

# Low-Density Lipoprotein Cholesterol Levels Among Individuals Receiving Statin Therapy: Real-World Evidence from India

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**Abstract:** Despite the established clinical effectiveness of statin therapy, a substantial proportion of patients fail to attain the target low-density lipoprotein cholesterol (LDL-C) levels and remain at risk for cardiovascular events. This study aimed to evaluate the proportion of patients achieving the guideline recommended LDL-C levels in real-world settings after receiving statins for primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) in India. The study included a cross-sectional retrospective analysis of medical records from 2281 private healthcare facilities between 2017 and 2018. Overall, 15879 patients aged 20-80 years irrespective of their ASCVD status were included. Mean ( $\pm$ SD) age of patients was 55.96 $\pm$ 10.41 years; 62.8% were men, and 44.6% (n=7076) had clinical ASCVD. Overall, 96.2% (n=15271) patients were receiving statins, 99.3% in the secondary prevention and 93.6% in the primary prevention cohort. Most patients were receiving moderate-intensity statins for primary (89.7%, n=7391) and secondary ASCVD prevention (73.4%, n=5159). None of the patients in the secondary prevention cohort achieved the recommended LDL-C level of <70 mg/dL. Approximately 25.3% (n=2089) individuals in the primary prevention and 20.2% (n=1418) in the secondary prevention cohort achieved LDL-C <100 mg/dL. Similar proportion (23.2%, n=3361) of patients with LDL-C control (<100 mg/dL) were found among the high-risk coronary heart disease (CHD) or CHD-equivalent group (including those with diabetes). This large real-world study demonstrated levels of LDL-C that were higher than guideline recommended targets, especially among ASCVD patients, despite receiving statin therapy. The results highlight major gaps in the real-world practice of prescribing statin therapy for both primary and secondary prevention of ASCVD. Concordance to guideline recommended therapy, timely dose titration, use of alternative drugs, and patient adherence can bridge this gap and help achieve optimal control of LDL-C. Further intensification of therapy with addition of non-statins is recommended if LDL-C goals are not achieved among high-risk population.

**Keywords:** Low-density Lipoprotein Cholesterol (LDL-C), Cardiovascular Diseases, Statin Therapy, Real-World Evidence, India

## 1. Introduction

Cardiovascular disease (CVD) is the leading cause of global mortality, accounting for 17.8 million deaths in 2017 [1, 2]. The high-income countries have witnessed a decline in cardiovascular death rates, but in contrast, a gradual but alarming increase was reported in recent decades from lower-income countries, including India [2]. CVD is accountable

for the highest burden related to mortality in India (2017), with an age-standardized death rate of 282.28 per 100000, which is higher than the global average of 233.07 [3]. Indians have a predisposition to central obesity and insulin resistance, which enhances the burden of CVD precursors such as dyslipidemia, hypertension, and dysglycemia. Recent studies from India have reported the prevalence of high cholesterol levels among 25% to 30% of urban and 15% to 20% of rural

populations [4]. The Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study demonstrated that Indians tend to have atherogenic dyslipidemia, encompassing high prevalence of low high-density lipoprotein cholesterol levels (HDL-C, 72.3%), accompanied with elevated levels of triglycerides (29.5%) and low-density lipoprotein cholesterol (LDL-C, 11.8%) levels [5].

Evidence from a meta-analysis demonstrated that lower LDL-C levels were significantly associated with reduced rates of major coronary events, both in primary (1.5% lower event rate per each 1-mmol/L lower LDL-C;  $p=0.008$ ) and secondary prevention trials (4.6% lower event rate per each 1-mmol/L lower LDL-C;  $p<0.001$ ) [6]. Standard treatment guidelines across geographies, including the American College of Cardiology and American Heart Association (ACC/AHA), European Society of Cardiology and European Atherosclerosis Society (EAS/ESC), and National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP), emphasize on reducing LDL-C levels as a key intervention for mitigating risk of cardiovascular events [7-10]. The guidelines follow a risk-based approach for recommending LDL-C goals. To achieve the LDL-C targets, the guidelines suggest a combination of lifestyle modification and lipid-lowering therapies. Statin therapy is the mainstay for LDL-C reduction; with one year of statin use, each 1 mmol/L (38.6 mg/dL) of reduction in LDL-C leads to a 20% to 25% relative reduction of global CVD risk and a 20% decrease in coronary mortality [11, 12].

Despite the established clinical effectiveness of statin therapy, considerable individuals undergoing treatment are unable to attain the target levels of LDL-C in the real-world, thus rendering them at risk of cardiovascular events. The prospective Centralized Pan-European survey on the Under-treatment of hypercholesterolemia (CEPHEUS) Pan-Asian study, reported LDL-C goal attainment in 51.2% of primary and 48.7% of secondary prevention patients [13]. The Dyslipidemia International Study (DYSIS) II reported that 48.3% and 37.5% of patients with coronary heart disease (CHD) and acute coronary syndrome from India had LDL-C  $<70$  mg/dL [14]. However, the study was conducted in a large single-center Multispecialty tertiary care hospital in India including 1049 patients, wherein the treatment pattern might be different from routine primary care practice. Large-scale real-world studies determining the LDL-C levels among individuals treated with lipid-lowering therapies are scarce in the Indian population. This pan-India study was conducted with an aim to evaluate the LDL-C control among individuals receiving statin therapy for the primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) in routine clinical practice.

