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ASSESSMENT OF DRUG UTILIZATION PATTERN OF STATIN THERAPY FOR PRIMARY PREVENTION OF CARDIOVASCULAR RISK IN DIABETIC PATIENTS ATTENDING TERTIARY CARE TEACHING HOSPITAL OF CENTRAL INDIA

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ABSTRACT **Background:** Diabetes Mellitus is one of the prevalent metabolic disease which is associate with dyslipidemia. This poses this patient for significantly increased cardiovascular risk events like stroke, myocardial infarction etc. Statins are widely used among these patients for primary prevention of cardiovascular risk. This study emphasizes on pattern of statin therapy being practiced in Indian setup and lacunae related to with aspect of improving public health **Methods:** This study was a crossectional observational study conducted in a tertiary care teaching hospital of central India. The study was started after obtaining clearance from Institute Ethics Committee. The patients satisfying the inclusion criteria were recruited in this study after obtaining Informed consent. The diabetic patients were assessed for statin therapy and intensity of statin therapy widely prescribed and practiced with respect to Indian population. **Results:** Of total 2680 diabetic patients recruited in this study, 1800 (67.16%) were prescribed with statin therapy, of which 41.5% were males and 25.66% were females. 1280 diabetic patients were prescribed with Atorvastatin and 520 were prescribed with Rosuvastatin.Of all the available statins, Two statins, Atorvastatin and Rosuvastatin, was prescribed to the diabetic patients the most. **Conclusion:** This study will be providing baseline data regarding drug utilization pattern of statins in diabetic patients. This study will help in assessing the statin eligibility and to determine data pertaining to overuse or underuse of statins in diabetic patients. It also emphasizes the pattern of statin being prescribed based on its intensity. The data of this study will be useful to plan further research related cardiovascular risk and statin considering various factors for Indian population.

KEYWORDS : Statins, Diabetes, Cardiovascular complications

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Of the several types of DM, Type 1 and Type 2 are the most common. The 2016 Global WHO Report on Diabetes estimated worldwide prevalence of diabetes as 422 million people in 2014 with global prevalence of 8.5% and 69.2 million cases takes India among top 3 countries of diabetic population.

The major complications of DM are Cardiovascular diseases. Adults with diabetes have a two- to three-fold increased risk for CVD compared with their non-diabetic counterparts.[2,] These are now the leading causes of diabetes-related morbidity and mortality. Risk factors which poses a person to CVD include hypertension, diabetes, tobacco/alcohol, physical inactivity, inappropriate diet, psychosocial stress, smoking, obesity, dyslipidemia etc.

The situation regarding CVD in diabetic patients is dismal, 10% diabetes account for 10-12% of vascular death and also increases two-fold increased risk for a wide range of vascular diseases which occurs as effect of dyslipidemia and hypercholesterolemia which is commonly seen in diabetics.

Primary prevention of CVD in terms of risk stratification is essential to identify the risk factors and intervene early in the natural course of the disease. One of the goal in risk factor research is prediction of CV risk in individuals who are more likely to develop CVD and who therefore should receive intervention for its prevention.

Statin therapy is considered as one of the important preventive measures and has been recommended for patients who are at high risk of CVD risk.[.]

Considering diabetes as one of the most important risk factors for ASCVD and to alleviate its complications, a group of drugs known as Statins are commonly prescribed. Statins are basically lipid lowering agents and acts by inhibiting HMG CoA reductase enzyme as well as have other beneficial pleiotropic effects like anti-inflammatory, anti-proliferative, antioxidant, immunomodulatory, neuroprotective, antithrombotic and also improves endothelial dysfunction. Few examples of statins are Atorvastatin, Rosuvastatin, Simvastatin, Pravastatin and Pitvastatin. These statins are categorized into high intensity, moderate intensity, low intensity statin therapy based on the amount of reduction in LDL values of patient. 15 Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of ASCVD. Statins are useful in lipid management as it decreases LDL by 25-55%, non-HDL by 15-51%, Triglycerides by 7-30% and causes increase in HDL by around 5-15%. Therefore "Statins" are considered as first line drug for lipid management and primary prevention of Cardiovascular diseases and Ezetimibe, Fibrates can be included as add-on therapy for effective management.

