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Recommended Guidelines and Efficacy of Statins in Case of Hyperlipidemia

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ABSTRACT

Background: Hyperlipidemia is manifested by increased lipids and lipoprotein. Elevated lipid levels in blood are attributed due to having sedentary lifestyle and environmental conditions. Hyperlipidemia is one of the contributing risk factor for cardio vascular diseases. Human health is remarkably compromised because of cardio vascular disorders and complications associated with it. Statins are the frequently prescribed drug for the management of hyperlipidemia.

Objectives: The main objective of the proposed investigation was to study the prescribing patterns of statins. Moreover, the outcome of statins on lipid profile in hyperlipidemia patients had also been evaluated.

Method: A retrospective study was designed where patient data was obtained from the different hospitals of the twin cities i.e. Islamabad and Rawalpindi namely RIC, CDA and PIMS. Samples were obtained by random sampling technique. A sample of 50 patients was obtained. Low density lipoproteins (LDL), high density lipoproteins (HDL), triglycerides (TG) and total cholesterol (TC) were evaluated for the study.

Result: We calculated results of 3 months statins therapy in reducing LDL, TG, TC levels and elevating HDL levels. Our results were comparable with the NICE guidelines.

Keywords: Arteriosclerotic cardiovascular disease, cardiovascular diseases, β-Hydroxy β–methylglutaryl CoA

INTRODUCTION

Hyperlipidemia is elevation of fasting total cholesterol concentration which may or may not be associated with elevated TG concentration. Cardiovascular disease (CVD) is the leading cause of death among adults in the United States, and people with hyperlipidemia are at roughly twice the risk of developing CVD as compared to those with normal total cholesterol levels [1]. Patients with familial hypercholesterolemia (FH) have an even greater risk of developing CVD at an earlier age; therefore, early detection and treatment are imperative to reduce cardiovascular events and premature death. Statins are the mainstay treatment for hyperlipidemia; however, the limitations of statins include treatment resistance, intolerance due to adverse events, and a lack of adherence which contribute to poor outcomes [2]. As such, many patients require adjunct therapies to properly control hyperlipidemia including niacin, bile acid sequestrants, fibric acids, and ezetimibe. FH can be even more challenging to treat, often requiring the use of lomitapide, mipomersen, proprotein convertase subtilisin/kexin type 9 inhibitors, or low-

density lipoprotein cholesterol apheresis, in addition to high dose conjunction with statins or other agents. Statins as a lipid lowering drug is also under concern in COVID-19 as statins increase the expression of ACE2 [3,4]. The approach to determining the appropriate treatment options has also undergone important changes. Guidelines for the management of patients with hyperlipidemia vary in their recommendations, with the American College of Cardiology/American Heart Association recommending that treatment decisions be based on the intensity of response associated with various statins, while multiple other guidelines (e.g., National Lipid Association (NLA) and the American Association of Clinical Endocrinologists and American College of Endocrinology) still support attaining pre-specified lipid values to reduce cardiovascular risk. This article will evaluate the epidemiology of hyperlipidemia and FH, risk factors associated with the development of disease, as well as the efficacy and safety of statins and adjunct treatment options. In the United States, more than 100 million, or roughly 53% of adults, have elevated LDL-C levels. Yet, fewer than 50% of patients with high LDL-C receive treatment to reduce their levels, and among those receiving treatment, fewer than 35% achieve adequate control. Further, approximately 3.1 million American adults have total cholesterol levels that exceed 240 mg/dL, placing them at about twice the risk of ASCVD compared to those with total cholesterol levels that are at goal [5].

Classes of Apolipoproteins

- Chylomicrons – Triglyceride rich carrier of dietary fats
- Very Low-Density Lipoprotein (VLDL) – Triglyceride rich carrier of hepatic synthesized triglycerides (TG)
- Intermediate and Low-Density Lipoprotein (IDL & LDL) – Cholesterol rich remnant particles derived from lipolysis of triglycerides in VLDL
- High Density Lipoprotein (HDL) – Cholesterol rich particle that transports cholesterol to liver for disposal or recycling (Table 1).