## 2. Research Design and Methodology

### 2.1. Study Design

This cross-sectional study included 2281 private healthcare centres across India between 2017 and 2018. The inclusion of

healthcare facilities was uniformly distributed across the different regions of the country (Southern India: 40%, Western India: 22%, Eastern India: 18%, Northern India: 14%, Central India: 4% and North-Eastern India: 2%). Healthcare providers, including physicians and cardiologists, retrospectively transcribed protocol-defined data on the Lipid and Risk Markers in Indian Population (LIPIMAP) data collection form based on the available medical records. Individuals of either sex, aged 20 to 80 years, irrespective of their ASCVD status were included. Data of individuals with missing or erroneous values were excluded. The study was approved by the local ethics committee and was granted a waiver for patient consent as it involved only retrospective chart review without direct patient involvement.

### 2.2. Study Outcomes

The primary outcome was to determine the proportion of individuals receiving statin therapy for the primary and secondary prevention of ASCVD achieving guideline recommended levels of LDL-C. The operational definitions for statin therapy, glycemic control, body mass index (BMI), blood pressure, and dyslipidemia are described in Table 1.

### 2.3. Data Collection and Statistical Analysis

Data collection comprised of demographic and clinical details such as diabetes or ASCVD history and tobacco use. In addition, anthropometric variables, alongside treatment history with antihypertensive, and statin therapy were recorded. The latest available laboratory results for glycated hemoglobin (HbA1c), total cholesterol (TC), LDL-C, HDL-C, and triglycerides were recorded. Continuous variables are presented as means with standard deviations (SD) and categorical variables are given as absolute values and percentages. Descriptive analyses and cross-tabulations were performed to estimate the LDL-C levels for the different risk groups. Statistical analyses were performed using SAS version 9.4 and  $p<0.05$  was considered statistically significant.

## 3. Results

### 3.1. Demographic and Clinical Profile

A total of 15879 records were found eligible for inclusion in the study between 2017 and 2018. Table 2 summarizes the demographic and clinical characteristics of the study population. The mean ( $\pm$ SD) age of study participants was  $55.96\pm10.41$  years; majority of individuals (91.4%  $n=14509$ ) were in the age group of 40 to 75 years. The study population had a male predominance (62.8%  $n=9977$ ), and 31.9% ( $n=5071$ ) were tobacco users at the time of data collection. The mean BMI of the study population was  $26.87\pm3.41$  kg/m<sup>2</sup> and more than half (58.7%,  $n=9325$ ) were obese. Overall, 44.6% ( $n=7076$ ) patients had a history of established ASCVD and 91.1% ( $n=14464$ ) of individuals had diabetes mellitus. About 77.1% ( $n=12235$ ) patients were receiving antihypertensive medications. Patients with prior ASCVD had a higher history of tobacco use (62.5%,  $n=3168$ ) and

hypertension (56.8%, n=3377) compared with individuals with prior history of ASCVD. However, obesity (54.1%, n=5036), prehypertension (62.3%, n=5947), and diabetes (54.6%, n=7894) were substantially high among individuals without ASCVD. Fifty-four percent (n=6603) of individuals in the ASCVD group were receiving antihypertensive medications (Table 1). The mean TC level among the study

population was 196.00±25.91 mg/dL, and 55.3% (n=8778) had TC <200 mg/dL. The mean LDL-C level in the overall population was 122.06±29.41 mg/dL, only 23.2% (n=3681) had LDL-C level <100 mg/dL, while 2.5% (n=404) had a LDL-C level of ≥190 mg/dL. The mean triglyceride level was 177.97±57.47 mg/dL, and only one-third (31.3%) of individuals (n=4976) had triglyceride level <150 mg/dL.

**Table 1.** Operational definitions for categorizing the study population.

Guideline	Categories
Statin therapy (2018 American College of Cardiology (ACC) and American Heart Association (AHA) guideline) [7]	<ol style="list-style-type: none"> <li>1. High-intensity statin (atorvastatin 40 and 80 mg, rosuvastatin 20 and 40 mg)</li> <li>2. Moderate-intensity statin (atorvastatin 10-20 mg, rosuvastatin 5 to 10 mg, simvastatin 20-40 mg and pitavastatin 2-4 mg)</li> <li>3. Low-intensity statin (simvastatin 10 mg)</li> </ol>
Glycemic control (American Diabetes Association 2018) [33]	<ol style="list-style-type: none"> <li>1. Controlled (HbA1c &lt;7%)</li> <li>2. Uncontrolled (HbA1c ≥7%)</li> </ol>
Body mass index (BMI) (Consensus Statement for Diagnosis of Obesity, Abdominal Obesity and the Metabolic Syndrome for Asian Indians and Recommendations for Physical Activity, Medical and Surgical Management) [34]	<ol style="list-style-type: none"> <li>1. Normal (18-22.9 kg/m<sup>2</sup>)</li> <li>2. Overweight (23-24.9 kg/m<sup>2</sup>)</li> <li>3. Obese (≥25 kg/m<sup>2</sup>)</li> </ol>
Blood pressure (BP in mmHg) (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) [35]	<ol style="list-style-type: none"> <li>1. Prehypertension (SBP=120-139 or diastolic BP [DBP]=80-89)</li> <li>2. Stage 1 hypertension (SBP=140-159 or DBP=90-99)</li> <li>3. Stage 2 hypertension (SBP ≥160 or DBP ≥100)</li> </ol>
Dyslipidemia Updated National Cholesterol Education Program Adult Treatment Panel [NCEP ATP III] guideline [10]	<ol style="list-style-type: none"> <li>1. Total cholesterol (TC) Desirable (&lt;200 mg/dL), borderline-high (200-239 mg/dL) and high (≥240 mg/dL)</li> <li>2. HDL-C: men (low (&lt;40 mg/dL), high (≥40 mg/dL) and women, low (&lt;50 mg/dL), high (≥ 50 mg/dL)</li> <li>3. Triglycerides: normal (&lt;150 mg/dL), borderline-high (150-199 mg/dL), and high (200-499 mg/dL)</li> <li>4. *LDL-C goals; 0-1 risk factor (&lt;160 mg/dL), 2+ risk factors (&lt;100 mg/dL), and CHD or CHD risk equivalents<sup>†</sup> (&lt;100 mg/dL) and (&lt;70 mg/dL)</li> </ol>

