ABSTRACT

Introduction: Notable lipid abnormalities in DM include elevated LDL-C which have been reported to be the prevalent lipid abnormality in DM and elevated total cholesterol levels. Although the Statins are widely used in the management of lipid abnormalities, their effects on the lipid abnormalities in Nigerians with DM has not been extensively evaluated. Objective: This report sets out to determine the effect of Simvor, a brand of Simvastatin in Nigerians with DM and abnormal lipid profiles. Materials and Methods: A total of 300 diabetic patients with abnormal lipid profile who were treatment naïve for lipid disorders were longitudinally recruited for the study. They were managed with Simvastatin (Simvor) in doses ranging from 20-40 mg alongside dietary counseling and exercise recommendation. Results: The mean age (SD) of the study subjects was 58.4 (10 years). The male; female ratio was 99:211. The proportions of lipid abnormalities for LDL-C, TCHOL, HDL-C and TG were 87%, 45%, 53% and 7% respectively. Following Simvastatin (Simvor) treatment, the mean LDL-C value was reduced by 16%, TCHOL by 23%, TG by 6% and HDL-C increased by 10%. Simvastatin (Simvor) was generally well tolerated and no cardiovascular events were noted in the study subjects during the period of the study. Conclusion: Simvastatin (Simvor) was effective and well tolerated in the management of lipid disorders in Nigerians with DM.

Key words: Diabetes mellitus, lipid abnormalities, simvastatin

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder that is associated with considerable morbidity and mortality and people with diabetes have been shown to have higher mortality rates than people without diabetes. Cardiovascular events have been noted to be important causes of DM deaths accounting for 15% of all DM deaths in Nigerians. The major risk factors for cardiovascular diseases (CVD), in addition to older age, are hypertension, diabetes mellitus, tobacco use, elevated total and low-density lipoprotein cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C). Dyslipidaemia or the “atherogenic triad” that occurs in DM is characterized by high serum triglyceride levels, low serum high-density lipoprotein cholesterol (HDL-C) levels, and a preponderance of small, dense, low-density lipoprotein cholesterol (LDL-C) particles. Many Reports abound on dyslipidaemia in Nigerians with DM. Commonly reported lipid abnormalities are elevated LDL-C and hypertriglyceridaemia. In one Report however, reduced HDL-C was the commonly documented lipid abnormality and this was found in 32.7% of the persons studied. To address the Dyslipidaemia aspect of CVD, lipid-lowering agents are typically used. The most potent lipid-lowering agents are the hydroxymethyl glutaryl coenzyme A reductase (HMG-CoA) reductase inhibitors (Statins). These medications are highly effective as monotherapy for dyslipidemia and may be combined with other agents, such as niacin or fibric acid derivatives.
(fibrates), when further reductions in triglycerides and/or elevations in HDL-C are required.

Correction of the atherogenic profile in DM dyslipidemia is often accomplished by usage of HMG-CoA reductase inhibitors. The recent CARDS (Collaborative Atorvastatin Diabetes Study) showed that atorvastatin can reduce cardiovascular events in a trial specifically designed for a diabetic population. Statins have been reported to lower LDL-C levels by 30-60%. Statins have proven to be extremely safe in the vast majority of patients receiving them though they are not entirely free of side effects. Adverse reactions of the Statins although occur rarely may affect the digestive system, musculoskeletal system, nervous system and skin and appendages.

Reports on the effect of Simvastain on DM dyslipidemia have been reported elsewhere and till date there has been no study addressing the effects of this drug on the atherogenic profile of Nigerians with DM. This Report was initiated by Ranbaxy Nigeria Limited and their brand of Simvastatin-Simvor was the lipid lowering agent used for the Study.

The study endpoints to be evaluated included safety and response rate of elevated LDL-C, TG, TCHOL and reduced HDL-C to treatment with Simvor. The secondary endpoint included the magnitude of the response of the abnormal lipid parameters to treatment.

**Primary endpoint**
Reduction of LDL-C to <100 mg%, TG to <150 mg%, TCHOL to <200 mg% and increase in HDL-C to ≥50 mg% in females and ≥40 mg% in males. The primary endpoints also included safety and tolerability.

**Secondary endpoint**
The magnitude of the responses of the abnormal lipid parameters to treatment with Simvastatin (Simvor).

**Materials and Methods**
This was an open labeled prospective study carried out at the Lagos State University Teaching Hospital (LASUTH), Diabetes Centre. Patients with DM who met the inclusion criteria were longitudinally recruited and screened for lipid abnormalities till a target number of 300 patients with such abnormalities were obtained. The study period was for a 6 months period.

The procedures followed were in accordance with the ethical standards of the Helsinki Declaration. Ethical consent was obtained from the Ethics committee of LASUTH and informed written consent was given by consenting patients before the commencement of the study.

