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RATIONAL PRESCRIPTION OF LIPID-LOWERING AGENTS - STATIN MONOTHERAPY AND COMBINATION OF STATINS WITH OTHER LIPID-LOWERING AGENTS IN THE TREATMENT OF DYSLIPIDEMIA

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ABSTRACT: Dyslipidemia is one of the leading causes of various cardiovascular and central nervous system disorders. Death from cardio-vascular disorders accounted for 36.3% of the 2.4 million deaths world-wide. Recognition that dyslipidemia is a risk factor has led to the development of drugs that modify cholesterol level. The intensity of therapy should be sufficient to achieve 30–40% reduction in LDL – C without side effects and low cost. The prescription order is an important therapeutic transaction between the prescriber and the patient. It has been well accepted that inadequate and irrational prescriptions could lead to serious consequences. The study was carried out by observing and analyzing data of 100 consecutive patients admitted in ICU and receiving lipid lowering agents for a period of eighteen months. From the study it is found that statins are the cornerstone of pharmacotherapy of dyslipidemias. At the same time the importance of dietary manipulations can't be ignored in management of dyslipidemias. Statins are relatively safe drugs however a few significant adverse reactions such as myalgia were also encountered during the course of the study.
KEYWORDS: Dyslipidemia; Statins; Lipid-lowering agents.

INTRODUCTION: The subject of drugs is as old as disease. Therapeutics appears to be the first of the medical sciences to come into existence. Dyslipidemia is one of the leading causes of various cardiovascular and central nervous system disorders. A diet rich in saturated fat and cholesterol along with genetic disorders contribute greatly to an increased plasma lipid level. It is a major cause of atherosclerosis and its associated complications such as coronary heart disease, peripheral vascular disorders and ischemic cerebro-vascular disorders.[1]

Death from cardio-vascular disorders accounted for 36.3% of the 2.4 million deaths worldwide. Recognition that dyslipidemia is a risk factor has led to the development of drugs that modify cholesterol level.[2] The intensity of therapy should be sufficient to achieve 30 – 40% reduction in LDL – C without side effects and low cost.[3,4]

The prescription order is an important therapeutic transaction between the prescriber and the patient.[5] So it should be scientifically legible, unambiguous, adequate and complete. It has been well accepted that inadequate and irrational prescriptions could lead to serious consequences[6] Many potent drugs such as Statins,[7] Fibrates, Niacin, Bile-acid sequestrants, Omega-3 fatty acids etc. are used in the management of symptomatic dyslipidemia.

The use of all these drugs warrants a big concern amongst clinicians, especially whence many consider it to be unnecessary, inappropriate and downright dangerous. Errors in prescription are not uncommon and could be due to ignorance[8] or inadequate knowledge about the disease and

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pharmacology of the drugs prescribed.[9] Erroneous prescriptions are recognized even in the tertiary care hospital.

Lipid-lowering agents such as Statins, Fibrates, Niacin, Omega-3 fatty acids etc. are prescribed for a number of cases in Cardiology practice like dyslipidemia, familial hypercholesterolemia, metabolic disorders etc. There is an extreme paucity in drug utilisation studies in the international scene and they are almost non-existent in our country.[10]

Recently an increased attention has been diverted to rational prescribing and drug utilisation studies play a major role in this regard. These studies not only detect flaws in the therapy, but also help to find out solution to rectify the same.

OBJECTIVES:
1. To evaluate the rational prescription of Lipid-lowering agents with regard to: a) Selection of specific drugs among the Lipid-lowering agents. b)Dose and mode of administration. c) Adverse Drug Reactions (ADR) if any.
2. To evaluate the utilisation of Statin monotherapy and combination of Statins with other Lipid-lowering agents in the treatment of dyslipidemia.
3. To analyse the trend in drug utilisation of Lipid-lowering agents in Cardiology clinical practice.

MATERIALS AND METHODS: This prospective, observational and analytical study was done to assess the pattern of hypolipidemic drug use in patients of medicine and cardiology units of BTGH, Gulbarga:

1. **Study subjects:** Patients admitted in ICU (MICU/ICCU) and receiving lipid – lowering agents at BTGH, attached to MRMC.
2. **Study period:** the study was carried out between December 2011 and May 2013 (18 months)
3.1 **Sampling:** 100 consecutive patients admitted in ICUs and receiving lipid - lowering agents were included in the study.
3.2 **Inclusion criteria:** a) Males and non-pregnant female patients aged between 25-75 yrs. b) Patients with/without history of hypertension and /or diabetes mellitus. c) Patients who presented with signs and symptoms of cardiovascular diseases admitted in ICU.
3.3 **Exclusion criteria:** a) Patients aged below 25 years and above 75 years. b) Terminally ill patients and pregnant and lactating women. c) HIV and HBs Ag positive cases.
4. **Study procedure:** Patients aged between 25 to 75 years of either gender and receiving lipid-lowering agents were included for the study. Patient's medical records were scrutinized for demographic data, provisional diagnosis, comorbid conditions, and duration of stay in ICU and results of laboratory investigation (fasting lipid profile).