\*The LDL-C goals were classified according to the presence of risk factors (tobacco use, hypertension [BP >140/90 mmHg or on antihypertensive medication]), low HDL cholesterol (<40 mg/dL), and age (men >45 years; women >55 years). Data on chronic kidney disease and family history of premature CHD were not available.

<sup>†</sup>CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia. CHD risk equivalents include clinical manifestations of non-coronary forms of atherosclerotic, diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%.

BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; DBP, blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density Lipoprotein Cholesterol

### 3.2. Statin Therapy

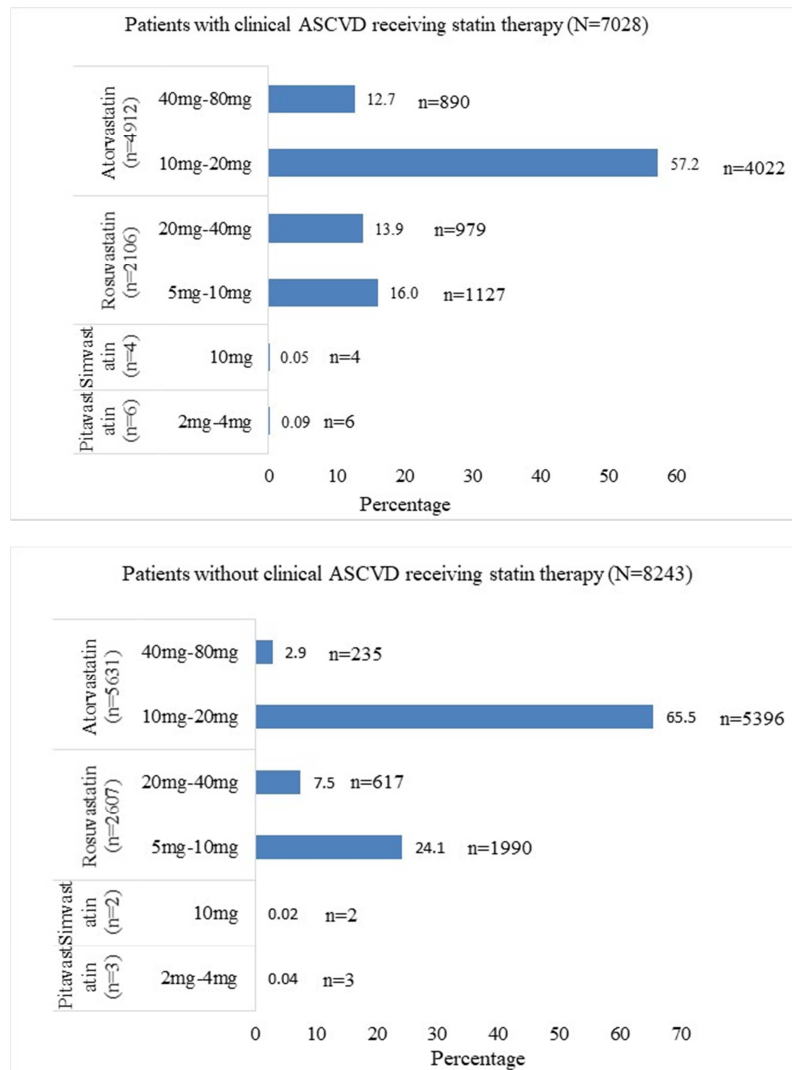
Overall, 96.2% (n=15271) of individuals in the cohort were treated with statin therapy on the day of data collection. Almost all (99.3%) (n=7028) patients with ASCVD and 93.6% (n=8243) without ASCVD were treated with statin therapy. The study population primarily received atorvastatin (69.0%, n=10543) and rosuvastatin (30.9%, n=4713); fewer patients were prescribed pitavastatin (n=9) or simvastatin (n=6). Of the patients in the ASCVD group eligible for high-intensity statins, only 26.6% (n=1869) adequately received high-intensity statin therapy: atorvastatin 40 to 80 mg (12.7%; n=890) and rosuvastatin 20 to 40 mg (13.9%; n=979). Most patients with ASCVD remained under-treated with moderate-intensity statins: atorvastatin 10 to 20 mg (57.2%; n=4022) and rosuvastatin 5 to 10 mg (16%; n=1127). Among non-ASCVD individuals, majority received moderate-intensity statins: atorvastatin 10 to 20 mg (65.5%, n=5396) and

rosuvastatin 5 to 10 mg (24.1%, n=1990) (Figure 1).

