

# 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



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**BACKGROUND:** Rates of atherosclerotic cardiovascular disease (ASCVD) are strikingly high in India compared to Western countries and are increasing. Moreover, ASCVD events occur at a younger age with only modest hypercholesterolemia, most commonly with low levels of high-density lipoprotein cholesterol. The course of ASCVD also appears to be more fulminant with higher mortality.

**OBJECTIVE:** In light of these issues, the Lipid Association of India (LAI) endeavored to develop revised guidelines with more aggressive low-density lipoprotein cholesterol (LDL-C) goals in secondary prevention and for patients with familial hypercholesterolemia compared to guidelines in the United States and other countries.

**METHODS:** Owing to the paucity of clinical outcomes data in India, it was necessary to place major emphasis on expert opinion as a complement to randomized placebo-controlled data generated mostly in non-Indian cohorts. To facilitate this process, the LAI conducted a series of 19 meetings among 162 lipid specialists in 13 cities throughout India over a period of 11 months before formulating this expert consensus statement.

**RESULTS:** The LAI recommends an LDL-C goal <50 mg/dL in all patients in secondary prevention or very high-risk primary prevention but proposes an optional goal  $\leq$ 30 mg/dL in category A extreme-risk patients (eg, coronary artery disease + familial hypercholesterolemia) and a recommended goal  $\leq$ 30 mg/dL in category B extreme-risk patients [coronary artery disease + (1) diabetes and polyvascular disease/ $\geq$ 3 major ASCVD risk factors/end organ damage, or (2) recurrent acute coronary syndrome within 12 months despite LDL-C <50 mg/dL, or (3) homozygous familial hypercholesterolemia].

**CONCLUSIONS:** More aggressive LDL-C goals are needed for prevention of ASCVD in India, as described in this expert consensus statement. Use of statins and ezetimibe needs to increase in India in combination with improved control of other ASCVD risk factors. Proprotein convertase subtilisin kexin type 9 inhibitors can improve LDL-C goal achievement in patients with refractory hypercholesterolemia.

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## Introduction

The incidence and prevalence of atherosclerotic cardiovascular disease (ASCVD) in India is alarmingly high and is increasing.<sup>1–4</sup> Coronary artery disease (CAD) manifests almost a decade earlier in India than in Western countries.<sup>3</sup> Although the incidence of CAD has been decreasing in Western countries for many years, deaths from CAD in India have almost doubled in the past 10 years.<sup>1,2</sup> The years of life lost because of ASCVD in India increased by 59%, from 23.2 million in 1990 to 37 million in 2010.<sup>3</sup> Even more worrisome is the finding that the incidence of CAD is increasing most rapidly among patients younger than 40 years of age. The results of recent studies demonstrated that 10% to 25% of myocardial infarctions (MIs) in India occur before the age of 40 years<sup>4,5</sup> and more than 50% of CAD-associated deaths in India occur before the age of 50 years.<sup>3–5</sup> These data identified a need for new strategies to help stem the rising tide of ASCVD in India, which prompted the Lipid Association of India (LAI) to endeavor to establish new guidelines for prevention of ASCVD among Indians, with a primary focus on achieving very low levels of low-density lipoprotein cholesterol (LDL-C) in the highest risk individuals. The purpose of this document is to provide updated recommendations for secondary prevention in Indians that have been derived from an analysis of the current scientific evidence.

Although dyslipidemia is highly prevalent in India, with 79% of subjects having at least one lipid abnormality, elevated LDL-C levels were identified in only 11.8% of subjects, whereas decreased high-density lipoprotein

cholesterol (HDL-C) levels were found in 72.3% of subjects and hypertriglyceridemia in 29.5% of subjects.<sup>6</sup> While dyslipidemia characterized by low HDL-C and hypertriglyceridemia is well recognized to be an atherogenic metabolic condition, the best proven strategies for primary and secondary prevention of ASCVD involve LDL-C lowering, particularly with statins.<sup>7–12</sup> ASCVD risk reduction has been documented regardless of baseline LDL-C levels, although the absolute benefit is greater in patients with higher baseline LDL-C levels. Moreover, treatment with statins has been proven to reduce ASCVD risk among individuals with average LDL-C and low HDL-C levels.<sup>13</sup> Hence, despite a relatively low prevalence of elevated LDL-C levels, Indians nonetheless have high risk of ASCVD and warrant aggressive LDL-C lowering, possibly to levels lower than those recommended by the AHA/ACC<sup>14</sup> for Americans. Although statins remain the drug of choice for lowering LDL-C to decrease ASCVD risk, there is increasing support for the necessity to use adjunctive therapies in combination with statins to achieve additional lipid lowering. Because most of the clinical trial data were generated in non-Indian populations, we had to extrapolate the data to develop recommendations that are applicable to the extremely high-risk Indian population.

## The need for adjunctive lipid-lowering therapies

A heart healthy dietary pattern and regular physical activity are the cornerstones of lipid-lowering therapy.<sup>15,16</sup>

A lifestyle management program for cardiometabolic management should include nutrition and lifestyle intervention for dyslipidemia, hypertension, type 2 diabetes, overweight, and obesity by a multidisciplinary team including a registered dietician, exercise specialist, and a behavioral psychologist. The drug therapy with statins is to be used in conjunction with lifestyle measures. However there are many limitations of statin therapy:

### Residual risk

There is a significant residual risk of ASCVD events despite patients being on high-intensity statin therapy. The results from various randomized placebo-controlled trials of statin therapy have demonstrated a roughly 25% reduction in risk of ASCVD events over 4–5 years of treatment,<sup>11</sup> which indicates that most patients treated with a statin are not protected from ASCVD events.<sup>17</sup> In some patients treated with statins, the residual risk may be related in part to inadequate LDL-C lowering. In the Heart Protection study, which randomized 20,536 patients with diabetes or CV disease to simvastatin 40 mg daily or placebo for 5 years, the mean achieved LDL-C of 63 mg/dL in the simvastatin arm resulted in 24% reduction in the ASCVD events (19.8% vs 25.2%;  $P < .0001$ ), with number needed to treat of 19 for 5 years to prevent one major adverse CV event. Importantly, 19.8% patients in the simvastatin arm still had CV events over 5 years, which is an unacceptable outcome for clinical care.<sup>11</sup>

