Do We Achieve target Lipid Levels with Statins in Patients with Coronary Artery Disease?

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ABSTRACT

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The lipid profile of 852 consecutive angiographically proven coronary artery disease(CAD) patients, who were on primary treatment with statins were analyzed to see whether they have achieved target Adult Treatment Panel III (ATPIII) goals. Mean age of the population was 53.6 +/- 7.9 years and there were 645 males (75.7%). These patients were on statins for a minimum period of 6 months (average 10.3 + 2.2 months). Lipid values before initiation of statin treatment were available only in 446 patients. 72% of the patients were taking atorvastatin (mean dose 15.9mg), 23% were on simvastatin (mean dose 16.0mg) and 4% were on lovastatin (14.5mg) at follow up. Only 359 (42.2%) of patients achieved low-density lipoprotein cholesterol goal of <100mg% on treatment with statins. 59.1% of the population were having a high density lipoprotein levels > 40 mg%. Triglyceride levels <150 mg% was seen in 81% of the study population. This data is in accordance with studies in the western population. This finding addresses to the need for better strategies in clinical practice to achieve lipid targets. The causes of the problem and the possible solutions are discussed.

Keywords: Statins, Cholesterol, Target Lipoprotein Levels, Coronary

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A history of coronary artery disease (CAD) increases the relative risk of subsequent cardiovascular morbidity and mortality by 5 to 7 times. Many large studies have shown the safety and efficacy of HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors, commonly known as statins, in CAD.[1,2,3] In a meta-analysis of 69511 individuals from 19 placebo-controlled studies on patients with CAD, it was found that statin therapy significantly reduced mortality and morbidity.[4]

Despite the large body of data demonstrating the impact of lowering low density lipo-protein cholesterol (LDL-C) on reducing CHD risk, current evidence suggests that statins are underutilized and many studies have shown that majority of the patients do not achieve target lipid levels[5,6,7,8,9,10,11,12] set by the National Cholesterol Education Program -Adult Treatment Panel III (NCEP - ATP III).[13]

The data on target lipid levels among patients from India are lacking. We took up this study to find out whether Indian patients with CAD are achieving target lipid levels and discuss the problems and the possible solutions.

MATERIALS AND METHODS

852 consecutive patients with angiographically proven coronary artery disease, who were on primary treatment with statins formed the patient population. There were 645 males in the study population (75.7%) and the mean age was 53.6 +/- 7.9 years. These patients were on statins for a minimum period of 6 months (average 10.3 $\pm$ 2.2 months). The study was during the period from January 2004 to November 2004.

NCEP ATP III guidelines defines a target of <100 mg/dL (2.6 mmol/L) for patients with CAD. Lipid profile was done by auto-analyzer Dade BehringTM. LDL-C values were calculated indirectly by Friedewald equation,14 LDL-C = Total Cholesterol – high density lipoprotein cholesterol (HDL-C) – triglycerides/5. Those patients who had triglycerides of more than 500 mg% were excluded from study. Values were expressed as mean +/- SD.

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RESULTS

Lipid values before initiation of statin treatment were available only in 446 patients. This was because, most of the patients were initiated on statins by primary treating physicians and later referred to our centre for further treatment of CAD. 72% of the patients were taking atorvastatin (mean dose 15.9mg), 23% were on simvastatin (mean dose 16.0mg) and 4% were on lovastatin (mean dose 14.5mg) at follow up. The pre-treatment values and lipid values at last follow-up is given in Table 1.

