Investigating the risk of Incident diabetes mellitus among primary care patients treated with simvastatin in North-Central Trinidad

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ABSTRACT

Aim: To determine the risk of new-onset diabetes mellitus in patients treated with simvastatin at primary healthcare clinics in North Central Trinidad. Materials and Methods: A retrospective descriptive case-series study design was applied to 384 conveniently sampled patient medical records from the cluster of primary healthcare centers during the period of February 2016–May 2016. Information from the patient files were then recorded using a systematic data extraction form. The major inclusion criteria were non-diabetic patients who were compliant with daily simvastatin for a minimum period of 1 year. The risk of incident diabetes mellitus was calculated, using SPSS version 20.0. Chi-squared ($\chi^2$) testing was performed to determine any association between new-onset diabetes mellitus and simvastatin use. Results: In all, 207 patients became diabetic during their treatment period translating into a 53.9% risk of incident diabetes mellitus ($\chi^2 = 2.3438, P = 0.1258$). A subgroup analysis of 133 subjects was performed to eliminate the confounders of family history of diabetes and age greater than 60 years. In this subgroup, 50 incident diabetics (37%) were identified and a statistically significant association was observed ($\chi^2 = 8.118, P = 0.0042$). Linear regression revealed that this association was dose-dependent with a corresponding 32% higher risk in patients taking 40 mg ($P = 0.001$) of simvastatin daily compared with 20 mg of simvastatin ($P = 0.094$). Linear regression also revealed that there was significant statistical association between onset of diabetes mellitus and duration of statin therapy ($P = 0.006$). Conclusion: In this population, simvastatin use is associated with a 53.9% increased risk of development of new-onset diabetes mellitus ($\chi^2 = 2.3438, P = 0.1258$). A statistically significant association was attained after subgroup analysis involving patients less than 60 years old and without a family history of diabetes with an incident risk of 37%. The increased risk of incident diabetes mellitus conferred by higher doses of simvastatin warrants consideration by physicians considering therapies for dyslipidemia in patients with multiple risk factors for diabetes mellitus.

Keywords: Diabetes, incident diabetes, simvastatin, Trinidad

Introduction

In Trinidad and Tobago, heart disease is ranked as the leading cause of death in patients according to the Pan American Health Organization.[1] Local healthcare providers prescribe statins to their patients to treat dyslipidemia. Dyslipidemia along with obesity, high blood pressure, family history of diabetes, unhealthy diet, increased age, and ethnicity are risk factors for developing diabetes.[2] In Trinidad, simvastatin is the only statin available to patients accessing government’s Chronic Disease Assistance Program.[3]

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Stats, as a class of cholesterol-lowering agents, are primarily administered for the treatment of dyslipidemia and the reduction in cardiovascular diseases that are atherosclerotic in nature. These drugs are among the most widely prescribed medications due to their high efficacy and broad effects on lipid profile. These drugs work primarily by reducing cholesterol levels, specifically low-density lipoprotein (LDL). While its actions are not limited, other effects of statins include reductions in total cholesterol and triglycerides with simultaneous increase in high-density lipoprotein (HDL).[^6]

Statins are described as having the ability to lower LDL through reversible competitive inhibition of the key enzyme HMG-CoA reductase. This enzyme is present in the first step of the biosynthetic pathway of cholesterol, which is also the rate-limiting step.[^7]

Statins structurally resemble the endogenous HMG-CoA moiety and competitively bind to the catalytic domain of HMG-CoA reductase.