The results of subsequent clinical trials, particularly those using proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, demonstrated that more aggressive LDL-C lowering through use of adjunctive treatment with ezetimibe<sup>18</sup> and/or PCSK9 inhibitors<sup>19</sup> in combination with statins was associated with further reductions in the risk of ASCVD events down to an LDL-C concentration of 20 mg/dL or lower. Both FOURIER and ODYSSEY Outcomes trials of evolocumab and alirocumab, respectively, showed relative risk reductions of 15% in their primary cardiovascular end points; however, indicating residual risk is still present in these studies.<sup>20,21</sup> Moreover, recent trials targeting inflammation,<sup>22,23</sup> despite significant reductions in cardiovascular events, show persistent residual risk.

### Statin intolerance

Statin intolerance has been documented to be very well tolerated with low rates of side effects in randomized placebo-controlled clinical trials, with <1% to 2% of patients experiencing statin-related muscle symptoms.<sup>24</sup> Despite the excellent safety data in clinical trials, many patients in clinical practice are unable to tolerate statins. The International Lipid Expert Panel has given a unified definition of statin intolerance: the inability to tolerate at least 2 different statins—one statin at the lowest average starting dose and the other statin at any dose, biomarker changes, or symptom/biomarker abnormality resolution after statin

discontinuation.<sup>25</sup> An observational study of 7924 patients with hyperlipidemia on high-dose statin therapy reported that 832 (10.5%) patients had muscular symptoms. The severity of symptoms was variable with 31 (4%) patients reporting severe pain and 315 (38%) patients reporting pain on moderate exertion.<sup>26</sup> The excellent safety of statins for clinical use was extensively reviewed in a scientific statement from the American Heart Association.<sup>24</sup> Although many patients with statin intolerance may have symptoms that are unrelated to the statin, statin intolerance nonetheless interferes with drug compliance and attenuates the ability of patients to achieve LDL-C goals.

### Variability in LDL-C response to statins

In the primary prevention JUPITER trial, the response to rosuvastatin 20 mg daily was highly variable despite a mean LDL-C reduction of nearly 60%. Among 7856 individuals assigned to rosuvastatin, LDL-C decreased  $\geq 50\%$  in 46%, <50% in 43%, and no meaningful reduction in 11% of individuals. Noncompliance could have contributed to diminished LDL-C lowering.<sup>27</sup> Importantly, individuals achieving the lowest LDL-C levels obtained maximal ASCVD benefit compared to individuals with lesser LDL-C reduction.

### Failure to achieve LDL-C goals

In the European Action on Secondary Prevention by Intervention to Reduce Events IV (EUROASPIRE IV) survey, 90.4% of 6648 patients from 24 European countries with CAD were taking statins but only 19.3% achieved LDL-C levels of <70 mg/dL.<sup>28</sup> The DYSIS II study included 10,661 patients: 6794 with stable CAD and 3867 with acute coronary syndrome (ACS), from 18 countries including India. Only 29.4% of stable CAD patients and 18.9% of ACS patients achieved LDL-C levels <70 mg/dL despite a mean daily atorvastatin dose equivalent of  $25 \pm 18$  mg.<sup>29</sup> More aggressive lipid guidelines, such as those from the Lipid Association of India<sup>16,30</sup> and the American Association of Clinical Endocrinology (AACE),<sup>31</sup> advocate for even lower LDL-C goals for very high-risk patients, <50 mg/dL and <55 mg/dL, respectively. The AACE guidelines define very high or “extreme-risk” as individuals with either (1) recurrent ACS after achieving an LDL-C <70 mg/dL, (2) CVD and diabetes mellitus, chronic kidney disease stage 3 or 4, or heterozygous familial hypercholesterolemia (HeFH), or (3) patients with premature CVD.<sup>31</sup>

In a recent study of 1669 patients with stable CAD, the prevalence of extreme CV risk based on the AACE criteria was 55% (32% diabetes, 33% premature CAD, and 9.2% HeFH). Of these extreme-risk patients, 87% were on lipid-lowering therapy. However, only 20.3% of patients had LDL-C <70 mg/dL and only 5.3% patients had LDL-C below the AACE-recommended goal of <55 mg/dL.<sup>32</sup>

Adherence to statin therapy is also important to achieve LDL-C goals. Although country-wide Indian data on statin usage for secondary prevention are not available, studies from selected parts of India report that only 3.3% to 5% of deserving patients are treated with statins.<sup>33,34</sup> In another study, the prevalence of statin prescriptions decreased from 82% in tertiary care facilities to 21% in primary care centers,<sup>35</sup> which suggests that primary care providers may need great encouragement to prescribe statins.

## The need for more aggressive LDL-C lowering in India

All the aforementioned data portray a dismal picture of dyslipidemia management in high-risk CAD patients in India under current strategies. The Lipid Association of India started the process of developing this updated consensus statement in August 2018. To ensure that the recommendations in this statement reflected expert opinion among lipid specialists throughout India, a series of 19 meetings were conducted in 13 cities involving 162 expert health care providers over 11 months. The recommendations presented in this document represent information collected during this series of meetings and summarized here in this consensus document.

## Strategies beyond statin therapy for prevention of ASCVD events in primary and secondary prevention

It is clear that additional strategies are needed to further reduce the risk of ASCVD events in many patients treated with statins in primary and secondary prevention, but particularly in secondary prevention. Achievement of additional LDL-C lowering is a key strategy, which can be achieved with the use of high-intensity statin therapy in combination with add-on treatment with ezetimibe, and possible treatment with PCSK9 inhibitors. The results of studies of treatment of low HDL-C and hypertriglyceridemia with fibrates, niacin, and other agents have yielded inconsistent and sometimes controversial data, resulting in a lack of agreement about the best strategies for addressing these lipid abnormalities. Treatments that target the inflammatory component of ASCVD also may have merit, but more work is needed to define which agents are appropriate and which patients warrant anti-inflammatory treatment. Management of other ASCVD risk factors, such as diabetes, hypertension, obesity and the metabolic syndrome, smoking, and sedentary lifestyle, is also important. For the time being, achievement of lower LDL-C goals is a primary strategy for ASCVD prevention. PCSK9 inhibitors are an important tool for achieving more aggressive LDL-C lowering in high-risk patients already treated with a high-intensity statin (or maximally tolerated dose) and ezetimibe, which is the focus of this document.

