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IMPACT OF DIFFERENT STARTING DOSES OF ATORVASTATIN ON REACHING TARGET LOW DENSITY LIPOPROTEIN CHOLESTEROL LEVELS AND HEALTH RELATED QUALITY OF LIFE IN DYSLIPIDEMIC PATIENTS

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Abstract : Objectives : 1. To compare the percentage of patients that reach target LDL-C goals with 10 mg Vs. 20 mg of atorvastatin as a starting dose. 2. To compare Health Related Quality of Life (HRQOL) in patients on 10 mg Vs. 20 mg of atorvastatin.

Methods : A prospective, double blind, parallel groups, unicentric study of patients of dyslipidemia, randomized to receive atorvastatin 10 mg (n=75) or atorvastatin 20 mg (n=75) once daily for 12 weeks. Safety reporting of incidence of adverse events was done.

Results : Significantly more number of patients ($P<0.05$) reached target LDL-C levels at the end of 12 weeks in the 20 mg group (77.27% in the high risk group, 100% in moderately high risk group and 100% in the moderate risk group) when compared to 10 mg group (32% in the high risk group, 75% in moderately high risk group and 83.33% in the moderate risk group). Increase in HRQOL at the end of 12 weeks was also significantly greater ($P<0.001$) in 20 mg group (27.89%) vs. 10 mg group (19.26%).

Conclusions : Selecting the starting dose of atorvastatin according to the patients risk category (by using the Framingham's algorithm for calculating cardiovascular risk) and the percentage reduction in LDL required, will result in greater success in achieving LDL goals and better quality of life.

Key words : atorvastatin dyslipidemia LDL-C goal quality of life

INTRODUCTION

Dyslipidemia is a broad term that refers to a number of lipid disorders. Eighty percent of the lipid disorders are related to diet and lifestyle, whereas the other twenty percent are familial disorders (1). Statins are the most effective and best-tolerated agents for treating dyslipidemia. Statins are a class of cholesterol-lowering drugs that are competitive inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-

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CoA) reductase, which catalyzes an early, rate-limiting step in cholesterol biosynthesis. Statins occupy a portion of the binding site in HMGCoA, thus blocking access to the active site (2). A number of trials have demonstrated the efficacy of statin treatment in reducing fatal and nonfatal coronary heart disease (CHD) events, strokes, and total mortality (3).

The effectiveness of statins in lowering low density lipoprotein cholesterol (LDL-C) varies per milligram dose. Hence, for each statin, the dose required to achieve a target LDL-C reduction varies. Achieving LDL-C targets can be a long and difficult process. Target LDL-C levels are frequently not achieved in patients who require large reductions in LDL-C. Several dose titrations, typically months apart, are often required and some patients still do not reach the target. A treatment strategy that helps patients quickly achieve their LDL-C target will therefore not only have a positive clinical impact, as illustrated by recent studies comparing aggressive atorvastatin treatment with usual care (4, 5), it may also increase adherence to treatment.

Current statistics show that many dyslipidemic patients are not even diagnosed with dyslipidemia (6, 7, 8). Of those patients that are diagnosed, only a few receive treatment for this condition (9, 10). Current management of dyslipidemia is sub-optimal. Treatment of dyslipidemia is likely to reduce preventive morbidity and premature mortality and decrease the health care costs of expensive cardiovascular and hence it is important to treat dyslipidemia aggressively (5, 6, 7).

Despite an increasing body of evidence on the benefit of lowering elevated levels of low-density lipoprotein cholesterol (LDL-C), there is still considerable concern that patients are not achieving target LDL-C levels (11). The INTERHEART study demonstrated that traditional cardiovascular disease risk factors play an important role in the prediction of myocardial infarction in populations around the world, including South Asians (12). Multiple studies of migrant South Asian populations have, however, confirmed a 3- to 5-foldincrease in the risk for myocardial infarction and cardiovascular death as compared with other ethnic groups (13, 14, 15). Hence it is extremely important to study the how many patients of dyslipidemia would reach their target LDL- goals in the Indian context. To our knowledge there is currently no such study to test the efficacy of atorvastatin to reach target LDL levels in statin naïve Indian patients.