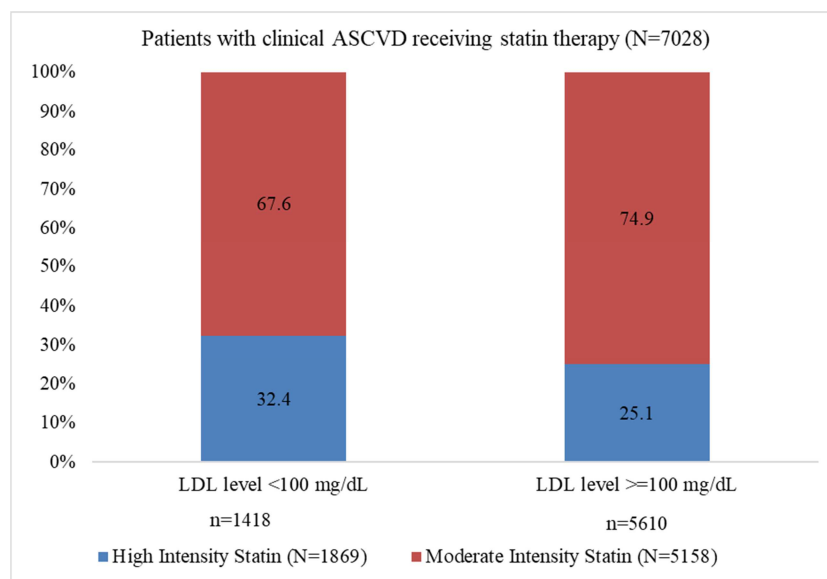
### 3.3. LDL-C level: Primary and Secondary Prevention Cohort

The mean LDL-C levels were 126.47±31.02 and 118.49±27.53 among patients with ASCVD and without ASCVD, respectively. None of the patients in the ASCVD group had LDL-C levels <70 mg per the recommended guidelines. Of the patients with ASCVD receiving statin therapy (n=7028), only 20.2% (n=1418) had LDL-C <100 mg/dL (Figure 2). Most of the ASCVD patients with LDL-C levels ≥100 mg/dL (n=5610) were treated with moderate-intensity statin therapy (74.9%; n=4200), while only 25.1% (n=1409) patients received high-intensity statins. Similarly, among individuals with non-ASCVD, 25.3% (n=2089) achieved LDL-C <100 mg/dL. Of the non-ASCVD individuals with LDL-C ≥100 mg/dL (n=6154), majority

(89.2%; n=6154) received moderate-intensity statin therapy. (n=3969) and 78.4% (n=1641) of males and females, Gender distribution of the study population revealed that 80.4% respectively, had LDL-C  $\geq 100$  mg/dL in the ASCVD group.



**Figure 1.** Distribution of statin therapy among the study population for primary and secondary prevention of ASCVD.



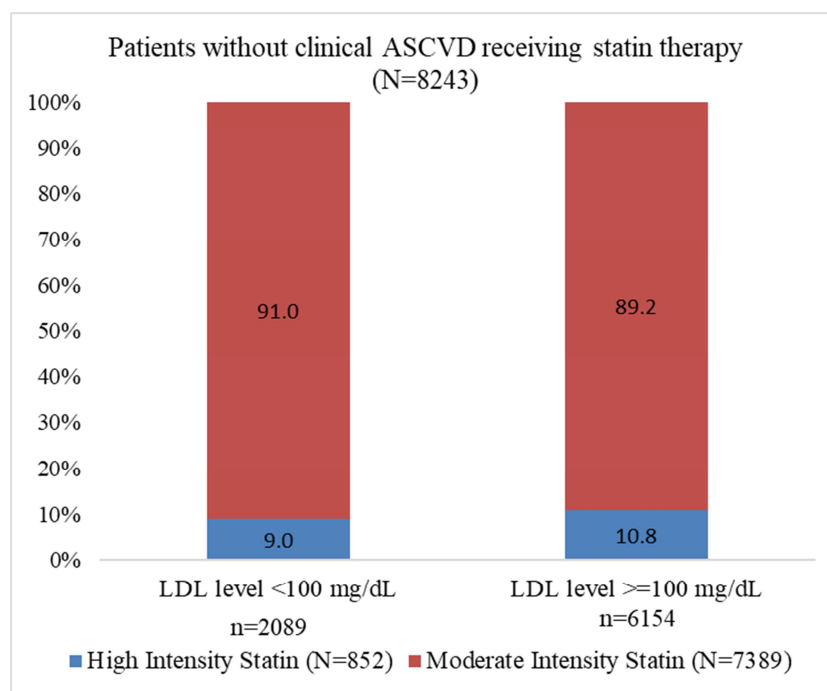


Figure 2. LDL-C level of patients receiving statin therapy for primary and secondary prevention of ASCVD.