Table 1: Intensity Of Statin Therapy

Low intensity (20-30%)	Medium intensity (31-40%)	High intensity (>40%)
Simvastatin 10mg	Atorvastatin 10-20mg	Atorvastatin 40-80mg
Pravastatin 10-20mg	Rosuvastatin 5-10mg	Rosuvastatin 20-40mg
Lovastatin 20mg	Simvastatin 20-40mg	
Fluvastatin 20-40mg	Pravastatin 40-80mg	
Pitvastatin 1mg	Lovastatin 40mg	
	Fluvastatin 80mg	
	Pitvastatin 2-4mg	

Note: Values in bracket indicates percentage reduction in LDL levels.

Evidence suggests that the clinical benefit of statins is largely independent of the type of statin used, but depends primarily on the extent of LDL-C reduction achieved. Hence, the type of statin and dose to be used should be based on the degree of LDL-C reduction that is required to reach the target LDL-C in a given patient. Meta-analyses, including data from over 18,000

patients with diabetes from 14 randomized trials of statin therapy (mean follow-up 4.3years), demonstrates 9% proportional reduction in all-cause mortality and 13% reduction in vascular mortality for each mmol/L (39 mg/dL) reduction in LDL cholesterol. There are some Adverse Drug Reactions (ADRs) associated with statins, the most frequently reported symptoms include myalgia, fatigue, weakness, generalized aching, and low back ache or proximal muscle pain. Other ADRs are hepatotoxicity, peripheral neuropathy, memory loss, peripheral neuropathy.[ii]

AIM
- To assess drug utilization pattern of statin therapy in diabetic patients attending tertiary care teaching hospital in central India

OBJECTIVES
- To assess drug utilization pattern of statins in diabetic patients
- To stratify statin therapy pattern based on its intensity charcterised by percentage reduction in LDL cholesterol
- To clinically assess the patients for adverse effects associated with statins

METHODOLOGY
This was a cross-sectional observational study of six-months duration in the outpatient department (OPD) of a tertiary care teaching hospital, after obtaining Institute Ethics Committee approval.

A convenient sampling method was used to recruit the patients. The study was conducted in a cohort of diabetic patients. The consecutive, diagnosed patients of Type – 2 diabetes mellitus, aged 25-84 years, of either sex and who did not have any history of cardiovascular disease like stroke, transient ischemic attack, myocardial infarction, angina, were included in this study after obtaining their written informed consent. Critically ill patients were excluded from the study. The demographic details and relevant health data were collected through a pre-validated structured questionnaire and from health record available with the patients. The medication data was recorded from their prescription and was screened for statin use. Body indices and current systolic blood pressure (SBP) were also recorded. The details were subsequently entered into a case record form. The values will be expressed as mean ± standard deviation for all continuous variables.The categorical data were analysed using Fisher's exact test. Pearson's correlation coefficient (r) was estimated to assess the relationship between various risk factors and 10-year CV risk score. A p-value <0.05 was considered statistically significant.

RESULTS
A total of 2680 diabetic patients were recruited during the study period. The demographic and clinical details of the study participants are shown in Table I.

Table 2: Demographic And Clinical Details Of The Study Participants

Variable	n (%)
Gender	
Male	1680 (62.69)
Female	1000 (37.31)
Age group (in years)	
≤ 39	260(9.70)
40 – 49	740 (27.61)
50 – 59	840 (31.34)
60 – 69	620 (23.13)
≥70	220 (8.21)
Age in years (Mean ± SD)	54.02 ± 11.02
Type of Diabetes	
Type 1	0
Type 2	2680 (100%)
Duration of Diabetes	
< 6 months	80 (2.99)
6 months – 1 year	140 (5.22)
1 – 5 years	840 (31.34)
> 5 years	1620 (60.45)
On BP treatment	
Yes	1320 (49.25%)
No	1360 (51.75%)
Body mass index (in kg/m2)	
<18.5	140 (5.22)
18.5 – 24.9	1620 (60.45)
25 – 29.9	600 (22.39)
>30	320 (11.94)

Statins Prescribed To Diabetic Patients
Of total 2680 diabetic patients recruited in this study, 1800 (67.16%) were prescribed with statin therapy, of which 41.5% were males and 25.66% were females. 1280 diabetic patients were prescribed with Atorvastatin and 520 were prescribed with Rosuvastatin.

Of all the available statins, Two statins, Atorvastatin and Rosuvastatin, was prescribed to the diabetic patients the most.