The structural similarities of statin drugs are described as being responsible for the steric hindrance and prevention of HMG-CoA from accessing the active site. This inhibition of the key enzyme then prevents the production of cholesterol in the liver. The reduction in cholesterol is detected by hepatocytes, which triggers upregulation of the LDL receptor expression to increase uptake of LDL and very low-density lipoprotein from systemic circulation, which are then internalized and the cholesterol is converted into bile salts and excreted. As a result of this, a significant portion of the cholesterol-lowering effects of the statin is attributed to the increased LDL clearance from the plasma and second to that is the inhibition of cholesterol biosynthesis.[^8]

Dyslipidemia is defined as an abnormally elevated level of plasma cholesterol – total cholesterol, LDL, and a decrease in HDL in the blood.[^8] The National Institute of Health establishes the range at which total cholesterol levels are considered normal or abnormal. Total cholesterol is normal when it is <200 mg/dL, while 200–240 mg/dL is classified as borderline, and >240 mg/dL is high.[^9]

A non-diabetic person will have an A1c result less than 5.7%, a pre-diabetic A1c level is 5.7%–6.4%, and a diabetic A1c level is 6.5% or higher.[^9] A person with a fasting blood glucose level of 70–100 mg/dL is normal, 100–125 mg/dL is pre-diabetic, and greater than 126 mg/dL is considered diabetic.[^10]

It is postulated that the mechanism by which patients are thought to develop diabetes through statin use is through the impairment of Beta cells in the pancreas, which decrease the amount of insulin that is stored and secreted, resulting in glucose levels remaining high.[^10]

The information gleaned from using a local population to conduct this study may be useful in assisting local healthcare providers to better assess the potential risks associated with the continued use of statin therapy. It can therefore benefit the local population by promoting a more judicious use of statin therapy to our at-risk population.

The prevalence of both hypercholesterolemia and diabetes has increased globally, regionally, and locally. The World Health Organization reported that in 2008, global prevalence of raised cholesterol among adults was 39% (37% males and 40% females). Between the years of 1980–2008, the mean total cholesterol level reportedly decreased by less than 0.1 mmol/L per decade.[^10] According to the International Diabetes Federation of North America and the Caribbean, as of 2015 in the North American and Caribbean region, there are more than 44.3 million people suffering from diabetes and this figure is expected to rise to 60.5 million by 2040.

In Trinidad and Tobago, as of 2015 there were 140,300 cases of diabetes mellitus and the prevalence of diabetes in adults (ranging 20–79 years) was reported to be 14.5%.[^11] The Ministry of Health of Trinidad and Tobago in 2010 reported that “1 in 8 (maybe 1 in 5) of all adults in the Caribbean has Diabetes” and “Diabetes is more prevalent in Females and in East Indians when compared to other ethnic groups.”[^12]

Evidence of the increased risk of diabetes conferred by the use of statin medication has been reported internationally. In 2010, a study published in the Lancet identified 13 statin trials comprising a total of 91,140 participants; 4278 (2226 assigned statins and 2052 assigned control treatment) of those participants developed diabetes over an average of 4 years. Statin therapy was associated with an increased risk for incident diabetes mellitus of 9% (odds ratio 1.09; 95% confidence interval 1.02–1.17) and little heterogeneity (I² = 11%) between the trials.[^12]

Preiss et al. concluded in a pooled analysis of data from five statin trials that intensive-dose statin therapy was associated with an increased risk of new-onset diabetes compared with moderate-dose statin therapy, suggesting that there was an association between incident diabetes mellitus and statin use and that the risk increased when the dosage of statin increased. Carter et al.[^9] reported similar findings and found that simvastatin (Zocor) and other statins raised the risk of diabetes by 10%–22%.[^8]
Materials and Methods

Study design
A retrospective descriptive case-series study design was used to examine the relationship between simvastatin use and the risk of incident new-onset diabetes mellitus. Data were collected from the medical records of patients attending primary healthcare-based chronic disease clinics in North Central Trinidad.

Medical records of patients were selected on the basis of the following criteria:

**Inclusion criteria**
1) Patients without diabetes mellitus prior to simvastatin treatment
2) Compliant with daily simvastatin therapy for at least 1 year
3) Between the ages of 40 and 64 years.

