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Review Article

Internal Medicine Section

Cholesterol Management in Indians: Should We Treat the Targets or Treat the Risk?

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ABSTRACT

Clinical evidence on relationship between cholesterol and Cardiovascular Disease (CVD) has highlighted the importance of all lipid components in the pathogenesis of CVD, thereby generating the concepts of "target". Low Density Lipoprotein Cholesterol (LDL-C) and Non High Density Lipoprotein Cholesterol (non HDL-C) have been identified as the main "targets" in the guidelines for lipid management. For the corresponding targets, different "target goals" have been defined in most guidelines according to the levels of risk, to guide the lipid management and to minimise CV events. In the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guideline abandoned the target goal. This caused confusion among physicians. Recent trials like Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) have brought back into focus the concept of LDL hypothesis. Subsequent guidelines for dyslipidaemia management have retained the target goal based approach. In India, there is a high prevalence of dyslipidaemia and many patients do not achieve their lipid target goals. In this article, we have reviewed the evidence base used by different guidelines on lipid targets along with newer studies; in order to bring clarity to the dyslipidaemia management approach of Indian physicians.

Keywords: Cardiovascular disease, Clinical trials, Dyslipidaemia, Low density lipoprotein

INTRODUCTION

Prevalence of hypercholesterolemia is about 25-30% in urban and 10-15% in rural populations in India [1]. According to a survey of 5400 Indian patients with Diabetes Mellitus (DM), 48.74% achieved LDL-C targets while HDL-C, Triglyceride (TG), and Total Cholesterol (TC) targets are achieved in 60.48%, 57.54% and 92.24%, respectively. Among those with overt CVD, target LDL-C level of <70 mg/dL was achieved in 22.87% patients [2]. In DIVERSE (Demographic Assessment and Evaluation of Degree of Lipid Control in High Risk Indian Dyslipidemia Patients) study, only 7.7% of the patients achieved LDL-C levels <70 mg/dL on lipid lowering therapy. Majority of these patients were on suboptimal dosage of statin [3].

LDL-C has been identified by the American/European dyslipidaemia guidelines as the primary target of cholesterol-lowering therapy [4,5]. The ACC/AHA (American College of Cardiology/American Heart Association) 2013 guidelines have recommended that reduction of Atherosclerotic CVD (ASCVD) risk should be achieved with moderate-intensity or high intensity statin treatment based on level of CV risk [4]. In contrast, the recent 2016 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines recommend a target based approach for management of dyslipidaemia [5]. Newer molecules and trials have brought back into focus the LDL hypothesis. We have reviewed the approach suggested and the studies analysed by guidelines on lipid targets. We have also reviewed studies that were published in during year 2016-2017 but not included in the guidelines through a search using PubMed, EMBASE and Google Scholar.

Abandon Low Density Lipoprotein Cholesterol Targets? Not Yet

Clinical trial data have demonstrated a clear linear relation between LDL lowering and ASCVD risk reduction. A 2012 meta-analysis of 27 Randomised Controlled Trials (RCTs) of statins including 174149 participants; by the Cholesterol Treatment Trialists (CTTs) collaborators found that a reduction of 38.7 mg/dL in LDL levels translates into 11 fewer major vascular events per 1000 treated over five years (a benefit that greatly exceeds any known hazards of statin therapy) [6]. According to a 2010 meta-analysis, high dose treatment was associated with a highly significant reduction in major vascular events of 28% per 38.7 mg/dL LDL reduction achieved compared with usual dose statin therapy [7].

Post publication of 2001 National Cholesterol Education Program (NCEP)- Adult Treatment Panel (ATP) III recommendations, 5 landmark clinical trials results evaluating the beneficial impact of aggressive statin therapy on clinical endpoints were out [8]. This forced major changes in the 2004 ATP-III recommendations. The LDL-C goal had to be reduced to less than 70 mg/dL in very high risk patient's and less than 100 mg/dL in high risk group [8].

