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A Review Study of HIST Usage in Indian Patients - What Plays a Pivotal Role in the Indian Setting. (PMS-HIST Study)

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ABSTRACT

Background: To examine the use of high-dose statin therapy in Indian patients, this post-marketing analysis aimed to understand physicians' responses to the use of HIST in CVD patients with high LDL cholesterol and triglycerides. Indians have a higher risk of CAD compared to Caucasians.
Main Body: A study was conducted in India where 1590 physicians received a questionnaire based on various parameters, data were collected and 1461 responses were finally included in the data analysis.
Recent lipid protocols recommend lowering low-density lipoprotein (LDL) cholesterol in patients with coronary heart disease. To validate the evidence for this recommendation, we conducted a clinical trial based on clinical experience in which physicians could share their views on statin use relative to their usual treatment.
Dyslipidaemia is the most important risk factor for myocardial infarction worldwide, Cholesterol levels are directly related to coronary artery disease in all studies.
A few years ago, randomized controlled trials showed that 1 mmol/L reduction in blood low-density lipoprotein (LDL) cholesterol with statin therapy was associated with a higher risk of heart disease. and death. Relative risk reduction (21% and 12%, respectively).
Conclusion: Overall, 87% of physicians prefer statin therapy for better clinical outcomes, as HIST is generally safe and effective. Compared with low-dose statin therapy for CAD and CVD, HIST provides additional benefits regardless of lower LDL cholesterol levels. Doctors recommend that patients at higher risk be treated with HIST.
More clinical studies are needed to determine which is the best LDL cholesterol target, the role of HIST in patients without heart disease, and the role of concomitant therapy.

Keywords: High-Intensity Statin Therapy, Cardiovascular Disease, Coronary Atherosclerosis Disease, Flat Pricing

List of Abbreviations:

PMS – Post Marketing Surveillance
HIST – High-Intensity Statin Therapy
LDL – Low-Density Lipid
CVD – Cardio Vascular Disease
CAD – Coronary Atherosclerosis Disorder
ACC – American College of Cardiology
AHA – American Heart Association
FRS – Framingham Risk Score

INTRODUCTION

This PMS study is focusing on the clinician's experience in an Indian setting regarding the use of HIST in Indian patients with risk factors and how is HIST impacting clinical outcomes. Total responses were taken for analysis the data representation is done in percentage to show the confidence and clinical experience of Indian clinicians regarding the use of HIST in their daily routine. Although several studies have compared high-intensity statins with low- or moderate-intensity statins, most have focused on evaluating the effectiveness of these therapies in reducing CVD events and improving prognosis. According to an analysis of safety data, high-intensity statin medication is also accompanied by an increase in adverse events and side effects, which could affect the adherence of CVD patients taking high-intensity statins. Although it is plausible that medication adherence may well be impacted by a higher possibility of adverse reactions from high-intensity statin therapy than those from low-intensity statin therapy, this topic has so far not received significant study attention in the literature. [1,2,3]

This has implications as healthcare providers adopt the recent cholesterol guideline into clinical practice. The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guideline on the treatment of blood cholesterol recommends high-intensity statin use in most patients with cardiovascular disease (CVD).

In addition to preserving the integrity of cell membranes and producing bile acid, steroid hormones, and vitamin D, cholesterol is crucial for the body's metabolism. [4,5,6]

Animal studies and genetic abnormalities affecting cholesterol metabolism are evidence that cholesterol is a significant risk factor in the development of atherosclerosis. Russian physician Nikolay Anichkow showed in 1913 that rabbits fed a diet high in cholesterol developed severe atherosclerosis of the aorta. In the absence of any other known risk factors, individuals with genetic forms of hypercholesterolemia develop premature atherosclerosis at a young age. Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and very LDL-C constitute 60–70%, 20–30%, and 10–15% of the total cholesterol. LDL levels and the rate of coronary heart disease (CHD) onset in men and women who are initially disease-free are directly correlated, according to large epidemiological studies like the Framingham Heart Study and Multiple Risk Factor Intervention Trial. [7]

Therefore, keeping the risk of ASCVD as a target to reduce LDL cholesterol. [8][21]

HIST OUTLOOK AND REVIEW

Coronary artery disease in Indians:

According to a gauge by the Public Health Foundation of India, in 2011; there were 30 million patients with CHD, in India. In urban areas, the rate of paralytic stroke is between 334 and 424 per 100,000 people, whereas in rural areas, it is between 244 and 262 per 100,000 people. By 2030, CVD-related mortality is expected to reach 4.2 million.