All the relevant data were entered and documented in case record forms (CRF).

Case records were thoroughly scrutinized for the intended purpose i.e., to assess the pattern of hypolipidemic drug use, the class of hypolipidemic drugs used, the formulations used, the doses used, route and frequency of administration. Any change in the drug use during the stay in ICU and the reason for the same was also evaluated:

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1. **Laboratory investigations:** a) Haematological: Haemoglobin(Hb%), Total and differential count (TLC/DLC), Erythrocyte sedimentation rate (ESR), Platelet count. b) Biochemical: Fasting lipid profile, Blood glucose level., Urine analysis, Renal function tests (RFT), Liver function tests (LFT), Creatinine phosphokinase MB (CPK-MB), Troponin I (Trop I), Serum electrolytes c) Microbiological: Blood culture, Urine culture, Peripheral smear for malarial parasites, HIV & HBs Ag. Hematological and biochemical investigations were done routinely for all patients, and microbiological tests were done selectively, wherever found necessary.

2. **Follow up:** The patients were re-evaluated for lipid profile after duration of three months post first report.

Statistical Analysis: the data collected was statistically analysed by using descriptive statistics. Wherever necessary the results are depicted in the form of percentages with graph and tables using MS word and Excel version 7.

RESULT: Table 1 displays the duration of stay of all the subjects in the study. It was found that most of the patients stayed in the ICU for 4 to 5 days (34), while the least number of patients were discharged early, within one day. It was observed that the longer duration stay was more common in males (24) compared to females (10).

Days	Males	Females	Total
0-1	4	6	10
2-3	20	7	27
4-5	24	10	34
>5	17	12	29
Table 1: Distribution of patients according to duration of stay			

Bar graph showing distribution of patients according to duration of stay:
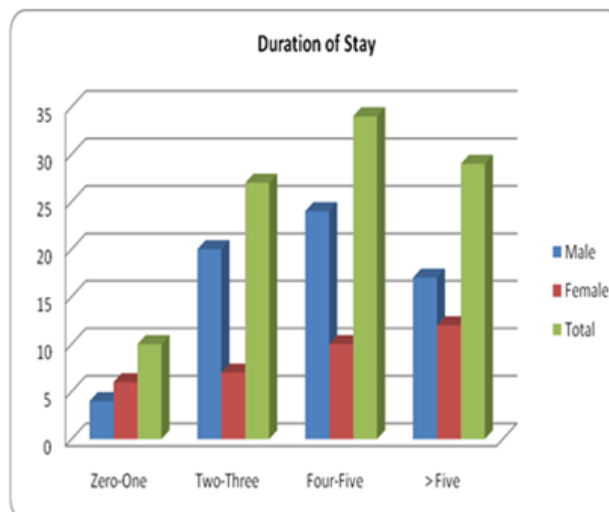
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Table 2 shows the change in lipid profile values from admission to follow up. A positive effect of the therapy was seen as we noted a general decline in the values of mean total cholesterol, mean LDL, and mean triglycerides along with improvement in the mean HDL values. There was a reduction of 25.4% in the total cholesterol values. A reduction of 20.2% was seen in mean LDL values. There was a 36.1% reduction in mean triglyceride levels post therapy, whereas HDL levels showed an improvement of 15% from pre- treatment values.