A meta-analysis of 38,153 patients from eight landmark RCTs {including AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study), LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease), JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), TNTs (Treating to New Targets), IDEAL (Incremental Decrease in Endpoints through Aggressive Lipid Lowering), SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels)} found a 56% reduction in major CV events among individuals who achieved LDL-C level less than 50 mg/dL [9]. Several newer landmark trials have also supported the benefits and safety of very low LDL levels [Table/Fig-1]. Various imaging trials like ORION (Outcome of Rosuvastatin Treatment on Carotid Artery Atheroma: a Magnetic Resonance Imaging Observation), YELLOW and PRECISE-IVUS (Plaque Regression with Cholesterol absorption Inhibitor or Synthesis inhibitor Evaluated by Intra Vascular Ultra Sound) have shown that more aggressive lowering of LDL-C level results in significant reduction in atheroma volume and CV events [1].

A 2017 pooled data analysis from 14 trials revealed that alirocumab induced LDL-C levels of <25 mg/dL do not increase overall adverse event rates or neurocognitive events. However, cataract incidence was apparently increased in this group

Study name	N	Patient population/study duration	Treatment groups	Achieved LDL-C Level with treatment (mg/dL)	Risk reduction (major CV events)	Safety
JUPITER	17802	Subjects without CVD (LDL-C ≤130 mg/dL and hsCRP ≥2 mg/L)	Rosuvastatin 20 mg vs Placebo	55	44% (p<0.00001)	Increases in the risk of DM, haematuria and certain musculoskeletal, hepatobiliary and psychiatric AEs in patients with LDL-C <30 mg/dL
		Median follow up: 1.9 years		<50	65%	No differences in the incidence of renal failure, cancer, memory impairment or haemorrhagic stroke across LDL-C levels
IMPROVE-IT	18144	Post-ACS LDL-C Median follow up: 6 years	Simvastatin 40 mg+ ezetimibe 10 mg vs Simvastatin 40 mg + placebo	53	6% (p=0.016)	No increase in AEs (including muscle, liver, gallbladder and neurocognitive AEs) or cancer across LDL-C levels
ODYSSEY LONG TERM	2341	High CV risk LDL-C ≥70 mg/dL Receiving statin treatment at maximum tolerated Dose Mean follow up: 1.5 years	Alirocumab 150 mg Q2W Placebo	48	48% (p=0.02)	Rates of AEs were similar in patients with LDL-C (<25 mg/dL) compared with the overall group
OSLER-1 and OLSER-2	4465	Varying Median follow up: 0.9 years	Evolocumab 140 mg Q2W or 420 mg QM+ST Placebo+ST	48	53% (p=0.003)	Rates of AEs (including muscle and neurocognitive AEs) were similar across LDL-C levels

[Table/Fig-1]: Main trials supporting very low LDL-C Levels [10].
N-Number of Participants, ACS-Acute Coronary Syndrome; HR-Hazard Ratio, hs-CRP-high-sensitivity C-reactive Protein, PCSK9-Proprotein Convertin Subtilisin/Kexin Type 9, Q2W-every 2 weeks, QM-Every Month; ST-Standard Therapy; IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial); AE-Adverse Event

[11]. Another 2017 pre specified analysis of the IMPROVE-IT trial revealed that patients who achieved LDL less than 30 mg/dL at one month had a similar safety profile over a six year period compared with those achieving higher LDL. These data provide some reassurance regarding safety of very Low-Density Lipoprotein (LDL-C) levels [12]. However, more data is required to determine whether LDL-C reductions to less than 25 mg/dL can be a recommendation.

Non-High Density Lipoprotein Cholesterol (Non-HDL)-Should We Target It?

