



Editorial

Expanding statin use for prevention of ASCVD in Indians: Reasoned and simplified proposals

A B S T R A C T

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Atherosclerosis, a systemic disease, is the predominant cause of cardiovascular disease (CVD) that far exceeds other causes (egs: congenital, hypertension, arrhythmia). CVD is the leading cause of mortality globally (18 million lives, including 9 million from coronary artery disease (CAD) annually).¹ The Global Burden of Disease study reported that in the year 2017, India had one of the highest mortality, most of them premature, from CVD (2.64 million, women 1.18, men 1.45) and CAD (1.54 million, women 0.62, men 0.92) in the world.² A systemic disease of this magnitude and impact warrants a proactive preventive strategy and not a reactive, invasive and focal approach. In this editorial, we call for a wider use of statins in Indians, explain our rationale based on risk factors and risk-enhancing factors, and present a simplified and cost effective approach to combat CVD.

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1. The centrality of low-density lipoprotein cholesterol (LDL-C) in ASCVD

The primary cause of atherosclerotic cardiovascular disease (ASCVD) is increased LDL-C and its retention within the arterial wall is the key initiating event in atherogenesis.^{1–5} LDL-C is a *necessary* and *sufficient* risk factor for ASCVD.⁵ Necessary as atherosclerosis does not develop in the absence of some elevation in LDL-C and sufficient risk factor as atherosclerosis and acute myocardial infarction (AMI) develop when LDL-C is markedly elevated.^{5,6} As examples, rare genetic mutations that cause reduced LDL receptor function leads to markedly higher LDL-C and a dose-dependent increase in the risk of ASCVD even in children whereas rare variants leading to lower LDL-C are associated with a correspondingly lower risk of ASCVD.⁶ Meta-analyses of over 200 prospective cohort studies, Mendelian randomization studies, and randomized clinical trials including more than 2 million participants with over 20 million person-years of follow-up and over 150,000 ASCVD events demonstrate a remarkably consistent dose-dependent log–linear association between the absolute magnitude of exposure of the vasculature to LDL-C and the risk of ASCVD.⁶ The INTERHEART study reported that LDL-C was as important a risk factor in Indians as in other ethnic groups,⁷ and The Prospective Urban Rural Epidemiology (PURE) study found increased non-high density lipoprotein - C to be the most important cardiovascular disease risk factor in South Asians.⁸ South Asians refer to people who have ancestral origin in the Indian subcontinent (mainly India, Pakistan, Bangladesh, and Sri Lanka).

2. Statins reduce LDL-C and ASCVD risk effectively and safely

Numerous studies over the past 50 years have conclusively shown that abnormal lipids account for more than one-half of

CAD and nearly one-half of cerebrovascular accidents (CVA) and that lipid-lowering therapy (LLT) with statins can reduce this risk by >50%.^{3,4} The effect is cumulative as long as statin continues to be taken and larger absolute benefits would accrue with more prolonged statin therapy.⁹ Typically, treatment of 10,000 patients for 5 years with an effective regimen (e.g., rosuvastatin 20 mg or atorvastatin 40 mg daily) prevents ASCVD events in 500 patients in primary prevention and 1000 patients in secondary prevention.⁹