Table 1. Lipid levels before and after treatment

	Pre treatment Values N=446	Follow up values (N=852)	Number of patients achieving target lipid levels
Total Cholesterol	248.6 + 29.3	178.7 + 29.4	
HDL cholesterol	41.4 + 8.8	43.7 + 7.7	(>40mg/dl) 503(59.1%)
LDL cholesterol	171.3 + 33.3	105.1 + 26.3	(<100 mg/dl) 359 (42.2%)
Triglycerides	163.7+ 53.2	133.2 + 54.0	(<150 mg/dl) 690(81%)

(All fasting values in mg/dl. HDL-High density lipoprotein cholesterol, LDL-Low density lipoprotein cholesterol)

Only 42% of patients achieved LDL-C goals on treatment with statins. Though a specific goal is not set by the NCEP -ATPIII, HDL-C level of >40 mg/dl is considered as desirable and triglyceride level of <150 mg% is considered normal. About 60% of the patients were having an HDL-C value of >40 mg/dl, on follow-up. Eighty one percent of the patients had triglyceride levels below 150 mg% at last follow-up.

DISCUSSION

Dyslipidemia is an established risk factor for CAD. Benefits of cholesterol lowering were reported in secondary-prevention trials[1,2,3] in which the incidence of recurrent myocardial infarction (MI) was decreased approximately by 30% and the risk for coronary death decreased by 20% to 40%. The results of the above landmark statin trials have formed the basis for the treatment guidelines for the prevention of CAD.[13]

Recent large trials have confirmed the safety and efficacy of statins.[15,16] Based on the results of recent trials the coordinating committee of the National Cholesterol Education Program has recommended that when risk is very high, even an LDL-C goal of <70 mg/dl is a reasonable clinical strategy.[17]

Despite the strong data of the benefit of cholesterol lowering, dyslipidemia is under-treated. In a study by Frolkis et. al. it was found that physicians obtain an LDL-C value in their high-risk coronary artery disease patients only 50% of the time.[18] In one study from Germany it was found that there was very low prevalence of lipid-lowering treatment[7] (65.5% of patients did not receive any medication at all)

The REALITY Study showed that only 20.2% of CHD/CHD equivalent patients attained LDL-C goal during the study period average study follow-up of 3.6 years.[6] In a study on secondary prevention from Germany, it was found that only 2.7% patients had LDL-C levels <100 mg/dl at 6 weeks of therapy.[7] In our study also, only 42% in the treated group reached target LDL-C levels, which means that majority of Indian patients are also not reaching target LDL-C goals.

Even though the NCEP- ATP III recommendation[13] is to begin statin therapy at low doses and to titrate if cholesterol goals are not met, most patients remain on initial doses of statins. In the LIPI-WATCH study,[20] 77% of patients were maintained on the starting dose. In another study by Marcallino et.al,[21] 88% of patients who did not achieve their LDL-C goal were maintained on the same dose of statin for at least 1 year, and only 3% were receiving the maximal dose. In our study also, the mean atorvastatin dose was 15.8 mg, which is much below the doses in major studies (80 mg/day). Persistence with therapy is another challenge, as more than 70% of patients fail to maintain their therapy beyond 12 months.[8] The data regarding persistence of therapy was not evaluated in our study as it was a "point of time analysis".

The mean basal HDL-C values were > 40 mg%, but after treatment with statins for about 10 months in our study, the percentage of patients with HDL-C > 40 mg% was 59%. Statins is supposed to increase HDL-C levels by 6%. In this study also there was 5.6 % increase in HDL-C. Still 40 % of the patients were having HDL values less than 40 mg%. After life style modification, the most effective means of elevating HDL is by nicotinic acid. Though the long acting preparations of nicotinic acid are comparatively safer and better tolerated, the chance of serious side effects especially in combination with statins and the need for frequent monitoring makes it less attractive.

Triglyceride levels also came down with statin treatment in our patient group. Statins are supposed to bring down triglyceride levels by 10-35%. Level of reduction will depend upon the basal triglyceride levels.[15] In this study triglycerides levels were brought down by 18.7 %. The lower magnitude of reduction is because the

baseline triglyceride values were lower. No target levels of triglycerides were proposed by NCEP-ATP III. But 81% of our patients were having a value of less than 150 mg%, which is considered normal. But in our study, patients with triglyceride levels more than 500mg% were excluded. So this study may not be reflective of the true picture regarding triglycerides.

There are concerns about the safety of statins. The publicity of cerivastatin withdrawal from the market following reports of deaths due to rhabdomyolysis and subsequent renal failure, made the physician community concerned about the safety of statins.