**Inclusion criteria** included ambulant patients with DM irrespective of treatment type of DM and aged between 22-75 years. Patients with DM who were treatment naïve for lipid abnormalities were included.

**Exclusion criteria** included patients who are undergoing dialysis or in whom nephropathy had been diagnosed and those with established hypothyroidism. Patients who had hypertension as a comorbidity were on beta blockers were excluded. Patients who were pregnant and those who were already on lipid lowering agents were also excluded.

Lipid abnormalities or Dyslipidaemia referred to the occurrence of the following abnormalities either singly or in combination viz; raised triglyceride (TG) levels ≥150 mg%, reduced high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) ≥100 mg%, Also considered abnormal is an elevated total cholesterol level ≥200 mg%.

Case Report Forms (CRF) and patients’ medical file records were used to obtain information on the clinical status of the patients. The CRF were designed to document biodata, duration of DM, treatment type for DM and the presence of hypertension. Other relevant clinical data included the weighted means of fasting blood glucose over a preceding 3 months period. The anthropometric indices viz, the weight, height and body mass indices and blood pressure were recorded.

All recruited and consenting participants for this Study were managed with Simvastatin (Simvor) and lifestyle modification. (There was no Placebo arm). The doses of Simvastatin (Simvor) administered ranged from 20 mg-40 mg at the instance of the investigator and subjects were asked to take the drugs at bedtime. Patients reported for the initial visit whereby Simvastatin (Simvor) was administered and a second and final visit at the end of six weeks. The patients were asked to note and subsequently report any side effects at the second visit. As the usual practice in our Centre all the study subjects were referred to the dietician for counselling on lipid lowering diet and those that were fit were asked to engage in physical exercise specifically brisk walking for at least two-three times a week for a 20-30 minutes period.

Cardiovascular events such as cerebrovascular accident and heart failure were sought out for at all visits.
Laboratory assessment
Fasting venous blood samples were taken for lipid and blood glucose assessment at the start of the study and six weeks post Simvor treatment. After centrifugation plasma samples were analysed within 48 hours. Total cholesterol assay was done using the modified Liebermann-Burchard’s method. LDL-C was calculated using the Friedwald’s formula and TG results were obtained using enzymatic colorimetric methods.

Statistical analysis
The Statistical package used for analysis was SPSS version 15.

Chi square analysis was used to determine significance if any in the proportions of reduction noted after treatment with Simvor in HDL-C, LDL-C, TCHOL and TG. Results were deemed statistically significant at a P value of ≤0.05

Data are displayed by means of tables and diagrammatic representations.

RESULTS

Clinical characteristics of the study subjects
An initial 425 people with DM were screened to obtain the required number of patients with dyslipidaemia.

A total of 300 subjects with dyslipidaemia were recruited for the study and the male:female ratio was 201:99. A large majority -189 (63%) of the subjects had hypertension. The biodata, anthropometrics and other clinical features of the subjects are shown in Table 1.

The pattern of diabetes treatment was such that the majority of the subjects-86% were on oral hypoglycaemic agents, 6% and 8% used insulin and a combination of insulin and oral hypoglycaemic agents respectively for the management of DM.

Biochemical parameters
The results of the correlation between TCHOL, and all other lipid parameters using bivariate correlation are displayed in Table 2.

Table 1: Clinical characteristics of the study subjects

| Variable    | Mean (SD) | Range  |
|-------------|-----------|--------|
| Age (yrs)   | 58.4 (10) | 22 ‑75 |
| BM (Kg/m²)  | 28.5 (5.8) | 17.34‑47.19 |
| FBS (mg%)   | 150.4 (68.9) | 44‑401.4 |
| Duration of DM (yrs) | 6.3 (6.2) | 0.3‑40 |
| Duration of HTN (yrs) | 7.4 (7.8) | 1‑42 |

Table 2: Correlation between TCHOL all three lipid parameters

| Variable | R   | P value |
|----------|-----|---------|
| HDL-C    | +0.16 | 0.005   |
| LDL-C    | +0.8  | 0.000001 |
| TG       | +0.3  | 0.05    |

Pretreatment and post treatment results
Of the lipid abnormalities documented, elevated LDL-C was the commonest abnormality and was noted in 87% of the study subjects. Reduced HDL-C, elevated triglyceride and elevated total cholesterol were documented in 53%, 7% and 45% respectively of the study subjects.

Primary endpoint: impact of simvor on the lipid abnormalities
Post treatment with Simvor, there was a significant reduction in the proportions of pretreatment lipid abnormalities. The mean post treatment elevated value of HDL-C was however not statistically significant. These results are displayed in Table 3.