\*None of the patients achieved the recommended LDL-C target of <70 mg/dL

†Overall (n=3) patients received low-intensity statins

LDL-C, low-density Lipoprotein Cholesterol; ASCVD, atherosclerotic cardiovascular diseases

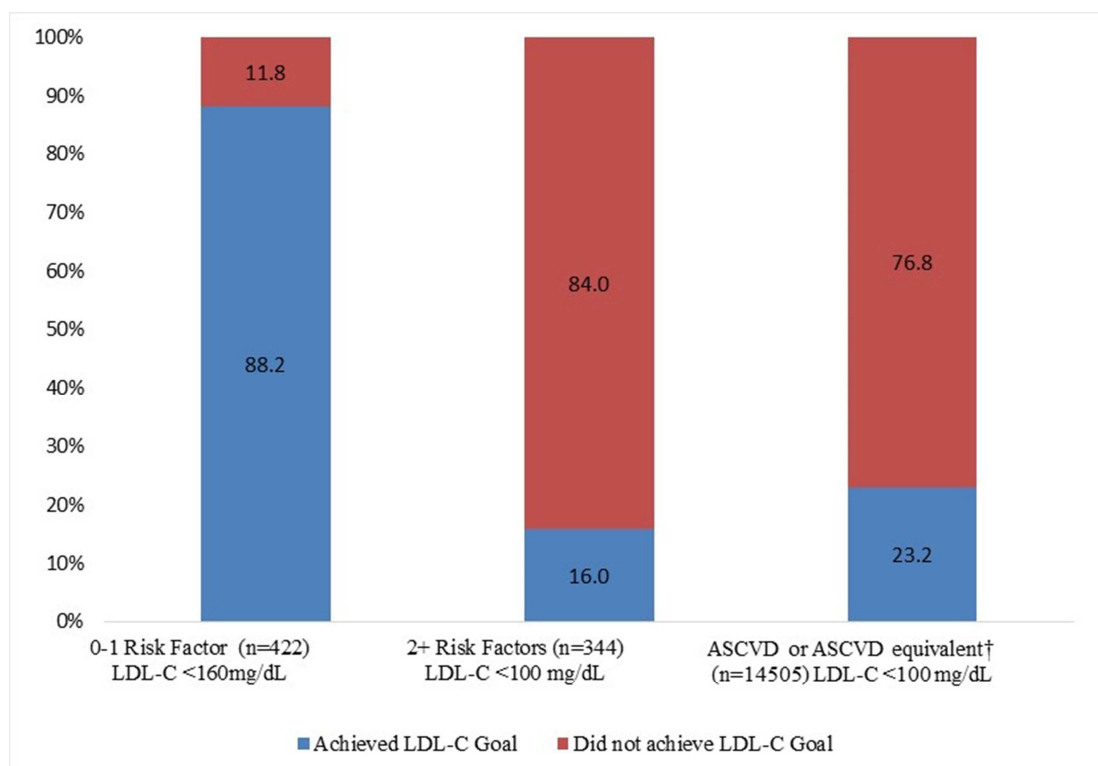


Figure 3. LDL-C level of patients receiving statin therapy segregated by risk groups based on the updated NCEP ATP 3 guideline.

None of the patients achieved the recommended LDL-C target of <70 mg/dL

\*Risk factors: Tobacco use, hypertension (blood pressure >140/90 mmHg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), and age (men >45 years; women >55 years). Data on chronic kidney disease, and family history was not available

†ASCVD-equivalent includes patients with diabetes based on the NCEP ATP guidelines.

LDL-C, low-density Lipoprotein Cholesterol; ASCVD, atherosclerotic cardiovascular diseases

**Table 2.** Demographic and clinical characteristics of the study population.

	Overall		Clinical ASCVD		No clinical ASCVD	
	N	%	n	%	n	%
Total	15,879		7,076		8,803	
Age (Mean±SD 55.96±10.41)						
<40 years	987	6.2	221	3.1	766	8.7
45-75 years	14,509	91.4	6,614	93.5	7,895	89.7
>75 years	383	2.4	241	3.4	142	1.6
Gender						
Male	9,977	62.8	4,963	70.1	5,014	57.0
Female	5,902	37.2	2,113	29.9	3,789	43.0
Tobacco use	5071	31.9	3,168	44.8	1,903	21.6
Body mass index (kg/m <sup>2</sup> ) (Mean±SD) 26.87±3.41						
Normal (18- 22.9 kg/m <sup>2</sup> )	1750	11.0	764	10.8	986	11.2
Overweight (23 - 24.9 kg/m <sup>2</sup> )	2,312	14.6	1028	14.5	1,284	14.6
Obesity (≥25)	9,325	58.7	4,289	60.6	5,036	57.2
Blood pressure						
Normal (SBP=<120 or DBP=<80)†	386	2.4	98	1.4	288	3.3
Prehypertension (SBP=120-139 or DBP=80-89)	9,548	60.1	3,601	50.9	5,947	67.6
Stage 1 Hypertension (SBP=140-159 or DBP=90-99)	5267	33.2	2,967	41.9	2,300	26.1
Stage 2 Hypertension (SBP≥160 or DBP≥100)	678	4.3	410	5.8	268	3.0
*Receiving antihypertensive treatment	12,235	77.1	6,603	93.3	5,632	63.9
Diagnosed as Diabetic	14,464	91.1	6,570	92.9	7,894	89.7
Receiving statin therapy	15,271	96.2	7,028	99.3	8,243	93.6
Total Cholesterol (Mean±SD) 196.00±25.91						
Desirable (<200 mg/dL)	8,778	55.3	3,558	50.3	5,220	59.3
Borderline-high (200-239 mg/dL)	5,902	37.2	2,873	40.6	3,029	34.4
High (≥240 mg/dL)	1,199	7.6	645	9.1	554	6.3
High-density Lipoprotein (HDL) (Mean±SD) 42.44±7.63						
Low (<40 mg/dL) - Male	3,716	23.4	1,901	26.9	1,815	20.6
(≥ 40 mg/dL) - Male	6,261	39.4	3,062	43.3	3,199	36.3
Low (<50 mg/dL) -Female	4,891	30.8	1,780	25.2	3,111	35.3
(≥ 50 mg/dL) - Female	1,011	6.4	333	4.7	678	7.7
Triglyceride (Mean±SD) 177.97±57.47						
Normal (<150 mg/dL)	4,976	31.3	1,928	27.3	3,048	34.6
Borderline-high (150-199 mg/dL)	6,333	39.9	2,834	40.1	3,499	39.8
High (200-500 mg/dL)	4,567	28.8	2314	32.7	2,253	25.6
Very high (≥500)	3	0.0	0	0.0	3	0.0