## Proprotein convertase subtilisin kexin type 9

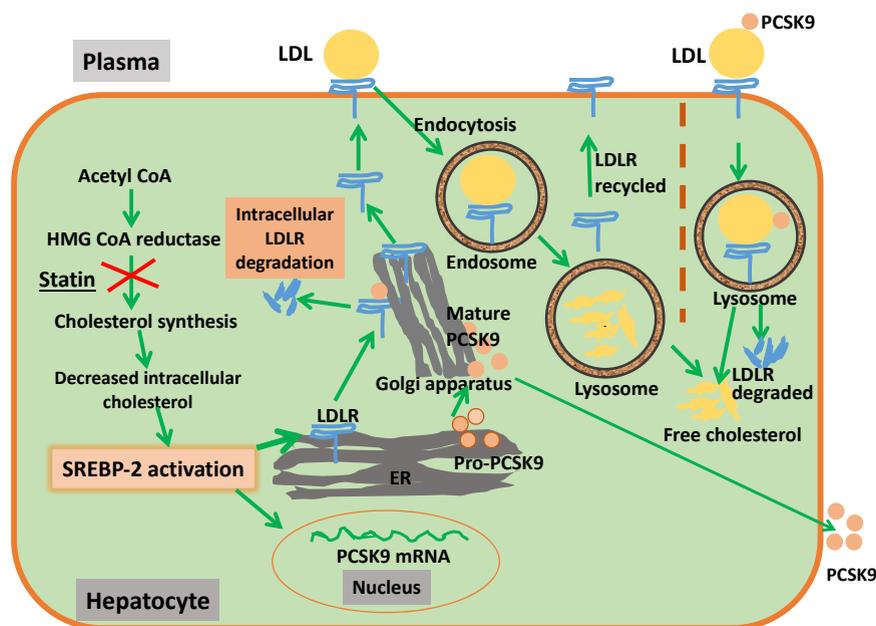
PCSK9 is the ninth member of a family of serine proteases that does not have significant proteolytic activity. Its discovery was first reported in 2003 by Nabil Seidah from Montreal, Canada.<sup>36</sup> PCSK9 is highly expressed in hepatocytes and to a lesser extent in small intestine and kidneys. Its physiologic function is unknown, but it plays a role in regulating activity of the LDL receptor (LDLR) and other lipoprotein receptors in the liver, with a possible role in lipoprotein assembly and secretion (Fig. 1).<sup>37</sup> Rare humans with total PCSK9 deficiency appear to be healthy and fertile adults but most notably have very low levels of LDL-C of 14 to 16 mg/dL.<sup>37–39</sup> The absence of discernible health problems in humans with total PCSK9 deficiency raises important questions about the role of PCSK9 in normal human physiology. PCSK9 is secreted by hepatocytes into the circulation where it binds to the LDLR resulting in lysosomal degradation of the LDLR in lieu of the usual recycling of the LDLR back to the cell surface to internalize more LDL particles dozens of times. The biology of PCSK9 regulation and its role in modulating LDLR activity have been extensively reviewed.<sup>37</sup>

## PCSK9 mutations

Until 2003, only 2 genes had been implicated as causing familial hypercholesterolemia, namely LDLR gene and ApoB gene. Simultaneous to reporting of the discovery of PCSK9 in February 2003, a mutation in chromosome 1 in 2 French families with familial hypercholesterolemia was identified through genotype sequencing.<sup>40</sup> The genetic polymorphism was subsequently documented to be a gain-of-function mutation in the PCSK9 gene, resulting in a rare cause of autosomal dominant familial hypercholesterolemia (<1%).<sup>37,40</sup> To date, more than 30 gain-of-function mutations in PCSK9 have been identified.<sup>37</sup> Two years after the identification of gain-of-function mutations in PCSK9, loss of function mutations were reported to be associated with reduced levels of LDL-C and reduced incidence of ASCVD. For example, in the Atherosclerosis Risk In Communities (ARIC) study, rare nonsense mutations in PCSK9 (2.6% of blacks) were associated with 28% lower mean LDL-C levels compared to unaffected individuals, but an 88% lower risk of CAD ( $P = .008$ ).<sup>41</sup>

## PCSK9 and triglyceride metabolism

Several lines of experimental evidence indicate that PCSK9 may have a role in regulating very low-density lipoprotein (VLDL) and triglyceride metabolism in addition to modulation of LDL-C levels in plasma.<sup>42</sup> For example, patients with gain-of-function mutations in PCSK9 have increased levels of VLDL-C, lipoprotein remnant-C, and triglycerides in addition to elevated LDL-C. These effects may be mediated by suppression of



**Figure 1** The role of PCSK9 in lipoprotein metabolism and effect of statins. PCSK9 is secreted from the ER to the Golgi apparatus as an inactive mature PCSK9/prodomain complex, which inhibits the protease activity of PCSK9 and prevents the binding of any other proteins to the catalytic site. From the Golgi apparatus, mature PCSK9 is secreted into circulation. In response to decrease in intrahepatocyte cholesterol levels, the expression of LDLR and PCSK9 is increased by SREBP-2, a membrane-bound transcription factor that controls cellular lipid homeostasis. The LDLR binds to the LDL and is internalized via endocytosis involving clathrin-coated vesicles. In the acidic compartment of the endosome, the affinity between LDLR and LDL particle becomes weaker and they dissociate. The LDL is degraded to free cholesterol while the LDLR recycles to hepatocyte surface. In the presence of PCSK9, affinity of PCSK9 toward LDLR is enhanced in endosomes, such that the LDLR is degraded along with LDL. Thus, PCSK9 disrupts the recycling of LDLR to the cell membrane. Intracellular PCSK9 directs some LDLRs toward lysosomal degradation. The binding of PCSK9 to some LDLRs in the hepatocyte is the reason some LDLRs are not released and therefore degraded in the lysosome. ER, endoplasmic reticulum; LDLR, low-density lipoprotein cholesterol receptor; PCSK9, proprotein convertase subtilisin kexin type 9; SREBP-2, sterol regulatory element binding protein-2.