Atherogenic lipoprotein pool in blood includes several non LDL lipoproteins [cholesterol-enriched remnants of TG-rich lipoproteins such as Very Low-Density Lipoprotein (VLDL), Intermediate Density Lipoprotein (IDL)] with LDL contributing about 75% of it. These non LDL lipoproteins may account for a significant ASCVD risk, especially when TG levels are elevated levels or LDL-C has been lowered with statins. The residual risk of ASCVD in statin-treated patients is 55%-70% and may be attributed to these non LDL lipoproteins. It is thus important to focus on all atherogenic lipoproteins, and not just LDL alone for effective CV risk reduction [1].

Evidence on Non HDL-C

Non HDL-C is measured as TC minus HDL. Non HDL-C is a much stronger predictor of CV mortality as compared to LDL and more so in diabetics. Not only has non HDL-C demonstrated predictive accuracy in elevated TG (>400 mg/dL) but also in relatively low TG (<200 mg/dL). However, LDL loses its predictive value when TG levels exceed 400 mg/dL [1]. A 2014 study conducted in Chandigarh (India) found that in the 75 angiographically proven Coronary Heart Disease (CHD) patients; serum non HDL-C is closely associated with severity of CHD being lowest in single vessel disease and highest in triple vessel disease [13].

A 2011 meta-analysis of 12 observational studies, including 233 455 subjects showed that over a 10-year period, a non HDL-C strategy would prevent 300,000 more events than a LDL strategy [14]. A 2012 meta-analysis of 25 trials including 131,134 patients suggested that non HDL-C outperforms Apo-B for prediction of CVD [15]. Another 2012 meta-analysis of 62, 154 statin treated patients in eight trials revealed that among statin treated patients uncontrolled non HDL-C is associated with increased risk of future CV events even if LDL-C is under control [16]. According to a 2016 prospective cohort study of 7, 216 patients with clinically manifest arterial disease in the Secondary Manifestations of AR Terial Disease (SMART) study, the LDL-C and non HDL-C relation with CV events was similar in all types of arterial diseases [17].

Do Guidelines Support Non-HDL-C?

The Joint British Societies (JBSs) prefers non HDL-C over LDL-C as the treatment goal [18]. The 2014 National Institute for Health and Care Executive (NICE) guidelines state that- "…Before starting lipid modification therapy for the primary prevention of ASCVD, take at least 1 lipid sample to measure a full lipid profile. This should include measurement of TC, HDL-C, non- HDL-C, and TG concentrations. A fasting sample is not needed" [19]. The American National Lipid Association (NLA) guidelines have given a greater weightage to non-HDL-C over LDL-C [20]. The International Atherosclerosis Society (IAS) has also recommended non HDL-C along with LDL-C as a target [21]. According to American Association of Clinical Endocrinologists (AACE) 2017 guidelines, if insulin resistance is suspected, the non-HDL-C should be evaluated to determine total atherogenic lipoprotein burden [22].

Non HDL-C and Indians

Indians have high prevalence of DM, obesity and metabolic syndrome characterised by high TG levels, low HDL-C and higher small dense LDL particles (atherogenic dyslipidaemia). Hence non HDL-C is an important target for therapy especially in Indians [1].

Triglycerides: Do They Matter?

TG is a core component of VLDL. TG does not directly contribute to atherosclerotic plaques but free fatty acids may activate pro-inflammatory signaling pathways leading to insulin resistance and atherogenicity [1].

A 2013 systematic review of 61 studies showed that the risks of CVDs and all-cause deaths were increased by 13% per 90 mg/dL TG increment [23]. A 2014 study found that those with mutations in the gene encoding Apolipoprotein C3 (APOC3) associated lifelong low levels of non fasting triglycerides have a reduced risk of ischaemic CVD. Participants with non fasting TG levels of less than

90 mg/dL had a significantly lower incidence of CVD than those with levels of 350 mg/dL or more [24].

