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Concordance to Guideline-recommended Statin Therapy: Real-world Evidence from India

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Abstract: To evaluate concordance to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline on treatment of blood cholesterol for primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) in India. Concordance to 2013 ACC/AHA guideline was assessed by retrospectively analyzing statin therapy prescribing practice as per ASCVD risk score in four statin-benefit groups in 23,295 patients aged 40-79 years from health facilities across India between 2017 and 2018. Mean (±SD) age of patients was 58.9 (±9.2) years; 62% were men; 60% (n=14,070) had clinical ASCVD. Among patients without ASCVD (n=7,122), 3.9% (n=278) had low-density lipoprotein-cholesterol (LDL-C) ≥190 mg/dL, 94.0% (n=6,694) had diabetes mellitus and 2.1% (n=150) patients had 10-year ASCVD risk ≥7.5%. Among 18,795 patients (81%) eligible for high-intensity statins, only 34% were concordant whereas 63% were treated with moderate-intensity statins. Among 2,290 patients eligible for moderate-intensity statins, 76% were concordant and 18% received high-intensity statins. Among patients with ASCVD (<75 years), 43% received high-intensity statins, 55% received moderate-intensity statins, while 2% did not receive statins. Among patients with diabetes and ASCVD risk <7.5%, 86% received moderate-intensity statins, but those with risk >7.5%, 83% remained under-treated. Most patients (82%) with LDL-C >190 mg/dL were prescribed with moderate-intensity statins. Most patients were receiving statins at dose non-concordant to 2013 ACC/AHA guideline, reflecting gaps in real-world practice of prescribing statins for primary and secondary prevention of ASCVD. Addressing care gaps and promoting compliance to optimize statin therapy will help reduce cardiovascular disease, especially in high-risk population among South Asians.

Keywords: Cardiovascular Disease, Statin Therapy, Real-world Evidence, Low-density Lipoprotein-Cholesterol, Cholesterol Guidelines

1. Introduction

Atherosclerotic cardiovascular diseases (ASCVDs) are the leading cause of mortality worldwide accounting for 18 million deaths every year [1]. Middle and low-income countries contribute to 75% of the global ASCVD burden [1]. ASCVD mortality has declined in high-income countries, while low-income countries, including India, continue to bear a high burden of cardiovascular events (6.43 events/1000 person-years) and case fatality rate (17.3%) [2]. The age-standardized ASCVD death rate in India is higher than the global average [3]. ASCVDs contributed to about 28.1% of total deaths and 14.1% of disability-adjusted life years in India in 2016, which is nearly double of that observed two decades ago [4]. ASCVD trajectory is a critical challenge in India as the death rate is higher among people <70 years (53.4%) [4].

Genetic susceptibility concomitant with factors such as aging population, thin-fat phenotype, higher prevalence of diabetes at a lower body mass index (BMI), dietary risks, and tobacco use act as catalysts for higher ASCVD risk among Indians [5]. Hypercholesterolemia (total cholesterol [TC] ≥200 mg/dL) occurs in 25%-30% of urban and 15%-20% of rural Indian population [6]. The most common pattern of dyslipidemia consists of border-line high low-density

lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), and hypertriglyceridemia [6]. The Prospective Urban Rural Epidemiological (PURE) study highlighted the paradox of a high cardiovascular burden in India, despite having a lesser risk factor burden [2]. The PURE study concluded that ASCVD burden in high-income countries may have been mitigated by the control of risk factors through pharmacologic therapies and improved lifestyles. Primordial prevention by reducing the onset of risk factors such as smoking or obesity in healthy individuals and primary prevention by preventing the development of CVD in at-risk persons with diabetes, dyslipidemia, and hypertension are crucial alongside secondary prevention [7]. Early assessment of cardiovascular risk followed by a healthier lifestyle and appropriate pharmacological interventions is imperative for ASCVD management among Indians.

Different tools have been devised for ASCVD risk assessment such as the Framingham Risk Score, QRISK, and Joint British Society risk score; however, there is no specific tool designed for the South Asian population. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines are the most widely used standards globally that predict the 10-year and lifetime ASCVD risks for an individual [8]. The 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce ASCVD risk in adults identified four statin benefit groups for the primary and secondary prevention of ASCVD, namely patients with (1) clinical ASCVD, (2) LDL-C ≥190 mg/dL, (3) diabetes and LDL-C 70-189 mg/dL, and (4) estimated 10-year ASCVD risk ≥7.5%. The guideline highlighted that addressing insufficient response to lipid reduction by optimizing statin therapy intensity or change in therapy is crucial for ASCVD risk reduction. The 2018 ACC/AHA guideline on management of blood cholesterol is an update to the 2013 guideline and emphasizes on a more intensive approach for reducing risk of ASCVD.

