Statin prescription among patients with type 2 diabetes at a specialised diabetes clinic, Botswana

by

Julius Chacha Mwita

A thesis presented in fulfilment of the requirements for the degree of Master of Science (MSc) in Clinical Epidemiology in the Faculty of Medicine and Health Sciences at Stellenbosch University

Supervisor: Tonya M Esterhuizen

Co-supervisor: Brian Godman

December 2019

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Date: December 2019
STELLENBOSCH UNIVERSITY
FACULTY OF MEDICINE AND HEALTH SCIENCES

TO WHOM IT MAY CONCERN

ASSIGNMENT/THESIS/DISSertation RELEASE

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<td>Tonya M Esterhuizen, Prof Brian Godman</td>
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<td>24/09/2019</td>
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Part A: Completed manuscript

Abstract

Background

There is evidence of statin benefit among patients with diabetes regardless of their cholesterol levels or prior cardiovascular disease history. Despite the evidence, there is under-prescription of statins in clinical practice. This study aimed to assess statin prescriptions and associated factors among patients with type 2 diabetes in Botswana.

Methods

The study was a secondary data analysis of 500 randomly selected type 2 diabetes patients at a specialised diabetes clinic at Gaborone Botswana. We assessed the proportion of statin-eligible patients who were prescribed statins and evaluated the adjusted associations between various factors and statin prescription.

Results

Overall, 477(95.4%) participants were eligible for a statin prescription. Clinicians prescribed statins in 217(45.5%; 95% confidence interval[CI]: 41.1%-50.0%) of eligible participants, and only one(4.4%) ineligible participant. The probability of statin prescription was high in participants with high baseline low-density lipoprotein cholesterol(risk ratio [RR]:1.49; 95%CI: 1.17 - 1.89), increasing duration of diabetes (RR: 1.01; 95%CI 1.00 - 1.03) and the presence of chronic kidney disease (RR: 1.35; 95%CI: 1.06 - 1.74).

Conclusion

Most patients with type 2 diabetes were not receiving statins. Clinicians did not consider most guideline-recommended indications for statin prescription. The findings call for improvement in diabetes quality of care by implementing evidence-based guideline recommendations.

Keywords: statin, type 2 diabetes mellitus, prescription and Botswana
# Table of Contents

**Part A: Completed manuscript**

- Abstract .............................................................................................................. 3
- Background ........................................................................................................ 5
- Methods ............................................................................................................ 6
- Statistical analysis .......................................................................................... 8
- Results ............................................................................................................. 9
- Discussion ....................................................................................................... 11
- Conclusion ...................................................................................................... 14
- Abbreviations ................................................................................................. 14
- Declarations ................................................................................................... 14
- References ...................................................................................................... 14
- Tables .............................................................................................................. 20
  - Table 1: Demographic and clinical characteristics of patients with type 2 diabetes at a specialised Diabetes clinic in Gaborone (N= 477) .............................................................................................................. 20
  - Table 2: Factors associated with statin prescription among statin-eligible patients with type 2 diabetes at a specialised Diabetes clinic in Gaborone (N= 477) .............................................................................................................. 21
  - Table 3 Adjusted relative risks for associations between various factors and statin prescription among statin eligible patients with diabetes at a specialised diabetes clinic in Botswana .............................................................................................................................................................................. 22

**Part B: Appendices**

- a. Relevant journal Instructions to Authors: .......................................................... 22
- b. Questionnaire/data capture instrument(s) (as prepared originally for protocol) .............................................................................................................. 31
- c. Ethics consent form(s) (as prepared originally for protocol) .................................. 31
- d. Selected tables or figures, .................................................................................. 35
- e. Any technical appendices needed – for example, laboratory techniques, statistical formulae .......................................................... 35
- f. Acknowledgements ......................................................................................... 35
- g. Turnitin report ............................................................................................... 35
Background
Cardiovascular disease (CVD), which includes coronary artery disease (CAD), cerebrovascular accident, and peripheral arterial disease (PAD), are common and contribute to over two-thirds of mortality among patients with type 2 diabetes mellitus [1-3]. Although the presence of type 2 diabetes alone confers the highest risk for CVD of any single risk factor, the coexistence of other cardiovascular risk factors is a common phenomenon [3, 4]. Consequently, guidelines advise screening and optimal treatment of CVD risk factors in people with diabetes [5, 6]. Besides, prescribing of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) among patients with type 2 diabetes reduces the risk of major CVD events by 23%-33% [7-9]. There is evidence of statin benefit among patients with diabetes regardless of their low-density lipoprotein cholesterol (LDL-C) values or prior CVD history [7, 9-14]. For each mmol/l reduction in LDL-C, there is evidence of a 9% relative reduction in all-cause mortality in patients with diabetes [15]. Irrespective of LDL-C, guidelines recommend statins for patients with diabetes aged ≥ 40 years without atherosclerotic cardiovascular disease (ASCVD), or those who are younger than 40 years but with existing ASCVD or additional risk factors [5, 6]. While some studies in developed countries have reported high use of statins among patients with type 2 diabetes, there has generally been under-prescription of statins across many countries [16-18]. Statin prescription ranges between 0% and 100% in developed countries [17-20]. The proportion of patients with type 2 diabetes in Africa receiving a statin currently ranges between 3 and 13% [21-23]. The suboptimal utilisation of statin therapy in Africa is due to many factors, but mainly limited access to standard diabetes care because of the high cost of tests and medications [22]. Affordability is a critical issue in several African countries where there is no universal healthcare, with the cost of medicines accounting for up to 70% of total healthcare expenditure, much of which is out-of-pocket [24, 25]. This is a concern given the high growth rates of cardiovascular diseases in sub-Saharan African countries and current poor control of cardiovascular diseases [26-30]. The underuse of statins significantly increases the incidence of cardiovascular events and associated mortality [31]. Although healthcare is free in Botswana, factors not related to cost may still affect the uptake of statins in patients with diabetes. This is an issue given current prevalence rates of diabetes in Botswana and the resultant impact on
morbidity and mortality[32]. Currently, there is no study assessing statin prescriptions among patients with type 2 diabetes in Botswana. We aimed to address this by evaluating the extent of statin prescriptions among patients with diabetes in Botswana. Our secondary aim was to determine factors associated with statin prescriptions among Type 2 diabetes. Subsequently, we will use the findings to develop appropriate strategies to address the situation identified concerns.