Results are presented as column percentages. The percentages may not total because of presence of missing values

\*The percentage of individuals receiving antihypertensive has been calculated from the total population

†SBP=Systolic blood pressure, DBP=Diastolic blood pressure

### 3.4. Individuals Achieving LDL-C Goal in the Different Risk Groups (Per Updated NCEP ATP Guidelines)

In our study, the patients with established ASCVD included those with CHD and non-coronary forms of atherosclerotic disease, whereas ASCVD-equivalent group included high-risk individuals with diabetes (based on the NCEP ATP 3 guidelines). Among the patients in the ASCVD or ASCVD-equivalent group (N=14505), 23.2% (n=3361) achieved the LDL-C threshold of <100 mg/dL (Figure 3). Of the patients in ASCVD or ASCVD-equivalent group with LDL-C ≥100 mg (N=11144), 82.3% (n=9167) received moderate-intensity statins. Among the non-ASCVD individuals with two or more risk factors (n=344), 16.0% (n=55) had LDL-C <100 mg/dL, while among those with 0 to 1 risk factor (N=422), 88.2% (n=372) had LDL-C <160

mg/dL.

### 3.5. LDL-C Goal Achievement in Individuals with Type 2 Diabetes Mellitus (T2DM)

Among the individuals with T2DM (N=14464), less than one-fourth (23.5%) achieved the LDL-C goal <100 mg/dL and amongst this population 17.5% and 78.4% were receiving high-intensity and moderate-intensity statins, respectively (Table 3). In very-high risk patients having comorbid ASCVD and T2DM, the majority had LDL-C level ≥100 mg/dL (79.9%) and amongst this population, 74% were receiving moderate-intensity, while 25.5% were receiving high-intensity statins. In patients with T2DM alone, 73.8% had LDL-C level ≥100 mg/dL with majority (85.3%) receiving moderate-intensity statins; however, 4.9% were not receiving any

statin therapy.

### 3.6. LDL-C goal and Duration of Statin Therapy

Among the individuals receiving statin therapy (N=15,271), 26.0% (n=3,972) were treated with statins for the previous 2 to 5 years, and 17.7% (n=2,699) individuals had been receiving statins for more than 5 years. Among

the high-risk patients in the ASCVD/ASCVD-equivalent group, the proportion of patients who achieved LDL-C level <100 mg/dL statistically increased with the duration of statin therapy: past 6 to 12 months (6.1%; n=507), past 1 to 2 years (28.1%; n=885), past 2 to 5 years (30.6%; n=962), and more than 5 years (25.2%; n=794) (p<0.01) (Table 4).

**Table 3.** LDL-C level of patients with type 2 diabetes mellitus in the study population.

LDL-C (mg/dL)	Total patients with T2DM (A+B)		NS (N=452)	Total (N=14464)	Patients with ASCVD and T2DM (A)	
	HIS (N=2498)	MIS (N=11511)			HIS (N=1765)	MIS (N=4769)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<100	595 (17.5)	2659 (78.4)	138 (4.1)	3392 (23.5)	427 (32.3)	884 (67)
≥100	1903 (17.2)	8852 (79.9)	314 (2.8)	11072 (76.5)	1338 (25.5)	3885 (74)

**Table 3.** Continued.

LDL-C (mg/dL)	Patients with ASCVD and T2DM (A)		Patients with T2DM alone (B)		NS (N=417)	Total (N=7894)
	NS (N=35)	Total (N=6570)	HIS (N=733)	MIS (N=6742)		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<100	9 (0.7)	1320 (20.1)	168 (8.1)	1775 (85.7)	129 (6.2)	2072 (26.2)
≥100	26 (0.5)	5250 (79.9)	565 (9.7)	4967 (85.3)	288 (4.9)	5822 (73.8)

T2DM, Type 2 diabetes mellitus; LDL-C, Low-density Lipoprotein Cholesterol; ASCVD, atherosclerotic cardiovascular diseases; HIS, High-Intensity Statins; MIS, Moderate-Intensity Statins; NS, Not on statins