2.1. Degree of ASCVD risk reduction relates to absolute LDL-C reduction

The evidence is incontestable that reducing LDL-C levels reduce ASCVD events. The Cholesterol Treatment Trialists' Collaboration (CTTC) reported a 22% reduction in major ASCVD events per 39 mg/dl (1 mmol/l) lowering of LDL-C in the middle-aged regardless of whether the patient's starting LDL-C was 132 mg/dl or 66 mg/dl.^{10–12} Since relative risk reductions are half as large in the first year as compared with subsequent years, the ASCVD risk reduction increases from 22% to 25% after 2 years (per 39 mg/dl reduction in LDL-C).⁹ An updated meta-analysis of 50,627 patients treated with statins and non-statin with a starting median LDL-C 63 mg/dl and achieved median LDL-C of 21 mg/dl has reproduced the same relationship between LDL-C reduction and ASCVD reduction.¹² Despite such ultra-low LDL-C levels there was a conspicuous absence of any serious consequence such as cancer, dementia, memory loss, intracranial hemorrhage, sexual and reproductive function.¹² Patients, notably those who are obese and sedentary, on statin treatment have a small increase in the risk of new-onset diabetes mellitus. But the overall absolute ASCVD risk reduction (5–10%) clearly outweighs the small increase in the incidence of diabetes (0.5–1%).⁹ Statin associated muscle symptoms muscle

pain, muscle weakness, or severe cramps (5–10% occurrence) call for temporary discontinuation of the drug.⁹ Restarting same or a different statin after the myalgia has subsided would allow most of the patients to stay on therapy. Statins very rarely cause serious muscle damage (1 in a million).⁹

2.2. Paradigm shift from LDL-C target to LDL-C threshold

Consequent to the plethora of evidence tying the efficacy of ASCVD event prevention to the absolute reduction of LDL-C, the guidelines have moved from a target number to the maximum reduction of LDL-C that can be safely achieved.^{3,4} Statin is the first-line of drug therapy for people with high ASCVD risk regardless of their LDL-C level (high, average, below average).^{3,4} What was considered to be a normal LDL-C level has dropped down with the increasing realization that “normal” is far from optimal.^{3,4} Throughout the range of LDL-C levels, ‘lower is better’ at least down to 40 mg/dl.^{3,4} The 2019 European guidelines have lowered the LDL-C target to <55 mg/dl for very high risk patients.⁴ The 2018 Clinical Practice Guidelines for the Management of Dyslipidemia by the American College of Cardiology/American Heart Association (ACC/AHA) recommend an LDL-C threshold of 70 mg/dl for initiating statin therapy in people with ASCVD risk from established and risk enhancing factors.³

2.3. Statin therapy in Indians: great benefits, but greatly underused

Reductions of ASCVD events with statin therapy vary up to 20-fold depending on the absolute reduction in LDL-C achieved as well as the baseline risk¹¹; the higher the risk greater the benefit for any given degree of LDL-C reduction.¹¹ Thus Indians would benefit more from statin therapy than other populations as Indians have a 1.5–2 fold ASCVD risk at any given combination of risk factors compared to whites.^{13–15} In addition, Indians have a 3–5-fold higher incidence and mortality from malignant CAD at a young age.¹⁶

Thus it is disconcerting and disappointing that the reported use of statin therapy in India is very low. In a large cross sectional study ($n = 6123$) at multiple sites in India, the age-adjusted level of cholesterol was 178 mg/dl with 25% having cholesterol >200 mg/dl and 50% having LDL >100 mg/dl; but the awareness, treatment, and control of cholesterol were 16%, 7% and 4 % respectively.¹⁷ In the PURE study the use of statin therapy among South Asian patients with ASCVD was 5%.¹⁸

The plausible reasons for this dismal number include poor understanding by the public and medical practitioners on the long natural history of ASCVD and the proven efficacy of statins, cost of statins, exaggerated concerns of safety, undue reliance on aspirin, penchant for surgical and invasive options, and the complexity and multiplicity of cholesterol guidelines and dosage of statin therapy.^{3,4,19}

3. Proposal: classify degree of risk and match it to intensity of treatment

As stated in 2.2, the need for statin and the intensity of therapy are now determined by the level of ASCVD risk.^{3,4,19} In the United States, the estimated 10-year risk for ASCVD event is determined using the Pooled Cohort Equation (PCE) and is stratified to 4 levels of risk (high, intermediate, border-line and low).²⁰ But the application of PCE and other risk estimation tools is virtually non-existent in clinical practice in India.