Management of ASCVD presents unique challenges in India such as inconsistencies among physicians regarding ASCVD risk estimation and suboptimal prescription of statins. A multisite prescription study in India demonstrated that statins are prescribed in only half of clinic-based patients [9]. Real-world data on ASCVD risk and the prescription pattern of statin therapy among Indian population are scarce. This study was conducted to determine and evaluate the concordance to statin therapy per the ASCVD risk score and recommendations of the 2013 ACC/AHA guideline for cholesterol management for the primary and secondary prevention of ASCVD in India.

2. Research Design and Methodology

2.1. Study Design and Settings

This cross-sectional study was conducted at 2,980 private healthcare facilities across India between 2017 and 2018. Protocol-defined data were retrospectively transcribed on the MORE (measurement of ASCVD risk parameters in Indian patients eligible for statin treatment) data collection form by healthcare providers (physicians, diabetologists, and cardiologists) based on the available medical records. Patients of either sex, aged 40-79 years, irrespective of their ASCVD status were included. Data of patients <40 years of age and those with missing or erroneous values were excluded. The study included retrospective data collection from anonymous patient records; hence, it was exempted from ethical clearance.

2.2. Study Outcomes

The primary outcome was to evaluate the proportion of patients' receiving statin therapy in concordance with the 2013 ACC/AHA guideline.

2.3. Operational Definitions

Clinical ASCVD was defined as acute coronary syndromes, a history of myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease [8]. The10-year risk of developing ASCVD was calculated using the ACC/AHA risk estimator: low (0%-5%), moderate (5%-7.5%), and high (≥7.5%). Statin therapy was classified as high-intensity (atorvastatin 40-80 mg and rosuvastatin 20-40 mg), moderate-intensity (atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, and pitavastatin 2–4 mg), and low-intensity (simvastatin 10 mg). The 2013 ACC/AHA guidelines were followed to ascertain the eligibility of patients for each statin therapy group: high-intensity statins (clinical ASCVD patients <75 years, adults >21 years with LDL ≥190 mg/dL and patients with diabetes having ASCVD risk ≥7.5%) and moderate-intensity statins (older ASCVD patients >75 years, patients with diabetes having ASCVD risk ≥7.5%, and patients with ASCVD risk >5% to <7.5%). The guidelines recommend submaximal statin therapy to reduce ASCVD risk in patients unable to tolerate moderate- or high-intensity statin therapy. Glycemic control was defined as controlled (glycated hemoglobin [HbA1c] <7%) or uncontrolled (HbA1c ≥7%) [10]. BMI was categorized as normal (18-22.9 kg/m^2), overweight (23-24.9 kg/m^2), and obese (≥25 kg/m^2) [11]. Blood pressure (BP in mmHg) was categorized as prehypertension (systolic BP [SBP]=120-139 or diastolic BP [DBP]=80-89), stage 1 hypertension (SBP=140-159 or DBP=90-99), stage 2 hypertension (SBP ≥160 or DBP ≥100) [12]. Dyslipidemia was classified according to National Cholesterol Education Program Adult Treatment Panel III guidelines as (a) TC: desirable (<200 mg/dL), borderline high (200239 mg/dL) and high (≥240 mg/dL); (b) HDL: men, low (<40 mg/dL), high (≥40 mg/dL) and women, low (<50 mg/dL), high (≥ 50 mg/dL); (c) LDL: optimal (<100 mg/dL), near optimal/above optimal (100-129 mg/dL), borderline high (130-159 mg/dL), high (160189 mg/dL), very high (>190 mg/dL); and (d) triglycerides: normal (<150 mg/dL), borderline-high (150-199 mg/dL), and high (200-499 mg/dL)

[13].