\*None of the patients achieved the recommended LDL-C target of <70 mg/dL

†Overall (n=3) patients received low-intensity statins

**Table 4.** LDL-C level based on the statin duration for the ASCVD or ASCVD-equivalent risk group.

	6-12 months		Past 1-2 years		Past 2-5 years		More than 5 years		p value
	N	%	N	%	N	%	N	%	
	<b>2,636</b>		<b>4,504</b>		<b>3,832</b>		<b>2,670</b>		
LDL <100 mg/dL	507	16.1	885	28.1	962	30.6	794	25.2	
LDL ≥100 mg/dL	2,129	20.29	3,619	34.5	2,870	27.4	1,876	17.9	<0.0001

\*ASCVD-equivalent includes patients with diabetes according to the NCEP ATP guideline

LDL-C, low-density Lipoprotein Cholesterol; ASCVD, atherosclerotic cardiovascular diseases

## 4. Discussion

This pan-India study evaluated the LDL-C control among a large, real-world cohort of individuals from routine clinical practice. Most individuals (79%) received moderate-intensity statins for primary and secondary prevention of ASCVD. None of the patients in the ASCVD group had LDL-C levels <70 mg per the recommended guidelines. Only one-fifth of ASCVD patients and one-fourth of non-ASCVD individuals achieved the LDL-C level <100 mg/dL. Similarly, only 1 in 5 patients with comorbid ASCVD and diabetes achieved LDL-C thresholds of <100 mg/dL.

The findings from our study are consistent with earlier studies on statin utilization among patients with high CVD risk. A real-world study from Germany reported a comparatively lower proportion of LDL-C goal achievement (albeit a higher percentage than our study), 30% patients in ASCVD group and 23.6% in the non-ASCVD group achieved LDL-C goals <100 mg/dL. [15]. The Demographic Assessment and Evaluation of DEgree of Lipid Control in High-Risk Indian Dyslipidemia Patients (DIVERSE) study, across 483 sites in India, reported that only 7.7% patients achieved LDL-C levels <70 mg/dL and 18.5% achieved

LDL-C levels between 70 to 100 mg/dL [16]. The Dyslipidemia International Study (DYSIS) II, a multinational study (including India), showed that among patients with CHD, 74.1% and 32.6% achieved LDL-C levels <100 mg/dL and <70mg/dL, respectively [14]. However, majority (91.7%) of the patients in the DYSIS study were using lipid-lowering therapy, including non-statin medications. The SURF study (SURvey of Risk Factors) conducted in 11 countries reported a higher usage of statins in Europe (86.8%) as compared with Asia (51%, p<0.001). It further highlighted that Asian patients were less likely to attain stringent LDL cholesterol target (14.6%) compared with European counterparts (32.9%) [17]. The SURF study revealed an inadequate control of cardiovascular risk factors (particularly smoking, obesity), insufficient achievement of therapeutic targets, and underuse of drugs among the study population. In our study, none of the patients achieved the recommended LDL-C <70 mg/dL. The poor control of LDL-C in our population is a matter of concern, highlighting gaps in prescribing adequate statin therapy, especially for the high-risk category. The SURF study elucidated that the poor control of lipids in Asia might be attributed to professional attitudes, patient preferences, ineffective implementation of guidelines, poor access to cardiac rehabilitation, and/or lack of professional guidelines

[17].

Only around a quarter of the patients in our study received adequate high-intensity statin therapy, reflecting lacuna in dose titration and clinical inertia of physicians while prescribing statin therapy. A retrospective cohort analysis found a graded association between intensity of statin therapy and mortality; patients treated with maximal doses of high-intensity statins had lower mortality compared with those receiving submaximal doses [18]. Barriers to guideline implementation for physicians might include complexity of guidelines, lack of training in CVD prevention, and time constraints [19]. Additionally, patient preferences, perceived side effects, and cost-effectiveness of maintaining optimal lipid levels might also influence the physician's decision for prescribing suboptimal statin therapy [20, 21]. Evidence from a study in Singapore revealed that reduction in LDL-C by statins was not influenced by Asian ethnicity or BMI, and recommended upward titration of statin dosages when target lipid levels are not achieved [22].

The DYSIS study highlighted that use of non-statins was lowest for Indian patients; majority (95.8%) were treated with statin monotherapy [14]. The 2018 ACC/AHA guidelines recommended addition of ezetimibe to maximally tolerated statin therapy when LDL-C level remains  $\geq 70$  mg/dL in very-high-risk patients (history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions). The guidelines also suggested adding ezetimibe and consequently a PCSK9 inhibitor in patients with severe hypercholesterolemia if LDL-C levels remain  $\geq 100$  mg/dL, after considering the long-term safety and cost-effectiveness [7]. A physician survey across India illustrated that only 52.4% doctors prescribed ezetimibe, despite its well-established effectiveness for reducing major cardiovascular events in combination with statins [23, 24]. The International Cholesterol management Practice Study (ICLPS), a retrospective study including India, reported that 32.1% of very high-risk and 51.9% of high-risk patients achieved LDL-C goals through combination therapies such as statin, statin plus fibrate, and statin plus cholesterol absorption inhibitor [25]. A retrospective study from Japan reported high goal attainment rates of LDL-C  $< 100$  mg/dL among 52.6% patients in primary and 69.9% in secondary prevention cohort. The study emphasized that high compliance rate of patients to appropriate therapy could have contributed to the relatively higher LDL-C control levels [26].

