International Journal of Pharmacology and Clinical Research (IJPCR)

IJPCR |Volume 3 | Issue 1 | Jan - Jun - 2019
www.ijpcr.net

ISSN: 2521-2206

Research article *Clinical research*

A study on prescription pattern and rational use of statins in tertiary care corporate hospital

M. Praveen Kumar[1], K. Bhanu Prasad[1], Afshan Naaz[2], Pooja Aksal[2], CH.Sri Nidhi[2], N.Sriram[1]

[1]*Assistant Professor, Department of Pharmacy Practice, Holy Mary Institute of Technology and Science, Bogaram, Keesara, Hyderabad, India- 501301*

[2]*PharmD Interns, Department of Pharmacy Practice, Holy Mary Institute of Technology and Science, Bogaram, Keesara, Hyderabad, India- 501301*

[*]**Address for correspondence: M. Praveen Kumar**

E-mail: praveen.pharmd16@gmail.com

ABSTRACT

Objectives

Our objectives are to evaluate prescription pattern and rational use of statins in a tertiary care corporate hospital.

Methodology

It was a prospective observational study conducted for a period of 6 months and included various departments of 300 bedded multi specialty tertiary care corporate hospital. A total of 200 patients were included and the study criteria was inpatients and induvial more than 18 years of either gender who are prescribed with HMG-CoA reductase inhibitors.

Results

In the present study 200 patients belonged to the age group of above 18 years, out of which about **65%** were male and **35%** were female. Atorvastatin **(67%)** was prescribed mostly and Rosuvastatin **(29.5%)** was also used.

Conclusion

It is finally concluded that Rational and prophylactic use of statins can reduce further complications of Diabetes Mellitus (DM) and cardiac events.

Statins treatment is favourable in long term treatment of diseases, it is most effectively used in treatment of serious disease conditions which has shown its immense therapeutic role in treatment.

Keywords: HMG-CoA reductase inhibitors, Prophylactic use, Diabetes mellitus, Cardiac events

INTRODUCTION

Medicines are an integral part of the health care, and modern health care is impossible without the availability of necessary medicines. They not only save lives and promote health, but prevent epidemics and diseases too. Accessibility to medicines is the fundamental right of every person. However, to bring optimal benefit, they should be safe, efficacious, cost-effective and rational

Prescription pattern and rational use

Prescription pattern monitoring studies (PPMS) are a tool for assessing the prescribing, dispensing and distribution of medicines. Prescription pattern

explain the extent and profile of drug use, trend, quality of drugs and compliance with regional, state or national guidelines like standard treatment guidelines, usage of drugs from essential medicine list and use of generic drugs. The main aim of PPMS is to facilitate rational use of medicines (RUM). There is paucity of published data analyzing the effectiveness of PPMS. The present review has been done to assess the effectiveness of prescription pattern monitoring studies in promoting RUM. Data search was conducted on internet. A multitude of PPMS done on different classes of drugs were collected and analyzed. PPMS using American College of Cardiology-American Heart Association (ACC-AHA) guidelines 2013 and recommendations from National Lipid Association (NLA) were included. It was observed in the majority of such studies that physicians do not adhere to the guidelines made by regulatory agencies leading to irrational use of medicines. This in turn leads to increased incidence of treatment failure, antimicrobial resistance and economic burden on the patient and the community as a whole. The treatment of diseases by the use of essential drugs, prescribed by their generic names, has been emphasized by the World Health Organization (WHO) and the National Health Policy of India. The prescription monitoring studies provide a bridge between areas like rational use of drugs, pharmacovigilance, and evidence based medicine, pharmacoeconomics. In India, this is the need of the hour to utilize the data generated by so many prescription pattern monitoring studies done in every state and on every drug, so that the main aim of promoting rational use of drugs is fulfilled [1].

The prevalence of Cardiovascular Diseases (CVD) is increasing in India. As per an estimate by Public Health Foundation of India, in 2011; there were 30 million patients with Chronic Heart Disease (CHD), in India. The prevalence of paralytic stroke is between 334 and 424 per 100,000 in urban areas and between 244 and 262 per 100,000 in rural areas. The mortality due to CVD is projected to rise to 4.2 million by 2030[8].

The aim of PPMS is to facilitate the rational use of drugs in a population. Irrational use of medicines is a major problem worldwide. WHO estimates that more than half of all medicines are prescribed, dispensed or sold inappropriately, and that half of all patients fail to take them correctly. The overuse, underuse or misuse of medicines results in wastage of scarce resources and widespread health hazards. The rational use of medicines (RUM) is defined as "Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community [1].

A large number of studies have been conducted to study the prescribing pattern of physicians across the country. The studies conclude the irrational prescribing practices of prescribers and suggest RUM at all levels of health care delivery system. However, no systematic reviews, meta-analyses, or randomized controlled trials are present about the relevance of PPMS in promoting rational use of drugs. The present review has been done to assess the effectiveness of PPMS in developing RUM. This study was conducted with the aim of analyzing the prescribing practices of physicians and to assess the extent to which the goal of RUM has been achieved. The drugs frequently prescribed by the physicians for disease conditions like diabetes, hypertension, coronary artery disease have been included in this study. An effort has been made to also include the prescribing trends of antiplatelet drugs due to the increased incidence of cardiovascular diseases [1, 2]**.**

The higher incidence of chronic diseases and degenerative pathologies increases demand for prescription medicines to treat these conditions, and to provide quality of life and well- being, which renders older susceptible to the risk of polypharmacy and drug- related illnesses. Aging related pathophysiologic changes also make them more prone to medication error. The resulting altered pharmacokinetics and pharmacodynamics due to these changes, makes them more susceptible to the adverse effects of drugs. Gaining insight into physicians prescribing pattern in order to identify prescribing problem is the fundamental step in improving the quality of prescription and patient care. This study gives an insight into the prevalence of prescribing error in one of the territory care corporate hospital with an aim to determine the nature and types of medication prescribing errors in territory care corporate hospital setting together with the pattern of drug use in elderly [2].

Initiation of statin therapy

Cardiovascular disease (CVD) is the leading cause of death worldwide. Many prospective cohort studies have shown that high levels of low-density lipoprotein cholesterol (LDL-c) are a major risk factor for CVD. 3-Hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) reduce all-cause mortality and major vascular events by approximately 23% for each 1.0 mmol/l lowering of LDL-c. The challenge of statin treatment is the identification of patients who would benefit from treatment. Various guidelines have been developed to guide physicians.