2.4. Data Collection and Statistical Analysis

Data collection included patient demographics, clinical history (including diabetes), ASCVD history, tobacco history, anthropometric measures, vital signs, physical examination, antihypertensive treatment, and statin pharmacotherapy. The latest available laboratory results for HbA1c, TC, LDL-C, HDL-C, and triglycerides were recorded. Summary statistics for quantitative variables included the frequency distribution, mean, and standard deviation (SD). Results are expressed as absolute values and percentages. Patients receiving statins at the recommended intensity were classified as concordant. This was primarily a descriptive study designed to determine the proportion of patients' receiving statin therapy in concordance with the 2013 ACC/AHA guideline. Descriptive analyses including cross-tabulations were performed for estimating the proportion of patients who were prescribed statin therapy in concordance with the guidelines. Statistical analyses were performed using SAS version 9.4.

3. Results

3.1. Demographic and Clinical Profile

A total of 23,295 records between 2017 and 2018 were found eligible for inclusion in the study. Table 1 summarizes the demographic and clinical characteristics of the study population.

Table 1. *Demographic and clinical profile in the overall population (N=23,295).*

	n	%
Age (Mean±SD)	58.89±9.21	
40 - 75 years	22540	96.8
> 75 years	755	3.2
Gender		
Male	14546	62.4
Female	8749	37.6
Current tobacco user	8256	35.4
Body mass index* (Mean±SD)	26.57±3.45 kg/m^2	
Normal (18- 22.9 kg/m^2)	2083	8.9
Overweight (23 - 24.9 kg/m^2)	3030	13.0
Obesity (≥25 kg/m^2)	11155	47.9
Total Cholesterol (TC)† (Mean±SD)	197.11±25.73	
Desirable (<200 mg/dL)	12489	53.6
Borderline high (200-239 mg/dL)	8897	38.2
High (≥240 mg/dL)	1909	8.2
High density Lipoprotein (HDL)‡ (Mean±SD)	39.49±8.34	
Low (<40 mg/dl) - Male	7120	30.6
(≥ 40 mg/dl) - Male	7426	31.8
Low (<50 mg/dl) -Female	7725	33.2
(≥ 50 mg/dl) - Female	1024	4.4
Low density Lipoprotein (LDL) § (Mean±SD)	126.07±32.47	
Optimal (<100 mg/dl)	5171	22.2
Near optimal/above optimal (100-129 mg/dL)	8091	34.7
Borderline high (130-159 mg/dL)	5219	22.4
High (160-189 mg/dL)	3622	15.5
Very high (≥190 mg/ dL)	1005	4.3
Triglyceride (Mean±SD) ‖	186.23±60.20	
Normal (<150 mg/dL)	6270	26.9
Borderline-high (150-199mg/dL)	8791	37.7
High (200-499 mg/dL)	8104	34.8
Diagnosed as Diabetic¶	17452	74.9
Diagnosed as Hypertensive**	18301	78.6
Anti-hypertensive treatment	17384	94.9

*BMI: Normal (18-22.9 kg/m^2), overweight (23 24.9 kg/m^2), and obese (≥25 kg/m^2).

†TC: Desirable (<200 mg/dL), borderline high (200-239 mg/dL) and high (≥240 mg/dL).

‡HDL: Men, low (<40 mg/dL), high (≥40 mg/dL) and women, low (<50 mg/dL), high (≥ 50 mg/dL)

§LDL: Optimal (<100 mg/dL), near optimal/above optimal (100-129 mg/dL), borderline high (130-159 mg/dL), high (160-189 mg/dL), very high (≥190 mg/dL).

‖Triglycerides: Normal (<150 mg/dL), borderline-high (150-199 mg/dL), and high (200-499 mg/dL).

¶Glycemic control: Glycated hemoglobin [HbA1c] <7%, uncontrolled (HbA1c ≥7%).

**Blood pressure (mmHg): Prehypertension (systolic BP [SBP]=120-139 or diastolic BP [DBP]=80-89), stage 1 hypertension (SBP=140-159 or DBP=90-99), stage 2 hypertension (SBP ≥160 or DBP ≥100).