Table 1. Classification of hyperlipidemia by The National Lipid Association and the National Cholesterol Education Program (NCEP).

Test's Name	Reference Range
Total Cholesterol	Desirable < 200 mg/Dl Borderline 200 - 239 mg/dL High > 240 mg/Dl
Triglyceride	Normal < 150 mg/dL Borderline High 150 - 199 mg/dL High 200 - 499 mg/dL Very High > 500 mg/dL
HDL Cholesterol	Adult: 40 - 60 mg/dL • An HDL cholesterol less than 40 mg/dL is • low and constitute a coronary heart disease • risk factor. • An HDL cholesterol greater than 60 • mg/dL is a negative risk factor for coronary • heart disease.
LDL Cholesterol	Desirable < 100 mg/dL Above desirable 100 - 129 mg/dL Borderline high 130 - 159 mg/dL High 160 - 189 mg/dL Very high > 190 mg/dL
Total Lipids	400 - 1000 mg/Dl
Cholesterol / HDL Ratio	Up to 05

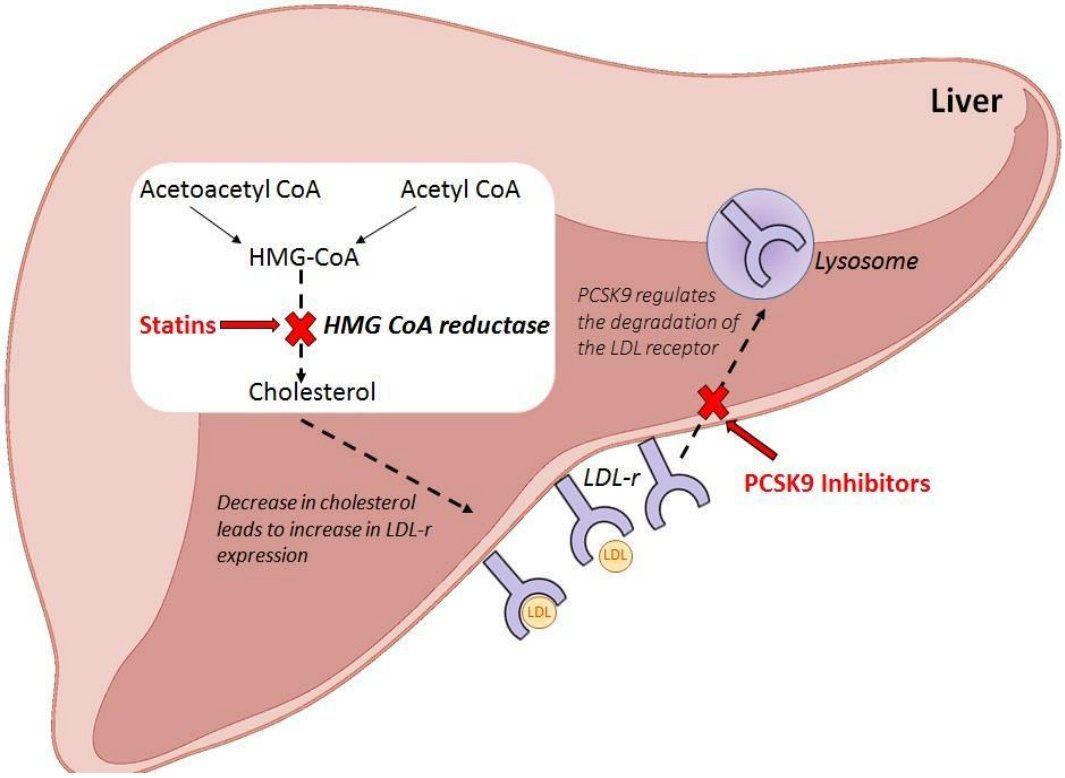

Figure 1. Mode of action of statins.