We would like to clear the morass of guidelines and simplify them to enable rational and wider use of statins through 2 largely self-explanatory tables. Table 1^{3,17,19,21–26} shows our

recommendations for statin therapy ranked in decreasing order (classes 1A, 1B, 2A, and 2B) of priority based on the strength of collected evidence. Our practical and cost-efficient classification (based mainly on clinical data) fills the void and places statin therapy on a rational footing. This strategy utilizes classifying ASCVD risks (Table 1) and then matching each to treatment appropriate for that class (Table 2).³

3.1. Patients with ASCVD (1A)

The highest priority for statin therapy based on the strength of evidence (1A) is for patients with ASCVD (egs: acute and previous MI, stroke, coronary stent or bypass surgery) as they are at high risk for recurrent events. Those who have had multiple previous events and major risk factors are at very high risk (10 year risk of 30–40%) for recurrence. Silent ASCVD may be manifest on ECG gated electron-beam computed tomographic assessment of coronary artery calcium (CAC) score; higher the score higher the risk.²⁴ (see footnotes under Table 1). However we currently do not recommend its routine use in India as a screening tool because of cost, access, complexity (use of risk score calculator for optimal use) and practicality.

3.2. Patients with major risk factors (1B)

Each of the major and well established risk factors (high cholesterol, diabetes, tobacco use and hypertension) is associated with a 2–3 fold risk of ASCVD²⁷ and merits much more therapeutic attention than they currently receive to make a dent in the morbidity and mortality caused by this disease.²⁸ Our Class 1A and Class 1B recommendations applied to the estimated prevalence cited on Table 1, would vastly increase the number of Indians who would benefit from statin therapy. One criterion alone cholesterol >170 mg/dl or LDL-C > 100 mg, projected from a cross sectional study, would increase it to nearly 50% of the adult population.¹⁷

Cholesterol >170 mg/dl (4.4 mmol/l): Compared to the cost of a lipid panel (cholesterol, triglycerides, LDL-C, very low density lipoprotein cholesterol (VLDL-C), and high-density lipoprotein cholesterol (HDL-C), the measurement of cholesterol alone is 3–4 times less expensive and does not require fasting. In order to reduce the financial burden of testing, we propose testing for total cholesterol, as a surrogate for LDL-C. Although the International Atherosclerosis Society (IAS) Global Recommendations for Management of Dyslipidemia recommend cholesterol ≥ 180 mg/dl (4.6 mmol/l) as the threshold for statin therapy,¹⁹ we propose a lower threshold of 170 mg/dl (4.4 mmol/l) for 3 reasons. First, Indians develop AMI at lower LDL-C and cholesterol⁷; and also are at increased ASCVD risk even after adjusting for all established risk factors.^{13–15} Second, PCE for estimating ASCVD risk uses a cholesterol threshold of >170 mg/dl.²⁰ Third, a cholesterol reading of 170 mg/dl corresponds to an LDL-C of 100 mg/dl.³ There should be no reticence to use statins in high-risk Indians, especially men, as young as 20 years of age as CAD death rates are 3 times higher in Indians <30 years of age,³⁹ and ASCVD risk from any given level of elevated cholesterol is double in those ≤ 45 years, compared to ≥ 60 years.²⁹ Caution is advised against the use of statins in females of childbearing age and in pregnancy. Statins are approved for use in children with persistent LDL-C > 160 mg/dl (e.g.: familial hypercholesterolemia).³⁰

Diabetes, tobacco use, and hypertension: These 3 conditions are so well established by several studies as major risk factors^{8,27} and therefore are used in all the ASCVD risk estimators in North America and Europe. Patients with diabetes *per se* are considered at intermediate risk and at high risk if other risk factors are present.³ The benefit and risk balance of statin therapy in these 3 conditions (alone or in combination) markedly favors therapy and

Table 1
Recommendations for statin therapy in Indians.