In the Randomized Control Trials (RCTs) reviewed, initiation of moderate-intensity therapy (lowering LDL-C by approximately 30% to <50%) or high-intensity statin therapy (lowering LDL-C by approximately ≥50%) is a critical factor in reducing Atherosclerotic Cardiovascular disease (ASCVD) events. Moreover, statin therapy reduces ASCVD events across the spectrum of baseline LDL-C levels ≥70 mg/dL. In addition, the relative reduction in ASCVD risk is consistent for primary and secondary prevention and for various patient subgroups [3].

On the basis of this large and consistent body of evidence, 4 major statin benefit groups were identified for whom the ASCVD risk reduction clearly outweighs the risk of adverse events based on a strong body of evidence.

These are:

1) Secondary prevention in individuals with *clinical* ASCVD,
2) Primary prevention in individuals with primary elevations of LDL-C ≥190 mg/dL,
3) Primary prevention in individuals with diabetes 40 to 75 years of age who have LDL-C 70 to 189 mg/dL, and
4) Primary prevention in individuals without diabetes and with estimated 10-year ASCVD risk ≥7.5%, 40 to 75 years of age who have LDL-C 70 to 189 mg/dL.

Moderate evidence supports the use of statins for primary prevention in individuals with 5% to <7.5% 10-year ASCVD risk, 40 to 75 years of age with LDL-C 70 to 189 mg/dL. Selected individuals with <5% 10-year ASCVD risk, or <40 or >75 years of age may also benefit from statin therapy. Clinicians and patients should engage in a discussion of the potential for ASCVD risk-reduction benefits, adverse effects, drug–drug interactions, and consider patient preferences for treatment. It also emphasize healthy-lifestyle habits and addressing other risk factors [3].

Intensity of statin therapy in primary and secondary prevention:

The Expert Panel defined the intensity of statin therapy on the basis of the average expected LDL-C response to a specific statin and dose. "High-intensity," "moderate-intensity," and "low-intensity" statin therapy definitions were derived from the systematic reviews. The basis for differentiation among specific statins and doses arose from the RCTs, where there was a high level of evidence that high-intensity statin therapy with atorvastatin 40 mg to 80 mg reduced ASCVD risk more than moderate-intensity statin therapy with atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20 mg to 40 mg twice daily [3].

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately ≥50%	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Daily dose lowers LDL-C, on average, by <30%
Atorvastatin (40†)–80 mg	Atorvastatin 10 (20) mg	Simvastatin 10 mg
Rosuvastatin 20 (40) mg	Rosuvastatin (5) 10 mg	Pravastatin 10–20 mg
	Simvastatin 20–40 mg	Lovastatin 20 mg
	Pravastatin 40 (80) mg	Fluvastatin 20–40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2–4 mg	

Women and men with clinical ASCVD (acute coronary syndromes; history of MI, stable or unstable angina) arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin are at increased risk for recurrent ASCVD and ASCVD death. An extensive body of evidence demonstrates that high-intensity statin therapy reduces ASCVD events more than moderate-intensity statin therapy in individuals with clinical ASCVD.

High-intensity statin therapy should be initiated for adults ≤75 years of age with clinical ASCVD who are not receiving statin therapy, or the intensity should be increased in those receiving a low- or moderate-intensity statin, unless they have a history of intolerance to high-intensity statin therapy or other characteristics that could influence safety. The high-intensity statins atorvastatin 80 mg and Rosuvastatin 20 mg daily reduce LDL-C ≥50% on average and have been shown to reduce ASCVD events in RCTs [3].

Stratifying by the type of prevention, atorvastatin was significantly more prescribed for secondary prevention than for primary. A recent meta-analysis on comparative benefits of statins on major cerebrovascular events suggested that, although any statin therapy is associated with a significant reduction in cerebrovascular events in secondary prevention, only atorvastatin resulted in significantly fewer events than controls [5].

Primary prevention in individuals with diabetes

A high level of evidence supports the use of moderate-intensity statin therapy in persons with diabetes who are 40 to 75 years of age. The only trial of high-intensity statin therapy in primary prevention was performed in a population without diabetes. However, a high level of evidence existed for event reduction with statin therapy in individuals with a ≥7.5% estimated 10-year ASCVD risk who did not have diabetes to recommend high-intensity statin therapy preferentially for individuals with diabetes and a ≥7.5% estimated 10-year ASCVD risk .This consideration for those with diabetes who are 40 to 75 years of age recognizes that these individuals are at substantially increased lifetime risk for ASCVD events and death. Moreover, individuals with diabetes experience greater morbidity and worse survival after the onset of clinical ASCVD. In persons with diabetes who are <40 years of age or >75 years of age, or whose LDL-C is <70 mg/dL, statin therapy should be individualized on the basis of considerations of ASCVD risk-reduction benefits, the potential for adverse effects and drug–drug interactions, and patient preferences[4].

2014 nla criteria for treatment initiation according to risk:

Clinicians have felt somewhat lost with the current ACC/AHA guidelines.

- In 2014, the National Lipid Association (NLA) published recommendations for identifying patients by risk-
- Moderate, high, or very high risk
- T2 Diabetes patients fit into high or very high risk categories. [11]

2014 NLA Criteria for Treatment Initiation According to Risk

Risk Category	Criteria	LDL-C/Non-HDL-C Levels for Treatment Initiation, mg/dL
Moderate	• 2 major ASCVD risk factors* • 10-y risk ≥ 7.5%† • Role of metabolic syndrome?	130/160
High	• ≥ 3 major risk factors* • CKD stage 3B/4 • T2D plus 0-1 other major risk factors • LDL-C ≥ 190 mg/dL • 10-y risk 10%†	100/130
Very high	• ASCVD • T2D plus ≥ 2 other risk factors* • End-organ damage (retinopathy or UACR ≥ 30 mg/g or eGFR < 60 mL/min/1.73 m²)	70/100

*Age > 45 y M/ > 55 y W; high BP; current cigarette use; family history CHD age < 55 y M/< 65 y W; HDL-C < 40 mg/dL M/<50 mg/dL W; †ATP III Framingham Risk Score.