activity of VLDL, apo E, and LDLR-related protein receptors in the liver by PCSK9.<sup>43</sup> One gain-of-function mutation in PCSK9 (S127 R mutation) was associated with increased production of apo B100 (3-fold), VLDL (3-fold), IDL (3-fold), and LDL (5-fold) compared with controls or subjects with LDL-R mutations.<sup>44</sup>

Despite the potential role of PCSK9 in aggravating hypertriglyceridemia and remnant lipoprotein accumulation, the results from clinical trials using PCSK9 inhibitors have demonstrated only modest triglyceride lowering (eg, 5%–18%) in patients with normal triglyceride levels.<sup>45,46</sup> In a study of 81 healthy normolipidemic nonobese men, it was shown that evolocumab (420 mg SQ every 4 weeks) for 8 weeks resulted in increased fractional catabolic rate for VLDL-apoB, IDL-apoB, and LDL-apoB, along with a decreased production rate for both IDL-apoB and LDL-apoB, which was associated with modest triglyceride (TG) lowering.<sup>47</sup> In addition, from the ODYSSEY LONG TERM study, alirocumab is shown to reduce triglycerides by 13% in those without and 17% in those with mixed dyslipidemia.<sup>48</sup> It is unclear whether treatment with PCSK9 inhibitors may have greater triglyceride-lowering efficacy among Indians in the context combined hyperlipidemia.

## PCSK9 and Lipoprotein(a)

Statins increase LDLR expression but have no effect on Lp(a) levels<sup>49</sup> or may even modestly raise the level by 11%. The regulation of Lp(a) production and clearance remains largely unknown. Lipoprotein(a) is formed in plasma from covalent binding of apolipoprotein(a) to apo B on LDL through sulfhydryl bonding. Lowering the LDL-C concentration with dietary interventions, statins, or ezetimibe does not lower the plasma concentration of lipoprotein(a), so the amount of LDL substrate in plasma and the level of LDLR activity do not appear to significantly influence the Lp(a) concentration.<sup>49,50</sup>

The 2 anti-PCSK9 monoclonal antibodies, alirocumab and evolocumab, lower Lp(a) levels an average of approximately 30%, which is far less than the 50% to 60% mean reduction in LDL-C.<sup>45</sup> Moreover, not all patients treated with PCSK9 inhibitors achieve Lp(a) lowering. Although the underlying mechanism for Lp(a) lowering is not clear, enhanced production of Lp(a) appears to be blunted by PCSK9 inhibition.<sup>51</sup>

Also of interest is that the relation of higher Lp(a) levels to cardiovascular events seems resistant to statin therapy; in fact, on-statin Lp(a) levels (especially above 50 mg/dL)

relate more strongly to cardiovascular events than do Lp(a) levels not on statin therapy as shown by a recent meta-analysis of Lp(a) levels in those on or not on statin therapy.<sup>52</sup>

## PCSK9 inhibition and inflammation

A meta-analysis of 16 treatment arms (2546 participants) did not show any significant effect of PCSK9 inhibitors on high-sensitivity C-reactive protein (hs-CRP) levels (weighted mean difference: 0.002 mg/L,  $P = .807$ ). There was no association of changes in hs-CRP levels with changes in plasma LDL-C concentrations ( $P = .697$ ), type of PCSK9 inhibitor, or cumulative dosage of the drug ( $P = .980$ ).<sup>53</sup>

## Anti-PCSK9 monoclonal antibodies

Monoclonal antibodies targeting PCSK9 include fully human (eg, alirocumab and evolocumab) and humanized (eg, bococizumab) antibodies. Currently alirocumab (Praluent; Sanofi Aventis) and evolocumab (Repatha; Amgen) are FDA approved for treatment of patients with ASCVD or familial hypercholesterolemia who require additional LDL-C lowering after lifestyle modification and treatment with maximal tolerable doses of statins.<sup>54,55</sup> Evolocumab is available for clinical use in India. Bococizumab has been dropped from clinical development. Alirocumab and evolocumab are commonly referred to as “PCSK9 inhibitors.” The dose of alirocumab is 75 mg or 150 mg administered SQ every 2 weeks or 300 mg every 4 weeks. The lower dose is generally recommended as the starting dose and is satisfactory in about two-thirds of patients, but the higher dose can be initiated directly. Monitoring of the effect on LDL-C is recommended, with measurement 14 days after the third biweekly dose. With the alirocumab 75-mg dose, LDL-C levels fall by 45% to 55%, and they fall by approximately 50% to 60% with the 150 mg dose. If sufficient LDL-C lowering has not been achieved after 8 weeks of treatment with the 75 mg dose, the dose can be titrated to 150 mg every 2 weeks. The evolocumab dose is 140 mg every 2 weeks or 420 mg monthly (injected by 3 separate subcutaneous injections of 140 mg or 420 mg administered by SQ infusion from a disposable autoinjector). Both dosing regimens of evolocumab achieve the comparable LDL-C lowering (approximately 50%–60%), but there may be more between-dose fluctuations of the LDL-C concentration with monthly administration.<sup>45,54,55</sup> Both agents lower triglycerides by about 15%, raise HDL cholesterol by 5% to 10%, and lower Lp(a) by 25% to 30%.<sup>45,46</sup>

