

Statins: Cholesterol guidelines and Indian perspective

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ABSTRACT

Statins have become an important drug in preventing the occurrence of atherosclerotic cardiovascular disease (ASCVD). The effectiveness of statins in reducing ASCVD has been established in large-scale clinical trials. The lipid management guidelines have been periodically modified due to accumulating evidence about the proportionate benefit achieved with a progressive reduction in cholesterol levels with higher doses of statins and even in those at low risk of development of ASCVD. The current American College of Cardiology/American Heart Association guidelines have based its recommendations from data gathered exclusively from randomized controlled trials. It has simplified the use of statins, but also raised questions regarding the validity of its cardiovascular event risk prediction tool. Epidemiology of cardiovascular disease in India differs from the western population; there is an increased the prevalence of metabolic syndrome and atherogenic dyslipidemia phenotype a group not addressed in the current guidelines. The guidelines are based on trials, which do not have a representative South Asian population. This article reviews the relevant literature, and examines the issues involved in adopting the guidelines to the Indian population.

Key words: Asian Indians, lipids, statins

INTRODUCTION

In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) published guidelines on treating blood cholesterol to reduce atherosclerotic cardiovascular disease (ASCVD) risk in adults.^[1] The guidelines generated a fair amount of attention among the scientific community (and media) and stirred controversy due to its radical departure from previous guidelines on the subject.^[2] This review examines the issues involved in the management of cholesterol by statins and examines the guidelines from the point of view of its applicability in the Indian subcontinent.

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LOW-DENSITY LIPOPROTEIN CHOLESTEROL AND ATHEROSCLEROSIS

Cholesterol is essential for body metabolism, and is responsible for maintaining the integrity of cell membrane and synthesis of bile acid, steroid hormones, and Vitamin D. The evidence that cholesterol is an important risk factor in development of atherosclerosis is supported by animal studies and genetic disorders affecting cholesterol metabolism. In 1913, Nikolay Anichkow a Russian pathologist demonstrated the occurrence of severe atherosclerosis of aorta in rabbits fed with cholesterol-rich diet.^[3] Individuals with genetic forms of hypercholesterolemia suffer from premature atherosclerosis at a young age in the complete absence

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of other well-established risk factors.^[4] Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and very LDL-C constitutes 60–70%, 20–30%, and 10–15% of the total cholesterol. Large epidemiological studies such as Framingham Heart Study and Multiple Risk Factor Intervention Trial have demonstrated that there exists a direct relationship between level of LDL, and the rate of onset of coronary heart disease (CHD) in men and women who are free of the disease to start with.^[5,6] Hence LDL cholesterol is targeted for reduction of risk of ASCVD.^[7]

Optimal level of low-density lipoprotein

Hunter-gatherer communities (Hazda, Inuit, Ikung, Pygmy, and San) following indigenous life style have an average total cholesterol of 100–150 mg/dl and yet show no evidence of atherosclerosis even in sixth or seventh decade of life. On the other hand an average adult American has total cholesterol of 200–210 mg/dl and 50% of the population have evidence of atherosclerosis by the age of 50 years. Studies using endovascular ultrasound for determining the degree of coronary and carotid artery stenosis in patients have shown that atherosclerosis does not progress if LDL-C levels are brought down to 67 mg/dl. Regression models have shown that CHD event rates were predicted to be zero in patients with LDL-C levels of 57 mg/dl in primary prevention trials and 30 mg/dl in secondary prevention trials.^[8]

STORY OF STATINS

In 1973, Dr. Akira Endo, a Japanese scientist at Sankyo Co., and a self-confessed admirer of Alexander Fleming extracted a molecule from the culture broth of *Penicillium citrinum*. He named the molecule ML-236B, which he showed was a potent inhibitor of cholesterol synthesis; officially considered the first statin. The blockade of rate controlling enzyme HMG Co-A reductase by statins leads to upregulation of LDL-C receptors on the liver leading to increase uptake of LDL-C and decrease in their levels in the circulation.^[9] Lovastatin was the first commercially marketed statin. Subsequently a number of statins have become available (Simva-, Atorva-, Fluva-, Rosuva-, Pitava-). Besides reduction of circulating LDL statins also exhibit a number of pleiotropic effects such as augmenting endothelial function (upregulation of endothelial nitric oxide synthase, increased nitric oxide synthesis), stabilizing vulnerable plaque (decreased matrix metalloproteinase activity), inhibition of macrophage migration, phagocytosis/lipid uptake, and foam cell formation (reduced vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin activity).^[10]