It is currently unknown whether aggressive lipid-lowering with a higher atorvastatin dose is indicated in Indian patients of dyslipidemia who have not had an acute coronary event (for e.g. myocardial infarction or stroke) in the past. Hence it would be worthwhile to compare the dose related effects of atorvastatin on lowering of lipid levels in patients of dyslipidemia who have not suffered from history or clinical evidence of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or clinically significant myocardial ischemia to determine the number of patients reaching the target LDL goals. It was also interesting to see the effect on the quality of life in patients receiving treatment at a

higher dose as compared to patients receiving treatment at a lower dose. The benefits of a higher dose therapy should be weighed carefully against the risk of adverse events. Hence, we also proposed to monitor the patients for the incidence of adverse events while on therapy with a higher dose and a lower dose of statin.

Hence the objectives of the above study were to compare the percentage of patients who reach LDL-C goals with 10 mg vs. 20 mg of atorvastatin as starting dose and to compare the incidence of adverse events in patients with 10 mg vs. 20 mg of atorvastatin in patients who had not suffered from an acute coronary event in the past; and to compare the improvement in Quality of life in patients on 10 mg vs. 20 mg of atorvastatin by calculating the Health Related Quality of life (HRQOL) score.

METHODS

The project was completed in Department of Pharmacology, Jawaharlal Nehru Medical College (J.N.M.C.) and Department of Medicine, Acharya Vinoba Bhave Rural Hospital (A.V.B.R.H.), Sawangi (Meghe), Wardha, Maharashtra, India.

The study was initiated after permission from the institutional ethics committee and written, informed consent from all participating subjects. The study was carried out according to the Indian Council of Medical Research (ICMR) guidelines for Biomedical Research in Humans (2006); and in compliance with the ICH/GCP Guidelines.

This study was comparative, randomized, double blind, parallel groups, single centre study. The patients of dyslipidemia attending outpatient department (O.P.D.) of Medicine were enrolled into the present study.

Inclusion criteria

1. Patients ≥18 years of age of either sex.
2. Patients who are willing to give written informed consent.
3. Dyslipidemic patients eligible for lipid lowering therapy at baseline, as determined by NCEP ATP III guidelines
   - ≥2 NCEP risk factors that confer a 10-year risk for CHD of >20%, LDL-C ≥100 mg/dL (2.6 mmol/L). - High risk group
   - Or ≥2 NCEP risk factors that confer a 10-year risk for CHD of 10% to 20%, LDL-C ≥130 mg/dL (3.4 mmol/L)- Moderately high risk group.
   - Or ≥2 NCEP risk factors that confer a 10-year risk for CHD of <10%, LDL-C ≥160 mg/dL (4.1 mmol/L)- Moderate risk group
4. Patients willing to adhere to a low fat diet as advised by the study investigator.

Exclusion criteria

1. Patients with history or clinical evidence of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.
2. Patients with history or clinical evidence

of non-coronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease, transient ischemic attacks or stroke of carotid origin or 50% obstruction of a carotid artery).

3. Patients with uncontrolled diabetes (i.e. fasting blood sugar > 140 mg/dl).

4. Impaired hepatic function (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥2 × the upper limit of normal [ULN]).

5. Uncontrolled hypertension (diastolic blood pressure >95 mm Hg).

6. Evidence of gastrointestinal disease limiting drug absorption or partial ileal bypass.

7. Secondary causes of hyperlipoproteinemia, defined as uncontrolled primary hypothyroidism (thyroid-stimulating hormone ≥1.5 × ULN).

8. Individuals with decompensated kidney function blood urea nitrogen ≥30 mg/dL, creatinine ≥1.2 mg/dL, or creatine kinase (CK) ≥3 × ULN.

9. Any decompensated metabolic/hormonal disorders.

10. Patients with clinically significant respiratory or haematological disorder or any other severe concurrent illness, or acute infection, gram negative sepsis or cancer within past 5 years.

11. Patients with current use of lipid lowering drugs (example- bile acid sequestrant, fibrate, nicotinic acid, fish oil), CYP 3A4 inhibitor (including cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, macrolide antibiotics) or oral corticosteroid.

12. Intolerance to statins at any time in the past.

13. Recent major surgery/illness/tissue injury/muscle injury/extensive burns.

14. Family history or past history of muscular disorders.

15. Excessive physical exercise of any form.

16. Patients who have experienced any unexplained muscle pain, tenderness or weakness in the past.

17. Participation in any clinical trial in the past six months.

18. Pregnant/Lactating mothers and women of childbearing potential not using medically accepted methods of contraception.