The mean (±SD) age of patients was 58.89±9.21 years; most patients (n=22,540, 96.8%) were in the age group of 40-75 years with male predominance (n=14,546, 62.4%). At the time of data collection, approximately one-third of the study population (n=8,256, 35.4%) were tobacco users. The mean BMI of patients was 26.57±3.45 kg/m^2 and almost half (47.9%, n=11,155) of them were obese. About 78.6% (n=18,301) of patients were diagnosed as hypertensive, of which 94.9% (n=17,384) were receiving antihypertensive medications. Overall, 74.9% (n=17,452) of patients were diagnosed with diabetes mellitus. The mean TC level among the study population was 197.11±25.73 mg/dL while 46.4% (n=10,806) had TC ≥200 mg/dL. Mean triglyceride level was 186.23±60.20 mg/dL, and nearly three-fourths of patients (72.5%, n=16,895) had triglycerides ≥150 mg/dL. Mean HDL-C level was 39.49±8.34 mg/dL. Among the men, almost half (n=7,120; 48.9%) had low HDL-C (<40 mg/dL), while among women, 88.3% (n=7,725) had low HDL-C (<50 mg/dL). The mean LDL-C level was 126.07±32.47 mg/dL, only 22.2% had optimal LDL-C level <100 mg/dL while 4.3% (n=1,005) had LDL-C ≥190 mg/dL. The prevalence of risk factors was highest among patients with ASCVD (tobacco use: 42%, obesity: 46.7%, diabetes: 73.6%, hypertension: 84.9%) while 96.0% were receiving antihypertensive medications (Table 2).

Table 2. *Demographic and clinical characteristics of the study population according to the four statin benefit groups*

	Clinical ASCVD (N=14,070)	No clinical ASCVD (N=7122)		
		LDL≥190 mg/dL* (N=278)	Diabetes† (N=6,694)	ASCVD Risk ≥7.5 (N=150) ‡
Age n (%)				
40-75 years	13,504 (96.0)	271 (97.5)	6,694 (100)	150 (100)
> 75 years	566 (4.0)	7 (2.5)	-	-
Gender n (%)				
Male	9,291 (66.0)	159 (57.2)	3,809 (56.9)	126 (84.0)
Female	4,779 (34.0)	119 (42.8)	2,885 (43.1)	24 (16.0)
Tobacco user n (%)	5,908 (42.0)	77 (27.7)	1,768 (26.4)	59 (39.3)
Body mass index (BMI) kg/m^2 (mean±SD)	26.77±3.46	26.34±3.89	26.23±3.40	26.04±2.48
Total Cholesterol (TC) mg/dL (mean±SD)	197.80±26.06	214.20±25.51	194.63±24.51	202.57±25.08
High density Lipoprotein (HDL) mg/dL (mean±SD)	38.88±8.60	36.18±6.88	40.20±7.75	42.17±7.70
Low density Lipoprotein (LDL) mg/dL (mean±SD)	129.55±32.96	193.53±3.39	117.59±27.66	120.18±23.92
Triglycerides mg/dL (mean±SD)	189.79±60.28	208.10±61.66	179.66±58.82	202.67±70.70
Diagnosed as Diabetic n (%)	10,353 (73.6)	188 (67.6)	6,694 (100)	-
Diagnosed as Hypertensive n (%)	11,942 (84.9)	183 (65.8)	4,860 (72.6)	79 (52.7)
Receiving antihypertensive treatment n (%)	11,417 (95.6)	174 (95.0)	4,512 (92.8)	69 (87.3)

*Includes patients aged 21 years and older with LDL ≥190 mg/dL.
†Includes diabetic patients with age 40-75 years and LDL-C 70-189 mg/dL.
‡Includes patients 40-75 years without diabetes and ASCVD risk ≥7.5.