2016 consensus statement from ACC/AHA and NLA

In 2016, a consensus guideline on the management of atherosclerotic cardiovascular disease (ASCVD) risk was published by the ACC/AHA and NLA

- Includes the same treatment recommendations
- Provides guidance for treatment after statin use or in cases of statin-intolerance. [3, 11]

2013 ACC/AHA Statin Benefit Groups[a]	2014 NLA Recommendations[b,c]
1. Any clinical ASCVD	• High-intensity statin if ≤ 75 y • Moderate-intensity statin if age is > 75 y or if not a candidate for statin therapy
2. LDL-C ≥ 190 mg/dL	• High-intensity statin
3. Diabetes, aged 40 to 75 y, LDL-C 70 to 189 mg/dL, no clinical ASCVD	• Moderate-intensity statin • High-intensity statin if ASCVD risk ≥ 7.5%
4. Estimated 10-y ASCVD risk of 7.5%, aged 40 to 75 y, LDL-C 70 to 189 mg/dL, no clinical ASCVD	• Moderate-to-high-intensity statin

Rationale for the expert panel approach to primary –prevention guidelines

1. Cholesterol-lowering medications, particularly statins, are efficacious and effective for reducing risk of initial cardiovascular events.
2. Statins are associated with similar relative risk reductions for cardiovascular events across the majority of primary-prevention patient groups studied.
3. The extent of relative risk reduction for ASCVD is proportional to the degree of LDL-C lowering observed on statin therapy. Therefore, more intensive statin therapy could reduce risk more than moderate- or lower-intensity statin therapy.
4. According to consistent findings, the absolute benefit in ASCVD risk reduction is proportional to the baseline risk of the patient

group or individual and to the intensity of statin therapy.

5. Patients or groups at higher baseline absolute risk, therefore, will derive greater absolute benefit from initiation of statin therapy over a period of 5 to 10 years.
6. The absolute risk for adverse outcomes, including a small excess in cases of newly diagnosed diabetes, also appears to be proportional to the intensity of statin therapy. However, the adverse outcome of incident (or earlier diagnosis of) diabetes must be weighed in the context of the potentially fatal or debilitating occurrence of MI or stroke that could be prevented by statin therapy.
7. The Expert Panel emphasizes that the occurrence of a major ASCVD event (MI or stroke) represents a much greater harm to health status than does an increase in blood glucose leading to a diagnosis of diabetes. The net absolute benefit of statin therapy can be considered as a comparison of the absolute risk reduction for ASCVD with the absolute excess risks, including that for diabetes. Benefit also could be understood as a comparison of the number of statin-treated patients that would result in the prevention of 1 case of major ASCVD with the number of statin-treated patients that would result in 1 excess case of diabetes.
8. Because the absolute benefit in terms of ASCVD risk reduction depends on the baseline absolute risk for ASCVD, the absolute benefit from initiation of statin therapy is lower and would approach the risk for adverse effects in patients with lower baseline levels of predicted ASCVD risk.
9. Available RCT evidence indicates a clear net absolute benefit of initiation of moderate-to-intensive statin therapy at a baseline estimated 10-year ASCVD risk of ≥7.5%.
10. Available RCT evidence indicates that when baseline ASCVD risk is 5.0% to <7.5%, there is still net absolute benefit with moderate-intensity statin therapy. However, the tradeoffs between the ASCVD risk-reduction benefit and adverse effects are less clear. Thus, a clinician-patient discussion is even more important for individuals with this range of ASCVD risk. The net benefit of high-intensity statin therapy may be marginal in such individuals [3].

This guideline recommends that initiation of moderate-intensity statin therapy be considered for patients with predicted 10-year "hard" ASCVD risk of 5.0% to <7.5%.

A conservative estimate of adverse events includes excess cases of new-onset diabetes and rare cases of myopathy and hemorrhagic stroke. The rate of excess diabetes varies by statin intensity. For moderate-intensity statins, approximately 0.1 excess case of diabetes per 100 statin-treated individuals per year has been observed, and for high-intensity statins, approximately 0.3 excess case of diabetes per 100 statin-treated individuals per year has been observed. The long-term adverse effects of statin-associated cases of diabetes over a 10-year period are unclear and are unlikely to be equivalent to an MI, stroke, or ASCVD death. Myopathy (~0.01 excess case per 100) and hemorrhagic stroke (~0.01 excess case per 100) make minimal contributions to excess risk from statin therapy [3].

Statin safety recommendation:

To maximize the safety of statins, selection of the appropriate statin and dose in men and non pregnant/ nonnursing women should be based on patient characteristics, level of ASCVD risk, and potential for adverse effects. Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin–associated adverse effects are present.

Characteristics predisposing individuals to statin adverse effects include but are not limited to:

- Multiple or serious co morbidities, including impaired renal or hepatic function.
- History of previous statin intolerance or muscle disorders.
- Unexplained ALT elevations ≥3 times.
- Patient characteristics or concomitant use of drugs affecting statin metabolism.
- Age >75 years.

Additional characteristics that could modify the decision to use higher statin intensities might include but are not limited to:

- History of hemorrhagic stroke.
- Asian ancestry.

For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for nonstatin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy.

It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm:

- To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiation of statin therapy.
- If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating Creatinine kinase (CK) and creatinine and performing urinalysis for myoglobinuria.
- If mild to moderate muscle symptoms develop during statin therapy:

– Discontinue the statin until the symptoms can be evaluated.

– Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases).

– If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy.

Individuals receiving statin therapy should be evaluated for new-onset diabetes according to the current diabetes screening guidelines. Those who develop diabetes during statin therapy should be encouraged to adhere to a heart-healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events.

Decreasing the statin dose may be considered when 2 consecutive values of LDL-C are <40 mg/dL. This recommendation was based on the approach taken in 2 RCTs. However, no data were identified that suggest an excess of adverse events occurred when LDL-C levels were below this level [3].

Recommendations for monitoring, optimizing and addressing insufficient response to statin therapy

Monitoring statin therapy

Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within 4–12 weeks after initiation or dose adjustment, and every 3–12 months thereafter. Other safety measurements should be measured as clinically indicated.

Optimizing statin therapy

The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended but not tolerated.

Insufficient Response to Statin Therapy

- In individuals who have a less-than-anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed:

- Reinforce medication adherence.
- Reinforce adherence to intensive lifestyle changes.
- Exclude secondary causes of hyperlipidemia [3].

Factors affecting statins prescribing pattern

- Lack of familiarity with the current clinical guidelines.
- Speciality of the prescriber.
- Lack of proper outcome anticipation.
- Practice setting related limitations.
- Patient related limitations.
- Presence of guidelines, concerns or disagreement [6].

Factors affecting patients compliance to statin therapy

Patient related factors

- Age.
- Addictions.
- Sedentary life style.
- Co morbidities.

- Satisfaction with the therapeutic efficacy.
- Tolerance issues.

