



RESEARCH ARTICLE

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Evaluation of statin utilisation in tertiary care teaching hospital: An observational prospective study, YSR Kadapa

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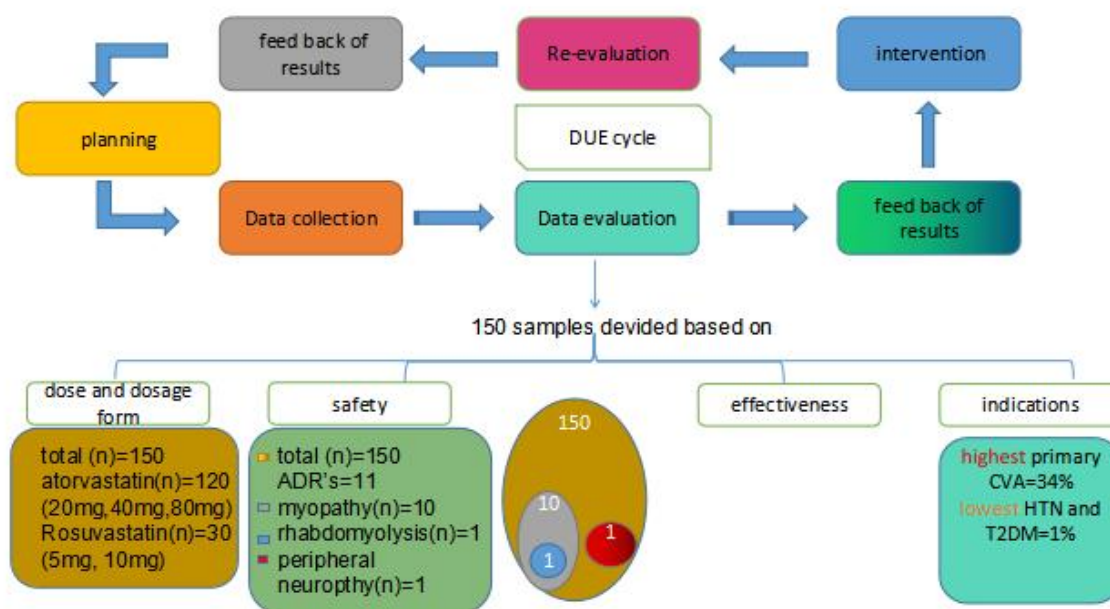
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Graphical abstract of a DUE study on statins



Received 12 March 2023;
Revised 27 April 2023;
Accepted 16 May 2023.

Keywords:

Atorvastatin,
cardiovascular and
cerebrovascular problems,
non-adherence, Re-
occurrence, Rosuvastatin.

Introduction: Statins are highly preferred drugs in the treatment and prevention of atherosclerotic diseases. Statins usage increased in the last two decades. DUE is a cyclic quality-enhancing procedure in the prescription of drugs.

Methods: Our study engaged in compiling various prescribing conditions for statins, assessing their effectiveness and safety, and comparing the lipid profile images of atorvastatin and rosuvastatin. A prospective observational study with the involvement of 150 volunteers. The complete data collected is analyzed using SAS and Microsoft Excel software. Statistical methods of mean, standard deviation, clinical significance, and Z value are calculated.

Results: Atorvastatin (20 mg, 40 mg, and 80 mg) and Rosuvastatin (5 mg and 10mg) are widely used in the primary, secondary, and tertiary prevention of atherosclerotic cardiovascular and cerebrovascular problems. Average reduction of LDL and total cholesterol levels to 106.5(SD $\pm$ 11.04) and 203.53 (SD $\pm$ 94) respectively.

Conclusion: Both drugs are equally effective in reducing cholesterol levels. adverse drug reactions observed on long-term usage of 2 to 6 years in 7.33 % of volunteers. Secondary and tertiary occurrences of CVA are observed due to non-adherence.

An official publication of the Global Pharmacovigilance Society.