19. Active alcohol intake.

20. Drug or medication abuse within the last 6 months or any condition that would indicate the likelihood of poor subject compliance.

21. Subjects not willing to comply with the procedures described in this protocol.

22. Any serious or unstable medical or psychological condition that in the opinion of the investigator would compromise the patients safety or successful participation in the trial for e.g. physical examination, laboratory test, ECG.

Study procedure

At baseline, a thorough clinical examination and ECG was done which was followed by the baseline investigations. Patients were evaluated for lipid profile, liver function tests (LFT), fasting and post prandial blood sugar level and serum creatinine. Blood samples were tested in the Central Research Laboratory, A.V.B.R. Hospital. The patients were advised a low fat diet and anthropometry measurements were taken. For each patient Health Related Quality of life (HRQOL) score was evaluated using SF 36-Item Health Survey questionnaire. Patients were classified into their risk category by using the online version of the 10-year risk calculator made available by The National Heart, Lung and Blood Institute based on the Framingham algorithm. [(hin.nhlbi.nih.gov/atpiii/calculator.asp)/ (hin.nhlbi.nih.gov/atpiii/riskcalc.htm)].

A total of one hundred and fifty (n=150) patients were enrolled in the study. They were randomly allocated into two groups of seventy five each, using a computer generated randomization chart. Drugs were in the form of tablets to be taken orally once a day, for a period of 12 weeks. Both 10 mg and 20 mg atorvastatin tablets for 12 weeks were packed in identical boxes. Allocation concealment was obtained by number coding the drug boxes containing 10 mg and 20 mg atorvastatin. Patients were given a unique alpha-numeric code consisting of their initials and the code of the drug box that they were given and a key to the code was prepared to identify the group to which the patients belonged after completion of the study. This key was not disclosed to the investigator during the conduction of the study. The drugs were given for 15 days to every patient by the clinical assistant. After every 15 days all patients were asked to come for follow up, refilling of medications and monitoring of adverse drug events. At the end of 4 weeks lipid profile estimation was done to ensure compliance to the medication and anthropometry measurement was done to ensure that the patient was following a low fat diet. At the end of study intervention (12 weeks) all the baseline investigations (lipid profile, liver function tests (LFT), fasting and post prandial blood sugar level, serum creatinine), anthropometry measurements , Health Related Quality of life (HRQOL) score evaluation using 36-Item Health Survey questionnaire were done (16). Patient counselling regarding diet and medication were done at the end of the study.

Testing for myalgia:

In order to test if the patients were suffering from myalgia; the power in the proximal muscles was tested by the investigator during each visit. A visual analogue scale was provided to determine the degree of myalgia experienced by the patients. Any patient experiencing myalgia was withdrawn from the study.

Outcome measures:

1. The percentages of subjects who reach LDL-C goals as per NCEP ATP III guidelines. [Time Frame: After 12 weeks of study drug]
2. Health Related Quality of life (HRQOL) score evaluation using SF 36-Item Health Survey questionnaire. [Time Frame: *Before* and at the *end* of the study after 12 weeks of study drug]

Sample size calculation :

A sample size of 120 subjects was considered adequate for the study statistical power (17). Assuming a dropout rate of 15 to 25% over a 12 weeks period, 150 patients were randomized to drug treatment to detect, with 90% power, a significant difference of 15% (P≤0.05) between each treatment arm.

Statistical analysis : Statistical analysis was carried out by using Student's unpaired t-test for comparing quantitative data between the 10 mg and 20 mg study groups after therapy. Comparison of categorical (qualitative) data between the study groups was done using Fischer's test.

RESULTS

In all, two hundred (200) patients were screened and after meeting the inclusion and exclusion criteria, a total of one hundred and fifty (150) patients were enrolled in the study. Of the 150 participants randomized to treatment, 119 completed the treatment phase successfully. The data of only these 119 patients was considered for statistical analysis. Out of the 31 patients who did not complete the study, 9 patients were lost to follow up. 22 patients were discontinued during the double-blind period, primarily as a consequence of treatment-emergent adverse event of myalgia (n=7); noncompliance to diet (n=10) and withdrawal of informed consent (n=5) (Fig. 1).