Trials in use of statins

The lipid-lowering drug cholestyramine was studied in the Coronary Primary Prevention Trial of 1984, and showed a modest reduction in total and LDL-C; reduction in coronary events barely reached statistical significance.^[11] The Scandinavian Simvastatin Survival Study published in 1994, was the first study that sought to evaluate the effect of statin therapy in the reduction of major coronary events. A total of 4444 men and women with angina or prior myocardial infarction (MI), and serum cholesterol levels of 5.5–8.0 mmol/L (212–309 mg/dL) were randomized to simvastatin (20–40 mg) or placebo for > 5 years. At the end of the study, total cholesterol was reduced by 25%, LDL-C by 35%, and deaths due to CHD by 42% ($P < 0.00001$).^[12] The benefits of statins in decreasing cardiovascular event rates thus became apparent. Since, then more than 20 large scale trials and several meta-analysis using pooled data have been published, which have demonstrated the effectiveness of statins in reducing cardiovascular events.

Cholesterol Treatment Trialists' Collaborators conducted a meta-analysis of data of 129,526 individuals from 21 randomized trials using statins, and showed that reduction of LDL by 1.07 mmol/L sustained for more than 5 years reduced the occurrence of major ASCVD event (MI, coronary mortality, coronary vascularization, fatal or nonfatal stroke) by one-fifth. These benefits were accrued irrespective of initial cholesterol level.^[13] The benefits of statins were observed even in those with low LDL-C at baseline prompting investigators to study the more intense reduction of LDL-C with higher doses of statins.

PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) trial randomized 4162 patients with the acute coronary syndrome and baseline cholesterol of 200 mg/dl to atorvastatin 80 mg or pravastatin 40 mg daily. At the end of 2 years, LDL-C was reduced to 62 mg/dl (decrease by 51%) for atorvastatin 80 mg and 95 mg/dl (decrease by 22%) for the pravastatin group. There was a significant 16% reduction ($P < 0.001$) in adverse CHD events and a 28% reduction in death due to cardiovascular events in the atorvastatin group.^[14] Another trial Treat to New Target (TNT) randomized 10,001 patients with stable CHD and LDL below 130 mg/dl to receive 10 mg/80 mg of atorvastatin and followed up for 4.9 years. At the end of the trial, LDL was 101 mg/dl and 77 mg/dl in low- and high-dose atorvastatin group, respectively. There was relative risk reduction of 22% in incidence of major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) in the high-dose atorvastatin group, ($P < 0.001$).^[15] In the subgroup of patients with diabetes in TNT study 25% reduction in the major cardiovascular event was noted in the

high dose atorvastatin group ($P < 0.026$).^[16] PROVE-IT and TNT confirmed results of previous studies that quantitative relationship in reduction of CHD events with lowering of LDL-C levels holds true even in those with low baseline LDL-C and “fixed high dose” atorvastatin reduced CHD event rates more than “moderate dose” statins.

Statins have been studied for the primary prevention of CHD events in those considered at low risk. JUPITER trial was conducted to study the effect of rosuvastatin 20 mg in prevention of vascular event in those with LDL-C < 130 mg/dl and high-sensitivity C-reactive protein (hs-CRP) > 2 mg/L a marker of increased cardiovascular risk. The trial was terminated prematurely, after 1.9 years of follow-up. LDL-C was reduced by 50%, and hs-CRP levels were reduced by 37%. The cardiovascular event rates were reduced by 44% and mortality by 20% in patients in rosuvastatin arm. The trial provided proof about statins being effective even in those with LDL-C in levels considered “within range”.^[17]