Introduction:

Atherosclerosis is a complex syndrome characterized by the formation of plaques, narrowing of the arteries (mainly the carotid artery, the abdominal aorta, the coronary artery, and the iliac arteries), and increased lipid levels in the body (high levels of cholesterol, LDL, triglycerides, VLDL, total cholesterol, and possibly a decrease in HDL levels) (Al-Shura et al., 2014; Gaddi et al., 2007).

Arteriosclerosis is the leading cause of death worldwide. Among several factors, elevated LDL levels are associated with the development of atherosclerotic plaque. The LDL maintenance target is less than 100 mg/dL (2.59 mmol/dL) (Chaiyakunapruk et al., 2011). Every 10 % reduction in cholesterol is associated with a 20–30 % reduction in the incidence of coronary heart disease (Pasha et al., 2006).

According to the World Health Organisation (WHO), drug use evaluation (DUE) or drug use review (DUR) is a continuous, licensed, and systematic process for quality improvement (Ransam et al., 2019). Our study is qualitative and involves gathering information through methods that include focus group discussions, open questionnaires, interviews, and in-depth observations. These examine the perceptions of prescribers, providers, and patients handling drugs and evaluate criteria such as indications for drug use, dose, frequency of dosing, duration of therapy, and adequacy of medical care. The European Medical Association (EMA) has proposed DUE as a strategic plan for proactive pharmacovigilance aimed at early diagnosis and minimizing the risks associated with drug use (Mazzaglia et al., 2016).

Our study involves collecting data, analyzing that data, obtaining results, and revealing the state of rationality in statins usage. DUE recommends necessary changes to essential medicine lists and prescription regimens to promote rational therapy and improve patient outcomes (Pasha et al., 2006). Of the various lipid-lowering drugs available, statins are highly selective and effective in

reducing high lipid levels and regulating normal levels. Statins (Atorvastatin, Rosuvastatin, Pitavastatin, Pravastatin, Lovastatin, and Fluvastatin) inhibit the enzyme HMG-CoA reductase and thereby inhibit the production of lipids (Praveen et al., 2013). In our study, we only discussed atorvastatin and Rosuvastatin. Statins are preferred in cardiovascular diseases (history of Angina pectoris and acute myocardial infarction), and arterial diseases (peripheral vascular disease, non-hemorrhagic stroke, or transient ischemic attack) (Praveen et al., 2013). In patients at risk of developing cardiovascular disease, the duration and complications depend on the age of diabetes and concomitant risk factors (patient age > 40 years, type 1 or type 2 diabetes), the youngest age of target organ damage, and poor glycemic control (HbA1c > 9 %). Low HDL cholesterol and high triglyceride levels, hypertension, or a family history of premature cardiovascular disease are recommended in primary prevention (Teeling et al., 2005). These drugs are also used in the secondary and tertiary prevention of ischemia associated with atherosclerosis. Statins are generally well-tolerated drugs. The incidence of adverse effects related to these drugs is very low < 3 %, but recent Studies show that the incidence of adverse effects is around 10.5 %. The most common side effects are gastrointestinal symptoms (constipation, flatulence, dyspepsia, and abdominal pain) and elevated levels of transaminases. These are reversible, but some have dose-dependent side effects, such as myopathy, Myositis, and rhabdomyolysis are observed when enzyme inhibitors are administered together. The myopathy of these adverse reactions is confirmed by clinical symptoms such as an inability to walk a limited distance; pain in the upper and lower limbs; decreased performance; or an inability to work effectively. Elevated creatine kinase levels are evidence of rhabdomyolysis (Bernini et al., 2001; Golomb et al., 2008). Kidney function tests are done to assess kidney function. The effect of the drug is determined by comparing the lipid profiles of two different drug regimens. The efficacy of

Statins in Reducing Lipid Levels in Newly Started individuals is assessed after 30 days.

Materials and Methods:

Study design and volunteers

a 6-month prospective observational study (November 2020 to April 2021) carried out at the Rajiv Gandhi Institute of Medical Sciences government general hospital (RIMS GGH) in YSR Kadapa, Andhra Pradesh. 150 volunteers older than 20 years, using statins with or without any co-morbidities, are included. Consent was obtained from the patient or their representative before the initiation of the study. Our project was approved by IEC (Ref. no. PRRMCP/IEC/2021/11/01).