Baseline characteristics :

Both the groups were similar in demographic profile and baseline CHD risk factors at the start of the study (Table I).

TABLE I : Demographic Characteristics; Baseline CHD risk factors and baseline lipid profile before study.

Parameters	*Atorvastatin 10 mg (Mean±SD) n=61*	*Atorvastatin 20 mg (Mean±SD) n=58*	*P value*
Age (years)	55.33±11.67	53.83±11.91	0.4891
Males	36 (59.02%)	32 (55.17%)	0.8117
Female	25 (40.98%)	26 (44.83%)	0.8117
Male ≥45 years	26 (42.62%)	19 (32.76%)	0.3575
Female ≥55 years	12 (19.67%)	09 (15.52%)	0.7235
Cigarette smoking	25 (40.98%)	27 (46.55%)	0.6692
Diabetics	13 (21.31%)	15 (25.86%)	0.7123
Hypertensive	23 (37.70%)	18 (31.03%)	0.5671
TC (mg/dL)	242.60±28.47	245.07±31.15	0.6533
TG (mg/dL)	201.97±34.14	208.53±29.65	0.2658
LDL (mg/dL)	167.46±32.30	167.83±32.65	0.9507
HDL (mg/dL)	34.75±3.21	35.53±3.11	0.1814
VLDL (mg/dL)	40.39±6.83	41.71±5.93	0.2658
Non HDL (mg/dL)	207.85±29.48	209.53±31.45	0.7638

TC - Total cholesterol, TG - triglycerides, LDL-C- Low Density Lipoprotein Cholesterol, HDL-C- High Density Lipoprotein Cholesterol, VLDL-C- Very low Density Lipoprotein Cholesterol, Non HDL-C = TC - HDL-C/LDL+VLDL.

Baseline laboratory parameters :

The baseline laboratory parameters between the two groups were similar at the start of the study. After treatment for 12 weeks, there were no important changes in haematology or biochemical laboratory values.

There were no significant differences in the mean baseline levels of lipid parameters TC, TG, LDL-C, VLDL-C and HDL-C at the start of study (Table I).

Efficacy : Changes in Serum Lipids :

Both doses of atorvastatin reduced the levels of TC, TG, LDL-C, VLDL-C, and Non-HDL-C from baseline to week 4 to week 12. (Table II) At both doses of 10 mg and 20 mg