Strength of recommendation	Underlying conditions	Prevalence (estimated)
Class 1A: Highly recommended	Atherosclerotic cardiovascular disease ^a	3–6% ²⁶
Class 1B: Recommended	Major risk factors (presence of 1 or more). The last 3 do not require initial cholesterol measurement. ¹⁹	
	Cholesterol ≥ 170 mg/dl or LDL-C > 100 mg/dl ¹⁹	50% ¹⁷
	Diabetes ¹⁹	6–10%
	Tobacco use (both active and passive smokers) ¹⁹	15–25%
	Systolic blood pressure ≥ 140 mg ¹⁹	20–25% ^{21,40}
Class 2A: Reasonable	Cholesterol ≥ 140 mg/dl or LDL-C ≥ 70 mg/dl plus ASCVD risk-enhancing factor(s). ³	
	Triglycerides ≥ 150 mg/dl	35–45% ¹⁷
	Metabolic syndrome (men 35%; women 50%)	35–45% ²³
	Elevated lipoprotein(a) ≥ 30 mg/dl	25% ²²
	Chronic kidney disease (estimated GFR 15–59)	9%
	Family history of premature ASCVD	20–25%
	Chronic inflammatory conditions (rheumatoid arthritis, psoriasis or chronic HIV)	N.A.
	High sensitivity C-reactive protein ≥ 2 mg/dl	N.A.
	Ankle-brachial index < 0.9	N.A.
	Women with premature menopause < 40 years or pre-eclampsia	5–10%
	Coronary artery calcium score $\geq 10,0$ ²⁴	N.A.
	Abdominal obesity (waist circumference ≥ 90 cm in men and ≥ 80 cm in women)	50–75% ²⁵
Class 2B: May be considered	Men > 45 and women > 55 years of age and cholesterol > 140 mg/dl or LDL-C > 70 mg/dl	N.A.

^a Includes those with silent ASCVD manifest only as high coronary artery calcium score ≥ 300 Angstrom units as they have a nearly 10 fold increased risk than those with 0 calcium.²⁴

Table 2
Matching the degree of ASCVD risk to the intensity of treatment.³

ASCVD risk	Intensity of therapy	Name and dose of statin mg/day	LDL-C reduction	ASCVD risk reduction
I A	HIST	Rosuvastatin 20–40 mg Atorvastatin 40–80 mg	> 50 –60%	25–55%
I B	HIST plus ¹ MIST ²	HIST plus Ezetimibe 10 mg Rosuvastatin 5–10 mg Atorvastatin 10–20 mg	+16% more than HIST alone 35–49%	+6% more than HIST alone 20–24%
2A	MIST	Same as above	Same as above	Same as above
2B	MIST	Same as above	Same as above	Same as above

HIST = high-intensity statin therapy; MIST = moderate-intensity statin therapy.

¹ add Ezetimibe if LDL-C remains ≥ 70 mg/dl.

² proceed to HIST if LDL-C > 70 mg/dl.

therefore we propose that cholesterol measurement need not be a requisite for initiating statin therapy. This is consistent with the Global Recommendations of the IAS¹⁹ and the results of the Heart Outcomes Prevention Evaluation (HOPE 3) study.³¹ ASCVD risk reductions of 24% achieved in intermediate risk patients (without factoring lipid levels), and 40% in those with hypertension on statins (rosuvastatin 10 mg/d) further support our proposal.³¹

3.3. Patients with cholesterol > 140 mg/dl (3.6 mmol/l) and ASCVD risk-enhancing factor(s) (2A)

The pool of Indians who may benefit from statin therapy is further increased when 2A and 2B – albeit with weaker strengths of recommendation than 1A and 1B – are also taken into consideration. The common denominator in both 2A and 2B is South Asian ethnicity.