The Indian population has CAD which is distinct from the Caucasian population in several ways. The Western cardiovascular risk prediction scores do not accurately reflect the cardiovascular risk of the Indian population. Khanna et al. discovered that FRS grossly underestimated the risk among young Indians with angiographically proven CAD. As previously mentioned, Indians develop coronary artery disease a decade earlier than Caucasians do, so FRS is of limited use in predicting cardiovascular risk. In contrast, a correlation with angiographically demonstrated CAD was significantly stronger when metabolic syndrome was present than when FRS was present. Three commonly used scores- FRS, British, and European - underestimated the risk in an Indian cohort with one family member with early-onset CAD in another study. Based on risk scores, the levels of plasma biomarkers like apolipoprotein A1 (Apo A1), Apo B, and lipoprotein (a) varied incrementally between the low, intermediate, and high-risk groups. Because

the inclusion age for individuals is greater than 40 years old and it does not include any non-traditional risk factors, the new risk prediction tool that was proposed by the ACC/AHA guidelines is likely to be inaccurate in predicting cardiovascular risk in Indians.

As a result, indigenous risk prediction scores are required for cardiovascular risk prediction in the Indian population. Indians use statins Pharmacokinetic studies indicate that when given the same doses, Indians have higher levels of circulating statins than Caucasians. A review directed in Singapore has uncovered that Asian Indians accomplished 1.68 the plasma levels of rosuvastatin when contrasted with the Caucasian populace when controlled a single 40 mg portion of rosuvastatin. For Asian Indians, the Food and Drug Administration of the United States recommends a starting dose of 5 mg of rosuvastatin.

Statins' efficacy and safety have only been the subject of a few studies in the Indian population. IRIS (Examination of Rosuvastatin in South Asian Subjects) preliminary was led in patients of South Asian beginning with hypercholesterolemia got comfortable US and Canada. They were randomly assigned to receive either 10 or 20 mg of Atorvastatin or 10 or 20 mg of Rosuvastatin for six weeks.

LDL-C diminished by 45% with rosuvastatin 10 mg versus 40% with atorvastatin 10 mg (P = 0.0023) and by 50% with rosuvastatin 20 mg Vs 47% with atorvastatin 20 mg (P = NS). Apart from this, both drugs were well-tolerated and no significant side effects were observed. The open-label PURE-ACS study compared the reduction in LDL-C levels of patients with acute coronary events presenting within 10 days in seven Indian cardiology centers. Atorvastatin 40 mg or 80 mg was assigned to each patient in a randomization scheme. A dose-dependent reaction was seen with a more noteworthy decrease of LDL-C in the atorvastatin 80 mg (27.5% versus 19.04%) than that of atorvastatin 40 mg bunch toward the finish of 12 weeks.

In either group, there were no significant side effects. The presence of variants of the solute carrier organic anion transporter family member 1B1 (SLCO1B1) is an important determinant of statin-induced myopathy.

SLCO1B1 quality encodes membrane-bound sodium-independent natural anion-moving polypeptide 1B1 that is associated with a functioning cell convergence of statin in hepatocytes. SLCO1B1 (c. 521T > C) C allele is a risk factor for simvastatin-induced myopathy and lowers liver statin uptake. More than 60% of cases of myopathy are caused by the variant, which is found in 15% of Caucasian people.

A survey of 15 percent of the population in Kerala found this variant to be present. Choudhry and co-analysed prescription data from 2006 to 2009 in India and discovered that 8000 out of every 100,000 CHD patients were taking statins.

According to the data, statins were being prescribed at a lower rate than in Western nations.