Clinicians related factors

- Clinical experience.
- Number of patients seen per month.
- Practice settings.
- Communication skills.
- Perception of statins adverse effects [6].

Rationale

Importance

Cardiovascular disease is a broad term that encompasses a number of atherosclerotic conditions that affect the heart and blood vessels, including coronary heart disease, as ultimately manifested by myocardial infarction (MI), and cerebrovascular disease, as ultimately manifested by stroke. Cardiovascular disease is the leading cause of morbidity and mortality in the United States, accounting for 1 of every 3 deaths among adults.

Statins are a class of lipid-lowering medications that function by inhibiting the enzyme (HMG-Co-A) 3-hydroxy-3-methyl-glutaryl coenzyme A reductase, which is involved in the rate-limiting step in the production of cholesterol. Statins reduce levels of total cholesterol and LDL-C and, to a lesser extent, triglycerides, and probably have anti-inflammatory and plaque stabilization effects as well [7].

Potential Benefits of Statin Use

The US Preventive Services Task Force (USPSTF) found adequate evidence that use of low- to moderate-dose statins reduces the probability of CVD events (MI or ischemic stroke) and mortality by at least a moderate amount in adults aged 40 to 75 years who have 1 or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year CVD event risk of 10% or greater.

The USPSTF found adequate evidence that use of low- to moderate-dose statins reduces the probability of CVD events and mortality by at least a small amount in adults aged 40 to 75 years who have 1 or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year CVD event risk of 7.5% to 10%.

The USPSTF found inadequate evidence to conclude whether initiating statin use in adults 76 years and older who are not already taking a statin is beneficial in reducing the incidence of CVD events and mortality [7].

Potential Harms of Statin Use

The USPSTF found adequate evidence that the harms of low- to moderate-dose statin use in adults aged 40 to 75 years are small. Randomized clinical trials (RCTs) of statin use for the primary prevention of CVD events have largely used low and moderate doses; under these conditions, statin use was not associated with serious adverse events such as cancer, severely elevated liver enzyme levels, or severe muscle-related harms. However, evidence concerning the association between statin use and diabetes mellitus is mixed, with 1 prevention trial suggesting that there may be a small increased risk of developing diabetes with use of high-dose statins. Myalgia is a commonly reported adverse effect of statins, but placebo-controlled trial data do not support the conclusion that statin use has a major causative role in its occurrence. Evidence for cognitive harms is relatively sparse; further research would be needed to more definitively establish the relationship between statin use and cognitive function. The USPSTF found no clear evidence of decreased cognitive function associated with statin use. These findings are consistent with those from a recent systematic review of RCTs and observational studies assessing the effect of statins on cognition that found no effect on incidence of Alzheimer disease or dementia. The recently published HOPE-3 (Heart Outcomes Prevention Evaluation 3) trial found that statin use increased risk of cataract surgery, which was unanticipated and not a predetermined outcome of the trial. None of the other primary prevention trials reported this outcome.

The USPSTF found inadequate evidence on the harms of statin use for the prevention of CVD events in adults 76 years and older without a history of heart attack or stroke [7].

Pharmacology of statins

Statins are the structural analogues of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A). Introduced in 1980's this class of compounds are

the most efficacious and best tolerated hypolipidemic drugs.

Different statins are

- Atorvastatin
- Rosuvastatin
- Lovastatin
- Simvastatin
- Pravastatin
- Pitavastatin
- Fluvastatin [9].

Mechanism OF ACTION

They competitively inhibit conversion of 3-Hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) to mevalonate (rate limiting step in CH synthesis) by the enzyme HMG-CoA reductase. Therapeutic doses reduce CH synthesis by 20-50%.This results in compensatory increase in LDL receptor expression on liver cells. 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). This competition reduces the rate by which HMG-CoA reductase is able to produce mevalonate, the next molecule in the cascade that eventually produces cholesterol [10].

In addition to lowering cholesterol levels, statins also reduce inflammation, which could be another mechanism by which statins beneficially affect atherosclerosis. This reduction of inflammation does not depend on statins ability to reduce cholesterol. Furthermore, these anti-inflammatory effects can be seen as early as two weeks after starting statins [9, 10].

Other effects include decreased oxidative stress and vascular inflammation with increased stability of atherosclerotic lesions. It has become a standard practice to initiate statins therapy immediately after acute coronary syndromes, regardless of lipid levels. Improvement in endothelial function due to increased NO production and reduction in LDL oxidation are proposed as additional mechanisms by which statins may exert anti atherosclerotic action [9].

Pharmacokinetics

- Absorption of ingested doses of the reductase inhibitors varies from 40%-75% with the exception of fluvastatin, which is completely absorbed.
- All statins have high first pass extraction by liver.
- Most of the absorbed dose is excreted in the bile; 5-20% is excreted in urine.
- Atorvastatin and rosuvastatin has a much longer plasma half life of 18-24 hours [9].

Adverse effects

- All statins are remarkably well tolerated; overall incidence of adverse effects not differing from placebo.
- Notable adverse effects are- Headache, Nausea, Bowel upset, Rashes, Sleep disturbances (probably more with lipophilic drugs)
- Rise in serum transaminase can occur, but liver damage is rare
- Muscle tenderness and rise in CPK levels occurs infrequently. Myopathy is the only serious reaction, but is rare (<1 per 100). Myopathy is more common when nicotinic acid/gemfibrozil or CYP3A4 inhibitor HIV protease inhibitor is given concurrently [10].

Interactions

- May increase risk of myopathy and rhabdomyolysis with CYP3A4 potent inhibitor (e.g. HIV or HCV protease inhibitors, itraconazole, clarithromycin), fenofibrate, colchicines, and fixed combination of lopinavir/ritonavir.
- May decrease plasma concentration with CYP3A4 inducer (e.g. rifampicin, efavirenz).
- May significantly increase Area under curve (AUC) and peak plasma concentration of Digoxin.
- Increased AUC for norethindrone and ethinyl estradiol.
- Gemfibrozil inhibits the hepatic uptake of statins by the organic anion transporter OATP2.
- Fenofibrate interferes least with statin uptake/ metabolism and should be preferred for combining with them. Hence a lower dose of statin is advised when fibrate is given concurrently.

Potentially fatal

- Increased risk of myopathy or rhabdomyolysis with ciclosporin, gemfibrozil, telaprevir, tipranavir.

- May increase risk of myopathy or rhabdomyolysis with grapefruit juice [10].