Safety of statins

The statins are relatively safe drugs; side effects being myositis, myalgia (1.0–1.5%), and elevation of liver enzymes. Rhabdomyolysis is extremely rare.^[13] Statin use is associated with an increase in the development of new onset diabetes, but the risk is low in absolute terms and when compared with the reduction in coronary events.^[18] New onset diabetes is more likely to occur in those treated with an intensive dose of statins as compared to those treated with moderate dose statins.^[19] The presence of a baseline fasting glucose > 100 mg/dl, fasting triglycerides > 150 mg/dl, body mass index > 30 kg/m², and a history of hypertension were each associated with a much higher risk of new onset diabetes.^[20]

STATINS IN LIPID GUIDELINES

The National Cholesterol Education Program (NCEP) was introduced in the USA by National Heart, Lung, and Blood Institute (NHLBI) of the National Institute of Health, in 1985 to educate general public and medical community alike about the need to identify and treat

elevated cholesterol to reduce risk of CHD. The Adult Treatment Panel (ATP) guidelines issued by NCEP for detection, evaluation, and treatment of elevated blood cholesterol was first published, in 1988, and has been periodically updated since then. Talwalkar *et al.* have chronicled the revisions in the ATP guidelines since their inception and readers may refer to their well-researched article on the subject.^[21] The ATP I and ATP II dwelled on dietary therapy as part of a strategy for managing elevated cholesterol in those with preexisting CHD; drugs were to be used only if cholesterol was still above target levels. The guidelines favored the use of nicotinic acid and bile acid sequestrants over statins. The use of hypolipidemic drugs in primary prevention was not recommended due to lack of safety data and adverse cost-benefit ratio.^[21,22] The updated ATP III guidelines of 2004, were till recently the most accepted guidelines for managing cholesterol. It involved the steps outlined in Table 1. It brought the concept of CHD risk equivalents, estimation of short-term, and lifetime risk of cardiovascular events and set targets for LDL-C lower than in previous guidelines. It defined the metabolic syndrome and discussed the strategies for managing hypertriglyceridemia.^[7,23]

In 2008, NHLBI started the process of revising the ATP III guidelines. In 2011, the Institute of Medicine, USA published a report on trustworthy guidelines, outlining that recommendations in guidelines should be “evidence-based” obtained from randomized controlled trials (RCTs).^[24] The NHLBI restricted its role to conducting a review of evidence while ACC/AHA was asked to frame the cholesterol guidelines based on the review of evidence.

American College of Cardiology/American Heart Association guidelines on management of lipids 2013

The ACC/AHA brought out the updated guidelines, in November 2013. The guidelines have emphasized the adoption of a healthy lifestyle as the foundation of cardiovascular health. The guidelines have identified four risk groups where lipid lowering measures have been found to be most effective. [Table 2]. Statins due to the overwhelming evidence have been recommended for treatment of elevated cholesterol. It has done away with

Table 1: Risk category and LDL-C (mg/dl) goals in NCEP ATP III

Risk category	Goal	Initiate TLC	Consider drug therapy
Very high: CHD plus either multiple risk factors (e.g., metabolic syndrome) or poorly controlled risk factors or smoking	$< 70^*$	All	≥ 100 (< 100 optional)
High: CHD or CHD risk equivalent	< 100	All	≥ 100 (< 100 optional)
Moderately high: ≥ 2 risk factors with 10 years risk 10–20%	< 130 (< 100) [*]	All	≥ 130 (100–129 optional)
Moderate: ≥ 2 risk factors with 10 years risk 10–20%	< 130	≥ 130	≥ 160
Low: 0–1 risk factors	< 160	≥ 160	≥ 190 (160–189 optional)

*Optional goal. TLC: Therapeutic Lifestyle Changes

titrating statin dose to achieve a desired LDL-C level. The dosing of statin has been fixed as “high intensity (ability to reduce LDL-C by > 50%)” and “moderate intensity” (ability to reduce LDL-C by 30–50%) [Table 3]. For primary prevention in patients considered at low risk (those without ASCVD, nondiabetics, LDL-C < 190 mg/dl) the guidelines recommend a discussion between the clinician and patient before initiating statin therapy. The guidelines recommend the use of Pooled Cohort Equation for assessing the 10 years risk of ASCVD. The Pooled Cohort Equations have been derived from cohorts of African Americans and White Americans who were part of five large NHLBI-sponsored observational studies on assessing cardiovascular health. Monitoring lipid profile is also not recommended as routine; except to ensure adherence to therapy.^[1]

Controversies

Since, its publication the guidelines have generated a fair amount of discussion right from the composition of expert panel (dominated by cardiologist), the risk estimation tool, financial implications, and applicability of the guidelines to populations other than White American and African American population. We examine these issues in succeeding paragraphs.