There are limited data on the potential benefit of adding a second drug in high-risk patients treated with a statin who continue to have high TG levels. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial did not find that fibrate therapy added to statin reduced CV events in DM patients except in one subgroup (TG ≥204 mg/dL and an HDL ≤34 mg/dL) [25]. These findings are particularly relevant for Indians because atherogenic dyslipidaemia is encountered quite frequently.

Has HDL-C Gone Out of Focus?

Large prospective epidemiological studies have found that low HDL-C is independently associated with increased risk for CHD. Based on this most guidelines continue to recommend HDL-C for CHD risk assessment. However, HDL-C may be influenced by several genetic and acquired factors [1].

Recent evidence has questioned the role of HDL as a risk factor. An observational analysis of 323 patients found that higher HDL-C level is associated with better survival in patients with Ejection Fraction reduced Heart Failure (EFrHF) complicating CHD [26]. In the Multi-Ethnic Study of Atherosclerosis (MESA) study participants (without clinical CVD) were followed for around 10 years. The primary low HDL cholesterol group showed higher risks of CVD than group with optimal lipid profiles but no difference in survival was noted [27].

A total of 3590 individuals from the Framingham Heart Study offspring cohort without known CVD were followed between 1987 and 2011 [28]. Compared with isolated low HDL-C, CVD risks were higher when low HDL-C was accompanied by LDL-C ≥100 mg/dL and normal TG, TG ≥100 mg/dL and normal LDL, or TG and LDL-C ≥100 mg/dL. In contrast, compared with isolated low HDL-C, high HDL-C was associated with 20% to 40% lower CVD risk except when TG and LDL-C were elevated. Interestingly TG levels were associated with CVD risk across HDL-C and LDL-C subgroups. At TG <100 mg/dL, CVD risk was low in presence of high HDL-C and LDL-C <100 (or <130) mg/dL. However, the presence of higher TG (>200 mg/dL) within this subgroup was associated with increased CVD risk comparable to the subgroup with higher LDL-C and lower TG. Hence, TG levels reclassify risk of CVD irrespective of HDL-C [28].

Surprisingly, a prospective cohort study of 1,829 patients found that in high-risk patients with DM and LDL-C levels <77 mg/dL, higher HDL-C at baseline is related to a higher risk for CV events and all-cause mortality in contrast to patients with LDL-C levels between 77 and 96 mg/dL [29]. This can be partly explained by impaired HDL function in DM patients irrespective of levels. Also this could reflect a decreased Hepatic Lipase (HL) activity secondary to use of statins. HL enhances the selective uptake of HDL esters by enzymatic modification of HDL.

The Cardiovascular Health in Ambulatory Care Research Team (CANHEART) study included 631,762 individuals without previous CVD followed up for 4.9 years [30]. Lower HDL-C levels were independently associated with higher risk of CV, cancer, and other mortality compared with normal HDL-C levels [30]. Also, higher HDL levels were associated with increased hazard of non CV mortality. HDL-C does not represent a CV specific risk factor or a target for intervention given similarities in its associations with non CV outcomes [30].

HDL cholesterol efflux capacity is the ability of HDL to accept cholesterol from macrophages in reverse cholesterol transport. In 2924 adults without CVD who were participants in the Dallas Heart Study, the cholesterol efflux capacity had minimal association with genetic/acquired factors compared to HDL-C levels and was inversely associated with the incidence of CV events [31]. Similar findings were also noted in the prospective European Prospective Investigation into Cancer (EPIC)-Norfolk study [32]. Another 2016 study found that anti atherogenic HDL functionalities were significantly impaired in Myocardial Infarction (MI) patients [33].

The levels of large HDL show inverse relationships with CV risk but concentrations of small HDL particles have positive correlations with the risk. Studies reveal that diminished HDL particle number can be superior to reduced HDL-C levels for predicting CV risk [34]. According to a 2017 nested case-control study of the JUPITER trial, HDL particle number was a stronger inverse predictor of incident events and biomarker of residual risk compared to cholesterol efflux capacity for both baseline and on-statin analyses [35].