Our study results found that a substantial proportion of individuals without ASCVD had a high prevalence of CVD risk factors such as obesity and prehypertension. In our attempt to minimize the cumulative lifetime exposure to atherogenic lipoproteins, experts recommend primordial and primary prevention strategies designed to lower lipid levels closer to optimal levels be initiated at an early age wherein such strategies would have the most impact. For instance, Ference, et al, argue that although the short-term risk of a CVD event is low during young adulthood and middle age, the risk of experiencing a CVD event increases log-linearly when the overall cumulative LDL threshold exceeds 5000

mg-years; thereby a decrease in LDL-C by 1 mmol/L at age 25 years should reduce the lifetime risk of CVD events by 50%, resulting in a 23% absolute risk reduction. [19]. It is imperative to adopt a focused and individualized approach to monitor and manage the 7 metrics of cardiovascular health, including cigarette smoking, obesity, hypertension, high cholesterol, physical inactivity, poor diet, and diabetes. Ference et al recommended that alongside lifestyle modifications, the addition of lipid-lowering therapy should begin early in adulthood for individuals with a high-inherited burden of LDL (patients with familial hypercholesterolemia) or patients with higher than optimal lipid levels [19].

Diabetes doubles the risk for CVD, independent of other conventional risk factors. Diabetes develops at a lower lean body mass and at earlier age among the Indian population. In our study, among individuals with comorbid ASCVD and diabetes, only one-fifth attained the LDL-C thresholds of  $< 100$  mg/dL. An observational study from Germany showed that the proportion of individuals with diabetes who achieved target LDL-C  $< 100$  mg/dL were lower than for the ASCVD cohort (18.5% and 22.4%) [15]. A real-world study involving 178 sites from India reported that among patients with diabetes and overt CVD, only 22.87% achieved LDL-C  $< 70$  mg/dL [27]. In a physician survey, Wander et al highlighted that 50% doctors in India chose not to use a statin in persons with diabetes, irrespective of their LDL-C levels [23]. For individuals with diabetes having CVD, most guidelines recommend intensive statin therapy alongside lifestyle modifications, or a 10-year risk of a cardiovascular event [28]. Addition of non-statins such as ezetimibe can be beneficial for the high-risk statin-treated patients with diabetes. The ACCORD-lipid trial suggested that addition of fenofibrate therapy may reduce CVD events in diabetic patients with hypertriglyceridemia and low HDL-C [28-30]. Evidence from multiple studies have evaluated the potential effect of PCSK9 inhibitors, bile acid sequestrants, niacin, omega-3-fatty acids as add-on therapies to statins for patients with diabetes [29, 30]. However, the incremental benefit of these drugs in patients with diabetes and comorbid ASCVD needs to be explored further.

Majority of our very-high risk patients with comorbid ASCVD and T2DM had LDL-C level  $\geq 100$  mg/dL, despite receiving moderate- or high-intensity statin therapy. These results are in alignment with a retrospective study from Italy, which showed relatively poor control rates of LDL-C in high or very high European SCORE risk individuals. Multivariate analysis in this study revealed that high-risk SCORE estimation was a strong and independent predictor for lack of achieving the predefined therapeutic targets of LDL-C [31]. Therapeutic inertia, gaps in disease monitoring, patient resistance to lifestyle measures and poor drug adherence in high-risk patients might be attributable for the elevated LDL-C levels. Data from TECOS, a clinical trial among patients with T2DM and established ASCVD, also demonstrated that although most high-risk patients with T2DM and cardiovascular disease were on lipid-lowering therapy, only one-third had LDL-C  $< 70$  mg/dL [32].



Our study is one of the largest real-world studies evaluating the LDL goal attainment in patients receiving statin therapy in India. However, the retrospective nature of the study was a limitation to ascertain the causal association between statin therapy and LDL-C levels. Data on ASCVD risk score, familial hypercholesterolemia, adverse effects of statin therapy, and other lipid-lowering strategies such as ezetimibe, fibrates or non-statins were not available. Segregated data on patients with CHD and non-coronary forms of atherosclerotic disease were not available. The study did not evaluate if statin intolerance, patient adherence, or cost-effectiveness affected the therapeutic decisions of doctors for prescribing statin therapy. Additionally, the study included patients only from the private sector, wherein the cost of the medication is primarily out-of-pocket expenditure by the patients. A significant proportion of the Indian population avails healthcare from public or government facilities, where the common lipid reducing medication such as statins are dispensed free of cost. Hence, the results may not be generalizable to the entire population in the country. The recent guidelines by the EAS/ESC recommend much lower LDL-C targets considering factors such as comorbid chronic kidney diseases (CKDs). However, the updated NCEP ATP guideline was used to determine the LDL-C goals in our study because of unavailability of data on CKD and the ambiguous validity of other guidelines for the Indian population.

## 5. Conclusion

This study presented real-world insights from a large subset of Indian population and demonstrated that levels of LDL-C that were higher than guideline recommended targets, especially among ASCVD patients, despite receiving statin therapy. The LDL control is a cause of concern, as majority of the patients remain at high-risk for poor CVD outcomes. There are pitfalls in the real-world management of prescribing statin therapy for primary and secondary prevention of ASCVD. It is imperative to formulate specific approaches that enhance concordance to guideline recommended statin therapy, including timely dose titration and use of alternative therapy for optimal management of dyslipidemia and CVD in the Indian subcontinent. The addition of non-statins can further provide a window of opportunity for the optimal control of LDL-C levels among the high-risk population in India.

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