of recurrent acute coronary syndrome or polyvascular disease (extreme risk group B), a target of 30 mg/dL or lower is recommended.
- In acute coronary syndrome, the lipid profile should be done at emergency triage and repeated within 2 weeks of initiating lipid-lowering therapy. All patients should be started on combination therapy with high-intensity statin plus ezetimibe at presentation to the emergency department. The treatment is intensified every 2 weeks until LDL-C goals are achieved, preferably by week 4.[18]
- Any form of subclinical atherosclerosis (including nonobstructive carotid, femoral, or coronary plaques or ankle-brachial index <0.9) is considered equivalent to ASCVD, with similar LDL-C targets as for clinically manifest ASCVD.
- Patients with CAC scores of 1–99 but <75th percentile for age, gender, and ethnic group are defined as a high-risk group with an LDL-C target of <70 mg/dL. Coronary calcium score values greater than the 75th percentile for age, gender, and ethnicity, or values between 100 and 299, are classified as a very high-risk group with an LDL-C target of <50 mg/dL. If the CAC score exceeds 300, then the individual falls into extreme risk group A with an optional LDL-C target of 30 mg/dL or lower.
- Heterozygous familial hypercholesterolemia (HeFH) without ASCVD is included in the very high-risk group with an LDL-C goal of <50 mg/dL, whereas HeFH with ASCVD is included in the extreme risk group A with an optional LDL-C target of 30 mg/dL or lower. HoFH is incorporated in the extreme risk group A with an LDL-C target of <50 mg/dL and an optional target of 30 mg/dL or lower, while HoFH with ASCVD is listed in the extreme risk group B with a mandatory LDL-C target of 30 mg/dL or lower.
- A new extreme risk group category C has been created for very few patients who continue to have recurrent ASCVD events despite holistic ASCVD risk reduction through optimal lifestyle intervention, aggressive lipid-lowering therapy, use of therapies targeting nonlipid risk (e.g., anti-inflammatory agents such as colchicine), and guideline-directed management of underlying conditions like diabetes and hypertension. In these patients, it is recommended to lower LDL-C to 10–15 mg/dL.

The LAI expert group envisages that these latest recommendations will facilitate more appropriate dyslipidemia management among Indian subjects, leading to a reduction in CV risk. At the same time, the LAI guidelines also emphasize comprehensive ASCVD risk reduction and management, beyond just lipid-lowering therapy.

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References

1. Iyengar SS, Puri R, Narasingan SN, et al. Lipid Association of India expert consensus statement on management of dyslipidemia in Indians 2016: part 1. J Assoc Physicians India 2016;64(3 Suppl):S7–S52.
2. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41(1):111–188.
3. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology solution set oversight committee. J Am Coll Cardiol 2022;80(14):1366–1418.
4. Puri R, Mehta V, Iyengar SS, et al. Low-density lipoprotein cholesterol targets in secondary prevention of atherosclerotic cardiovascular disease. J Assoc Physicians India 2020;68(11):21–34.
5. 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.
6. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376(18):1713–1722.
7. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379(22):2097–2107.
8. Giugliano RP, Pedersen TR, Park JG, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a pre-specified secondary analysis of the FOURIER trial. Lancet 2017;390(10106):1962–1971.
9. Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomized controlled trial. Lancet Diabetes Endocrinol 2017;5(12):941–950.
10. Sabatine MS, De Ferrari GM, Giugliano RP, et al. Clinical benefit of evolocumab by severity and extent of coronary artery disease: an analysis from FOURIER. Circulation 2018;138(8):756–766.
11. Bonaca MP, Nault P, Giugliano RP, et al. Low density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER trial (further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk). Circulation 2018;137(4):338–350.
12. Puri R, Mehta V, Iyengar SS, et al. Non-HDL cholesterol and atherosclerotic cardiovascular disease. J Assoc Physicians India 2020;68(11[Special]):54–58.
13. Puri R, Mehta V, Iyengar SS, et al. Apolipoprotein B as a predictor of CVD. J Assoc Physicians India 2020;68(11):50–53.
14. Mehta V, Puri R, Duell PB, et al. Unmet need for further LDL-C lowering in India despite statin therapy: Lipid Association of India recommendations for the use of bempedoic acid. J Assoc Physicians India 2022;70(9):67–75.
15. Puri R, Mehta V, Duell PB, et al. Management of diabetic dyslipidemia in Indians: expert consensus statement from the Lipid Association of India. J Clin Lipidol 2023;17(2):e1–e14.
16. Modi KD, Chandwani R, Ahmed I, et al. Discordance between lipid markers used for predicting cardiovascular risk in patients with type 2 diabetes. Diabetes Metab Syndr 2016;10(1 Suppl 1):S99–S102.
17. Puri R, Bansal M, Mehta V, et al. Lipid Association of India 2023 update on cardiovascular risk assessment and lipid management in Indian patients: consensus statement IV. J Clin Lipidol 2024;18(3):e351–e373.
18. Puri R, Mehta V, Duell PB, et al. Evidence for intensive LDL-C lowering for acute coronary syndrome: recommendations from the Lipid Association of India. J Clin Lipidol 2022;16(3):261–271.