A 2012 Mendelian randomisation analyses showed that genetic mechanisms that raise plasma HDL cholesterol do not seem to lower the risk of MI [36]. A 2014 meta-analysis of 39 clinical trials (117411 patients) looking at benefit of raising plasma HDL levels revealed that niacin, fibrates and Cholesteryl Ester Transfer Protein (CETP) inhibitors failed to reduce all-cause mortality or CV events [37]. There is no evidence to support HDL-C as a target for therapy. A better approach would be to shift the target from increasing HDL-C level to that of increasing functional HDL particles. Further studies would reveal whether therapeutic modulation of HDL function markers translates to clinical benefits.

Targets from Guideline Perspective

ACC/AHA 2013 cholesterol guidelines [4]: The RCTs conducted on statins were fixed dose trials. The patients did not receive therapy titrated to achieve a specific goal and targets were also not compared. Hence, the Expert Panel did not support optimal LDL/non HDL levels. The additional reduction in non HDL-C levels with niacin therapy in one RCT also did not further reduce ASCVD risk in individuals treated to LDL-C levels of 40 to 80 mg/dL. They identified four major primary- and secondary-prevention patient groups who should be treated with statins on the basis of RCTs [Table/Fig-2].

S No.	Benefit groups
1.	Individuals with clinical ASCVD
2.	Individuals with primary elevations of LDL-C ≥190 mg/dL
3.	Individuals 40 to 75 years of age with diabetes and LDL-C 70 to 189 mg/dL without clinical ASCVD
4.	Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age and have LDL-C 70 to 189 mg/dL and an estimated 10-year ASCVD risk of ≥7.5%. This requires a clinician-patient discussion.

[Table/Fig-2]: Four statin benefit groups [4].

ESC-EAS 2016 cholesterol guidelines [5]: The European task force panel considered a wider range of available studies (basic science, clinical observations, genetics, epidemiology, and RCTs) compared to American guidelines. Post publication of the American guidelines, IMPROVE-IT showed a modest benefit with the addition of ezetimibe to statin therapy in post ACS patients reiterating the importance of lower LDL levels. Also, there are no RCTs to support the ACC recommendation for the use of high-dose statins in all high-risk people irrespective of baseline LDL-C level. The benefits related to LDL-C reduction are not specific for statin therapy.

Total CV risk reduction needs to be individualised, and better achieved if goals are defined. Goal approach will aid patient-doctor communication as well as facilitate adherence to treatment. Hence, they retained a goal approach with treatment goals tailored to the total CV risk level. Currently there are no specific goals for HDL-C or TG levels determined in RCTs. They have described the risk categories [Table/Fig-3] and the targets [Table/Fig-4].

Risk category	Disease conditions
Very high-risk	Subjects with any of the following: • Documented Cardiovascular Disease (CVD), clinical or unequivocal on imaging. Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia. • Severe CKD (GFR <30 mL/minute/1.73 m^2). • A calculated SCORE ≥10% for 10-year risk of fatal CVD.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >310 mg/dL (e.g., in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk). • Moderate CKD (GFR 30-59 mL/minute/1.73 m^2). • A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	• SCORE is ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	• SCORE <1% for 10-year risk of fatal CVD.

[Table/Fig-3]: Risk categories (ESC-EAS 2016 Cholesterol Guidelines) [5].
ACS-acute coronary syndrome; AMI- acute MI; BP- blood pressure; CK-chronic kidney disease; DM-Diabetes Mellitus; GFR- Glomerular Filtration Rate; PAD- Peripheral Artery Disease; SCORE-Systematic Coronary Risk Estimation; TIA- Transient Ischaemic Attack

Target	Risk category	Recommendation
LDL-C (primary target)	Very high-risk	LDL-C <70 mg/dL or a reduction of at least 50% if the baseline=70-135 mg/dL.
	High-risk	LDL-C <100 mg/dL or a reduction of at least 50% if the baseline is 100-200 mg/dL.
	Low to moderate risk	LDL-C< 115 mg/dL.
Non-HDL-C (secondary target)	Very high-risk	<100 mg/dL
	High-risk	<130 mg/dL
	Low to moderate risk	<145 mg/dL
HDL-C	-	No target (>40 mg/dL in men and >48 mg/dl in women indicates lower risk.)
TG	-	No target (<150 mg/dL indicates lower risk and higher levels indicate a need to look for other risk factors.)