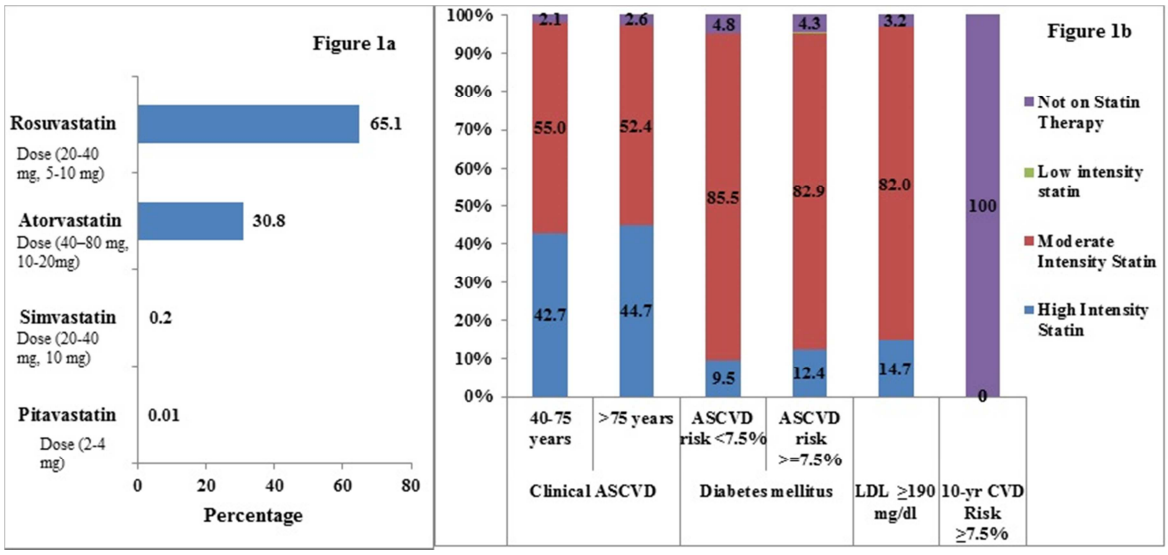

Figure 1. *Distribution of statin therapy in the study population.*

a Distribution of statin therapy in the study population.
b Distribution of statin therapy in the 4 statin benefit groups.
Patients with clinical ASCVD n=14,070 (age 40-75 years, n=13,504; age >75 years, n=566), patients with diabetes and ASCVD risk <7.5% n=1681, patients with diabetes and ASCVD risk ≥7.5% n=5013, LDL >190 mg/dL n=278, 10-year ASCVD risk ≥7.5% n=150.

3.2. ASCVD Risk Scores

Of the study population (N=23,295), 17.4% (n=4,051) had a history of acute MI, 8.6% (n=1,994) had stroke, while 17.2% (n=4,007) and 10.4% (n=2,414) reported unstable and stable angina, respectively. Additionally, 7.3% (n=1,694) had undergone arterial revascularization while 4.4% (n=1,025) had a history of peripheral arterial disease (data not shown). Overall, 78.8% (n=18,347) of patients had an ASCVD risk of ≥7.5%, while 8.3% (n=1,928) had a moderate risk of 5%-7.5%. Among diabetes patients without ASCVD (n=6,694), 74.9% (n=5,013) had a risk score of ≥7.5% while 9.9% (n=664) had risk between 5% and 7.5%.

3.3. Statin Therapy

The statin therapy in our study population was primarily comprised of rosuvastatin (65.1%, n=15,168) and atorvastatin (30.8%, n=7,173); some patients were also prescribed pitavastatin (n=3) and simvastatin (n=35) as monotherapy or combination therapy. The proportion of individuals receiving moderate-intensity statins included atorvastatin 10-20 mg (24.8%, n=5,784), rosuvastatin 5-10 mg (40.4%, n=9,417), simvastatin 20–40 mg (n=4), and pitavastatin 2-4 mg (n=3), while those receiving high-intensity statins included atorvastatin 40-80 mg (6.0%, n=1,387) and rosuvastatin 20-40 mg (24.6%, n=5,736) (Figure 1a).

3.4. Concordance to Statin Intensity Per 2013 ACC/AHA Guidelines

Of the patients eligible for treatment with high-intensity statins (80.7%, n=18,795), only 34.2% (n=6,436) received high-intensity statin therapy (Table 3). Most patients (62.9%, n=11,820) remained under-treated with moderate-intensity statins and a small proportion (2.7%, n=511) did not receive any statins.

Table 3. *Statin eligibility in study population according to the 2013 ACC/AHA guideline*

Recommend Statin Therapy Intensity per ASCVD Risk	High-intensity Statins	Moderate-intensity Statins	Moderate- or High-intensity Statins	Statins Initiated After Physician Patient Dialogue §	Total
	18,795	**2290**	**150**	**2060**	**23,295**
Actual statin intensity					
Received high-intensity* n (%)	6436 (34.2)	413 (18.1)	0	273 (13.3)	7122 (30.6)
Received moderate-intensity † n (%)	11,820 (62.9)	1735 (75.8)	0	1632 (79.2)	15,187 (65.2)
Received low-intensity ‡ n (%)	28 (0.2)	3 (0.1)	0	0	31 (0.1)
Not on Statin Therapy n (%)	511 (2.7)	139 (6.1)	150 (100.0)	155 (7.5)	955 (4.1)

*High-intensity statins (atorvastatin 40-80 mg and rosuvastatin 20-40 mg)

†Moderate-intensity statins (atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, and pitavastatin 2–4 mg)

‡Low-intensity statins (simvastatin 10 mg).