One subcutaneous injection of alirocumab 150 mg results in undetectable free PCSK9 levels within 2–4 hours of injection which remain undetectable for about 2 weeks, after which they start rising and correlate inversely with alirocumab levels. The LDL-C level starts falling within 2 to 3 days and remains low for 2 to 3 weeks when it starts

rising again, reaching baseline levels at 4 to 6 weeks. In one study, administration of evolocumab 140 mg fortnightly reduced the mean LDL-C concentration by about 65% on day 14. In another study, patients treated with atorvastatin 10 mg/d were randomized to either tripling of the dose of atorvastatin to 80 mg/d, adding alirocumab 150 SQ every 2 weeks, or both. Atorvastatin dose escalation to 80 mg/d reduced LDL-C by an additional 17% (as predicted), whereas the addition of alirocumab reduced LDL-C an additional 66% from the baseline achieved with atorvastatin 10 mg/d. When alirocumab was combined with atorvastatin 80 mg/d, the incremental reduction in LDL-C was 73% compared to atorvastatin 10 mg/d.<sup>45</sup>

## Evolocumab clinical trials

Evolocumab was initially evaluated in a dose finding MENDEL trial in statin-naïve patients. The maximum LDL-C reduction of 51% was seen with 140 mg every 2 weeks.<sup>56</sup> The LAPLACE TIMI 57 trial demonstrated that evolocumab reduced LDL-C levels in a dose-dependent manner in patients on statins ranging from 41.8% to 66.1% with 2 weekly dosing and 41.8% to 50.3% with 4 weekly dosing at 12 weeks.<sup>57</sup> DESCARTES trial demonstrated that mean reduction in LDL-C with evolocumab in patients on lipid-lowering therapy was 57% from baseline compared to placebo ( $P < .001$ ) and was sustained at 52 weeks.<sup>46</sup>

In the FOURIER study, 27,564 patients with prior MI, prior stroke, or symptomatic peripheral arterial disease and LDL-C levels of  $\geq 70$  mg/dL or non-HDL  $\geq 100$  mg/dL on maximal statin therapy were randomized to injection evolocumab (either 140 mg every 2 weeks or 420 mg every 4 weeks) or matching placebo.<sup>20</sup> The median LDL-C decreased by 59% from baseline of 92 mg/dL to 30 mg/dL ( $P < .001$ ) in the evolocumab group. The non-HDL levels decreased by 52% and Apo B levels decreased by 49% ( $P < .001$ ). Evolocumab significantly reduced the risk of 5-point primary end point (9.8% vs 11.3%; HR 0.85;  $P < .001$ ) and secondary end point (a composite of CV death, MI, or stroke) (5.9% vs 7.4%; HR 0.80;  $P < .001$ ) at a median follow-up of 2.2 years predominantly driven by reduction in the risk of MI, stroke, and coronary revascularization. The serious adverse events including new-onset diabetes and neurocognitive events were similar between the study groups. However the injection-site reactions were more common with evolocumab (2.1% vs 1.6%).<sup>20</sup>

Major CV events progressively declined with decreasing achieved LDL-C concentrations, with adjusted HR in the group with LDL-C  $< 10$  mg/dL of 0.69 for the primary and 0.59 for secondary end points compared with the reference group (LDL-C  $\geq 100$  mg/dL) (Table 1). No serious adverse events occurred in excess in the group with ultra-low achieved LDL-C.<sup>19</sup> In the FOURIER study, certain high-risk subgroups such as those with recent MI or multivessel disease,<sup>58</sup> diabetes mellitus,<sup>59</sup> or peripheral arterial disease<sup>60</sup> had higher event rates and consequently greater

**Table 1** Incremental benefit of lower achieved LDL-C in FOURIER study<sup>19</sup>

Achieved LDL-C at 4 wk	No. of patients (%) Total = 25,982 patients	5-point MACE (primary efficacy end point)	HR (95% CI)	RRR
<20 mg/dL	2669 (10%)	10.3%	0.76 (0.64–0.90)	24%
20–49 mg/dL	8003 (31%)	12.4%	0.85 (0.76–0.96)	15%
50–69 mg/dL	3444 (13%)	13.6%	0.94 (0.82–1.09)	6%
70–99 mg/dL	7471 (29%)	13.7%	0.97 (0.86–1.09)	3%
>100 mg/dL	4395 (17%)	15.5%	Reference	

LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event.

The primary efficacy end point was a composite of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospital admission for unstable angina.  $P_{\text{trend}} < .0001$  for Kaplan-Meier event rates at 3 y across 5 groups of achieved LDL-C from lowest to highest.

absolute benefit with evolocumab. The OSLER-1 (Open-Label Study of Long-term Evaluation Against LDL-C) study of 1255 patients reported 58% reduction in LDL-C at the end of 5-year follow-up period without any increase in the incidence of adverse events.<sup>61</sup> Please refer to [supplementary material](#) for more details about evolocumab.

### Alirocumab clinical trials

Alirocumab has also been tested in multiple clinical trials (see [Supplementary material](#)). The most recent large ODYSSEY Outcomes trial randomized 18,924 patients in 57 countries with history of an ACS within the previous 12 months to either alirocumab 75 mg every 2 weeks ( $n = 9462$ ) or placebo ( $n = 9462$ ). Inclusion criteria included either LDL-C levels  $\geq 70$  mg/dL, or non-HDL-C  $\geq 100$  mg/dL, or Apo B  $\geq 80$  mg/dL after maximal statin therapy (atorvastatin or rosuvastatin). The on-treatment LDL-C target was 25 to 50 mg/dL. After a median follow-up of 2.8 years, LDL-C levels were 53.3 mg/dL in the alirocumab group compared with 101.4 mg/dL in the placebo group (54.7% decrease) with on-treatment analysis. The primary end point of major adverse cardiovascular events (MACEs) was significantly lower in the alirocumab group vs placebo group (9.5% vs 11.1%, HR 0.85,  $P = .0003$ ), with benefit seen only after one year of treatment as in statin trials.<sup>21,62,63</sup>