The 2018 ACC AHA guidelines adopted the pioneering findings of the Coronary Artery Disease in Indians (CADI) research³² and included South Asian ethnicity as a risk-enhancing factor, in recognition of their heightened risk of ASCVD.^{13–15} The distinction between these 2 sub-classes is that all the risk-enhancing factors listed in Table 1 under 2A have in addition to ethnicity one or more of the following 3: lipid abnormalities, vascular disease, inflammatory disease and therefore has a higher priority for statin therapy than 2B. These risk-enhancing factors are listed in the

2018 ACC/AHA Task Force on Clinical Practice Guidelines on the Management of Blood Cholesterol.³ A few additional comments on abdominal obesity (also called central or visceral obesity) and family history are warranted. Abdominal obesity *per se* was not listed in the guidelines as it is conventionally considered a part of metabolic syndrome (a combination of metabolic risk factors associated with a 2-fold risk of CAD and 5-fold risk of diabetes).^{23,33} However, a multi-specialty expert panel has opined that inclusion of abdominal obesity need not be an obligatory component of metabolic syndrome.³³ Since a single set of cut points for waist circumference could not be determined, they urged further work and the interim use of gender and ethnic specific cut points proposed by International Diabetic Federation (IDF) and/or national guidelines.³³ Abdominal obesity was an important ASCVD risk factor in 2 landmark studies that used waist to hip ratios.^{8,34} Waist circumference has been proposed as a surrogate for cultural and practical reasons in Indians. In an in-depth review Misra and Shrivastava³⁵ reasoned for a cut off of waist circumference of ≥ 90 cm in men and > 80 cm in women for abdominal obesity in Indians. Of note, these cut points are 12 cm lower in men 8 cm lower than that recommended for Americans.³³

Family history of premature ASCVD (men < 55 and women < 65 years of age) is an important risk factor as those with such a history have a 2–7 fold increased risk of premature ASCVD and this range is dependent on the number of first degree relatives (parents and

siblings) who have had premature MI. While shared social and environmental factors are contributors to this risk, genetic factor(s) are the foremost to consider in those with a history of premature MI in multiple first degree relatives at a young age. One such genetic factor – lipoprotein(a) – has received a great deal of attention and was the subject of recent reviews in this journal.^{16,36}

3.4. Indians (men >45 and women >55 of age) and cholesterol > 140 mg/dl (>3.6 mmol/l) or LDL-C >70 mg/dl (>1.8 mmol/l) (2 B)

Our recommendation that statin therapy “may be considered” for this class, at first look, may seem an overreach and therefore is in need of an explanation. Our rationale is based on the natural history of atherosclerosis, cumulative effects of risk factors and importantly our ethnicity. Atherosclerosis, mistakenly, is considered a disease that affects only the middle-aged and elderly whereas the natural history of atherosclerosis is life-long. The onset is early in life but the clinical manifestations of atherosclerosis are delayed for many decades. Coronary atherosclerosis by intravascular ultrasound has been shown in teenagers and young adults.³⁷ The prevalence of clinical CAD in men in the US increases from <1% at ages 20–39 to 6% at ages 40–59 to 20% at ages 60 to 79 and 31% at ages ≥80 and fatal and non-fatal AMI increases from 25 per thousand at ages 35 to 44, to 75 per thousand at ages 45 to 54, to 130 at ages 55 to 64 and 155 per thousand at ages 65 to 74.³⁸

The development of clinical CAD is delayed 10–15 years in women: the rate of AMI in 45 year old men is higher than that of 55 year old women (75 versus 70/1000) and the rate in 65 year old men higher than that of 85 year old women (155 versus 125/1000).³⁸ Aging is associated with the acquisition of and increments in the most modifiable risk factors of ASCVD. Thus, age may be considered as the best surrogate for the length of exposure to risk factors and a consistent contributor to plaque formation—the precursor to CAD and AMI.³⁸