Indications

Statins are the first choice drugs for primary hyperlipidaemias with raised LDL and total cholesterol levels, with or without raised TG levels as well as for secondary (diabetes, nephritic syndrome) hypercholesterolaemia. Beneficial effects in subjects who have raised CH levels but no evidence of CAD may relate to improved coronary artery compliance and atheromatous plaque stabilization due to suppression of macrophage mediated inflammation, reducing chances of plaque rupture and thrombus formation.
Statins are used in the treatment of

Hyperlipidemia (Primary hypercholesterolemia and mixed dyslipidemia)

- Indicated as an adjunct to diet for treatment of elevated total-C, Apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson type IIa and IIb).

Hypertriglyceridemia

- Adjunct to diet for elevated TG levels (Fredrickson type IV).

Homozygous familial hypercholesterolemia

- Reduction of total-C and LDL-C in Homozygous familial hypercholesterolemia as an adjunct to other lip-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable.

Cardiovascular disease prevention

- Reduction of risk of stroke and heart attack in type 2 diabetes patients without evidence of heart disease but with other CV risk factors.
- Reduction of risk of stroke, heart attack, and revascularization procedures in patients without evidence of coronary heart disease (CHD) but with multiple risk factors other than diabetes (eg, smoking, HTN, low HDL-C, family history of early CHD).
- Patients with CHD, to reduce risks of MI, stroke, revascularization procedures, hospitalization for Congestive heart failure(CHF), and angina[9,10].

Contraindications

Statins are contraindicated in case of

- Pregnancy and lactation as there is no data available regarding their safety.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Concomitant use with cyclosporine, gemfibrozil, Telaprevir, tipranavir [9, 10].

METHODOLOGY

It was a prospective observational study conducted for a period of 6 months and included various departments of 300 bedded multi specialty tertiary care corporate hospital. A total of 200 patients were included and the study criteria was inpatients and indivuals more than 18 years of either gender who are prescribed with HMG-CoA reductase inhibitors. Patient data was obtained form patient consent form, patient profile form

RESULTS

Table 1: Age Wise Distribution of Statins Used

Age(years)	No. Of Patients(n)	Percentage (%)
21-30	03	1.50
31-40	05	2.50
41-50	22	11.00
51-60	58	29.00
61-70	**60**	**30.00**
71-80	44	22.00
81-90	07	3.50
91-100	**01**	**0.50**
Total	**200**	
Mean± SD	**25± 25.26**	

The above table it is inferred that out of 200 patients, we conclude that the age group to which statins were mostly prescribed was between 61-70 years are **60 (30%)** and leastly prescribed age group being 91-100 years is **1(0.5%).**

TABLE 2: GENDER WISE DISTRIBUTION

Gender	No. Of Patients(n)	Percentage (%)
Male	130	65.00
Female	70	35.00
Total	**200**	
Mean± SD	**100± 42.42**	

The above table it is inferred that out of 200 patients, statins were highly prescribed among males 130(65%) whereas in females it was found to be 70(35%).

TABLE 3: DEPARTMENT WISE DISTRIBUTION

Departments	No. Of patients (n)	Percentage (%)
Cardiology	**128**	**64.00**
Neurology	27	13.50
Vascular surgery	7	3.50
Pulmonology	11	5.50
General medicine	11	5.50
Orthopaedics	**5**	**2.50**
Others	11	5.50
Total	**200**	
Mean± SD	**28.57±44.41**	

The above table it is inferred that statins were prescribed in various departments of which **Cardiology** department being mostly prescribed with statins i.e. **128 (64%)** and leastly prescribed department was **Orthopaedics** i.e.**5 (2.50%).**

TABLE 4: WEIGHT WISE DISTRIBUTION OF STATINS

Weight intervals	No. Of patients(n)	Percentage (%)
41-50	15	7.50
51-60	53	26.50
61-70	**66**	**33.00**
71-80	45	22.50
81-90	18	9.00
>90	**3**	**1.50**
TOTAL	**200**	
Mean ±SD	**33.3±24.8**	

The above table it is inferred that statins were prescribed for patients with different weights in which highest no of patients belonged to weight interval of **61-70** i.e. **66(33%)** and least number of patients belonged to weight interval of **(>90)** i.e. **3(1.5%).**

TABLE 5: DIAGNOSIS WISE DISTRIBUTION:

Diagnosis	No Of Patients(n)	Percentage (%)
CAD	**71**	**35.50**
MI	20	10.00

NSTEMI	07	3.50
CHF	**03**	**1.50**
Stroke	20	10.00
Cellulitis	**03**	**1.50**
DVT	04	2.00
LRTI	06	3.00
Others	66	33.00
Total	**200**	
Mean± SD	**22.22±27.09**	

The above table it is inferred that out of 200 cases the highest no. of patients were diagnosed with **CAD** i.e. **71(35.5%)** and least no. of patients were diagnosed with CHF i.e. 03(1.50%), **Cellulitis** i.e. **3(1.50%).**

TABLE 6: TYPES OF STATINS PRESCRIBED

Drug name	**No. of patients(n)**	**Percentage (%)**
Atorvastatin	**134**	**67.00**
Rosuvastatin	59	29.50
Atorvastatin+ Rosuvastatin	4	2.00
Atorvastatin/ Rosuvastatin	2	1.00
Rosuvastatin/ Atorvastatin	1	0.50
Total	**200**	
Mean± SD	**40±58.004**	

The above table it is inferred that out of 200 prescriptions frequently prescribed statin was **Atorvastatin 134(67%)** and **Rosuvastatin 59(29.5%)** where as 2 patients where switched from atorvastatin to rosuvastatin (1%) and 1 patients was switched from rosuvastatin to atorvastatin (0.5%). During our study we encountered 4 prescriptions with a case of therapeutic duplication in which atorvastatin and rosuvastatin were prescribed simultaneously (2%).