Post treatment fasting plasma glucose levels were comparable to pre ‑treatment levels and there was no statistically significant difference (150.4 mg% (68.9) vs 149.2 mg% (69.8), P ≥0.05)

As at the end of the study period, a total 243 persons making up 81% of the Study subjects had met the Primary (biochemical) endpoints.

Secondary Outpoint: Magnitude of the impact of Simvor on abnormal lipid parameters
Simvor had an impact on all abnormal lipid parameters and the extent of these changes are shown in Figure 1.

Table 4 depicts, the actual mean differences and SD in pre and post treatment results using the paired student’s test and these were statistically significant only for LDL-C and TCHOL.

There was a noted reduction in LDL-C, TG-C, TG, and elevation of HDL-C following treatment with Simvor but actual reduction in abnormalities to normal values were achieved chiefly with TCHOL and LDL-C. These results are displayed in Figure 2.
Reported/Documented adverse effects
Two study subjects reported general muscular weakness but Creatinine phosphokinase levels could not be assessed. There was no noted cardiovascular events and none of the subjects developed jaundice in the course of treatment.

Discussion
The pattern of lipid abnormalities in our subjects with DM was such that the proportions of abnormalities documented with LDL-C, TCHOL, HDL and TG were 87%, 45%, 53% and 7%, respectively. LDL-C, the prevalent abnormality in this report was also reported as the prevalent abnormality in a previous Nigerian report\(^8\) and an Indian report.\(^1^2\) Simvor, a brand of simvastatin is a first generation Statin that is extremely potent in reducing TCHOL and LDL and also increasing the HDL and TG levels. It does this by inhibiting the enzyme 3-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase which is the key and rate limiting enzyme in cholesterol synthesis. This study has shown that all lipid abnormalities are corrected in varying degrees by Simvor. Similar report\(^1^3\) on the effectiveness of Simvastatin in the reversal of lipid abnormalities exist in literature. Although all lipid parameters were affected positively by usage of Simvor, it was only reductions in LDL-C and TCHOL that were significantly reduced to optimal levels as recommended by the WHO/IDF criteria. This study has also showed that though the greatest mean difference between pre and post treatment values were documented for LDL-C, the greatest reduction in proportions of abnormalities was noted for TCHOL. (LDL-C was reduced by 16% and TCHOL by 23%). This scenario may be explained by the correlation between total cholesterol and low density lipoprotein cholesterol since the correlation between these parameters was greater and more statistically significant between than that obtained between TCHOL and HDL and TG.

The percentage correction of the lipid abnormalities observed in this report are lower than that reported by an Indian research.\(^1^2\) In their report, they noted a 41.2% reduction in LDL-C, 24.3% reduction in TG, a reduction in TCHOL of 29.3% and an elevation of HDL-C of 19.8%. One possible explanation for this comparable difference in our report and theirs may well be due to the differences in the criteria used in the diagnosis of dyslipidaemia/lipid abnormalities. The earlier stated Report employed the use of the 2001 American diabetes association (ADA) criterion to define DM dyslipidaemia. Obviously our criteria for the diagnosis of dyslipidaemia which is a recent one is a more stringent one. Another possible explanation for the aforesaid scenario may be due to the difference in the study period. In our study, the time period for which Simvor was administered prior to

| Table 3: Comparison of pretreatment and Post-treatment lipid results |
|-----------------|----------------|----------------|----------------|----------------|
| Variable       | Pretreatment   | Post treatment | \(P\) value   |
| LDL-C          | 138.1 (40)     | 111.76 (30.6)  | 0.00001       |
| TG             | 89.1 (41)      | 85.5 (21)      | >0.05         |
| TCHOL          | 196 (45)       | 178.4 (26)     | 0.0001        |
| HDL-C          | 45.8 (18.3)    | 47.4 (13.9)    | >0.05         |

Results are in mg% and displayed as means and standard deviation.

| Table 4: Mean differences of Post and Pretreatment results |
|-----------------|----------------|----------------|----------------|
| Variable       | Mean difference | \(P\) value   |
| Posttreatment LDL-C - Pretreatment LDL-C | 26.3 (38) | 0.0001 |
| Posttreatment TG - Pretreatment TG | 3.6 (39) | >0.05 |
| Posttreatment TCHOL - Pretreatment TCHOL | 17.5 (40) | 0.0001 |
| Posttreatment HDL-C - Pretreatment HDL-C | +1.6 (28) | >0.05 |

Results are in mg% and displayed as means and standard deviation.

Figure 1: Percentage changes in abnormal lipid parameters

Figure 2: Pre and Post treatment percentages of lipid abnormalities
the second evaluation of the biochemical parameters was six weeks while in the earlier stated report(12) evaluation post treatment with a lipid lowering agent was after a 12 week period.