§The 2060 patients who received statins after physician-patient dialogue included the following: Diabetic patients >75 years, diabetic patients with LDL <70 mg/dL, nondiabetic patients >75 years, nondiabetic patients with LDL <70 mg/dL, nondiabetic patients aged 40-75 years with 10-year ASCVD risk <5% who were not on statins, nondiabetic patients aged 40-75 years with LDL 70-189 mg/dL who were receiving statin therapy because of a high ASCVD risk score or clinical discretion.

The 155 patients who did not receive statins after physician-patient dialogue included the following: Nondiabetic patients aged 4075 years with a 10-year ASCVD risk <5%, n=133; diabetic patients with LDL <70 mg/dL, n=1; diabetic patients with LDL <70 mg/dL, n=2; nondiabetic patients with LDL <70 mg/dL, n=8; and nondiabetic patients aged >75 years, n=11.

Of the 2,290 patients (9.8%) eligible for moderate-intensity statins, 75.8% (n=1,735) were concordant with the guideline; however, 18.1% (n=413) were over-treated with high-intensity statins and 6.1% (n=139) did not receive any statins. Overall, 2,060 patients were eligible for statins after shared discussion with physicians, of which 155 did not receive any statins.

3.5. Concordance to Statin Therapy in the 4 Statin Benefit Groups

Of the total 23,295 patients, 60.4% (n=14,070) patients with a history of clinical ASCVD were eligible for secondary prevention. Of these patients, 42.8% (n=6,027) received high-intensity statins, more than half (55.0%, n=7,732) received moderate-intensity statins, and 2.2% (n=303) did not receive any statin therapy. Of patients with ASCVD in the older age group >75 years (n=566), 44.7% (n=253) were treated with high-intensity statins (Figure 1b). Interestingly, among the high-risk ASCVD patients receiving maximal intensity statins (n=6,027), most patients (98.9%, n=5962) had LDL-C ≥70 mg/dL (Figure 2a).

Among patients without clinical ASCVD (n=7,122) who were eligible for primary prevention because of coexisting risk factors, 3.9% (n=278) had LDL-C ≥190 mg/dL, 94.0% (n=6,694) had diabetes, and 2.1% (n=150) patients had 10-year ASCVD risk of ≥7.5%. Of the diabetic patients having low ASCVD risk <7.5% (n=1,681), 85.5% (n=1,438) received the apt moderate-intensity statins. However, among diabetic patients with high ASCVD risk ≥7.5% (n=5,013), 82.9% (n=4,157) remained under-treated with moderate-intensity statins (Figure 1b). Similarly, most patients (82.0%, n=228) with LDL-C ≥190 mg/dL (n=278) were inappropriately prescribed moderate-intensity statins (Figure 1b). About 2.1% (n=150) patients with high ASCVD risk ≥7.5% eligible for primary prevention with moderate-high

intensity statins were not receiving any statin therapy. Additionally, n=43 patients with ASCVD risk 5%-7.5%, who were eligible for moderate-intensity statin therapy were not receiving any statins (data not shown).

Among the people in the high-risk group, the proportion of patients achieving an optimal LDL-C level of <100 mg/dL was low despite receiving statin therapies of various intensities: high-intensity 18.6% (n=1,199), moderate-intensity 21.9% (n=2590), and low-intensity 71.4% (n=20) (Figure 2b). Very high LDL-C level (≥190 mg/dL) was present in 5.2% (n=338) patients receiving high-intensity statins and 5.3% (n=623) patients receiving moderate-intensity statins.