Table 2. Popular Statin Brands in Pakistan.

BRAND NAME	GENERIC NAME	COMPANY NAME	STRENGTH
ROVISTA	Rosuvastatin	Getz pharma	5,10,20mg
LIPIREX	Atorvastatin	Highnoon	10,20,40mg
LIPIGET	Atorvastatin	Getz pharma	10,20,40mg
ROSULIN	Rosuvastatin	Highnoon	5,10,20mg

Mode of Action of Statins

Statins act by competitively inhibiting HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway. Because statins are similar in structure to HMG-CoA on a molecular level, they will fit into the enzyme's active site and compete with the native substrate (HMG-CoA) (Figure 1).

Current and future treatment of Hyperlipidemia and the role of statins

Hyperlipidemia is recognized as one of the major risk factors for the development of coronary artery disease and progression of atherosclerotic lesions. Dietary therapy together with hypolipidemic drugs are central to the management of hyperlipidemia, which aims to prevent atherosclerotic plaque progression, induce regression, and so decrease the risk of acute coronary events in patients with pre-existing coronary or peripheral vascular disease [6,7]. In patients at high risk of coronary artery disease but without evidence of atherosclerosis, treatment is designed to prevent the premature development of coronary artery disease, whereas in those with hypertriglyceridemia, treatment aims to prevent the development of hepatomegaly, splenomegaly, and pancreatitis [8]. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are the most potent lipid-lowering agents currently available, and their use in the treatment of Hyperlipidemia provides the focus for this review.

Particular emphasis is given to cerivastatin, a new HMG-CoA reductase inhibitor that combines potent cholesterol-lowering properties with significant triglyceride-reducing effects. Recently completed primary and secondary intervention trials have shown that the significant reductions in low-density lipoprotein (LDL) cholesterol achieved with statins result in significant reductions in morbidity and mortality associated with coronary artery disease as well as reductions in the incidence of stroke and total mortality (Table 2). Such benefits occur early in the course of statin therapy and have led to suggestions that these drugs may possess antiatherogenic effects over and above their capacity to lower atherogenic lipids and lipoproteins [9]. Experimental studies have also shown statin-induced improvements in endothelial function, decreased platelet thrombus formation, improvements in fibrinolytic activity, and reductions in the frequency of transient myocardial ischemia [10,11] .

NICE Guidelines

When a decision is made to prescribe a statin, the guideline recommends using a statin of high intensity (more than 40% LDL-cholesterol reduction) and low acquisition cost.

The guideline recommends offering atorvastatin 20 mg daily for primary prevention. Secondary prevention should usually start with atorvastatin 80 mg daily. However, in people with CKD, the initial dose should be 20 mg daily, and in other people, a dose lower than 80 mg daily NICE recommends measuring total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol) and non-HDL-cholesterol in all people who have been started on high-intensity statin treatment as above after 3 months of treatment, aiming for a greater than 40% reduction in non-HDL-cholesterol. The only high-intensity statin specifically named in the NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification is atorvastatin 20–80 mg daily. Other high-intensity statins are rosuvastatin 10–40 mg daily and simvastatin 80 mg daily [12].

In the May 2010 edition of Drug Safety Update, the Medicines and Healthcare products Regulatory Agency (MHRA) advised that there is an increased risk of myopathy associated with simvastatin 80 mg daily, and that this dose should be considered only in people with severe hypercholesterolemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risk.

Rosuvastatin was not recommended in the guideline because, at the time of publication, it was considerably more expensive than atorvastatin, with no evidence of greater effectiveness. Since then, the price of rosuvastatin has reduced. The surveillance review carried out in 2018 notes a potential need to update the guideline for various reasons, including the availability of rosuvastatin in a generic form [13].

METHODOLOGY

Phase 1 (Design)

Patients taking statins from 2017-2019 were selected retrospectively from the database of the Hospital. Selected patients were further clarified to see if they fulfilled the inclusion or exclusion criteria.