Methods

Complete demographic, medical, and surgical information is collected on specially designed data collection forms. Effectiveness is determined by performing cholesterol tests. Tests are recommended for newly advised individuals one month after initiation. ADRs like myopathy, myositis, and rhabdomyolysis are confirmed by performing a creatine kinase test, and other differential diagnostic tests like a cardiac troponin test, liver function tests (LFT), and renal function tests (RFT) were also performed. Interactions among drugs in polypharmacy are checked by interaction checkers at Medscape and drugs.com.

Statistical methods: the obtained data is analyzed by SAS (mean, standard deviation, and Z-correlation were determined) and graphical designs are made using MS Excel.

Results

Table 1: Distribution based on re-occurrence of disease

Sl No.	Past illness	Reoccurred disease	Duration from initiation of therapy	Frequency	Discontinuation period	Frequency	Total
1	CVA	Hypertensive heart failure	3years	1	0		2
2	CAD	CHF	7years	1	0		
			9years	1	2years	1	
			4years	2	0		4
			2years	1	0		
	CAD angioplasty		4years	3	7months	3	
3		IHD	7years	1	6months	1	
			2years	1	8months	3	8
			1years	1	4months	1	
			3years	2	0		
4	CAD	CCF	7years	2	7months	2	
			6years	1	0		3
			4years	2	2 – 3months		
5	CVA	HF	4years	3	3–8months	5	
			9years	1	0		7
			11years	1	4months	2	
6	CVA	CAD	3years	2	0		2
7	CVA	IHD	6years	1	3months	1	
			2years	9	6months	9	1
			6years	2	12months	2	
			10years	1	18months	2	
8	CVA	CVA	5years	1	7months	1	
			7years	1	18months	2	17
			9years	2	9months	2	
			1years	1	0		
9	IHD	CHF	5years	2	2months	2	
			1year	1	9months	1	3

Demography

In a study duration of 150 patients, 80 (53.33 %) from the OPD (outpatient department) and 70 (46.66 %) from the IPD (inpatient department) of general medicine are enrolled as per the criteria. Among them, male patients are greater in number at 105 (70 %) and the remaining are females at 45 (30 %), indicating a male double in number in usage when compared to females. The age group of 51–60 years is 58 (38.66 %), followed by 41–50 years at 24 (16 %); 21 (14 %), between 71–80 years; 10 (6.66 %), between 31–40 years; and the least number 1 patient in between 21–30 years. The dose pattern of usage of statins is shown in Figure 1. The ratio of atorvastatin to rosuvastatin is 3:1.

Indications of statin usage:

In this tertiary care hospital, statins were prescribed mostly for secondary prevention of CVA (cerebrovascular accident) or treatment of primary CVA (34%), followed by CAD (18%), CCF (congestive cardiac failure), and CAD other diseases as summarised in Figure 2.

Re-occurrence of disease:

Divergent ischemic disease recurrence was observed in 57 samples due to treatment discontinuation in 39 samples, despite treatment recurrence in 18 samples. Non-adherence for an average period of 0 to 6.23 months

(SD±4.279) accelerates the recurrence of atherosclerotic diseases, as summarised in Table 1. To determine the effectiveness of statins, lipid profile tests were performed in 81 patients (41 samples using atorvastatin and 40 samples using rosuvastatin). Lipid profile tests were performed after 30 days of initiating statin therapy in newly prescribed patients.

The mean value of LDL-C is 106.5 mg/dl (SD±8.834) and total cholesterol levels are 199 (SD±11.18) in atorvastatin usage.

In patients using rosuvastatin, mean LDL-C levels were found to be 106.36 (SD±11.04), and total cholesterol levels were 203.53 (SD±94).

The Z-statistics are 0.063 and the P-value is 95 at a significance level of 0.5, which indicates both are equally effective.