[Table/Fig-4]: Recommendations for treatment goals for lipid parameters (ESC-EAS 2016 Cholesterol Guidelines) [5].

Lipid Association of India Expert Consensus Statement 2016 [1]: This statement on dyslipidaemia management was a result of opinion of 153 experts from 18 states and 30 cities of India. The approach to ASCVD risk assessment in Indians was outlined [Table/Fig-5]. The treatment goals for therapy in various risk categories were recommended [Table/Fig-6]. None of the available risk algorithms has been validated in Indian populations and therefore accurate ASCVD risk assessment in Indians is currently not possible.

American Association of Clinical Endocrinologists (AACE) 2017 guidelines [22]: In individuals who are at extreme, very high, high/moderate, and low risk for CV events should have of <55 mg/dL, <70 mg/dL, <100 mg/dL, and <130 mg/dL, respectively. They have included a new risk category called 'extreme risk category'. This category includes progressive ASCVD (including unstable angina) in patients after achieving an LDL-C <70 mg/dL, established clinical CV disease in patients with diabetes, chronic kidney disease stages 3/4, or heterozygous familial hypercholesterolemia and history of premature ASCVD (<55 years of age in men, <65 in women).

CONCLUSION

Among the lipid parameters LDL-C and non HDL-C are the most important targets of therapy. Even though we understand the significance of "target" in dyslipidaemia therapy, clinical situations tend to be complex. It is also not possible to determine the threshold value of LDL at which there would be no reduction in CV events using a large-scale RCT.

By abandoning the targets, the doctors as well as patients cannot easily adjust the statin dose based on laboratory values. However, without targets the physicians don't know where they are with a patient. Recent trials have once again highlighted the importance of lower LDL goals with use of non statin therapies. Both the risk based as well as target based approach has to be considered on individual case to case basis.

Risk category			
'Very high risk'	Pre-existing ASCVD, Or Diabetes with ≥ 2 other major ASCVD risk factors or evidence of target organ damage, Or Familial homozygous Hypercholesterolemia	*Major ASCVD risk factors	1. Age ≥ 45 years in males and ≥ 55 years in females 2. Family history of premature ASCVD 3. Current cigarette smoking or tobacco use 4. High blood pressure 5. Low HDL-C
'High risk'	≥ 3 major ASCVD risk factors* Or≥ 1 other high-risk features	Other high-risk features	1. Diabetes with 0-1 other major ASCVD risk factors and no evidence of target organ damage 2. CKD stage 3B or 4 3. Familial hypercholesterolemia (other than familial homozygous hypercholesterolemia) 4. Extreme of single risk factor 5. Coronary calcium score ≥ 300 6. Non-stenotic carotid plaque 7. Lipoprotein (a) ≥ 50 mg/dL
'Moderate risk'	2 major ASCVD risk factors*		
'Low risk'	0-1 major ASCVD risk factor*		

[Table/Fig-5]: ASCVD risk stratification in Indians (Lipid Association of India Expert Consensus Statement 2016) [1].

Risk category	Treatment goal LDL-C (mg/dL)	Non-HDL-C (mg/dL)
Very high risk	<50	<80
High risk	<70	<100
Moderate risk	<100	<130
Low risk	<100	<130

[Table/Fig-6]: Lipid treatment goals in Indians (ASCVD Risk Based) (Lipid Association of India Expert Consensus Statement 2016) [1].

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