62 manufacturers were producing atorvastatin, which was responsible for 80% of all prescriptions during that time. According to a different study, the prices of five brands of atorvastatin 10 mg varied by 1108.33 percent.

Studies on the bioequivalence of various generic statin preparations and a price cap are required considering the likely rise in CHD patients and statin prescriptions. [9]

MATERIALS & METHODS

A structured questionnaire was developed and designed and then given to trained people to gather the data from selected clinicians pan India. Once we received the data sheets filled and signed and stamped by the designated clinicians.

The filled data sheets were taken into consideration for final analysis. Each parameter is analysed and posted in the analysis segment for understanding. The Percentage of Clinicians who agreed or disagreed with the questions asked is posted here in graphical tables for further understanding.

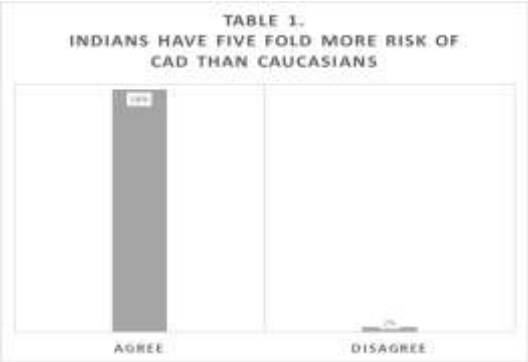
However, further exhaustive PMS is advisable to make a definitive conclusion for the larger good and better patient care management in Indian settings.

STATISTICAL ANALYSIS

The survey questionnaire was given to the clinician who treats CVD as one of their main chronic conditions among patients [8,9,10,11,12,13,14].

The Indian population is at a multi-fold more risk of developing Coronary arteries Disorder than Caucasians which is evident from the response we got from the clinicians. As per the response, 98% of clinicians agree (Table. 1) that Indians are prone to develop CAD.

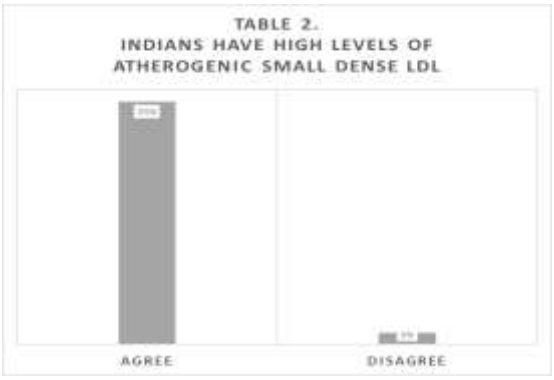
RESULTS



Recent data suggest that both genetic and epigenetic factors might induce the expression of this specific lipid pattern (Atherogenic).

In addition, a typical finding of an increase in small, dense LDL particles was confirmed in various groups of patients who had a higher risk of cardiovascular disease. The fact that small dense LDL is a distinct cardiovascular disease risk factor emphasizes the clinical significance of both the quantity and quality of LDL.

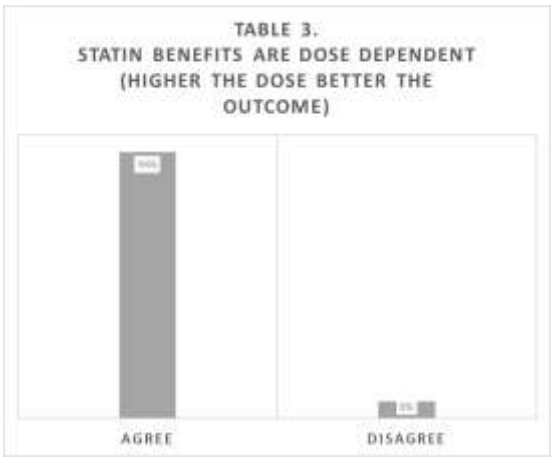
To avoid cardiovascular problems, atherosclerotic disease management should be taken into account the presence of small dense low-density lipoprotein (LDL).[15]



These findings are reiterated by the finding in PMS that Indians do have high levels of atherogenic small-dense LDL which could be one of the risk factors prevailing in Indian settings with 95% of clinicians (Table. 2) finding in their patients during their clinic practicing days.