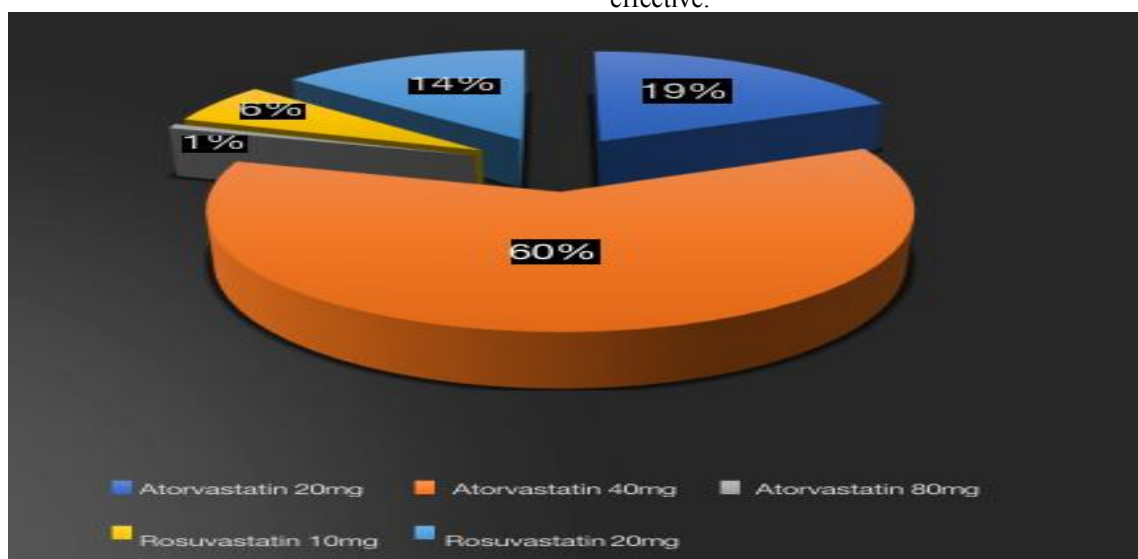


Figure 1: Distribution based on the dose of statins

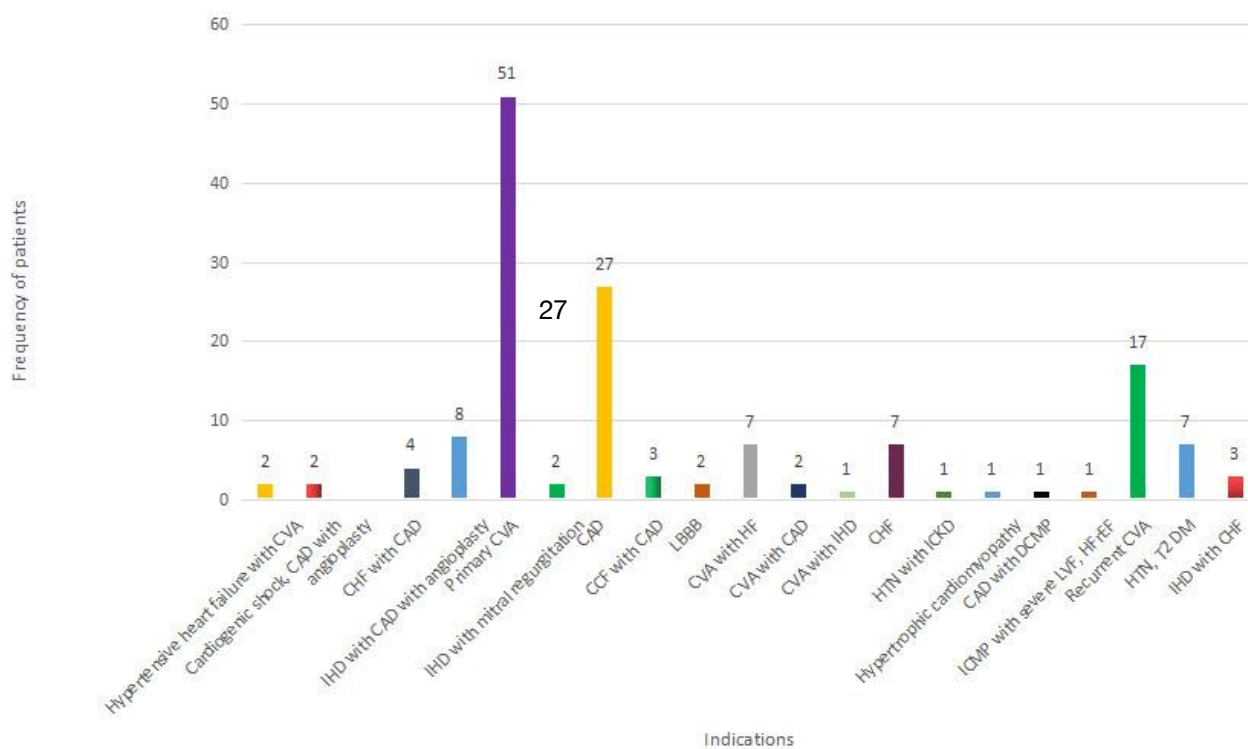


Figure 2: Distribution based on indication

Adverse drug reactions found in statin therapy:

Out of 150 patients, 11 subjects from the OPD of general medicine who have been using statin therapy for various indications over the long term and are complaining of symptoms of muscle wasting were tested for myopathy and rhabdomyolysis.

8 % of the total sample had an adverse drug reaction. 6 % of the total samples were associated with ADRs

Table 2: adverse drug reaction found in statin therapy

S.no	Drug name	Disease	Duration of therapy	Frequency	Percentage	ADR
1.	Atorvastatin	CAD	7years	1	0.6%	Myopathy
		CVA	4years	2	1.4%	
		CVA	6years	2	1.4%	
		CVA	2years	2	1.4%	
		CAD	8years	1	0.6%	
		TIA	3years	1	0.6%	
2.	Atorvastatin	CVA	5years	1	0.6%	Peripheral neuropathy
3.	Atorvastatin	CVA	9years	1	0.6%	Rhabdomyolysis

myopathy, and peripheral neuropathy was observed in 1 % of all exposures; rhabdomyolysis was observed in 1 %.

Continuous use of statins for about 2–6 years and above shows adverse reactions. This study shows the mean period of ADR development is 5.4 years (SD $\pm$ 2.5) after the initiation of therapy. Results are shown in Table 2

Laboratory tests for the confirmation of ADRs:

Eleven people who had signs of rhabdomyolysis and myopathy were tested for their kidney function (RFT) and liver function (LFT). Creatine kinase and cardiac troponin (Tni, Tnt) tests were done on five people whose creatinine levels were high.

One patient's creatine kinase levels increased to 6000 U/L, and cardiac troponin levels revealed a normal level. This indicates rhabdomyolysis.

The remaining ten patients were confirmed as having myopathy. Results are shown in Table 3

Table 3: laboratory test for confirmation of adverse drug reactions

Sl.No.	LFT					RFT		CARDIAC TROPONIN		Creatine kinase
	S.G.O.P	S.G.P.T.	ALP	TOTAL PROTEIN S	TOTAL BILIRUBIN	BUN (mg/dl)	Creatinine (mg/dl)	CTnT (ng/L)	CTnI (ng/L)	Normal (U/L)
						Normal: 15- 45	Normal:0.5-1.5	Normal : <3	Normal : <1.8	52- 336
1	30	20	80	6.6	0.8	35	1.5	1.4	0.7	220
2	36	21	90	6.5	0.6	16	2.5	1.2	0.6	120
3	38	25	83	7	0.9	23	2.0	1.1	1.2	176
4	23	25	92	6.9	0.5	15	3.5	1.0	1.4	227
5	34	27	78	6.8	0.6	50	3.8	2.5	1.3	6000

6	29	29	82	6.6	0.7	18	0.6	-	-	-
7	28	20	88	6.8	0.6	20	0.5	-	-	-
8	29	22	73	7.1	0.5	22	0.7	-	-	-
9	31	26	63	6.7	0.8	30	0.8	-	-	-
10	30	26	90	6.4	0.7	28	0.9	-	-	-
11	21	25	85	7	0.2	32	0.5	-	-	-

There are 120 samples in our study of social habits: among males, there are 110 with smoking (32), alcohol consumption (37), both smoking and alcohol consumption (25), and betel nut chewing (6); among females, there are 10 with betel nut chewing (6).