The committee framing previous ATP guidelines was from a diverse spectrum of specialties (metabolic diseases, cardiology, and public health) as against the current guidelines, which have representatives from cardiology. The assimilation of evidence for previous

ATP guidelines included epidemiological, observational, genetic studies, and RCT's. The current guidelines following the mandate of IOM report on guidelines restricted itself to evidence garnered from RCT's. The evidence favors, the use of statins in all clinical settings (preexisting ASCVD, primary prevention, diabetes, and high LDL-C). The exclusion of nonstatin drugs from cholesterol guidelines for lack of RCT data has made a leading expert in lipidology to comment that the guidelines were for the use of statins rather than reducing cholesterol. The exclusion of management of the metabolic syndrome has also been pointed out.^[25] A global position paper on management of dyslipidemia has been published by the International Atherosclerosis Society and expressed its dissatisfaction with the ACA/AHA guidelines. It is interesting to note that some members of the panel of International Atherosclerosis Society were part of the panel, which framed the ATP III guidelines.^[26]

The new ASCVD risk calculator “Pooled Cohort Equation” has also come under scrutiny. The ATP III guidelines used Framingham Risk Score (FRS) to compute the 10 years risk of ASCVD. Ridker and Cook used the new risk calculator to predict the risk of cardiovascular events in three American cohorts and concluded that it overestimated the risk by two-fold; increasing the numbers of low-risk individuals eligible for statin study.^[27] Pencina *et al.* used the US National Health and Nutrition Examination Surveys of 2005, and compared the number of individuals who would be eligible for statin therapy under ACA/AHA guideline with those who would be eligible under the ATP III guidelines. They extrapolated the results to the current US population of individuals between the ages of 40 and 75 years, and concluded that the number of adults who require statin therapy would increase by 2.8 million if current ACC/AHA guidelines were used with increase in use in mostly elderly individuals without cardiovascular disease (CVD).^[28]

The new ACC/AHA guidelines have been studied for cost-effectiveness in simulation models. Zhuo studied two groups in particular; diabetic individuals without ASCVD and nondiabetics with LDL-C between 70 and 189 mg/dl and ASCVD risk above 7.5% by the pooled cohort equation. Using the benchmark of cost-effectiveness as \$50,000 expenditure per quality adjusted life year gained, intensive statin use was cost-effective in diabetic patients only if their CVD risk was > 10% (as against 7.5% recommended by the guidelines) while moderate statin use was not cost-effective if CVD risk was between 7.5% and 10% in nondiabetic, non-ASCVD group of patients.^[29]

Table 2: Risk groups which benefit with statin usage

Clinical ASCVD
Primary prevention: LDL-C level \geq 190 mg/dl
Primary prevention: Patients with diabetes age 40–75 years and LDL-C levels between 70 and 189 mg/dl*
Primary prevention: Patients aged 40–79 years without diabetes and LDL-C levels between 70 and 189 mg/dl*
*Estimate 10 years risk using Pooled Cohort Equation
Intensity of statin according to level of risk

Table 3: High and moderate intensity statins

Statin therapy	Daily dose	
	High intensity* (mg)	Moderate intensity** (mg)
Atorvastatin	40–80	10 (20)
Rosuvastatin	20 (40)	(5) 10
Simvastatin	-	20–40
Pravastatin	-	40 (80)
Lovastatin	-	40
Fluvastatin	-	40
Pitavastatin	-	2–4

*Reduce LDL-C by \geq 50%, **Reduce LDL-C by 30–<50%. Doses in bracket approved by FDA but not proven in trials. Adopted from Stone *et al.*^[1] LDL-C: Low-density lipoprotein cholesterol, FDA: Food and Drug Administration

INDIAN PERSPECTIVE

Coronary artery disease in Indians

The prevalence of CVD is increasing in India. As per an estimate by Public Health Foundation of India, in 2011; there were 30 million patients with CHD, in India. The prevalence of paralytic stroke is between 334 and 424 per 100,000 in urban areas and between 244 and 262 per 100,000 in rural areas. The mortality due to CVD is projected to rise to 4.2 million by 2030.^[30] Certain characteristics of CAD in Indian population differ from the Caucasian population [Table 4].