But recent large trials showed that statins are well tolerated and the incidence of adverse effects is low. Rhabdomyolysis is the most significant adverse effect associated with statin therapy. In the Heart Protection Study, rhabdomyolysis occurred in 0.05% of patients receiving simvastatin (40 mg/d) compared to 0.03% of those receiving placebo.[15] Serious hepatic toxicity is also reported to be very rare.[15]

The cost of the drug is also a factor especially in developing countries like India. Statins also require regular laboratory checks to monitor drug toxicity. This is difficult in third world countries due to cost factors and also due to lack of patient motivation. These factors may also discourage dose titration to achieve LDL-C treatment goals.

How can we tackle this problem?

Most of the plasma LDL-C–lowering effect with a statin is achieved with the starting dose, with each subsequent doubling of dose producing 6% greater reduction in level of plasma LDL-C.[22] Dose titration increases the cost of the drug, additional costs are involved for follow-up hospital visits for consultation and laboratory monitoring and there is increased chance of drug toxicity.

Treating with more potent statins is an option to overcome this. The CURVES trial[23] and a study by Ernst J. Schaefer et al,[24] showed that atorvastatin produced significantly greater reductions in levels of plasma LDL-C than did the other statins (fluvastatin, pravastatin, lovastatin, and simvastatin) at all milligram-equivalent doses.

The STELLAR trial[25] and a post-hoc analysis of data from 6 randomized, double-blind, active-controlled trials[26] demonstrated clinical superiority of rosuvastatin over atorvastatin, pravastatin, and simvastatin in reducing LDL-C levels and in enabling patients to reach goals.

Switching to a more potent statin was tried in Mercury study[27] and it was found that that switching to a more efficacious statin like rosuvastatin is an effective strategy to improve lipid goal achievement in patients requiring lipid-lowering therapy.

Since the cost do not vary much among different statins in Indian market, it will be more cost-effective to start a potent statin like atorvastatin or rosuvastatin. It is said that the best approach in achieving LDL-C goals may be the use of a statin with maximal efficacy for LDL-C reduction, enabling most patients to achieve their treatment target with a low dose of a single drug, a simple regimen, and a low risk of side effects.[8]

Another option to achieve lipid goals is to try combination therapy. Many combination treatments have been tried with statins like niacin, fibrates and the cholesterol absorption inhibitor, ezetimibe.

The benefit of combination therapy is that the dose of the statin can be kept low, thereby reducing the potential for causing dose-related adverse effects. Disadvantages to using combination therapy are the added risk of hepato-toxicity and myo-toxicity. The need for frequent monitoring and the potency to side effects makes the combination of statin-fibrate and statin-niacin, a difficult option in India.

But the combination of cholesterol absorption inhibitor, ezetimibe with statin, with its minimal incidence of side effects may hold promise, as another option for adding to a statin's LDL-C-lowering efficacy. The Ezetimibe study group found that the addition of ezetimibe to atorvastatin provides a more effective and safe means for reducing LDL-C levels than doubling the dosage of atorvastatin.[28]

Another method to achieve LDL-C goals is to have an aggressive focused treatment strategy. The Alliance study sought to determine if an aggressive, focused (LDL-C)-lowering strategy was superior to usual care for patients with CAD. NCEP-ATP III goals were more likely to be met in patients on aggressive focused therapy compared with those receiving usual care.[29]

CONCLUSION

This data in Indian patients is in accordance with studies in the western population, which shows that majority of patients with CAD are not achieving target LDL-C levels with treatment with statins. This finding addresses to the need for better strategies in clinical

practice to achieve lipid targets. The best strategy may be to initiate treatment with a more potent statin and to add ezetemibe if LDL goals are not achieved. For those patients already on statins, if goals are not achieved, switching to a more potent statin is an option. Aggressive focused therapy by the physician is important. Patient education to initiate lifestyle modification with diet and exercise must be an integral part of the strategy. Physician awareness should increase.

END NOTE

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