The reduction in MACE with alirocumab was primarily because of reduction in ischemic events: nonfatal MI was reduced by 14%, stroke by 27%, and unstable angina by 39% (all significant). All-cause mortality was significantly lower by 15% with alirocumab vs placebo (3.5% vs 4%,  $P = .026$ ). However, CAD death (2.2% vs 2.3%) and CV death (2.5% vs 2.9%) were similar in both groups. The adverse events were similar between groups except more minor injection-site reactions in alirocumab (3.1%) than in the placebo group (2.1%). In patients with baseline LDL-C  $\geq 100$  mg/dL (30% of total), the MACE reduced by 24% with all end points showing significant reduction, including CAD death and CV death reduction by 28% and 31% respectively.<sup>21,63</sup> In a prespecified analysis of Odyssey Outcomes study, alirocumab decreased not only the occurrence of first serious CV adverse event but also subsequent adverse events.<sup>64</sup>

### Regulatory approval

The US Food and Drug Administration (FDA) approved alirocumab injection on July 24, 2015 and evolocumab injection on August 27, 2015 for use in adult patients with HeFH or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C as an adjunct to diet and maximally tolerated statin therapy. In addition, evolocumab is approved for adjunctive LDL-C lowering in patients with HoFH. More recently, both drugs were approved for the expanded indication of reducing the risk of MI, stroke, and coronary revascularization (evolocumab only), or unstable angina hospitalization (alirocumab only) in adults with established cardiovascular disease.<sup>54,55</sup> Evolocumab and alirocumab were given market authorization throughout European Union on July 17, 2015 and September 23, 2015, respectively, in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) or mixed dyslipidemia as an adjunct to diet and statins. In statin-intolerant patients, both are approved either alone or in combination with other lipid-lowering therapies. Evolocumab is also indicated in patients aged 12 years and over with HoFH in combination with other lipid-lowering therapies.<sup>65,66</sup> The new indication for evolocumab and alirocumab in adults with established ASCVD to reduce CV risk by lowering LDL-C levels was given on March 22, 2018 and January 31, 2019, respectively, as an adjunct to maximally tolerated statin or other lipid-lowering therapy.<sup>65,66</sup> The Central Drugs Standard Control Organization (CDSCO), India approved evolocumab for use in Indian patients with HoFH on February 21, 2017 and for clinical ASCVD on March 27, 2018.<sup>67–69</sup> Alirocumab is as yet not approved in India.

### Economics of PCSK9 inhibitors

PCSK9 inhibitors significantly reduce LDL-C with consequent reduction in major adverse CV events. However, they have not been shown to reduce mortality. The list price of PCSK9 inhibitor in India is about Rs. 19,400 (about \$270 USD) for one 140 mg dose, resulting in an annual cost of above Rs. 5 lakhs ( $> \$7000$  USD). It has been reported in multiple cost-benefit analyses in the United States that only a small fraction of their higher cost is likely to be recovered

**Table 2** Proposed LDL-C goals in very high-risk and extreme-risk group patients

Risk group		
Very high-risk group (VHRG)	Extreme-risk group Category A	Category B
LDL-C goal		
LDL-C goal of <50 mg/dL	LDL-C goal of <50 mg/dL (indispensable) LDL-C goal of ≤30 mg/dL (optional)*	LDL-C goal of ≤30 mg/dL*
High-risk conditions		
Any one of the following: ASCVD (CAD/PAD/TIA or stroke) Homozygous familial hypercholesterolemia Diabetes with ≥3 major ASCVD risk factors†/target organ damage	CAD† with ≥1 of the following: Diabetes without target organ damage/0–2 major ASCVD risk factors Familial hypercholesterolemia ≥3 major ASCVD risk factors CKD stage 3B and 4 ≥2 major ASCVD risk factors with ≥1 moderate nonconventional risk factor‡ Lp(a) ≥50 mg/dL Coronary calcium score ≥300 HU Extreme of a single risk factor PAD H/o TIA or stroke	CAD† with ≥1 of the following: Diabetes + polyvascular disease/≥3 major ASCVD risk factors‡/target organ damage Recurrent ACS (within 12 mo) despite on LDL-C goal Homozygous familial hypercholesterolemia

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; polyvascular disease, evidence of atherosclerotic disease in at least 2 vascular territories; CAD, coronary artery disease; PAD, peripheral arterial disease and history of (H/o) transient ischemic attack (TIA) or stroke; CKD, chronic kidney disease; Lp(a), lipoprotein(a); LDL-C, low-density lipoprotein cholesterol.

\*The LDL-C goal of ≤30 mg/dL must be pursued after detailed risk-benefit discussion between the physician and patient.

†Clinical judgment to be used in decision making if the patient has disease/risk factors not covered in the table, for example, PAD or cerebrovascular disease.

‡Major ASCVD risk factors: (1) age-male ≥45 y, female ≥55 y, (2) family h/o premature CAD-male <55 y, female <65 y, (3) smoking/tobacco use, (4) systemic hypertension, (5) low HDL (males <40 mg/dL and females <50 mg/dL).

§Moderate nonconventional risk factors: (1) coronary calcium score 100–299, (2) increased carotid intima-media thickness or aortic pulse wave velocity, (3) Lp(a) ≥20–49 mg/dL, (4) metabolic syndrome.

by prevention of cardiovascular events for the general population of patients with ASCVD,<sup>70</sup> but the results of more recent analyses performed after recent reductions in the cost of these medications in the United States have suggested greater cost-effectiveness.

In India, the penetration of health insurance is low, and when insurance is available, it is generally limited to hospitalizations and not outpatient medications. Hence, for most patients in India, the cost of medications has to be paid out-of-pocket, which is often unaffordable. Therefore, high cost of PCSK9 inhibitors is a major impediment to accessibility in India and will reduce long-term adherence.