Among these two, Atorvastatin was the most commonly prescribed statin with frequency of 71.11%. Among the different doses of Atorvastatin prescribed, 92.19% were of medium intensity and 7.81% were of high intensity whereas out of Rosuvastatin prescribed, most i.e. 92.31% were of high intensity and 7.69% were of medium intensity. There was no low intensity statin prescribed.

Table 3: Statins Prescribed To Diabetic Patients

Statins prescribed	Frequency of prescription (%)	Intensity
Atorvastatin	1280 (71.11)	Low = 0 (0%)
		Medium = 1180 (92.19%)
		High = 100 (7.81%)
Rosuvastatin	520 (28.89)	Low = 0 (0%)
		Medium = 40 (7.69%)
		High = 480 (92.31%)

Adverse Drug Reactions And Statin Therapy
The data of adverse drug reactions in stain users and non-users is depicted in table. Of 1800 diabetic patients receiving statin, 660 (36.67%) patients complained of muscle pain while 380 (21.11%) patients complained of tingling and numbness.

Table 4: Adverse Drug Reactions In Statin Users And Non-users

ADRs	Patients receiving statin (n = 1800)	Patients not receiving statin (n=880)	p value	Relative risk (95% CI)
H/o muscle pain	660 (36.67%)	120 (13.64%)	0.0079	2.68(1.218 – 5.935)
H/o Tingling and numbness	380 (21.11%)	140(15.91%)	0.6424	1.32 (0.6033 – 2.919)

DISCUSSION
In our study, we attempted to find the drug utilization pattern of statin therapy in diabetics patient receiving treatment from a tertiary care hospital. Of total diabetic patients recruited in this study, 67.16% of patients were receiving statin therapy of which Atorvastatin (47.76%) was the most frequently prescribed statin followed by Rosuvastatin(19.4%). Average

duration of statin use was 26 months in overall users.

The majority of patients were aged ≥40 years (90.30%) with an average age of 54.02 years. Physical obstruction of coronary arteries due to atherosclerosis attributes to age-related increase in the severity of cardiovascular diseases

Statin therapy associated with two important adverse effects – increased risk of adverse effects and increased cost of treatment. Although statistically insignificant, the common adverse effects associated with statin use like peripheral neuropathy and myopathy observed more in statin users. Diabetic patient population and advanced age could be the potential confounders for these finding. Moreover, we could not measure serum creatinine kinase activity and vitamin D levels, which could have given a better correlation.

AHA guidelines recommend moderate-intensity of statin therapy in all diabetic patients with age group 40-75 years and high-intensity statin therapy .There are no defined criteria for patients with age group <40 years and >75 years in AHA guidelines and suggests statins to be prescribed based on clinical judgement of physician.

Though Diabetes mellitus is itself a risk factor for cardiovascular disease but could not be a single criterion for prescription of statins in diabetics as in AHA guidelines. Hence, considering several parameters could be a better criterion for deciding statin eligibility in diabetics as well in other patients.(considering AHA recommends statin therapy to all diabetic aged 40-70 years). On the contrary, NICE guidelines recommend Atorvastatin 20 mg for the primary prevention of CVD to people who have ≥10% 10-year risk of developing CVD.[12] The intensity of statins is based on percentage reduction of LDL-C by a statin and its various doses and categorization into low, medium and high is based on NICE guidelines.[15] However, appropriateness of use of different intensity of statins could not be ascertained in our study, as we did not have baseline lipid profile data. Therefore, it was inappropriate to miss these potential candidates who are actually at risk of CVD.

As per latest Indian Lipid guidelines Non-high-density lipoprotein cholesterol (Non-HDLC) is now, considered to be a better predictor of cardiovascular risk, because it contains cholesterol of all atherogenic particles, including low-density lipoprotein(LDL), lipoprotein A, very-low-density lipoprotein(VLDL), VLDL remnant an intermediate-density lipoprotein. In a study by Ram N et al, the author showed a correlation between non-HDLC and LDL. NICE guidelines recommend that before starting lipid modification therapy for the primary prevention of CVD, take at least one lipid sample to measure a full lipid profile and this should include measurement of total cholesterol, HDL cholesterol, non-HDL cholesterol and triglyceride concentrations.