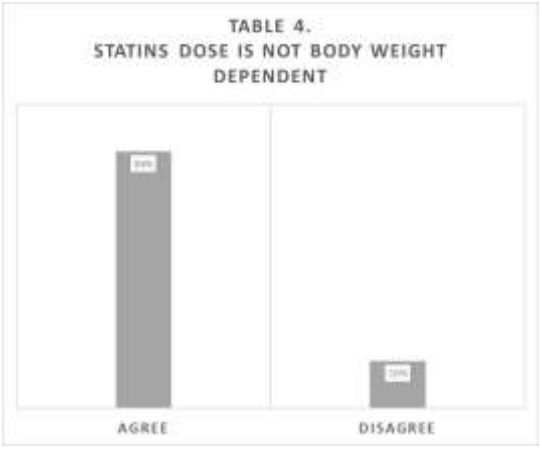
There is now compelling evidence that Asians benefit clinically from taking a higher statin dose than they do from taking a lower one, just like white people do.

When compared to using a statin at a lower dose, there was no evidence of significant side effects. Those taking a higher dose of statins had a significantly lower risk of experiencing an ASCVD event in addition to a greater reduction in LDL cholesterol. [16]



94% of Indian clinicians (Table. 3) have agreed that the higher doses of statin outweigh the risks and benefits as per their individual clinical experience with dyslipidaemia patients over the years of clinical practice in the Indian demographic region.

The higher the statin dose better the outcome can be seen in (Table. 4) wherein 84% of clinicians agreed that a higher dose of statins would give better outcomes in managing dyslipidaemia in Indian patients.

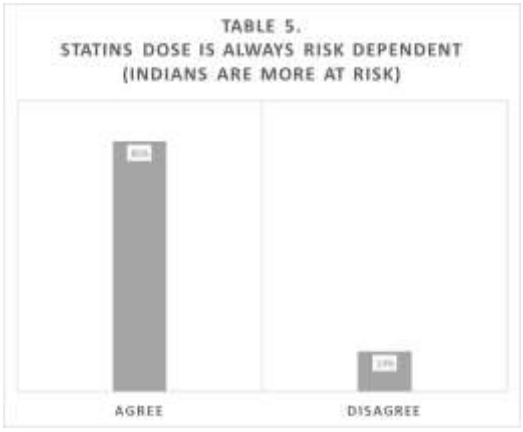


Notwithstanding this cost is one more central point that becomes possibly the most important factor with statin treatment in emerging countries. Rosuvastatin, which costs a lot, can be replaced at a lower cost with generic Atorvastatin. This distinction is crucial in a setting with low to moderate income because higher costs may result in low adherence and even unreported discontinuation. Atorvastatin might be a more cost-effective option in such a scenario if it turns out to be comparable in terms of effectiveness. The comparative effectiveness of the two high-dose statins on cardiovascular outcomes in developing countries remained largely unknown.

The most effective medications for lowering LDL cholesterol are statins. There is a lot of evidence to suggest that statin therapy significantly reduces mortality and morbidity for primary and secondary cardiovascular disease prevention.

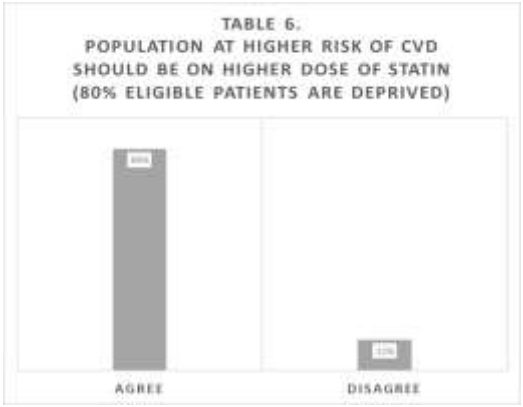
The most common side effect of taking statins is myalgia, which affects anywhere from 1% to 10% of patients. The most serious side effect of taking statins is rhabdomyolysis, which occurs in less than 1% of patients. [17]

Statin dose is always risk dependent, that is what Indian Clinicians feel as 86% of clinicians (Table. 5) have observed over the years of their clinical practice in an Indian Setting.