Lipid Profile Values (mg/dl)	At Admission (mg/dl)	On Follow-up (mg/dl)
Mean Total Cholesterol	254.58	192.46
Mean HDL	41.83	48.66
Mean LDL	144.88	115.39
Mean Triglycerides	264.14	168.6
Table 2: Distribution of patients according to average lipid profile values		

Bar graph showing distribution of patients according to average lipid profile values:
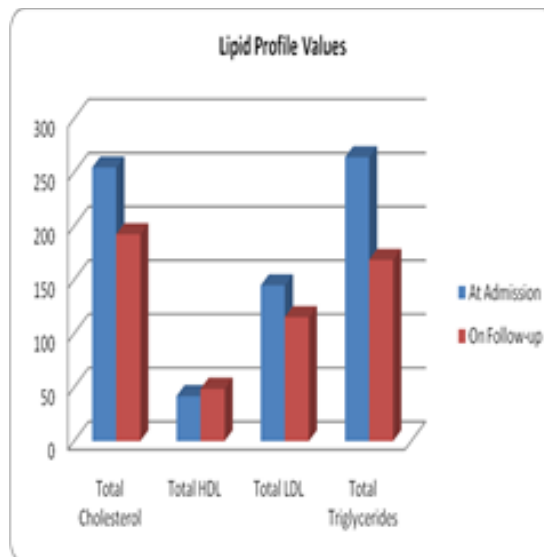
From table 3 we concur that out of the 66 patients who were prescribed statin monotherapy, a majority i.e; 33 were prescribed Atorvastatin (50%).

Statin	Number of Patients (n=66)
Atorvastatin	33
Rosuvastatin	25
Simvastatin	8
Table 3: Distribution of patients according to Stain received	

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Pie chart distribution of patients according to Statin received:

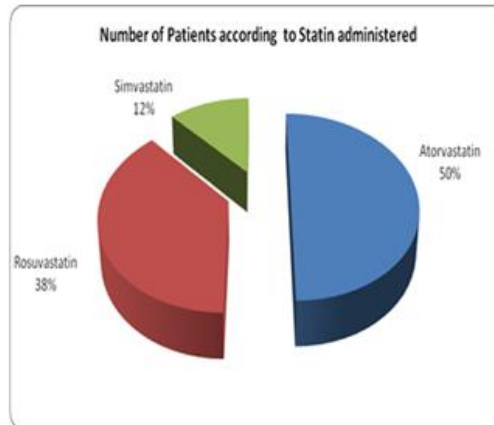Number of Patients according to Statin administered

Table 4 we conclude that the favoured polytherapy combination was atorvastatin and fenofibrate which was prescribed in 54% of the patients on polytherapy.

Drug Combinations	Number of Patients (n=24)
Atorvastatin + Fenofibrate	13
Atorvastatin + Ezetimibe	3
Atorvastatin + Niacin	1
Rosuvastatin + Fenofibrate	2
Simvastatin + Ezetimibe	3
Simvastatin + Niacin	2
Table 4: Distribution of patients according to polytherapy administered	

Bar graph showing distribution of patients according to polytherapy administered:
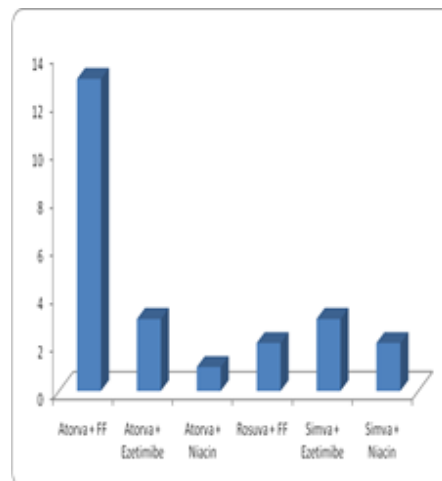
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Table 5 shows the final outcome of therapy in all the subjects involved in the study. 90% of the total patients showed improvement in our study.

Outcome of Therapy	Number of Male Subjects	Number of Female Subjects
Improved	58	32
Left Against Medical Advice (LAMA) / Loss to Follow-up	5	2
Death	2	1
Total	**65**	**35**
Table 5: Distribution of patients according to outcome of therapy		

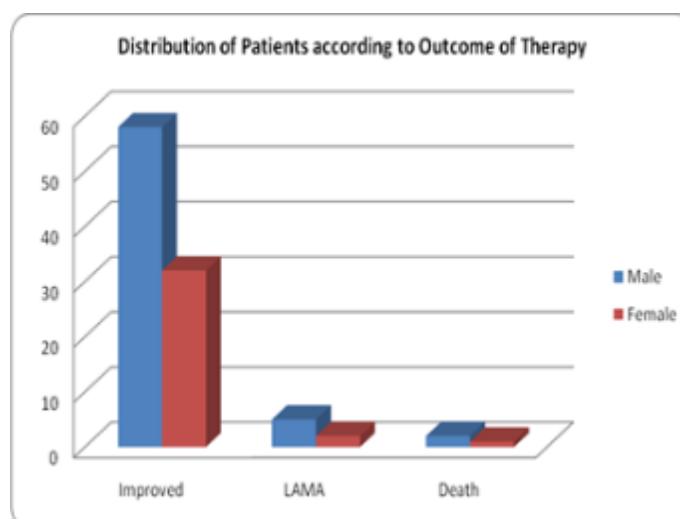**Bar graph showing distribution of patients according to outcome of therapy:**

Table 6 indicates the incidence of ADRs in our study. Most common ADR recorded was myalgia (48%).