### Lipid Association of India recommendations for secondary prevention of ASCVD

Indian patients have ASCVD at lower LDL-C levels and at a younger age than Western populations. Because the ratio of LDL-C to HDL-C may be important in determining the benefit of LDL-C lowering, and low HDL-C being the most common lipid abnormality in India, further lowering of LDL-C will help achieve the recommended ratio of ≤1.5.<sup>16</sup> Accordingly, these observations and the data

presented in the introduction suggest that lower LDL-C goals are likely to be needed for Indians. Although limited data regarding the impact of various interventions on ASCVD risk in India are available, most of the studies suffer from one or more major limitations that include small numbers of subjects, inadequate statistical power, short-term follow-up, absence of hard outcomes, and no comparison or placebo group.<sup>71–73</sup> Although more studies are needed to prove that achieving more aggressive LDL-C lowering goals in high-risk Indians prevents ASCVD events, aggressive action needs to be implemented now to help reign in the rising tide of ASCVD morbidity and mortality in India. On the basis of the best available evidence, guided by expert opinion, the LAI recommends more aggressive lowering LDL-C goals for very high-risk and extreme-risk secondary prevention patients in India (Table 2). The reader is referred to LAI expert consensus statement 2016 for dyslipidemia management of patients in low-, moderate-, and high-risk categories.<sup>16</sup>

### Strategies for ASCVD prevention

The LAI recommends that lifestyle measures remain the key intervention for both primary and secondary prevention

of ASCVD<sup>15,16</sup> followed by lipid-lowering drug therapy, as indicated. For secondary prevention, achievement of LDL-C goals is an indispensable part of management. All efforts must be made to achieve recommended LDL-C goals. Management options to decrease blood LDL-C levels will also result in decrease in non-HDL-C and remnant cholesterol levels.

The results from 2 large outcome studies evaluating the role of PCSK9 inhibitor monoclonal antibodies have been published<sup>20,21</sup> since the publication of the LAI Part I consensus statement in 2016.<sup>28</sup> Both studies demonstrated that reduction of LDL-C to very low levels was associated with further reduction of MACE, with no significant safety concerns. The safety was also shown in the pooled clinical trial data of up to 5 years of PCSK9 inhibitor therapy.<sup>61</sup> Furthermore, patients in the IMPROVE-IT trial with polyvascular disease with concomitant type 2 diabetes were at very high risk (60% MACE rate at 7 years) compared to those without diabetes and polyvascular disease (29.6% MACE rate at 7 years),  $P < .0001$ . The absolute risk reduction with ezetimibe 10 mg/d on the background of simvastatin 40 mg/d was 9.1% in polyvascular disease with concomitant type 2 diabetes compared to 1.7% in those without diabetes and polyvascular disease over 7 years,  $P < .0001$ .<sup>74</sup>

The LAI notes that longer term data regarding safety and efficacy will be helpful, as well as additional studies specifically in Indian patients. In the meantime, however, it is pertinent to incorporate data from these studies into consensus statement of LAI so that larger number of patients with ASCVD can achieve cardiovascular benefit of further reduction of LDL-C. Stratified-treatment algorithms have been suggested to define highest risk patients who are likely to benefit from larger absolute LDL-C reductions.<sup>75</sup> Based on the aforementioned information, the LAI proposes that among patients with ASCVD, there is a subgroup of very high-risk patients, termed “extreme risk,” who are likely to benefit from further lowering of LDL-C, possibly with PCSK9 inhibitors. We propose 2 categories of extreme risk, category A and category B (defined in Table 2). The LDL-C goal recommended by the LAI for category A patients is  $<50$  mg/dL with an optional LDL-C goal of  $\leq 30$  mg/dL. For category B patients, the LDL-C goal recommended by the LAI is  $\leq 30$  mg/dL. These goals should be first achieved utilizing ezetimibe after maximally tolerated statin therapy, and then with PCSK9 monoclonal antibodies therapy if additional LDL-C lowering is still required to reach goal. There should be a detailed discussion between the physician and the patient regarding the benefits, costs, and side effects of aggressive lipid-lowering therapy before initiating such therapy.

### Justification for extreme risk category

CAD is designated as very high-risk category in 2016 LAI consensus statement on management of

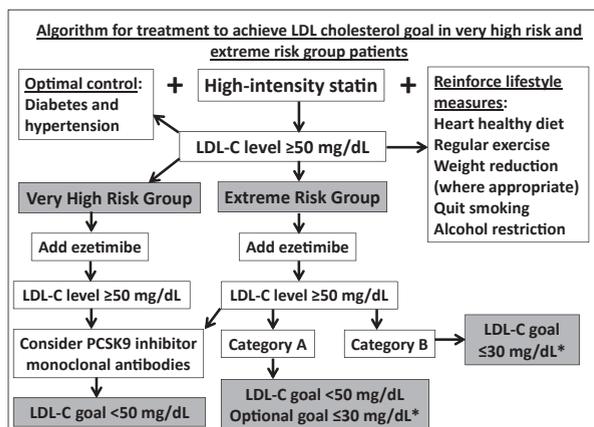
dyslipidemia.<sup>16</sup> However, all CAD patients do not have the same prognosis. Selected CAD patients have higher risk of future adverse CV events because of the coexistence of disease in other vascular territories (eg, prior stroke or peripheral artery disease) and/or the presence of other risk factors. The number, type, and severity of risk factors determine the risk of subsequent adverse CV events. Based on the presence of risk factors, LAI proposes a new category—extreme risk. These “extreme-risk” patients require aggressive management to decrease future ASCVD events.

The rationale for our lower recommended targets for those at extreme risk stems mainly from evidence from the PROVE-IT TIMI 22 trial showing the lowest event rates in those who achieved LDL-C  $<40$  mg/dL,<sup>76</sup> meta-analysis of 8 major statin trials showing lowest event rates in those who achieved LDL-C  $<50$  mg/dL,<sup>77</sup> as well as from the prespecified analysis of IMPROVE-IT trial showing the lowest event rates in those who achieved LDL-C  $<30$  mg/dL.<sup>18</sup> Moreover, FOURIER study showed a continuous gradient in lower event rates by achieving LDL-C down to 20 mg/dL without evidence of a threshold effect.<sup>19</sup> These data help justify an LDL-C  $<50$  mg/dL for most extreme-risk patients (extreme risk category A), with an optional target of  $\leq 30$  mg/dL. For those who continue to suffer events despite achieving an LDL-C  $<50$  mg/dL or having one or more features of very high-risk group with CAD (extreme risk category B), LDL-C goal of  $\leq 30$  mg/dL is recommended (Table 2).