The Inclusion Criteria

1) Receiving one fixed dose of one of the specific statins (atorvastatin, fluvastatin, lovastatin, pravastatin or simvastatin) for at least 3 months in the period of 2002/9/1 to 2003/12/31 in NTUH;

2) Having related lipid profiles at baseline and after the statin therapy for at least three months.

The Exclusion Criteria

1) The type or dosage of statin was switched during the 3-month treatment period

2) Used other lipid-lowering therapy during the treatment period

3) Enrolled in other clinical trials during the treatment period

4) Diagnosed as familial hypercholesterolemia or other secondary Hyperlipidemia.

Method: Random sampling

Sample Size: 50

Phase 2 (Conduct)

The eligible patients were divided into 4 groups (Figure 2)

Group 1 Patients with diabetes mellitus (DM) and cardiovascular disease (CVD).

Group 2 Patients who were non-DM, non-CVD

Group 3 Patients with DM but non-CVD

Group 4 Patient with CVD but non-DM

Phase 3 (Analysis)

The eligible patients were enrolled in this study and the basic demographic data and laboratory data including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), Triglyceride (TG), GOT, GPT and CPK was recorded at baseline and after the statin therapy. Information such as cardiovascular diseases, risk factor status, statin type and dosage taken, and adverse events was reviewed to the end of the treatment. Percentages of the patients achieving their TC and/or LDL-C target with various kinds of statins in different risk categorical groups were compared. The target level used was according to the American NCEP ATPIII guideline. The changes of TC, LDL-C, HDL-C and TG from pre-treatment to post-treatment were compared among different statin groups. The incidence of muscle pain and allergic reaction to statin was collected.

Statistical Analysis

Statistical analysis was performed using SPSS Version 20. Descriptive statistics were used to explain and evaluate the clinical and demographic characteristics of different groups. An independent sample T-test was utilized for continuous variables, and percentages were calculated.

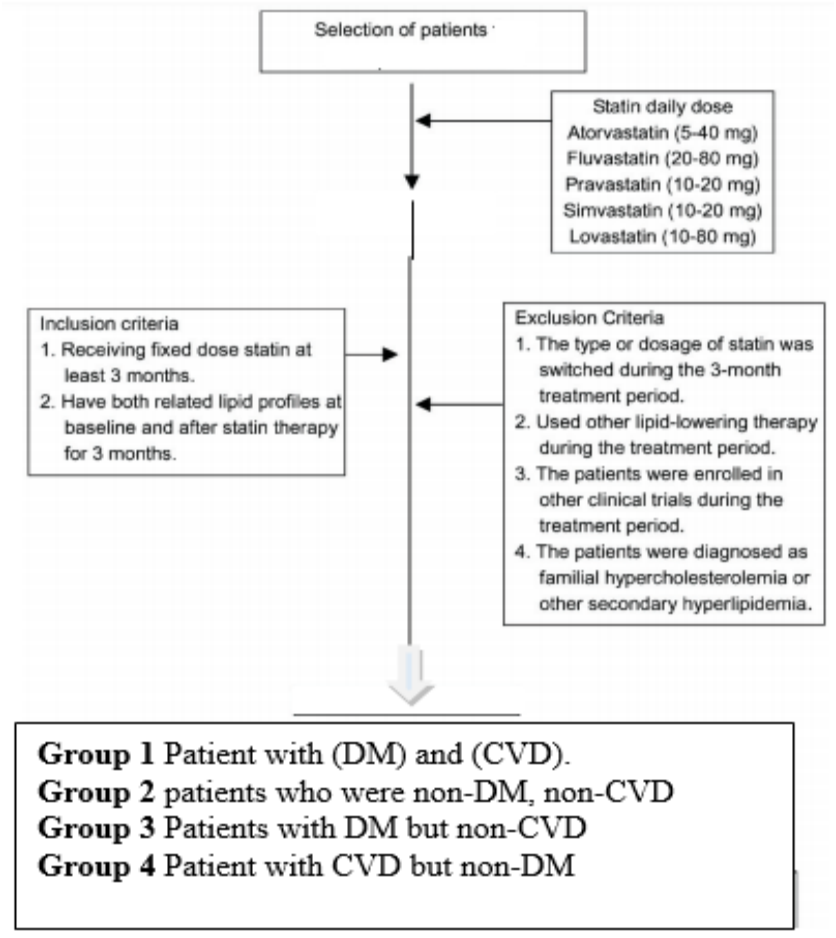

Figure 2. Method of data collection.