The cardiovascular risk prediction scores used in the west do not predict accurately the cardiovascular risk in Indian population. Khanna *et al.* found FRS grossly underestimated the risk in young Indians with angiographically proven CAD. As discussed Indians develop CAD a decade earlier as compared to Caucasian population, hence, FRS is of limited use in predicting cardiovascular risk. The presence of metabolic syndrome, on the other hand, provided a much stronger correlation than FRS with angiographically proven CAD.^[39] In another study on an Indian population, three commonly used scores (FRS, British, European), underestimated the risk in a cohort whose one family member had early onset CAD. The plasma biomarkers such as apolipoprotein A1 (Apo A1), Apo B, lipoprotein (a) showed incremental levels between low, intermediate, and high risk groups (based on risk scores).^[40] The new risk prediction tool proposed by the ACC/AHA guidelines is likely to be inaccurate in predicting cardiovascular risk in Indians as the inclusion age for individuals is more than 40 years and does not include any nontraditional risk factors. Thus, it is apparent that indigenous risk prediction scores are required for prediction of cardiovascular risk in Indian population.

Statin use in Indians

Pharmacokinetic studies suggest that Indians achieve higher levels of circulating statins compared to the Caucasian population when administered equivalent doses. A study conducted in Singapore has revealed that Asian Indians achieved 1.68 the plasma levels of rosuvastatin when

compared to the Caucasian population when administered single 40 mg dose of rosuvastatin.^[41] The United States Food and Drug Administration recommends a starting dose of 5 mg for rosuvastatin for Asian Indians.

There are limited studies, which have tested efficacy and safety of statins in Indian population. IRIS (Investigation of Rosuvastatin in South Asian Subjects) trial was conducted in patients of South Asian origin with hypercholesterolemia settled in United States and Canada. They were randomized to receive rosuvastatin 10 or 20 mg or Atorvastatin 10 or 20 mg for 6 weeks. LDL-C decreased by 45% with rosuvastatin 10 mg versus 40% with atorvastatin 10 mg ($P = 0.0023$) and by 50% with rosuvastatin 20 mg versus 47% with atorvastatin 20 mg ($P = \text{NS}$). In addition, both drugs were well-tolerated and were without significant side effects.^[42] PURE-ACS study was an open label study, which compared the reduction in LDL-C levels in patients with acute coronary event presenting within, 10 days to seven cardiology centers across India. The patients were randomized to receive either atorvastatin 40 mg or atorvastatin 80 mg. A dose-dependent response was observed with a greater reduction of LDL-C in atorvastatin 80 mg (27.5% vs. 19.04%) than that of atorvastatin 40 mg group at the end of 12 weeks. No significant adverse were observed in both groups.^[43]

One of the important determinants for statin induced myopathy is the presence of solute carrier organic anion transporter family member 1B1 (SLCO1B1) variants. SLCO1B1 gene encodes membrane-bound sodium-independent organic anion-transporting polypeptide 1B1 that is involved in an active cellular influx of statin in hepatocytes. The SLCO1B1 (c. 521T > C) C allele causes lower statin uptake in the liver and is a risk factor for simvastatin induced myopathy. The variant, prevalent in 15% of the Caucasian population, is responsible for more than 60% of cases of myopathy.^[44] A study from Kerala showed the presence of this variant in 15% of population, which was surveyed.^[45]

Choudhry *et al.* analyzed prescription data in India, during the period 2006–2009 and found that 8000 per 100,000 patients with CHD were receiving statins. The data indicated that a statin were being under prescribed as compared to western countries. Atorvastatin accounted for 80% of all prescriptions and was being produced by 62 manufacturers during that period.^[46] Another study showed a disparate price variation of 1108.33% between five brands of atorvastatin 10 mg.^[47] With a likely increase in patients with CHD and increase in the frequency of statin prescription, studies on the bioequivalence of various generic preparation of statins and a cap on prices is needed.