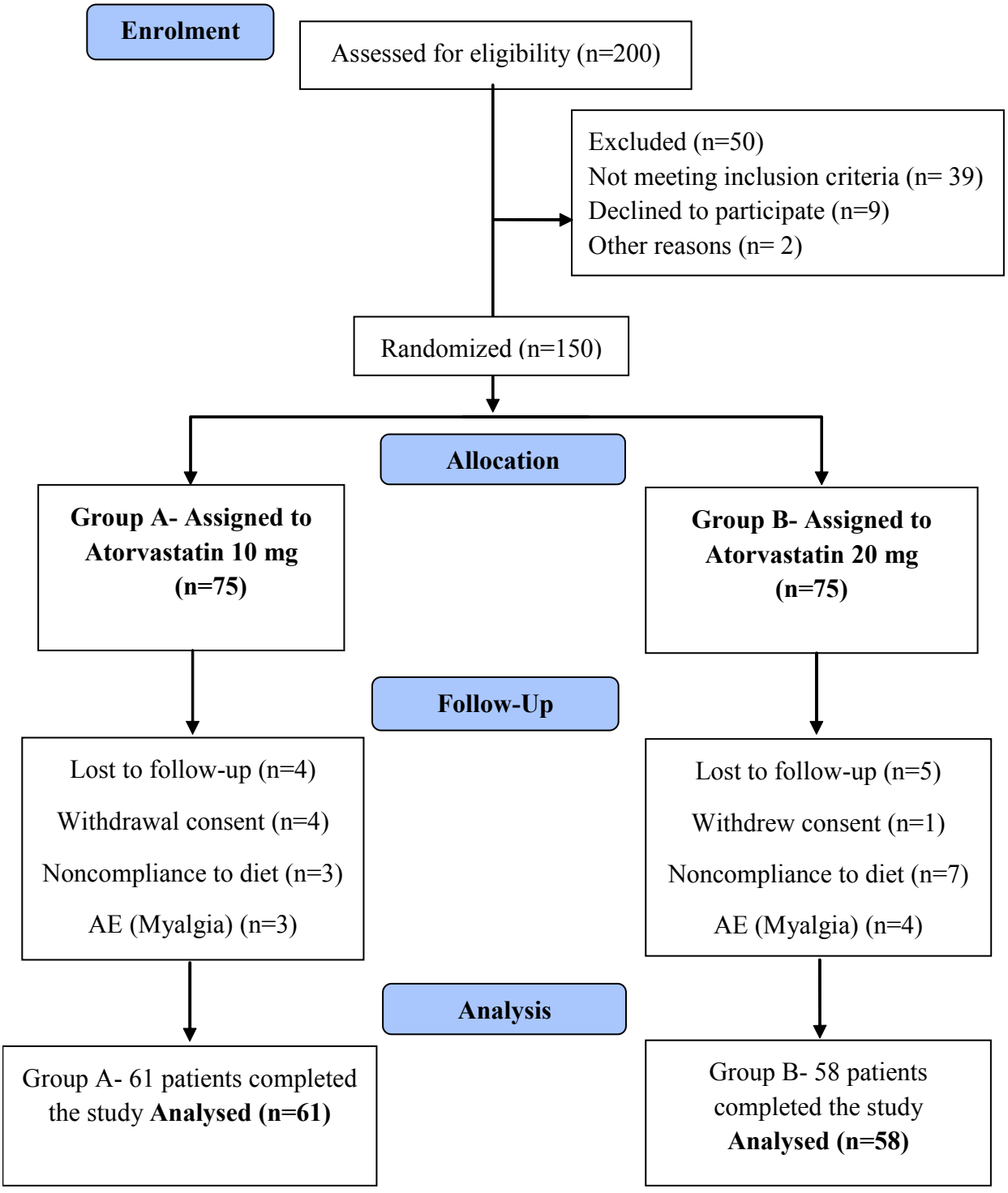

Fig. 1 : Study flow diagram.

TABLE II : Percent reduction in lipid profile with atorvastatin 10 mg and 20 mg doses at 4 and 12 weeks (values are mean±SD).

Lipid profile	*Atorvastatin 10 mg (n=61)*				*Atorvastatin 20 mg (n=58)*			
	At baseline	*At 4 weeks*	*Mean change*	*Percent change (%)*	*At baseline*	*At 4 weeks*	*Mean change*	*Percent change (%)*
TC mg/dL	242.60±28.47	201.59±20.61	41.02±13.96	16.91	245.07±31.15	189.85±22.58	55.22±14.05**	22.53
TG mg/dL	201.97±34.14	187.54±32.83	14.43±13.14	7.14	208.53±29.65	186.72±28.34	21.81±19.21*	10.46
LDL mg/dL	167.46±32.30	128.36±23.25	39.10±14.31	23.35	167.83±32.65	115.90±21.14	51.93±15.39**	30.94
HDL mg/dL	34.75±3.21	35.71±3.30	0.967±0.26	2.78†	35.53±3.11	36.60±3.2	1.07±0.41†	3.01
VLDL mg/dL	40.39±6.83	37.5±6.57	2.89±2.63	7.16	41.71±5.93	37.35±5.67	4.36±3.84*	10.45
Non HDL mg/dL	207.85±29.48	165.87±21.44	41.98±13.96	20.20	209.53±31.45	153.24±22.77	56.29±13.98**	26.86
Lipid profile	*At baseline*	*At 12 weeks*	*Mean change*	*Percent change*	*At baseline*	*At 12 weeks*	*Mean change*	*Percent change*
TC mg/dL	242.60±28.47	169.25±17.48	73.35±16.85	30.23	245.07±31.15	156.04±19.54	89.03±16.99**	36.32
TG mg/dL	201.97±34.14	134.67±23.21	67.30±20.59	33.32	208.53±29.65	133.06±21.01	74.87±32.14	35.90
LDL mg/dL	167.46±32.30	105.38±18.94	62.08±18.66	37.07	167.83±32.65	91.16±18.8	76.67±17.87**	45.68
HDL mg/dL	34.75±3.21	36.96±3.42	2.20±0.57	6.36†	35.53±3.11	38.15±3.42	2.61±0.51†,**	7.35
VLDL mg/dL	40.39±6.83	26.97±6.64	13.46±4.11	33.33	41.71±5.93	26.74±4.20	14.97±6.43	35.89
Non HDL mg/dL	207.85±29.48	131.70±17.86	76.15±16.67	36.64	209.53±31.45	117.89±19.79	91.65±16.9**	43.74