Table 3. Prescribing Pattern Observed.

Groups	Criteria	Prescribed Drugs	Dose Ranges	Reported Patients	% Of Patients
1	both DM and CVD	atorvastatin OD	10-40mg	12	24
2	without DM and CVD	Rosuvastatin	5-20mg	3	6
3	with DM but no CVD	Atorvastatin	10-40mg	27	54

4	with CVD but no DM	Atorvastatin	10-40mg	8	16

Table 4. Outcomes of 3 Month Statin Therapy.

Drug	Trade Name	Dose Range	% LDL-C Decrease	% HDL-C Increase	% TG Decrease
Atorvastatin	Lipirex	10–40 mg	39–60	5–9	19–37
Rosuvastatin	Rovista	5–40 mg	45–63	8–10	10–30

RESULTS

Prescribing pattern of the statins in different groups revealed that atorvastatin was prescribed in the dose of 10 – 40 mg while rosuvastatin was prescribed in the dose of 5 – 20 mg (table 3).

Atorvastatin significantly decreased LDL Cholesterol and Triglycerides (39 – 60%) and (19 – 37%). Remarkable increase was observed in HDL Cholesterol (5 – 9%). Similarly, Rosuvastatin also decreased LDL Cholesterol (45 – 63%) and Triglycerides (10 – 30%) as shown in table 4.

DISCUSSION

Statins are potent candidates for the reduction of serum cholesterol levels. Despite of efficacy they are associated with severe adverse effects that may contribute to heart failure. Hypertrophy and inhibition of CoQ10 production may increase the risk of heart failure in patients taking statins [14].

The dose-dependent possessions of statins on the NLRP3 complex are linked to their danger signals, pharmacokinetic properties and chemistry. As compared to hydrophilic statins, lipophilic statins have more pleiotropic effects on the NLRP3 complex. An immune response is created in shift to an anti-inflammatory response due to suppression of TLR4/MyD88/NF-κB signaling caused by statins. Besides, decrease in the expression of TLRs 2 by statins there is also inhibition of the NF-κB pathway. Statins due to both their lipid-lowering effects and immune-modulation they are a choice of agent in the treatment of atherosclerosis with an added advantage of cost effectiveness [15]. The efficacy of the statins is also altered by environmental and other factors [16].

Another study has reported that in the patients with chronic heart disease the phenotypic IL-8 and the transcriptomic appearance declined considerably in patients who were assigned statins. For evaluating the therapeutic effect of statins and to illustrate the pathology of CHD treatment the IL-8 must provide as a feasible marker [17]. Another study has also reported that more than forty percent of individuals taking statins persist with long term healthy arterial aging and have very low risk of Atherosclerotic cardiovascular disease [18].

Values observed by collected data were compared with NICE guidelines, 2019. Following three comparisons were made:

1. According to this guideline, LDL levels should be reduced to 40% and in our findings we observed that levels were reduced to 40% in 3 months therapy.
2. Dose of atorvastatin was in compliance to nice guideline.
3. We also noticed that simvastatin was not prescribed because of the adverse effects as mentioned in NICE guidelines.

CONCLUSION

Prescribing of medications as per the standard guidelines promote patient well being and improve quality of life. The present study concluded statins when prescribed in accordance with the NICE guidelines can significantly reduce elevated lipid levels in cardiovascular disease patients. They are also beneficial in reducing elevated lipid levels in patients having co-morbidities such as diabetes mellitus.

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