The first objective for patients with ASCVD, as stated in the AHA/ACC/MS guidelines, is to reduce LDL-C levels by 50% or more. In the US, numerous clinicians accept that a sensible LDL-C objective for patients with ASCVD is under 70 mg/dL. This conviction depends on past proposals from public associations for patients who have ASCVD and various high-risk conditions. An LDL-C threshold of 70 mg/dL was specified in the 2018 AHA/ACC/MS guidelines for the consideration of the addition of non-statin therapy to a maximal-dose statin when treating ASCVD patients at very high risk. Patients at very high risk should aim for an LDL-C level below 70 mg/dL, according to this value. [18]

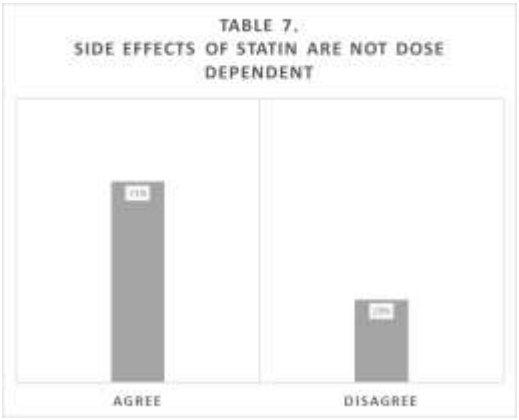
This also implies the data that confirms that 88% of clinicians (Table. 6) have an experience that ~80% of their patients may be eligible for HIST.



However, this is noteworthy that in a developing country like India, most of the patients may be eligible for high-intensity statin therapy but are not prescribed owing to the cost of the therapy which in turn increases the disease burden on society at large.

Statins, or 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, have been shown to lower the risk of death and cardiovascular events in ACS patients.

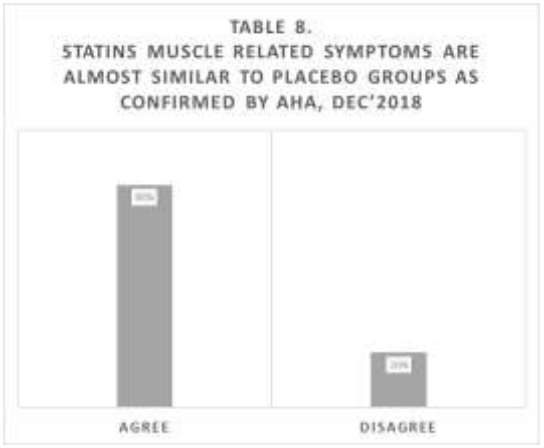
The American College of Cardiology recommended high-intensity statin treatment for ST-elevation myocardial infarction (MI) management in ACS cases, with a level of evidence of B, based on the MIRACL study, which evaluated the effects of atorvastatin at 80 mg versus (vs.) placebo, and the Prove-it trial, which compared pravastatin (40 mg) and atorvastatin (80 mg). [19]



While 71% of clinicians (Table. 7) agree that the high statin therapy may not be associated with a major side effect profile. Hence, the benefits versus side effect ratio should be considered while prescribing high doses of statins to eligible patients.

However, the muscle-related symptoms were almost similar to the placebo which is what 80% of clinicians (Table. 8) have experienced during their clinical practice over the years.

Myalgia and other symptoms associated with it have been observed and reported in a few studies involving high doses of statins. Five of the 16 trials reported that 164 people (4.99%) who received high-intensity statin therapy developed myopathy or myalgia, while 97 people (2.98%) received standard statin therapy.