Of 920 patients whose lipid profile were available, only 680 patients were receiving statin therapy. Mean non-HDL C was 120.15± 56.63 mg/dL whereas mean LDL was 101.86±48.72 mg/dL. Both LDL<100mg/dL and Non-HDL-C<130mg/dL targets were achieved in 520 (56.52%) patients. However, precise correlation of these values with statin therapy is out of the scope of this study, since we do not have their base-line data. Moreover, the temporal relationship of statin therapy and lipid profile could not be established.

It is also worthwhile to understand the basis of prescription of statins if the other risk factors taken into account. These factors will also help in decision making for primary physician to initiate statins.

The primary limitation of our study was that findings from a small group of the population cannot be generalizable, this study showed an overview of drug utilization pattern in Indian scenario Another important limitation was the cross-sectional design of this study. Non-availability of baseline data of few parameters hinders correlation. Cross-sectional data can be verified from prospective studies with larger sample size. Moreover, the data from this study is limited to a particular geographical area. Hence, the results may or may not be generalizable to the rest of the parts of India.

CONCLUSION

This study will be providing baseline data regarding drug utilization pattern of statins in diabetic patients. This study will help in assessing the statin eligibility and to determine data pertaining to overuse or underuse of statins in diabetic patients. It also emphasizes the pattern of statin being prescribed based on its intesity. The data of this study will be useful to plan further research related cardiovascular risk and statin considering various factors for Indian population.

REFERENCES

1. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2014;37(Suppl.1): S81-S90.
2. World Health Organization (WHO). Global Report on Diabetes 2016; WHO: Geneva,
3. Switzerland, 2016.p21-33.
4. Goldberg RB. Cardiovascular disease in diabetic patients. Med Clin North Am 2000 Jan;84:81-93.
5. Bertoluci MC, Rocha VZ. Cardiovascular risk assessment in patients with diabetes. Diabetol Metab Syndr. 2017 Apr 20;9:25. doi: 10.1186/s13098-017-0225-1.eCollection 2017.
6. Shah Bela, Mathur Prashant. Surveillance of cardiovascular disease risk factors in India: The need & scope. Indian J Med Res 2010;132: 634–642.
7. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;376:958.
8. S Kanjilal, VS Rao, M Mukherjee, BK Natesha, KS Renuka, K Sibi, SS Iyengar, Vijay V Kakkar. Application of cardiovascular disease risk prediction models and the relevance of novel biomarkers to risk stratification in Asian Indians. Vasc Health Risk Manag 2008;4:199–211.
9. Ludwig Sora, X Shen Garry. Statins for Diabetic Cardiovascular Complications. Current Vascular Pharmacology 2006;4:245-51
10. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, Ward K, Ebrahim S. Statins for the primary prevention of Cardiovascular Disease. Cochrane Library 2013;24(5):40
11. Bedi O, Dhawan V, Sharma PL, Kumar P. Pleiotropic effects of statins: new therapeutic targets in drug design. Naunyn Schmiedebergs Arch Pharmacol. 2016;389:695-712.
12. National Institute for Health and Care Excellence.[Accessed 8 October 2018]. NICE Guidelines 2014. Cardiovascular disease: risk assessment and reduction, including lipid modification. Available from: https://www.nice.org.uk/guidance/cg181.
13. Kannel WB, Gordan T. Evaluation of cardiovascular risk in the elderly: the Framingham study. Bull N Y Acad Med. 1978; 54:573–91.
14. Shah M, Sikkel MB. Coronary artery disease and age: beyond atherosclerosis. J Physiol 2013;591:5807-8.
15. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to reduce Atherosclerotic Cardiovascular risk in Adults. Circulation [Internet]. Ahajournals.org.2018 [cited 9 October 2018]. Available from https://www.ahajournals.org/doi/abs/10.1161/01.cir.0000437738.63853.7a
16. Grundy SM. Low-Density Lipoprotein, Non–High-Density Lipoprotein, and Apolipoprotein B as Targets of Lipid-Lowering Therapy. Circulation. 2002;106:2526-9.
17. Virani SS. Non-HDL cholesterol as a metric of good quality of care: opportunities and challenges. Tex Heart Inst J 2011;38:160-2.
18. Ram N, Ahmed B, Hashmi F, Jabbar AB. Importance of measuring non-HDL cholesterol in type 2 diabetes patients. J Pak Med Assoc 2014;64:124.