**Exclusion criteria**
1) Patients who were pregnant.
2) Patients who were smokers.

Sample size and sampling methodology
A sample size of 384 files were chosen based on an equation for calculation of a sample size from an unknown population. The sample size for unknown population:

\[ Z\text{-score: } 95\% - Z\text{-score} = 1.96 \]

\[ \text{Necessary sample size} = \frac{(Z\text{-score})^2 \times \text{StdDev} \times (1\text{- StdDev})}{(\text{margin of error})^2} \]

\[ = \frac{(1.96)^2 \times 0.5 (0.5)}{(0.05)^2} \]

\[ = 0.9604/0.0025 \]

\[ = 384.16 \]

384 (385) respondents are needed.

Data collection and analysis
Information from the patient files were extracted in a systematic manner by application of a standardized data extraction form during the period February–May 2016. Data were analyzed using IBM Statistical Program for Social Sciences version 20.0. Subgroup analysis to eliminate confounding factors of age and family history of diabetes was also performed. Ethical approval was conveyed by the Campus Ethics Committee of the University of the West Indies and the North Central Regional Health Authority.

Results
Data from 165 (43%) male and 219 (57%) female chronic disease clinic attendees were analyzed [Table 1]. Of the study population (N = 384), 207 became diabetic and 177 remained non-diabetic translating into a 53.9% risk of incident diabetes mellitus (\( \chi^2 = 2.34, \text{df} = 1, P = 0.126 \)).

Of the 207 new-onset diabetics, 86 (41.5%) were males and 121 (58.4%) were females. The non-diabetic population was in the order of 79 (44.6%) males and 98 (55.3%) females. No statistically significant association between gender and new onset of diabetes mellitus was observed as seen in Table 1.

Table 1 also compared the incidence of new-onset diabetes within the various ethnicities in the study population (N = 384). About 50.3% were of East Indian descent, 42.4% were of African descent, 1% was Chinese, 0.5% was Caucasian, and 6.5% were of mixed ethnicities. Of the East Indian ethnicity, 54.1% of individuals developed diabetes after using statin therapy, while 45.8% of individuals did not. With respect to the individuals of African descent, 41.5% of individuals developed diabetes while 43.5% did not. Of the individuals with mixed ethnicities, 6.5% developed diabetes while 10.7% did not. A statistically significant association between ethnicity and onset of new diabetes mellitus was observed (\( \chi^2 = 13.26, P = 0.010 \)) favoring its occurrence among those of East Indian heritage.

To adjust for baseline diabetes risk factors of age and family history, the case-series sample size was reduced by eliminating the confounding factors of age greater than 60 years and family history of diabetes mellitus. The elimination of these confounders resulted in a subgroup analysis of 133 patients (n = 133). From the subpopulation of \( n = 133 \), 50 patients developed new-onset diabetes mellitus and 83 patients did not result in an incident risk 37% (\( \chi^2 = 8.118, P = 0.004 \)).

| Demographic   | n (%) | Developing diabetes, n (%) | Not developing diabetes, n (%) | \( \chi^2 \) | P* |
|---------------|-------|-----------------------------|-------------------------------|-------------|----|
| **Gender**    |       |                             |                               |             |    |
| Male          | 165 (43) | 86 (41.5)                  | 79 (44.6)                     | 0.256 (df=1) | 0.613 |
| Female        | 219 (57) | 121 (58.4)                 | 98 (55.3)                     |             |     |
| **Ethnicity** |       |                             |                               |             |    |
| East Indian   | 193 (50.3) | 112 (54.1)                | 81 (45.8)                     | 13.26 (df=4) | 0.010 |
| African       | 163 (42.4) | 86 (41.5)                  | 77 (43.5)                     |             |     |
| Mixed         | 25 (6.5)  | 6 (2.9)                     | 19 (10.7)                     |             |     |
| Caucasian     | 2 (0.5)   | 2 (1)                       | 0 (0)                         |             |     |
| Chinese       | 1 (0.3)   | 1 (0.5)                     | 0 (0)                         |             |     |