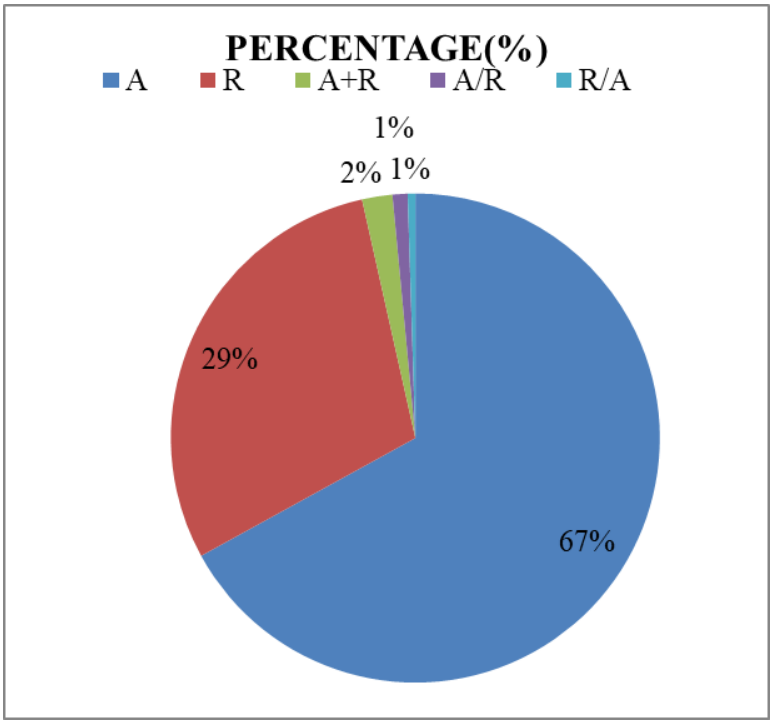

TABLE 7: PRESCRIPTION WISE DISTRIBUTION:

Prescribed as	No of prescription(n)	Percentage (%)
Brand names	162	81.00
Generic names	38	19.00
Total	**200**	
Mean± SD	**100±87.681**	

Out of 200 cases, a majority of the drugs were purely prescribed based on the **Brand names i.e., 162 (81%)** followed by **Generic names i.e., 38 (19%).** The pattern of prescription in terms of the generic name was found to be low and should be encouraged more.

TABLE 8: BRANDS THAT ARE PRESCRIBED:

Brands	No of Patients(n)	Percentage (%)
Aztor	**64**	**32.00**
Atorva	43	21.50
Storvas	14	7.00
Lipicure	01	0.50
Tonact	12	6.00
Clopitorva	01	0.50
Ecosprin AV	01	0.50
Atocar	02	1.00
Remetor	02	1.00
Rosuvas	**57**	**28.50**
Rosuvast	01	0.50
Rozavel	02	1.00
Total	**200**	
Mean± SD	**16.66±23.77**	

From the above table it is inferred that **AZTOR** was commonly prescribed brand of Atorvastatin **64 (32%)** followed by **ROSUVAS** brand of Rosuvastatin **57 (28.5%)**.

TABLE 9: PRESCRIPTION PATTERN OF STATINS:

Prescribing Pattern Of Statins	No Of Patients(n)	Percentage (%)
Monotherapy	25	12.50
Dual therapy	**79**	**39.50**
Triple therapy	70	35.00
Polytherapy	26	13.00
Total	**200**	
Mean± SD	**50±28.53**	

The above table it is inferred that from 200 patients about 79 (39.5%) patients were prescribed with dual therapy followed by 70 (35%) patients who received triple therapy and 26(13%) patients received polytherapy, 25 (12.5%) patients received monotherapy

TABLE 10: DURATION OF STATIN USE

Time period	No. of patients(n)	Percentage (%)
No history	**108**	**54.00**
Up to 1year	24	12.00
1-5 years	38	19.00
6-10years	24	12.00
>10 years	**6**	**3.00**
Total	**200**	
Mean± SD	**40±39.67**	

In our study we found that out of 200 patients, **108(54%)** patients were found with **no history of statin use.** And about **24 (12%)** patients were prescribed with statin for **1 year**.

TABLE 11: DRUG INFORMATION WISE DISTRIBUTION:

Information given to	No. of patients(n)	Percentage (%)
Patient	115	57.50
Patient Representative	81	40.50
Nurse	4	2.00
Total	**200**	
Mean± SD	**66.66±56.87**	

The above table it is inferred that out of 200 patients most of the information was given to the **patients i.e. 115(57.5%)** followed by patient representatives 81 (40.5%) **and nurse 4 (2.00%).**

TABLE 12: DIFFERENT CATEGORIES OF DRUGS PRESCRIBED TO PATIENTS

Category	No. of patients(n)	Percentage (%)
Oral hypoglycaemic agents	113	32.94
Anti hypertensive's	150	43.73
Anti platelet agents	80	23.32
Mean ±SD	**114.3±35.01**	

In our study we found that out of 200 patients Oral hypoglycemic agents were mostly prescribed drugs i.e., 113 (32.94%) followed by Anti hypertensive's 150(43.73%), Anti platelet agents 80 (23.32%).

TABLE 13: INTENSITY WISE DISTRIBUTION

Intensity	Atorvastatin	Rosuvastatin
Low	0	0
Moderate	28	12
High	107	49
Total	135	61

The above table, it is inferred that out of 200 prescriptions, majority of statins prescribed were of high intensity i.e., Atorvastatin 107 and Rosuvastatin 49 followed by moderate intensity Atorvastatin 28 and Rosuvastatin 12 respectively.

TABLE 14: RATIONALITY WISE DISTRIBUTION:

Rationality	No. of Patients(n)	Percentage (%)
Irrational	51	25.50
Rational	149	74.50
Mean± SD	**100±69.2**	

In this study, it was found that out of 200 patients who were given statins, 149 patients (74.5%) were prescribed rationally while 51 patients (25.5%) were prescribed irrationally.

Comparision of drugs based on department

Department	Atorvastatin	Rosuvastatin	P- Value
Cardiology	104	18	
Neurology	04	23	
Vascular surgery	0	07	P<0.001
Orthopaedics	02	03	
General medicine	07	03	
Pulmonology	10	01	
Others	12	06	

Comparision of drugs based on disease

Diseases	Atorvastatin	Rosuvastatin	P- Value
CAD	75	14	
MI	13	01	
Stroke	02	19	P<0.3421
DVT/PVD	05	02	
Cellulitis	02	01	
LRTI	04	02	

Comparisions of gender based on departments

DEPARTMENTS	MALE	FEMALE	P-value
Cardiology	89	39	
Neurology	06	11	
Vascular surgery	06	01	
General medicine	04	07	P<0.0001
Pulmonology	05	06	
Orthopaedics	01	04	
Others	09	02	

DISCUSSION

In the present study 200 patients belonged to the age group of above 18 years, out of which about **65%** were male and **35%** were female. It shows that in this study, males were mostly prescribed with statins shown in Table.no.2 with bar diagram. The mean± SD value of this distribution was **100±42.42.**