ADRs	No. of patients (n=90)
Myalgia	13
Constipation	2
Headache	6
Nausea, vomiting	5
Dark, red urine	1
Total	**27**
Table 6: Distribution of patients according to ADRs observed	

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Pie chart distribution of patients according to ADRs observed:
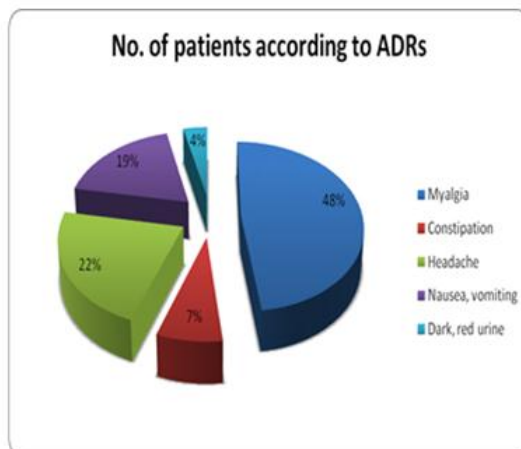
DISCUSSION: Dyslipidemia is a common ailment afflicting millions of people both in the developed world as well as in developing countries. The morbidity, mortality and the socioeconomic implications associated with this disease process is tremendous. Therefore a systematic review of drugs used to treat dyslipidemias is of utmost importance in medical, social and financial aspects. Statins have emerged as the primary choice of physicians worldwide for the treatment of this ailment. Other treatment options available include non-pharmacological dietary interventions and pharmacological agents such as Niacin, Fenofibrates, Bile sequesterants etc,

The study states that the most common duration of stay in the ICU was from 4-5 days in either sex (Table 1). This is evidently required for stabilizing the patients with co morbid conditions. At admission the values of lipid profile recorded are summarized in Table 5. When these values are compared with the values on follow up (Table 2) it was observed that there was a decline in mean total cholesterol, mean LDL and mean triglyceride along with an increase in mean HDL values.

These desirable results prove the efficacious attribute of the pharmacotherapy employed in the present study. Our findings are in concordance with the guidelines issued by NCEP.[11]Atorvastatin was the most commonly prescribed statin in our study (Table 3) and was closely followed by rosuvastatin. Simvastatin was comparatively less frequently prescribed.

Out of the total patients receiving statin monotherapy 50% were treated with atorvastatin alone. A study conducted by Fodor et al also reiterates our findings and states that atorvastatin (Lipitor) is the favoured statin among physicians for the treatment of dyslipidemia.[12]

From table 4, it is derived that the number of patients receiving various drug combinations and the most favoured combination amongst the various options available to the physicians was atorvastatin and fenofibrate which was prescribed in 54% of the patients on polytherapy. Koh et al in their study also described the beneficial effects of combination of atorvastatin with fenofibrate for the treatment of combined hyperlipidemias.[13]

The final outcome of therapy in all the subjects was observed in table no 5. 90% of the total patients showed improvement while 7 subjects were left against medical advice (LAMA) and 3 deaths were recorded. This shows that there was an overwhelmingly positive response to the treatment provided.

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The distribution of patients according to the ADRs was observed in table no 6. The study reinstates the findings of Langsjoen et al and shows myalgia to be the most common ADR to be observed in statin therapy.[14]

CONCLUSION: The study shows that statins to be the cornerstone of pharmacotherapy of dyslipidemias. At the same time the importance of dietary manipulations cannot be ignored in the management of dylipidemias. Statins are relatively safe drugs however a few significant adverse drug reactions such as myalgia were also encountered during the course of the study.

The most commonly prescribed statin was Atorvastatin. It was prescribed in 33 patients which is equivalent to 50% of patients receiving pharmacological therapy. The most commonly prescribed combination therapy was atorvastatin and fenofibrate, and was prescribed to a total of 13 patients enrolled in the study.

Early recognition and treatment of dyslipidemia will drastically reduce the burden of the disease and awareness of this disease process amongst the general population is of utmost importance.

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