Recent 2019 European Society of Cardiology (ESC) dyslipidemia guidelines recommend a lowered LDL-C target of  $<55$  mg/dL in very high-risk patients<sup>78</sup>, which is similar to very high-risk group patients as per the LAI risk algorithm. In patients who experience recurrent vascular events while taking maximally tolerated statin therapy, an LDL-C target  $<40$  mg/dL has been recommended by the ESC vs  $\leq 30$  mg/dL by Lipid Association of India.<sup>78</sup>

### Treatment options

High-intensity statins (atorvastatin 80 mg/d and rosuvastatin 40 mg/d) are the drugs and dosages of choice for initial management of dyslipidemia in patients with established ASCVD to achieve the proposed LDL-C goals. Physician inertia in using high-intensity statins was felt to be an important factor responsible for patients in India not achieving LDL-C goals. It was noted during expert discussions that often statin dosages are reduced in ACS patients after the first few months. In patients who are unable to tolerate these highest doses of statin, lower doses may be used. Ezetimibe 10 mg/d is the drug of first choice for adjunctive treatment in combination with statins for patients who are unable to achieve LDL-C goals after  $>6$ – $8$  weeks of treatment with a high-intensity statin. If LDL-C goals are not achieved after treatment with a high-intensity statin in combination with ezetimibe, PCSK9 inhibitors may be considered for addition as a third LDL-C-lowering



**Figure 2** Algorithm for treatment to achieve LDL cholesterol goal in very high-risk and extreme-risk group patients. \*Detailed discussion between the physician and patient is must regarding the benefits, cost, and side effects of aggressive lipid-lowering therapy before initiating such therapy. LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin kexin type 9.

medication in combination with a high-intensity statin and ezetimibe (Fig. 2). At the time of this publication, only evolocumab is approved by CDSCO, India.

## Strategies for managing statin intolerance

All efforts must be made to continue treatment with statins. In most cases, the symptoms related to statin use, typically muscle pain, are transient and mild in severity.<sup>24</sup> Detailed discussion with the patient regarding the benefits of statin will encourage him/her to continue statin treatment. Before a patient is labeled as statin intolerant, the criteria described must be met and statin intolerance clearly established.<sup>25</sup> If high-intensity statin treatment cannot be tolerated, lower doses of statin may be better tolerated and is preferable to no statin treatment for prevention of ASCVD events.

For secondary prevention, the LDL-C goals are same as for statin-tolerant patients. Ezetimibe 10 mg/d is recommended as adjunctive treatment followed by PCSK9 inhibitor monoclonal antibodies. A detailed discussion between physician and patient regarding the benefits, costs, and side effects of PCSK9 inhibitor therapy before initiating such therapy must be undertaken. It must be reemphasized that PCSK9 inhibitors are not substitutes or alternatives to statin therapy.

## Familial hypercholesterolemia

Familial hypercholesterolemia (FH) is a common (estimated ~1:250 individuals with heterozygous FH in the general population) and very high-risk condition that is associated with a 10- to 20-fold increased risk of ASCVD events.<sup>79,80</sup> Patients with the rarer and most severe form of FH, homozygous FH, can present with MI in the first decade of life and have a mean age of death of about 18 years if untreated.<sup>81</sup> There is uncertainty about optimal

LDL-C goals for patients with FH, but the results from population-based studies have demonstrated high rates of ASCVD events among patients with FH despite LDL-C lowering treatment.<sup>82,83</sup> More recent data from the CASCADE FH patient registry in the United States suggested that an LDL-C goal of  $< 70$  mg/dL may be appropriate even in primary prevention among patients with heterozygous FH.<sup>84</sup> In light of the need for lower LDL-C goals in Indians compared to Western populations, a correspondingly optimal but hypothetical LDL-C goal for Indian FH patients may be  $< 50$  mg/dL in primary prevention. Further studies are needed to verify optimal LDL-C goals in Indian FH patients, but in the meantime, patients with FH warrant aggressive LDL-C lowering.<sup>85</sup>

Proposed LDL-C treatment goals for patients with familial hypercholesterolemia are listed in Table 2. High-intensity statins followed by ezetimibe remain the standard of care but are often insufficient to achieve LDL-C goals in patients with familial hypercholesterolemia. PCSK9 inhibitors may be added after detailed discussion with the patient to achieve LDL-C goals. The CDSCO, India, has approved evolocumab for the treatment of adult patients with familial hypercholesterolemia and pediatric patients  $\geq 12$  years of age with HoFH in combination with other lipid-lowering drugs. LDL/lipoprotein apheresis is also very effective for LDL-C lowering in patients with HeFH and HoFH, but its availability is limited.

## Conclusions

ASCVD has reached epidemic proportions in India and continues to increase. Not only the incidence of ASCVD is increasing because of the presence and inadequate control of conventional risk factors, but also the disease is more malignant with a high case fatality rate. This is in the backdrop of lower LDL-C levels compared to Western populations. All of the above point to the need for lower LDL-C goals in Indians compared to Western populations, particularly among ASCVD patients with comorbidities who have much higher risk of ASCVD events compared to those with established ASCVD but without comorbidities. We have proposed aggressive LDL-C goals that are proportional to the lower LDL-C levels observed among Indians with ASCVD compared to Western populations. Very low achieved LDL-C levels have been shown to be not only safe but also efficacious for prevention of ASCVD events. High-intensity statins along with ezetimibe, possibly in combination with PCSK9 inhibitor monoclonal antibodies when needed, are recommended for achieving LDL-C goals. However, statin therapy is currently grossly underutilized in India, so a major focus on increased use of statins is needed. Multifaceted approaches are also required to induce positive lifestyle changes, control other ASCVD risk factors, and increase optimal use of lipid-lowering therapies to control the rising incidence of ASCVD in India.

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## Supplementary data

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.jacl.2020.01.006>.

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