†-percent increase for HDL, *P<0.0154, **P<0.0001 when mean change of atorvastatin 10 mg and 20 mg doses were compared.

atorvastatin, a large percentage of the total decrease in LDL-C was evident by week 4, and this decrease was sustained at week 12. A dose-dependent response was apparent, with greater decreases achieved by patients receiving the 20 mg as compared to 10 mg of atorvastatin. On comparison of the changes in the lipid levels at week 4 brought about by 10 mg of atorvastatin vs. 20 mg of atorvastatin, there was a highly significant decrease in the levels of TC, LDL-C, VLDL-C, and Non-HDL-C (P<0.001); significant decrease in the levels of VLDL-C (P<0.05) while changes in the levels of HDL were not significant. However at week 12, on comparison of 20 mg vs.10 mg of atorvastatin; there was a highly significant decrease (P<0.001) in the levels of TC, LDL-C, and Non-HDL-C and there was also a highly significant increase (P<0.001) in the levels of HDL-C.

Efficacy : NCEP ATP III LDL-C Goals :

Patients were classified according to their level of CHD risk based on the Framingham's risk algorithm to determine the percentage of patients that attained their NCEP ATP III LDL-C goal by the end of the study (Table III).

High risk category :

There was a statistically significant

TABLE III : Number of patients achieving NCEP-ATP III LDL goal at end of 12 weeks.

Risk category	*Risk of developing CHD in the next 10 years*	*Target LDL Level*	*Atorvastatin 10 mgn=61*			*Atorvastatin 20 mgn=58*		
			Total number of patients	*Number reaching target*	*Percentage of patients reaching target (%)*	*Total number of patients*	*Number reaching target*	*Percentag of patients reaching target (%)*
High Risk (CHD or CHD risk equivalents)	10-year risk >20%	Target LDL-100 mg/dL	25	8	32	22	17	77.27*
		Optional target LDL - <70 mg/dL	25	0	0	22	8	36**
Moderately High Risk (2+ risk factors)	10-year risk >10%–20%	Target LDL-130 mg/dL	24	18	75	26	26	100*
		Optional target LDL - <100 mg/dL	24	12	50	26	21	80.77*
Moderate Risk (2+ risk factors)	10-year risk <10%	Target LDL-130 mg/dL	12	10	83.33	10	10	100

*P<0.05, **P<0.001 (Fischer's test).

(P<0.05) higher percentage of patients with CHD or CHD risk equivalents i.e. high risk group (n=25 in 10 mg group and n=22 in 20 mg group) to reach goal LDL of 100 mg/dL at higher starting dose of 20 mg than at lower starting dose of 10 mg (32% at the 10-mg dose, 72.77% at the 20-mg dose). In high-risk persons, the recommended LDL-C goal is < 100 mg/dL. An LDL-C goal of < 70 mg/dL is a therapeutic option on the basis of available clinical trial evidence, especially for patients at very high risk. There was statistically highly significant difference (P<0.001) in achieving the optional goal of < 70 mg/dL (n=25; 0% patients attaining the goal at the 10-mg dose, n=22; 36.36% patients attaining the goal at the 20-mg dose.

Moderately high risk category :

Similar trends of statistically significant difference between the two groups (P<0.05) were also apparent for individuals at moderately high risk for CHD (≤2 CHD risk factors) (n=24; 75% patients attaining the goal at the 10-mg dose, n=26; 100% patients attaining the goal at the 20-mg dose).The optional LDL-C goal for the moderately high risk category is < 100 mg/dl. There was statistically significant difference (P<0.05) in achieving the optional goal of < 100 mg/dL between the two groups (n=24; 50% patients attaining the goal at the 10-mg dose, n=26; 80.77% patients attaining the goal at the 20-mg dose).

Moderate risk category :

For patients at moderate risk for CHD (<2 risk factors) (n=12, 83.33% patients attaining the goal at the 10-mg dose, n=10; 100% patients attaining the goal at the 20-mg dose); the difference was not statistically significant, but it is noteworthy that 100% of patients attained their goal LDL-C when they were on 20 mg dose.