This study observe that age distribution to which statins were mostly prescribed was between 61-70 years i.e., 60 (30%) followed by 51-60 years i.e., 58(29%), 71-80 years i.e., 44(22%) and 41-50 years i.e., 22(11%) leastly prescribed age group being 91-100 years is 1(0.5%) shown in Table.no.1 with bar diagram. The mean± SD value of this age distribution was **25±25.26.**

Department wise distribution of this study population shows that statins were prescribed in various departments of which cardiology department being mostly prescribed with statins i.e., 128 (64%) followed by neurology 27(13.5%), pulmonology 11(5.50%), general medicine 11(5.50%), vascular surgery 7(3.5%), orthopaedics 5(2.50%) and others including nephrology, gastroenterology, urology, endocrinology were shown in the table.no.3 with bar diagram. The mean± SD value of department wise distribution was **28.57±44.41.**

Weight wise distribution of this study population for different weights in which highest no of patients belonged to weight interval of 61-70 i.e. 66(33%) followed by 51-60 -53 (26.5) were shown in the Table.no.4 with bar diagram. The mean± SD value of weight distribution was found to be **33.3±24.8.**

Out of 200 cases the highest no. of patients were diagnosed with CAD i.e. 71(35.5%) followed by MI 20(10.0%) and stroke 20(10.0%) , NSTEMI 07(3.50%),CHF 03(1.50%), Cellulitis 03(1.50%) ,DVT 04(2.00%), LRTI 06(3.00%) and others include bronchial asthma, osteoarthritis, renal calculi, encephalopathy, etc were shown in the Table.no.5 with bar diagram. The mean± SD value of diagnosis wise distribution was **22.22±27.09.**

Out of 200 prescriptions frequently prescribed statin was Atorvastatin 134(67%) and Rosuvastatin 59(29.5%) where as in 2 patients were switched from atorvastatin to rosuvastatin (1%) and 1 patients was switched from rosuvastatin to atorvastatin (0.5%) were shown in the Table no.6 with bar diagram and pie chart. During our study we encountered 4 prescriptions with a case of therapeutic duplication in which atorvastatin and rosuvastatin were prescribed simultaneously (2%). The mean± SD value of frequently prescribed was found to be **40±58.004.**

Out of 200 cases, a majority of the drugs were purely prescribed based on the Brand names i.e., 162 (81%) followed by Generic names ie.,38 (19%).The pattern of prescription in terms of the generic name was found to be low and should be encouraged more which was shown in the Table no.7 with bar diagram. The mean± SD value of types of prescription was **100±87.681.**

Out of 200 cases, it is inferred that Aztor was commonly prescribed brand of atorvastatin 64 (32%) followed by Rosuvas brand of rosuvastatin 57 (28.5%) and Atorva being 43(21.5%), Storvas 14(7%), Tonact 12(6%), Atocar 2(1%), Remetor 2(1%) and Lipicure 1(0.5%), Rozavel 2(1%), Rosuvast 1(0.5%) were shown in the Table no.8 with bar diagram and pie chart. The mean± SD value of brands prescribed was found to be **16.66±23.77.**

The prescribing pattern of statins is shown in the Table, no.9 shows that in Monotherapy the no of prescriptions are 25 followed by in dual therapy 79 prescriptions were prescribed followed by triple therapy 70 prescriptions and in poly therapy 26 prescriptions were prescribed and it was shown with bar diagram from Table.no.9.The mean± SD value of prescription pattern of statins was found to be **50±28.53.**

Out of 200 patients, 108(54%) patients were found with no history of statin use. And about 24 (12%) patients were prescribed with statin for 1 year, about 38 (19%) were prescribed with statins from 1-5 years, about 24(12%) were prescribed with statins from 6-10 years and 6(3%) patients were prescribed with statins for more than 10 years which was shown with bar diagram from Table.no.10. The mean± SD value of duration of statin use was **40±39.67.**

Out of 200 patients most of the drug information was given to the patients i.e. 115(57.5%) followed by patient representatives 81 (40.5%) and nurse 4 (2.00%) which was shown with bar diagram from Table no.11. The mean± SD value of drug information wise distribution was found to be **66.66±56.87.**

Out of 200 patients Oral hypoglycemic agents were the mostly prescribed drugs i.e., 113 (32.94%)

followed by Anti hypertensive's 150(43.73%), Anti platelets 80 (23.32%) which was shown with bar diagram from Table no.12. The mean± SD value of different categories of drugs prescribed to patients was **114.3±35.01.**

Out of 200 prescriptions, majority of statins prescribed were of high intensity i.e., Atorvastatin 107 and Rosuvastatin 49 followed by moderate intensity Atorvastatin 28 and Rosuvastatin 12 respectively were shown with bar diagram from Table.no.13.

Out of 200 patients who were given statins, 149 patients (74.5%) were prescribed rationally while 51 patients (25.5%) were prescribed irrationally were shown with bar diagram from Table.no.14. The mean± SD value of Rationality wise distribution was **100±69.2.**

Two dimensional studies were also conducted on Department, Disease, Drugs and Gender.

Comparision of drugs based on departments **(P<0.001).**

Comparision of drugs based on diseases (**P=0.3421).**

Comparision of drugs based on gender (**P<0.0001).**

CONCLUSION

Present study was conducted in a tertiary care corporate hospital located in secunderabad. This study was aimed at assessing the prescription pattern of statins and we found that majority of the people belongs to an age group of between 61-70 **(30%).** The male patients were **65%**and **35%** were female patients and it was found that patients are mostly suffering from **CAD (35.5%).**

Atorvastatin **(67%)** was prescribed mostly and Rosuvastatin **(29.5%)** was also used. Brand names were purely prescribed about 81% where as generic names were prescribed for around **19%.** This concludes that generic name was found to be low and should be encouraged more. Aztor **(32%)** and Rosuvas **(28.5%)** are the brands which were mostly prescribed.

Based on prescription pattern of statins about **39.5%** of patients were prescribed with Dual therapy and Monotherapy **(12.5%)** was leastly prescribed through which we conclude that prophylactic use of statins would have reduced further cardiac events and complications of the disease.

Finding of the project indicates a significance reduction in rational prescribing which include multiple prescribing.

Assuring the safe medications to the patients, this study has created awareness among the medical practitioners on the necessity of the clinical pharmacist in the institutional healthcare setup to prevent irrational prescribing and to promote rational use of drugs.

It is finally concluded that Rational and prophylactic use of statins can reduce further complications of Diabetes Mellitus (DM) and cardiac events.