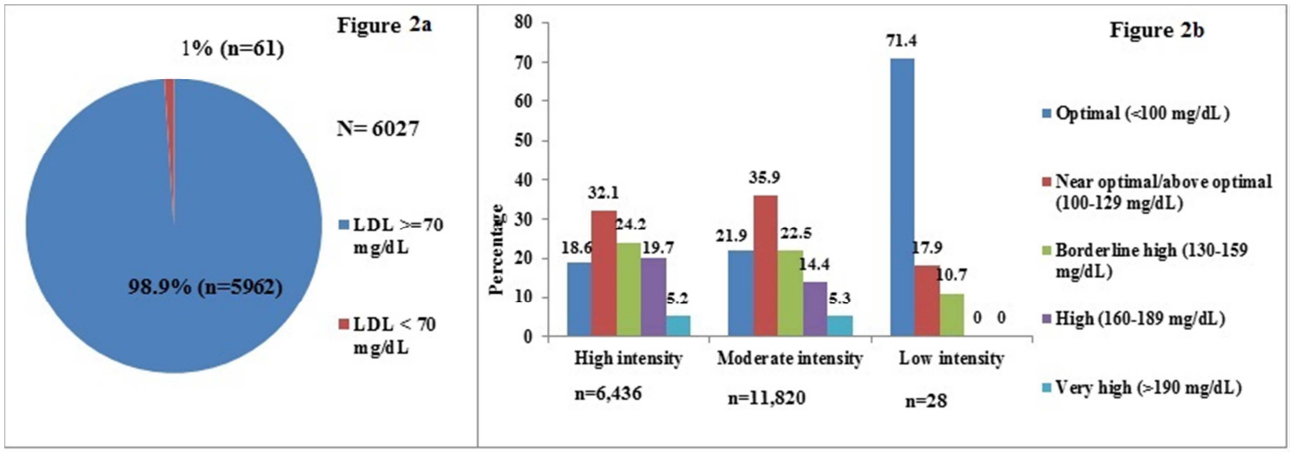

Figure 2. *Distribution of LDL-C levels of patients in the study population*

a LDL-C levels of patients with clinical ASCVD receiving high-intensity statins.
b LDL-C levels achieved in high-risk groups with various statin intensities.
LDL-C: Low-density lipoprotein cholesterol.

4. Discussion

This nationally representative real-world study assessed the 10-year ASCVD risk among Indian patients and evaluated the concordance to 2013 ACC/AHA statin therapy guideline for the primary and secondary prevention of ASCVD.

Fewer than 5% people achieve the 7 metrics of ideal cardiovascular health including regular exercise, no smoking, low saturated fats, TC <200 mg/dL, BP <120/80 mmHg, glucose <100 mg/dL, and BMI <25 kg/m^2 [14]. Nearly one-third of our study population were tobacco users, half were obese, and three-fourths had diabetes and hypertension, whereas 46.3% had TC ≥200 mg/dL. A cross-sectional study in India by Guptha et al demonstrated that the prevalence of TC ≥200 mg/dL was 25.0% and that of triglycerides ≥150 mg/dL was 36.9% [15]. Heterogeneity in risk factors, accelerated build-up with an early age of onset, high fatality rate, and suboptimal treatment in lower socioeconomic strata, alongside low awareness and treatment of hypercholesterolemia are major concerns for ASCVD management in India [3, 6].

Maintaining optimal lipid levels is an important component of ideal cardiovascular health. Statins are the cornerstone for dyslipidemia management. About 12.6% of annual ASCVD deaths can be prevented if eligible people receive statin therapy [16]. However; physician adherence to dyslipidemia guidelines presents a crucial challenge [17]. Our study found major gaps in prescription practices for statin therapy; only one-third patients eligible for high-intensity statins received treatment in concordant with guidelines. Most patients with ASCVD received moderate-intensity statins while 2.2% did not receive any statins. A registry-based study from the United States revealed that in cardiovascular practice 32.4% of statin-eligible patients were not receiving the recommended therapy, and only 49.9% of ASCVD patients were receiving statin therapies [18]. Wander et al conducted a survey of 404 physicians across India and reported that high-intensity statins were preferred by 73.7% of physicians in post-acute coronary syndrome patients, while 50% doctors chose not to use statins in diabetic patients [19]. In our study, most diabetics with high ASCVD risk ≥7.5% (82.9%) remained under-treated. The India Heart Watch-2 study also revealed that statins are prescribed in only 55% of diabetes patients [9].