Health Related Quality of Life Score (HRQOL score) :

As shown in Table IV, there was no statistically significant difference in the HRQOL score before treatment. The mean increase in HRQOL score at the end of 12 weeks was significantly greater (P<0.001) in patients receiving 20 mg dose as compared to patients on 10 mg dose.

Adverse events :

There were 24 incidences of adverse events in the 10 mg group and 26 incidences of adverse events in the 20 mg group. There were 7 cases of myalgia; with 3 cases of myalgia in the 10 mg Group and 4 cases of myalgia in the 20 mg Group (Table V). The most common adverse event in the both the groups was paresthesias with 4 patients in the 10 mg group and 6 patients in the 20 mg group suffering from paresthesias. The other adverse events noted in the 10 mg group were headache, asthenia, constipation, diarrhoea, dyspepsia, nausea, flatulence and dizziness. In the 20 mg group all the above adverse events were seen except for constipation. One patient in the 20 mg group also suffered from depression. Overall all the adverse events were mild or moderate in nature and no incidence of death or serious adverse events were observed during the study period.

TABLE IV : Mean increase in 'Health related quality of life' (HRQOL) score.

HRQOL Score	*Atorvastatin 10 mg (Mean±SD) n=61*	*Atorvastatin 20 mg (Mean±SD) n=58*
At baseline	65.44±11.05	65.69±8.56
Mean increase after 12 weeks	12.84±4.94	18.32±5.81*

*P<0.0001 (unpaired t test).

TABLE V : Incidence of Adverse events (AE).

Incidence of AE	*Atorvastatin 10 mg n=61*	*Atorvastatin 20 mg n=58*
Headache	2	3
Asthenia	2	3
Digestive system		
Constipation	1	0
Diarrhoea	2	1
Dyspepsia	3	2
Nausea	2	1
Flatulence	3	4
Nervous system		
Dizziness	2	1
Paresthesia	4	6
Depression	0	1
Musculoskeletal system		
Myalgia	3	4
Total	**24**	**26**

DISCUSSION

Atorvastatin has a long $t_{1/2}$ (14 hours), which allows administration of this statin at any time of the day. Rosuvastatin and pravastatin also have long $t_{1/2}$ of 19 hours and 22 hours respectively; however rosuvastatin is a very expensive drug and pravastatin had been implicated for serious

adverse drug events (e.g.,breast cancer) in the past; hence, we selected atorvastatin as our study medication.

LDL-C target goals :

At 4th week, atorvastatin 10 mg reduced LDL levels by 23.35% and atorvastatin 20 mg reduced LDL levels by 30.94%. Similarly, at 12 weeks atorvastatin 10 mg reduced LDL levels by 37.07 % and atorvastatin 20 mg reduced LDL levels by 45.68%. The reductions in LDL reported in this study are consistent with previously published values (18). In 2004 modifications were recommended to the NCEP ATP III guidelines which proposed reduced LDL target levels in patients at risk for CHD – in high-risk subjects – LDL target of less than 100 mg/dL and optional LDL target of < 70 mg/dL; in moderately high risk subjects – LDL target of less than 130 mg/dL and optional LDL target of < 100 mg/dL; in moderate risk subjects – LDL target of less than 130 mg/dL (19). In our study, across all the risk categories, in total 40.98% of patients did not reach the goal LDL levels at the 10 mg dose (i.e. 25 out of 61 patients did not achieve their goals). Compared to this, only 8.62% of the patients did not reach the goal LDL levels at the 20 mg dose (i.e. 5 out of 58 patients did not achieve their goals).

Health related quality of life score :

Many researchers looking at cardiac populations have used the generic SF-36 as their measurement tool of choice when assessing the Health Related Quality Of Life (HRQOL) (20, 21, 22, 23). The SF 36 questionnaire measures eight concepts: Physical Functioning, Role limitations due to physical health, Bodily pain, General health perceptions, Vitality, Social functioning, Role limitations due to emotional problems, and General mental health. The reliability of the eight scales has been estimated using both internal consistency (reliability co-efficient greater than 0.75 for all dimensions except social functioning which is 0.74) and test–retest methods (24). SF-36 has content validity in the field of heart disease because it covers the areas of energy/vitality and bodily pain. Besides SF 36 is very user friendly and requires approximately ten minutes for completion (25). The 10 mg group displayed an increase of 19.62% and the 20 mg group displayed an increase of 27.89% in the Health related Quality of Life score. The mean increase in the Health related Quality of Life score between the two groups was statistically significant ($P<0.0001$).