Physicians and pharmacists should also adopt interventions that are designed to help patients remember to keep their clinic appointments and to take their medications as prescribed by the doctor and promote rational use of drugs in all the departments.

REFERENCES

[1]. Shipra Jain, Prerna Upadhyaya, Jaswant Goyal, Abhijit Kumar, Pushpawati Jain, Vikas Seth**,** et al. A systematic review of prescription pattern monitoring studies and their effectiveness in promoting rational use of medicines. Perspect Clin Res. 6(2), 2015, 86–90.

[2]. Sujat Sakpota, Nawin Pudaisini, Chandan Singh, Sagar, Drug Prescribing Pattern and Prescription error in Elderly: A Retrospective study of inpatient record, ajpcr; l4(3), 2011.

[3]. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014, 63, 2013, 2889–934.

[4]. Roy Eldor, MD and Itamar Raz, MD, American Diabetes Association Indications for Statins in Diabetes. Diabetes Care. 32(2), 2009, S384–S391.

[5]. Degli Esposti L, Saragoni S, Batacchi P, Benemei S, Geppetti P, et al. Adherence to statin treatment and health outcomes in an Italian cohort of newly treated patients: results from an administrative database analysis. Clin Ther 34, 2012, 190–199.

[6]. Elnaem, M. H., Mohamed, M. H. N., Huri, H. Z., Azarisman, S. M., & Elkalmi, R. M. Statin Therapy Prescribing for Patients with Type 2 Diabetes Mellitus: A Review of Current Evidence and Challenges. Journal of Pharmacy & Bioallied Sciences, 9(2), 2017, 80–87.

[7]. Kirsten Bibbins-Domingo et al, Statin Use for the Primary Prevention of Cardiovascular Disease in Adults US Preventive Services Task Force Recommendation Statement. *JAMA.* 316(19), 2016, 1997–2007.

[8]. Menon AS, Kotwal N, Singh Y, Girish R. Statins: Cholesterol guidelines and Indian perspective. Indian Journal of Endocrinology and Metabolism. 19(5), 2015, 546-553.

[9]. Katzung Bertram G, Susan B, Trevor Anthony J, Basic and Clinical Pharmacology, 11th Edition. New Delhi: Tata Mc Graw Hill Education Private Limited; Agents Used in Dyslipidemia 35, 2009, 612-613.

[10]. KD Tripathi, Essentials of Medical Pharmacology 7th Edition. New Delhi: Jaypee; Hypolipidemic Drugs and Plasma Expanders; 45, 2015, 636-638.

[11]. Svensson, Elisabeth et al. "Statin Prescription Patterns, Adherence, and Attainment of Cholesterol Treatment Goals in Routine Clinical Care: Danish Population-Based Study." Clinical Epidemiology 7, 2015, 213–223. PMC.

[12]. Park ZH, et al, Statin-associated incident diabetes: a literature review. Pub med, 29(5), 2014.

[13]. H.-S. Kim et al, Analysis and comparison of statin prescription patterns and outcomes according to clinical department, Journal of clinical pharmacy and therapeutics, 41(1), 2016.

[14]. Anfossi G et al, Prescription of statins to dyslipidemic patients affected by liver diseases: a subtle balance between risks and benefits, Nutrition, metabolism& cardiovascular diseases, 14(4), 2004.

[15]. G.ErezE. Leitersdorf et al, The Rationale for Using HMG-CoA Reductase Inhibitors ('Statins') in Peripheral Arterial Disease, European Journal of Vascular and Endovascular Surgery, 33(2), 2007.

[16]. Kei A, Rizos EC, et al, Statin use in prediabetic patients: rationale and results to date. Therapeutic Advances in Chronic Disease.6(5), 2015, 246-251.

[17]. Collins R et al, Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet. ; 363(9411), 2004, 757-67.

[18]. Elnaem, M. H., Mohamed, M. H. N., Huri, H. Z., Azarisman, S. M., & Elkalmi, R. M. Statin Therapy Prescribing for Patients with Type 2 Diabetes Mellitus: A Review of Current Evidence and Challenges. Journal of Pharmacy & Bioallied Sciences, 9(2), 2017, 80–87.

[19]. Kirsten Bibbins-Domingo et al, Statin Use for the Primary Prevention of Cardiovascular Disease in Adults US Preventive Services Task Force Recommendation Statement. *JAMA.* 316(19), 2016, 1997–2007.

[20]. Eldor, R., & Raz, I. et al, American Diabetes Association Indications for Statins in Diabetes: Is there evidence? Diabetes Care, 32(2), 2009, S384–S391.

[21]. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G et al, Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 31(1), 2013.

[22]. Chou R, Dana T, Blazina I, Daeges M, Bougatsos C, Grusing S et al, Statin Use for the Prevention of Cardiovascular Disease in Adults: A Systematic Review for the U.S. Preventive Services Task Force Agency for Healthcare Research and Quality (US); 1(2), 2016.

[23]. Silva M, Matthews ML, Jarvis C, Nolan NM, Belliveau P, Malloy M et al, Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. Clin Ther. 29(2), 2007, 253-60.

[24]. Nichols GA, Koro CE. Does statin therapy initiation increase the risk for myopathy? An observational study of 32,225 diabetic and nondiabetic patients. Clin Ther. 29(8), 2007, 1761-70.

[25]. McClure DL, Valuck RJ, Glanz M, Hokanson JE. Systematic review and meta-analysis of clinically relevant adverse events from HMG CoA reductase inhibitor trials worldwide from 1982 to present. Pharmacoepidemiol Drug Saf. 16(2), 2007, 132-43.

[26]. Pierre Amarenco; Philippa C Lavallëe; Mikael Mazighi; Julien Labreuche. Statins in Stroke Prevention. Future Lipidology. 3(3), 2008, 319-325.

[27]. Hong, K.-S., & Lee, J. S. et al, Statins in Acute Ischemic Stroke: A Systematic Review. Journal of Stroke, 17(3), 2015, 282–301.

[28]. Castilla-Guerra L, Del Carmen Fernandez-Moreno M, Colmenero-Camacho MA. Statins in Stroke Prevention: Present and Future. Curr Pharm Des. 22(30), 2016, 4638-4644.

[29]. Harris SK, Roos MG, Landry GJ. Statin use in patients with peripheral arterial disease. J Vasc Surg. 64(6), 2016, 1881-1888.

[30]. Yan Y, Qiu B, Wang J, et al, High-intensity statin therapy in patients with chronic kidney disease: a systematic review and meta-analysis. BMJ Open 5, 2015, e006886.