* n: The number of patients in this group; %: Percentage of patients in this group; **P<0.05, a significant difference in development of diabetes
Table 2 illustrates the relationship between duration and dosage of simvastatin and new-onset diabetes mellitus within the subpopulation of 133. It was observed that the dosage prescribed was either 20 or 40 mg. Of the 50 diabetic patients, 33 (66%) were prescribed the higher dosage of 40 mg of simvastatin. Of the 83 non-diabetic patients, 52 (62.6%) patients were also prescribed a higher dosage of 40 mg of simvastatin. A Pearson’s Chi-squared test was used to compare dosage of drug and onset of diabetes mellitus using the study population N = 384. The corresponding results showed that there was no statistical significance between those two variables alone ($\chi^2 = 0.041288, P = 0.839$).

However, a comparison between these variables and duration of simvastatin therapy using a linear regression model revealed statistically significant results [Table 3 and Graph 1]. It was also observed that patients prescribed 40 mg of daily simvastatin had a 46% increased mean fasting blood glucose and a 24% increased mean HbA1c level.

Of the 50 diabetic patients in the subgroup analysis, only 72% had fasting blood glucose records available for analysis. Analysis of these records before and after simvastatin treatment revealed mean values of 94.11 and 137.41 mg/dL of fasting blood glucose, respectively. A mean difference of 43.3 mg/dL translated into an absolute increase of 46% in fasting blood glucose levels.

About 86% of these 50 records contained blood test results for HbA1c test before and after statin treatment. The average total mean HbA1c value before statin treatment was 5.53%, while the mean value after statin treatment was 6.86%. This accounted for a relative increase of 24% in HbA1c values over a period of 1–7 years [Tables 4 and 5].

**Discussion**

This retrospective case-series resulted in a relative risk for incident diabetes mellitus among simvastatin users of 53% ($\chi^2 = 2.3438$, $P = 0.1258$). However, statistically significant results were attained through a subgroup analysis performed on patients who had no family history of diabetes and were less than 60 years of age. This subgroup analysis of 133 patients revealed a risk of incident diabetes mellitus of 37% ($P = 0.004$). These findings are consistent with studies performed elsewhere in the world, but the magnitudes of our findings were comparatively greater. This may have occurred as a consequence of a smaller sample size and convenient sampling. The study conducted by Beckett et al. examined previous studies on the association between statins and new-onset diabetes and found that although the association between the two was small, it

| New onset of diabetes mellitus | Statin therapy (years), n=133 | Total |
|-------------------------------|--------------------------------|-------|
| Statin dosage                  |                               |       |
| 20 mg                          | 1 6 6 8 7 0 2 1 0 0 0 0 31 |       |
| 40 mg                          | 0 11 10 4 3 5 1 6 3 4 2 52 |       |
| Total                          | 1 17 16 12 10 3 7 2 6 3 4 2 83 |       |

Yes

| Statin dosage                  |                               |       |
| 20 mg                          | 1 3 5 3 2 2 1 - - - - - 17 |       |
| 40 mg                          | 1 5 2 10 12 3 0 - - - - - 33 |       |
| Total                          | 2 8 7 13 14 5 1 - - - - - 50 |       |

Total

| Statin dosage                  |                               |       |
| 20 mg                          | 2 9 11 11 9 2 3 1 0 0 0 0 48 |       |
| 40 mg                          | 1 16 12 14 15 6 5 1 6 3 4 2 85 |       |
| Total                          | 3 25 23 25 24 8 8 2 6 3 4 2 133 |       |

**Table 3: Comparison between statin dosage and new-onset diabetes during the treatment period using a linear regression model**

| Statin dosage (mg) (diabetic patients) | Linear regression (coefficient $P$ values) |
|----------------------------------------|--------------------------------------------|
| 20                                     | 0.09142                                    |
| 40                                     | 0.00142                                    |