Table 4: Unique features about CAD in South Asians

Five-fold more prone to myocardial infarction and cardiovascular death compared to Caucasians^[31]

Prone to develop CAD before 40 years of age^[32]

High prevalence of highly atherogenic small dense LDL^[33,34]

Higher incidence of metabolic syndrome and atherogenic dyslipidemia (small dense LDL, high triglyceride, and low HDL)^[35,36]

High levels of lipoprotein(a) a potent atherogenic lipoprotein^[37]

Elevated prothrombotic and pro-inflammatory markers^[38]

CAD: Coronary artery disease, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

APPLICABILITY OF CHOLESTEROL GUIDELINES IN INDIANS

The management of dyslipidemia in Indians has been along lines of NCEP ATP III recommendation. The recent ACC/AHA guidelines have made a radical departure from previous guidelines and have brought forth few issues, which need to be addressed. It has simplified the management of dyslipidemia by identifying the groups most likely to benefit [Table 2]. Whereas, the use of statins in certain population (preexisting ASCVD, diabetics, LDL > 190 mg/dl) is proven, the dosage recommended (high intensity vs. moderate intensity) needs deliberation. The IRIS trial has demonstrated Indians achieve up to 50% reduction in LDL levels even with moderate intensity statins. The risk of new onset diabetes has been noted to be more in the inpatients on higher intensity statins as compared to moderate intensity statins; the incidence was increased in those with metabolic syndrome.^[20] The Asian Indians have not constituted significant numbers in the major statin trials using high intensity statins.^[36] Will higher doses of statin in Indian population have a favorable cost-benefit ratio or would it increase the risk of side effects? Beyond scientific evidence, it has financial implication in a developing country like India.

The predictive value of Pooled Cohort Equation has not been tested in Indian population; hence its utility is limited. There is an urgent need to develop a cardiovascular risk prediction model tailored for Indian population. The ACC/AHA guideline favor use of statins over all other drugs affecting lipid metabolism; however the “atherogenic dyslipidemia” that is seen in Indian population is less likely to be affected, as statins exert its effect through reduction of LDL-C. Drugs like fibrates or niacin have been used to manage this “residual CVD risk,” but ACC/AHA guidelines do not favor their use due to lack of evidence for cardiovascular protection. Saroglitazar a molecule with agonistic activity on peroxisome proliferator-activated receptors α and γ receptors has been shown to have a favorable effect on atherogenic dyslipidemia, however, the evidence of cardiovascular benefit is lacking at this stage.^[48] The NCEP ATP III guidelines are still relevant in this subset of individuals with metabolic syndrome and atherogenic dyslipidemia. The guidelines dwell at length on the lifestyle measures to be followed; a useful tool for clinician managing such patient’s.

RECOMMENDATIONS

Making recommendations is a difficult task considering the complexity of the topic. The authors, however, suggest the following:

Table 5: Recommended areas of research for lipid management in Indians

Pharmacokinetic studies of statins in Indian population
Pharmacogenomic study for prevalence of SLCO1B1 gene variants in Indian population
Adverse events data of patients already on high intensity statins
Large studies on applicability of cardiovascular risk calculators to Indian population (Framingham, QRISK 2,^[49] and the newly introduced Globorisk^[50])
Cost-effectiveness studies on use of statins in primary prevention of cardiovascular disease in Indian population

SLCO1B1: Solute carrier organic anion transporter family member 1B1

- Forming a multi-disciplinary task force on formulating guidelines for lipid modification in Indian population
- In the intervening period, it may be prudent to follow NCEP ATP III guidelines for managing lipid abnormalities in Indian population
- Intensification of statin therapy to be considered in those with documented ASCVD and genetic hypercholesterolemia
- Certain area, where uncertainty exists, requires further research [Table 5].

CONCLUSION

The new ACC/AHA guidelines for managing have marked a radical change from previous guidelines on this subject. One needs to follow a pragmatic approach; there is no denying that it has simplified managing patients in the high risk group, however, dosage need not be the same as recommended. The previous ATP III guideline is still relevant to managing dyslipidemia in Indian population. There is an urgent need for research in key areas of lipid metabolism and assessing cardiovascular risk in Indian population. There is also a need for a multi-disciplinary task force to formulate guidelines for managing lipids to reduce cardiovascular risk in Indians.

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