Discussion

As per IMS statistics, statin consumption increased from 45.8 to 84.1 per 1000 patients in the interval of February 2006 to January 2010 for CAD in India, and the use of statins increased globally (Choudary et al., 2014). In this study, the age group 51-60 years has a higher (38.66 %) count than the age group 21-30 years. Some other studies display the age group of 51-70 as having higher statin consumption (Yourman et al., 2021). but the age group of less than 80 years is very small (Sundvall et al., 2019).

Statin utilization is higher in males (70%) when compared to females (30%), similar to that study by Michael G. Nana et al., 2019. The ratio of usage of Atorvastatin to Rosuvastatin is 3:1; Atorvastatin is highly preferred in our study even though both are equally effective in reducing LDL-C levels. However, according to the URANUS study, rosuvastatin is more effective than atorvastatin in lowering lipid levels and meeting European guidelines (Berne, C., 2005).

Statins' wide range of indications includes hypertensive heart failure with CVA, cardiogenic shock, CAD with angioplasty, CHF with CAD, IHD (ischemia of the heart) with CAD, treatment of primary CVA, CVA with CHF, CVA with IHD, CVA with CAD, CHF, HTN (hypertension) with CKD (chronic kidney disease), treatment of recurrent CVA, HTN with type 2 diabetes, etc. Statins are majorly prescribed for primary CVA treatment or secondary prevention (34 %), followed by treatment of secondary CVA or tertiary prevention (11.31%), in high-risk HTN and type 2 diabetes patients, given for primary prevention of atherosclerotic problems of the cardiovascular and cerebrovascular systems (Yebyo et al, 2019). Statins are prescribed to patients with CKD who are 5 to 30 times more likely to develop CVA (Nayak-Rao et al., 2019).

Among the 150 patients in our study, 57 patients had recurrent atherosclerotic problems. The discontinuation of therapy is visualized in 39 samples. Even though adhering to therapy re-occurred in 18 samples, this may be due to social habits, age, food habits, style of living, and other co-morbidities (Vitturi et al., 2020; El-Gohary, et al., 2019). Discontinuation occurred for a mean period of 6.23 months (SD $\pm$ 4.25). According to Meng Lee et al. 2017 and Vitturi, B.K. et al. 2020, discontinuation for 2 to 7 months or > 1 year and sub-optimal use lead to the re-occurrence of the disease.

Elevation of LDL and total cholesterol is considered hyperlipidemia; lipid profile tests are performed on all patients and are all within the normal limit. This indicates both are equally effective in reducing elevated lipid levels, as said by Berne. C et al., 2005. Statins are well tolerated and have few side effects, but long-term and high-dose usage causes myopathy and rhabdomyolysis in 1-10% of total volunteers (Manoj et al., 2017; Ramkumar et al., 2017), and peripheral neuropathy is an adverse drug reaction (ADR) of statin long-term use, according to a press release by Paul Minn.

In our study, myopathy developed in 6% and peripheral neuropathy in 1%, as confirmed by clinical manifestations, and rhabdomyolysis was confirmed by a creatine kinase test that was elevated by 10 times more than normal (Golomb et al., 2008). Cardiac troponin tests are performed to rule out increased creatine kinase levels due to cardiac problems. but troponins are within normal ranges. In our study, 80 patients had social habits related to smoking (32), alcohol consumption (37), both smoking and alcohol consumption (25), and betel nut chewing (6). In our study, we discovered 83 DDI, three of which are potential and moderate in severity.

Conclusion

According to our regional study, patients with primary CVA are the most likely to take statins. Non-adherence causes recurrence. Counseling patients about the importance of therapy prevents recurrence. Monitoring of systemic changes every six months, pertaining to ADRs

of statin usage, through laboratory tests after two years of therapy initiation reduces the risk of unnecessary complications and economic burden. Both drugs are equally effective in reducing LDL and total cholesterol levels.

Acknowledgment

We are grateful to the patients given consent for this study and Dr. Padmakar who helped with journal selection and manuscript preparation.

Conflict of Interest

No conflict of interest

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