At every risk factor level and at every age group South Asians have higher rates of CAD than whites. In the 10-year follow-up of a large prospective UK study ($n = 16,774$ South Asians and 7032 Europeans) the prevalence of CAD increased progressively from 2% at age 45 to 12% at age 75 in whites, whereas the prevalence increased from 3% to 32% in South Asians. Between the ages of 45 and 75 there was a >2- fold prevalence in South Asians in every age group compared to whites.¹⁴ CAD mortality rates in South Asians <30 years of age was 3.13 times that of whites in the UK.³⁹ Premature deaths (in people < 70 years of age) accounted for 62% of the deaths due to CAD in India¹ which is double that for the same age group in the US.³⁸

The enormity of the consequences of ASCVD, such as mortality, morbidity and loss of productive years of life (65million disability-adjusted life years), calls for action. Although the major risk factors for ASCVD has been identified for years, with the exception of smoking cessation efforts, the detection and control of other factors—high cholesterol, hypertension and diabetes are still low in India (it is estimated that detection rates are less than 50%).¹⁷⁴⁰ It is only reasonable then to assume even lower rates of detection of the less known risk-enhancing factors listed in Table 1. Given the proven benefits of statins in reducing ASCVD events and its marked under-use in India expanding its use to people in Class 2B would be a step worthy of consideration.

4. Matching the degree of ASCVD risk to intensity of statin therapy

Two basic tenets of preventive medicine are that the benefits are greater in populations at higher risk (South Asians have a 1.5 to 2 times ASCVD risk than whites)^{13–15} compared to those at lower

risk and that the degree of risk should be matched with the intensity of the preventive therapy. Thus as shown in Table 2, patients in Class 1A are highly recommended for high-intensity statin therapy (HIST). If the patient rejects or if the physician is uncomfortable initiating HIST one could start MIST, repeat lipid panel in 2 months, and increase the dose incrementally to reach the desired result. If the desired objective of LDL-reduction (<70 mg/dl) is not reached on HIST addition of ezetimibe is recommended (HIST plus). De-escalation of the intensity of statin therapy is warranted only if LDL-C is persistently <25 mg/dl.³

For patients in all other classes (1B, 2A and 2B) moderate-intensity statin therapy (MIST) is recommended (1B), reasonable (2A) or may be considered (2B). MIST alone suffices in the vast majority of these patients. An exception that requires a change to HIST is in Class 1 B patients with high cholesterol or LDL-C plus additional major risk factors who inadequately responded (less than 50% reduction) to MIST. It is worth highlighting that aspirin is not a valid substitute for a statin for ASCVD prevention. The 2019 ACC/AHA Guideline on the Primary Prevention of ASCVD severely restricted the use of aspirin in recognition of the dangers of severe bleeding, the magnitude of which exceeded that of ASCVD events prevented in primary prevention populations.^{27,41,42}

5. Summary and conclusion

We have presented our risk-based recommendations for statin therapy and for ease and practicality propose:

- 1) the use of total cholesterol (instead of a lipid panel) to cut costs and to simplify decision-making and
- 2) the use of statin therapy without cholesterol or lipid panel tests in patients with major risk factors - diabetes, tobacco use, hypertension.

We further propose that primary physicians (generalists) in India take an active role in statin therapy (MIST), as is the norm in the USA and most Western countries. This empowerment of primary physicians will markedly increase the number of patients treated with statins. Referral to cardiologists would be appropriate for the smaller number of patients who require HIST or statin plus ezetimibe or additional drug(s).

To combat ASCVD, a disease of vast magnitude and impact in Indians, requires a multi-pronged approach that includes primordial prevention (dietary habits, exercise, life style) and primary prevention (detection and elimination or control of major risk factors as well as a host of risk-enhancing factors).²¹ While recognizing statin therapy, that lowers LDL-C and consequently lowers ASCVD risk, is only one of the weapons against ASCVD, we must also acknowledge the indisputable evidence that it is the one that is the most proven and most effective.⁴³ As such, statin is the drug of choice for prevention of ASCVD. We earnestly urge our physician colleagues to heed our proposals and translate them into action.

Conflict of interest

The authors have no conflict of interest.

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