Our study results also highlight a possible gap in the dose titration and clinical inertia among physicians while prescribing statin therapy. Most patients taking low- or moderate-intensity statins were not titrated to a high dosage following an episode of ASCVD irrespective of their diabetes status, leaving residual risk for recurrent CVD events [20]. Lack of training, time constraints, complex guidelines, patient preferences, and perceived side effects are few reasons for suboptimal provider compliance to clinical guidelines [21, 22]. A physician survey in the United States revealed that 27.8% of physicians believed statins caused diabetes and 97.2% believed that statins cause myopathy [23]. A physician survey from Singapore reported that low awareness of standard guidelines, disagreement with

guideline recommendations, and concerns about statin intolerance in Asians were the major impediments to guideline implementation [24]. However, the REAL-CAD trial in Japan showed that compared with low-intensity statins, high-intensity statins reduced MACE (major adverse cardiovascular events) with no added risk of serious adverse events [25]. A study from Singapore also demonstrated that the reduction in LDL-C by statins was not influenced by Asian ethnicity or BMI, suggesting that statin dosages should be titrated upward when target lipid levels are not achieved [26]. It is crucial to formulate strategies that increase physician awareness and enhance physician compliance for statin guidelines while accounting for issues like patient intolerability and cost-effectiveness. Distributing educational materials, conducting periodic audits, providing feedback and continuity of care, and establishing communication between distant healthcare professionals can enhance guideline adherent prescription of statins/lipid lowering agents (OR 1.23; 95% CI 1.07-1.42, p=0.004) among physicians [27].

The most effective strategy to prevent cardiovascular events would be to achieve optimal lipid levels early in life and maintain them throughout life, thus reducing exposure to cumulative LDL-C and slowing plaque progression [14]. Most ASCVD patients in our study receiving high-intensity statins had LDL ≥70 mg/dL, highlighting a room for improvement in this population. Similar findings of persistent residual cholesterol risk have been demonstrated in PROVE-IT, IMPROVE-IT, and VIRGO registry studies [28]. The 2018 ACC/AHA guideline recommends addition of non-statins, such as ezetimibe, to maximally tolerated statin therapy in patients at very high ASCVD risk with LDL-C levels ≥70 mg/dL. In patients with severe hypercholesterolemia, if LDL-C levels remain ≥100 mg/dL, adding ezetimibe and consequently a PCSK9 inhibitor may be considered in addition to high- or moderate-intensity statins. However, a survey from India showed that only 30% doctors preferred ezetimibe in patients with uncontrolled LDL-C alongside a maximum-dose statin therapy, whereas 34% did not use ezetimibe in clinical practice [19].

The 2018 ACC/AHA guidelines recommend screening and management of adults above 20 years for dyslipidemia. A study from Kerala in India estimated that 61% of individuals aged 18 to 39 years had a high lifetime predicted risk of developing ASCVD [29]. The India Heart Watch-2 study demonstrated that statin prescriptions are lower in patients aged <40 years [9]. The MORE study primarily focused only on patients aged 40-79 years. Early risk assessment followed by timely implementation of primordial and primary prevention strategies can provide a window of opportunity to mitigate the burden of ASCVD. Early prevention by optimizing health behaviors such as smoking or physical activity and primary prevention among patients with dyslipidemia, hypertension, or diabetes must begin during adolescence and early adulthood. Furthermore, the implementation of guideline-adherent pharmacological interventions is vital for secondary and tertiary prevention to prevent the progression and development of additional CVD [30]. The retrospective cross-sectional design of our study was a limitation to evaluate the long-term impact of statin therapies on dyslipidemia. Data on younger population aged <40 years, renal dysfunction, statin intolerance, and prescription of non-statin cholesterol-lowering drugs were missing. Additionally, the study did not collect information on socioeconomic status and statin therapy cost; therefore, we could not ascertain if patient income or insurance may have influenced clinicians' decision to prescribe high-intensity statins. Nevertheless, our study is by far the largest real-world study in India assessing the ASCVD risk and evaluating concordance to the recommended statin therapy guidelines.

5. Conclusion

This large real-world study evaluated the concordance of statin therapy to the recommended guidelines among Indian population. Most patients were receiving statins at an inappropriate intensity, especially patients with diabetes. This reflects major gaps in the real-world practice of prescribing statins for the primary and secondary prevention of ASCVD. High LDL-C levels despite maximal intensity statins highlight the need for addition of non-statin cholesterol-lowering drugs. Regular monitoring and addressing insufficient response by dose titration or change in statin therapy is crucial for ASCVD management. Addressing care gaps and promoting compliance through enhanced physician awareness to optimize statin therapy will help prevent cardiovascular disease, especially in high-risk population among South Asians.

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