**Table 4: Mean fasting blood glucose levels in relation to daily statin dosage within the subpopulation**

| Drug history of statin dosage | Prestatin FBS (mg/dL) | Poststatin FBS (mg/dL) | Mean percentage increase |
|-------------------------------|-----------------------|------------------------|--------------------------|
| 20                            | Mean 93.2500          | Mean 136.250           | 46.1                     |
| n 16                          | 16                    | 16                     |                          |
| SD 6.79706                    | 6.19139               |                        |                          |
| 40                            | Mean 94.8000          | Mean 138.350           | 45.9                     |
| n 20                          | 20                    | 20                     |                          |
| SD 11.2792                    | 9.42714               |                        |                          |
| Total                         | Mean 94.1111          | Mean 137.4167          | 46.0                     |
| n 36                          | 36                    | 36                     |                          |
| SD 9.45902                    | 8.11128               |                        |                          |

FBS: Fasting blood glucose; SD: Standard deviation
was still significant. Another study supported this finding with a significant association between the onset of diabetes mellitus and statin use in postmenopausal women. They found that there was a range of risk of incidence of 3.1%–22.7%. \cite{13}

Our findings also revealed that new-onset diabetes mellitus was dose-dependent, since it was noted that a higher percentage of patients who developed diabetes mellitus (66%) were prescribed a higher dosage of 40 mg \( (P = 0.001) \) compared to those prescribed 20 mg \( (P = 0.091) \). Incident diabetes mellitus was also found to be associated with the duration of statin therapy when data were analyzed using linear regression \( (P = 0.006) \). These findings are consistent with a study performed by Navarese \textit{et al.}\cite{16} with respect to statin potency and risk of incident diabetes along with duration of statin therapy and incident diabetes. They found an increased risk of new-onset diabetes in patients prescribed higher potency statins compared with lower potency statins. \cite{17}

Further evidence of this dose-dependent association is documented by Navarese \textit{et al.}\cite{18} whose meta-analysis revealed a correlation between the potency of statins and the risk of diabetes mellitus. They reported a 12% higher relative risk for developing diabetes mellitus on intensive-dose statin therapy compared with moderate-dose therapy.\cite{19}

The investigators deemed it prudent to embark upon a subgroup analysis to address the effect of confounding factors. These confounding factors were age greater than 60 years and family history of diabetes. Age is known as a risk factor for diabetes. Indeed, it has been reported that the prevalence of diabetes mellitus increases with age and peaks at 60–74 years.\cite{18} It is with these findings in mind that patients from the study population who were on statins and were ≥60 years of age were excluded from our subgroup analysis as they were already predisposed to developing diabetes mellitus. Patients with a family history of diabetes were also excluded from analysis as this is well-established risk factor for developing diabetes.

In our study, ethnicity was found to be associated with new-onset diabetes \( (\chi^2 = 13.26, P = 0.010) \). Indeed, a larger percentage of new-onset diabetics (54%) were found to be of East Indian origin when compared with other ethnicities. This is consistent with findings of a study done by Mohan \textit{et al.}\cite{20} which revealed that the reason for increased risk of diabetes in people of Indian origin may be due to increased insulin resistance, stronger genetic factors, and environmental factors such as diet and lifestyle.\cite{21}

With respect to the duration of statin use, the majority (44 of 50) of the patients within the subgroup who used statin therapy for a period of 5 years or less developed diabetes. This is at variance to a study conducted by Macedo \textit{et al.}\cite{22} which showed an increased risk that was only apparent after 5 or more years of treatment with statins. This may be due to other potential and unknown confounders.

Hyperglycemia was also noted in the subgroup whereby increased mean fasting blood sugars (46%) and HbA1c (24%) levels were observed in both diabetic and non-diabetic patients. This trend suggests that the continued use of statin therapy may impair glycemic control.

Our findings are supportive of the increased risk of incident diabetes among statin users. The risk appears to be dose-dependent with a corresponding higher risk (32%) in patients taking 40 mg \( (P = 0.001) \) of simvastatin compared with 20 mg of simvastatin \( (P = 0.094) \).