Elevated triglyceride which is one of the metabolic syndrome defining criterion was the least noted abnormality in this report. Okafor et al(8) reported elevated TG as the least documented abnormality in their report on the pattern of lipid abnormalities in Nigerians with DM. The percentage reduction of this abnormality that was noted with Simvor usage was 6%. The percentage elevation of HDL, the other metabolic syndrome defining criterion as noted in our reports 10%.

Simvor was generally well tolerated and this is despite the fact that Statins may be associated with side effects that range from gastrointestinal tract disturbances such as nausea, dyspepsia, constipation and flatulence to sleep disturbances, dizziness and skin rash. In only 2 (0.6%) of the study subjects was tolerable general weakness noted. Since this was not evaluated for using Creatine Phosphokinase, it is difficult to say with certainty that this emanated from the usage of Simvor. It is pertinent to note that no adverse cardiovascular event was recorded during the period of usage of Simvor.

In our report, we found that Simvor had no effect on glycaemia as pre and post treatment glycaemia were comparable.

**Limitations of the study**
Liver function tests and Creatine Phosphokinase were not carried out.

**Conclusion**
The study has shown that Simvor is not only effective in the reversal of lipid abnormalities in our DM patients with dyslipidaemia but is associated with a high degree of tolerability. Its effectiveness is noted particularly in reducing not only the all too common elevated LDL-C that is the prevalent lipid abnormality in DM but also in correcting the other abnormal lipid components that make up the deadly atherogenic triad of DM.

**Acknowledgement**
Department of Medicine, Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria. C/o Structured Healthcare Initiatives, Po Box, 579, Ikeja, Lagos State, Nigeria.

**REFERENCES**

1. Fuller JH. Mortality trends and causes of death in diabetes patients. Diabet Metab 1993;19(1 Pt 2):96-9.
2. Ogbera O. Burden of diabetic illness in an urban hospital in Nigeria. Trop Doct 2007;37:153-4.
3. Ogbera AO, Chinemeje S, Onyekwere A, Fasanmade O. Prognostic indices of diabetes mortality. Ethn Dis 2007;17:721-5.
4. Yach D, Hawkes C, Gould CI, Hofman KJ. The global burden of chronic diseases: Overcoming the impediments to prevention and control. JAMA 2004;291:2616-22.
5. Nesto RW. Beyond low-density lipoprotein: Addressing the atherogenic liid triad in type 2 diabetes mellitus and the metabolic syndrome. Am J Cardiovasc Drugs 2005;5:379-87.
6. Ogbera AO, Fasanmade OA, Chinemeje S, Akinlade A. Characterization of lipid parameters in diabetes mellitus—A Nigerian report. Int Arch Med 2009;2:19.
7. Idogun ES, Unuigbe EI, Ogunro PS, Akinola OT, Famodu AA. Assessment of serum lipids in Nigerians with type 2 diabetes mellitus complications. Pak J Med Sci 2007;23:708-12.
8. Okafor CI, Fasanmade OA, Oke DA. Pattern of dyslipidaemia among patients with type 2 diabetes mellitus. Niger J Clin Pract 2008;11:25-31.
9. Edo A, Adediran OS. Dyslipidaemia among Nigerian oil workers with type 2 diabetes mellitus. West Afr J Med 2011;30:206-9.
10. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998;279:1615-22.
11. Newman CB, Palmer G, Silbershatz H, Szarek M. Safety of atorvastatin derived from analysis of 44 completed trials in 9416 patients. Am J Cardiol 2003;92:670-6.
12. Udwat H, Goyal RK. Lipid lowering effect of simvastatin in patients of type 2 diabetes mellitus. Indian Heart J 2001;53:172-6.
13. Hydrie ZI, Qasim R, Ahmadoni Y, Miyaz Z, Miyaz Y, Fawwad A, et al. Effect of Simvastatin on insulin sensitivity in type 2 diabetic subjects. Pak J Med Sci 2007;23:755-9.
14. Alberti KG. IDF Consensus on the metabolic syndrome: Definition and treatment. Available from: http://www.idf.org/webcast. [Last accessed on 2012 Feb 01].
15. Abel LL, Levy BB, Brodie BB, Kendall FE. A simplified methods for the estimation of the total cholesterol in serum and demonstration of specificity. J Biol Chem.1952;195:357-66.
16. Friedwald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma, without use of the preparative ultra centrifuge. Clin Chem 1972;18:499-502.
17. McGowan MW, Artiss JD, Strandergh DR, Zak B. A peroxidase-coupled method for the calorimetric determination of serum triglycerides. Clin Chem 1983;29:538-42.

Cite this article as: Okeoghene, OA, Alfred A. The efficacy and safety of Simvastatin in the treatment of lipid abnormalities in diabetes mellitus. Indian J Endocr Metab 2013;17:105-9.

Source of Support: Ranbaxy, Conflict of Interest: None declared.