Adverse events :

It has been observed from various randomized clinical trials (26, 27, 28, 29, 30, 31) that statin therapy reduces the relative risk of major cardiovascular events or death in relation to the absolute magnitude of LDL reduction and across wide range of cholesterol levels irrespective of history of any coronary artery disease. But, to use high dose statins to reach LDL goals physicians require robust safety data in addition to the efficacy data. Statins are well tolerated in majority of patients and the benefits far outweigh the potential risks. Patient differences in drug pharmacokinetics could make certain patients more vulnerable to the adverse effects of statin therapy (32, 33). Seven patients in our study suffered from myalgia. In a 5 year trial, involving 20,000

subjects, randomized to statin or placebo, it was found that one-third of patients complained of myalgia at least once, whether taking statins or placebo (24). Serum creatinine kinase (CK) levels need not be monitored routinely in patients taking statins, as an elevated CK in the absence of symptoms does not predict the development of any myopathy and also does not necessarily suggest the need for discontinuing the drug. Hence, we clinically evaluated our patients for myalgia, by checking the power in their proximal muscles and assessing if they were having myalgia, using a visual analogue scale.

Use of risk algorithm for prescribing the correct dose of statins by physicians:

Risk for CHD is calculated using the Framingham Study criteria and incorporates age, gender, total cholesterol, HDL, systolic blood pressure, hypertension treatment, and cigarette smoking (34, 19, 35). Despite the availability of guidelines for calculating risk, the use of the Framingham's risk algorithm has lagged in primary care. The number and complexity of the guidelines impede their implementation. Lack of time for physicians to act on guidelines presents an additional hurdle (36). The education regarding prescribing according to guidelines and the publication of guidelines is not adequate (36, 37). Hence many doctors do not use risk charts to assess a patient's risk for CHD, thereby underestimating many asymptomatic patients susceptibility for CHD events, and consequently under-treating these patients. Physicians tend to take the decision to initiate statin therapy based on high cholesterol levels. However the decision to initiate statin therapy should be based on the patients overall cardiovascular risk profile rather than abnormal lipids. A patient having relatively lower level of LDL, may still fall in the high risk category because of his other risk factors such as diabetes, smoking, etc. It would become necessary for such a patient to keep his LDL below target levels for his risk category to prevent cardiovascular morbidity and mortality. Thus, benefit from high dose statin therapy is possible, and is a viable therapeutic option for those patients who are at risk for CHD and/or have high LDL levels. Increasing the level of LDL target attainment and thus reducing the risk for the occurrence of cardiovascular events are likely to have significant economic benefits both at the level of the individual and society as a whole. In addition to the economic benefits of reducing CHD mortality and morbidity, mainly apparent as a decreased requirement for expensive revascularization procedures, treating patients to goals more efficiently will be associated with the use of fewer medical resources including laboratory tests, medication, and hospital visits. Indirect costs such as patient travel time, waiting time, or time to undergo examinations and tests are also likely to be reduced (38).

Limitations:

The present study has certain limitations. In this study short-term end points were studied, and thus the long-term rates of development of AEs could not be assessed. Also compliance with the higher dose of the drug over a long period of time could not be studied. Rather, the trial was designed to examine the efficacy of a treatment schedule-based assignment of drug dose according to patient's cardiovascular

risk rather than the traditional approach of starting at a low dose and gradually titrating the dose upwards. Such a trial design has been adopted by researchers in the past (39, 40).

Conclusions :

A significantly greater number of patients are not achieving the ATP III guideline specified LDL goal levels with lower dose of statin. More patients are attaining goal LDL levels with higher dose therapy.Selecting the starting dose of atorvastatin according to the patients risk category (by using the Framingham's algorithm for calculating cardiovascular risk) and the percentage reduction in LDL required, will result in greater success in achieving LDL goals and may result in better quality of life. Patients in the high risk category should be considered for a higher dose of atorvastatin, without compromising safety.

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