Primary care physicians (PCPs) often encounter patients with dyslipidemia, often as part of the metabolic syndrome or within the context of increased risk of adverse cardiovascular outcomes. It is therefore of great clinical importance that notwithstanding the benefits of reducing lipid levels and by extension of cardiovascular risk with statin medication, the findings of this study along with others which support the link between new-onset diabetes mellitus and statin therapy be shared so that PCPs may be aware of their potential risks.

Increasing awareness among PCPs of these findings will serve to further enhance risk assessment particularly as it relates to the development of impaired glycemic values. It should therefore prompt the PCP to establish baseline blood sugar indices that may reveal previously undiagnosed diabetes or can be used to monitor for glucose impairment post-statin initiation.

These findings also warrant the need for PCPs to consider alternatives to statin therapy for reducing lipid levels. Very often, simple lifestyle interventions such as reducing the intake of saturated fats, oils, and other unhealthy components of food and increasing exercise levels are overlooked in favor of statin therapy. PCPs should also recall the useful roles of ezetimibe, bile acid sequestrants, and fibrates in reducing LDL levels, creating a more favorable lipid profile and reducing cardiovascular risk. At the very least, PCPs should become more acutely aware of the potential

### Table 5: Mean glycated hemoglobin levels in relation to daily statin dosage within the subpopulation

| Drug history of statin dosage | Prestatin HbA1c results (mg/dL) | Poststatin HbA1c R results (mg/dL) | Mean percentage increase |
|------------------------------|---------------------------------|-----------------------------------|-------------------------|
| 20 mg                        |                                 |                                   |                         |
| Mean                         | 5.5714                          | 6.8714                            | 23.3                    |
| n                            | 14                              | 14                                |                         |
| SD                           | 0.3023                          | 0.25549                           |                         |
| 40 mg                        |                                 |                                   |                         |
| Mean                         | 5.5103                          | 6.8552                            | 24.4                    |
| n                            | 29                              | 29                                |                         |
| SD                           | 0.42057                         | 0.35009                           |                         |
| Total                        |                                 |                                   |                         |
| Mean                         | 5.5302                          | 6.8605                            | 24.0                    |
| n                            | 43                              | 43                                |                         |
| SD                           | 0.39008                         | 0.31933                           |                         |

HbA1c: Glycated hemoglobin; SD: Standard deviation.
harms of statin therapy but recall that statin use is generally justified as first-line therapy in cases with sufficient cardiovascular risks.

The limitations of this study included its retrospective descriptive case-series design, which may be affected by unknown and known confounding factors such as lifestyle factors. Potential biases include information and selection bias as a result of inconsistent documentation of compliance with prescribed statin and convenience sampling, respectively, which in terms limits the generalizability of our findings.

Conclusion
In this primary care-based patient population, simvastatin use was associated with a 53% increased risk of development of new-onset diabetes mellitus ($\chi^2 = 2.3438, P = 0.1258$). A statistically significant association was attained after subgroup analysis involving patients less than 60 years old and without a family history of diabetes. This association was dose-dependent with a corresponding higher risk of 32% in patients taking 40 mg ($P = 0.001$) of simvastatin compared with 20 mg of simvastatin ($P = 0.094$). The increased risk of incident diabetes mellitus conferred by higher doses of simvastatin warrants consideration by physicians considering therapies for dyslipidemia in patients with multiple risk factors for diabetes mellitus.

The increased risk of incident diabetes conferred by prescription of statin therapy should promote more judicious use of these drugs especially for those patients with concomitant risk factors for diabetes mellitus. Trinidad and Tobago’s unique population, diversity of lifestyle, and dietary habits warrant a study of this kind on a larger scale especially in a growing population and increased life expectancy worldwide.\(^9\)

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Conflicts of interest
There are no conflicts of interest.

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