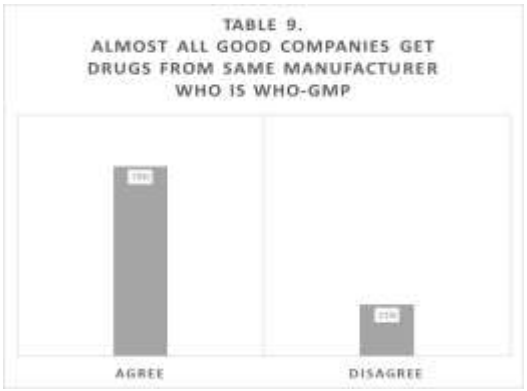
Rhabdomyolysis was seen in one patient in the IDEAL subgroup concentrate on who got standard statin treatment. In contrast, 42 individuals (0.84 percent) in the standard statin group had elevated serum aminotransferase and/or liver aminotransferase levels, compared to 96 individuals (1.84 percent) in the high-intensity statin group. [19]

In the Indian market where you can find three types of medicines being marketed, branded, branded generics, and generics. However, one can get the quality in branded and branded generics however generic medicines doesn't have any check, unlike the West.

Therefore, branded generics remain mostly an option for clinicians to prescribe to patients where quality remains a priority.

That is why 79% of clinicians (Table. 9) have confidence in WHO-GMP manufacturing practices and they are more likely to prescribe these types of medicines to their patients.

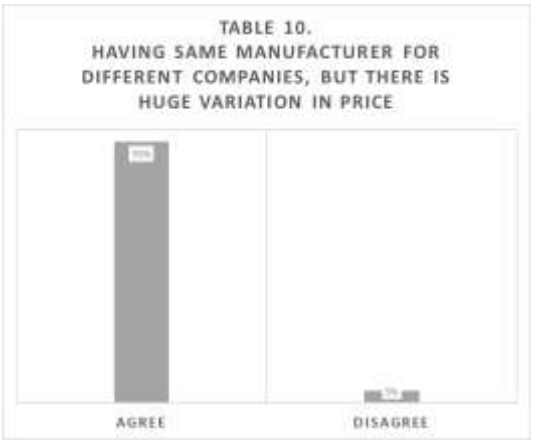
Now, price parity remains another challenge for practicing clinicians who see hundreds of patients on a daily basis. Same manufacturer when offers to many marketing companies. Hence, it is imperative that marketing companies put up MRP as per their need and wants. In the end, patients are paying a high price for that same branded generic medicine.



In India, 95% of clinicians (Table. 10) agree that even with the same manufacturer for different companies, there is a huge variation in price. This calls for the Flat Pricing strategy which is evidence-based and globally practiced.

Multiple dosage forms, or different concentrations of the active ingredient in a single tablet or capsule, are frequently available for medications. Offering various measurement structures represents varieties in human physiology, guarantees that the item is accessible to many possible clients, and builds the potential market size for the medication.

At the point when new brand-name numerous measurements drugs are at first showcased valuing procedures, or the steepness of evaluating, the organizations use can go from making each of the doses accessible at a similar cost, wonderful level estimating, to consummate monotonic evaluating by which the cost is corresponding to the strength of the prescription, e.g., as the dose doubles so does the cost. [20]



Companies spend more money on provincial governments when they use monotonic pricing instead of flat pricing. Because the cost is the same regardless of the prescribed dosage, public drug plans benefit from flat pricing. [20]

Flat Pricing may play a vital role in deciding the statin therapy dose and will help clinicians to increase the adherence levels in developing countries like India which is evident from the data collected. Keeping in mind that the manufacturing cost of all strengths is almost similar from the same manufacturing unit thus patient need not bear the extra cost burden when the clinician is titrating to the right dose. And 90% of clinicians (Table. 11) agree that doubling the dose should not lead to doubling the price of the same medicine.

CONCLUSION

This PMS study sheds light on the use of statins in clinical practice and suggests that patients might benefit from high-intensity statin therapy. However, the cost has a significant impact on adherence and addressing the clinicians' clinical inertia. As a result, Flat Pricing offers price parity which will undoubtedly contribute to the reduction of clinical inertia and the facilitation of patient compliance with medically recommended treatments for better clinical outcomes.

Declaration by Authors

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