Methods

Study design
We conducted a secondary analysis of data from a previous study among type 2 diabetics at a specialised diabetes clinic in Gaborone, Botswana. Any concerns with the management of diabetic patients in this dedicated leading clinic are likely to be exacerbated in non-specialist centres such as primary healthcare centres.

Participant recruitment and data collection
The original study took place between August 2017 and February 2018[33]. The primary objective of the original study was to assess glycemic, low-density lipoprotein, and hypertension control in patients with type 2 diabetes. The study included 500 randomly selected patients with type 2 diabetes aged ≥ 18 years who had received care from the clinic for at least three months before data collection. Demographic data (age, sex, occupation, educational attainments, and marital status), duration of diabetes, and the type of diabetes medications were collected. Other information was the history of hypertension, lipid disorders, ischemic heart diseases, stroke or peripheral vascular disease. We also recorded data on the use of medications for hypertension and lipid disorders (including statins), and anthropometric measurements (weight, height, hip and waist circumferences).

For the present study, we evaluated the extent of statin prescriptions among the participants in the dataset. The primary outcome measure was receiving a statin prescription among statin-eligible participants. We assessed statin eligibility based on the Society for Endocrinology, Metabolism, and Diabetes of South Africa (SEMDSA) guidelines[6]. According to SEMDSA, the eligibility for statin prescribing included any cardiovascular disease (CVD) or chronic kidney
disease (CKD), participant's age above 40 years, and diabetes duration longer than ten years. Also, the presence of one or more additional cardiovascular risk factors, i.e. hypertension, cigarette smoker, low high-density lipoprotein cholesterol (HDL-C) level, family history of early CAD, and any albuminuria were the other eligibility criteria [6]. Thus, we assessed the association of the above eligibility criteria for statin prescribing. Other independent variables included baseline serum LDL-C, body mass index (BMI), waist-hip ratio (WHR) and education attainment.

**Definition of terms**

The diagnosis of hypertension was based on the self-reported history of hypertension, the use of hypertension-lowering medications or sustained blood pressure ≥140/90 mmHg in more than one visit [34]. We defined CVD as the history of CAD, cerebrovascular diseases (ischemic stroke, transient ischemic attacks), or peripheral vascular diseases (PAD) [6]. CAD was any documented definite or probable myocardial infarction, CAD-related revascularisation (surgery, angioplasty, stenting, or any combination of these), or stable angina in patients’ medical records [35]. Cerebrovascular and peripheral vascular diseases were extracted from patients’ medical records as defined by the treating physician. Smoking status was a documented self-report of current smoking habits. We estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD), and classified patients with eGFR < 60 ml/minute/1.73m² as having chronic kidney disease and an increased risk of a cardiovascular event [5, 6, 36]. Body mass index (BMI) was categorized into underweight for BMI <18.5 kg/m²; normal for BMI of 25.0–29.9 kg/m²; or obese for BMI ≥30 kg/m² [37]. We measured waist and hip circumferences using standard procedures and defined WHR ≥ 0.85 for women and ≥ 0.90 for men as high [38]. Dipstick proteinuria appeared as negative (−), trace, (+), (++) or (+++) in the dataset. We classified proteinuria in individuals with ≥ (+) dipstick proteinuria results. For patients already on lipid-lowering medications and whose baseline 'untreated' levels of lipid profile were not available, we estimated the LDL-C levels before the initiation of statin treatment as in previous studies [39]. The adjustment was made based on the assumption that most patients received atorvastatin (the only statin available in the public sector in Botswana) at a dosage of at least 10mg per day. With an estimated adherence of 58.2 %, we calculated the
baseline LDL-C levels by assuming that the measured LDL-C is a result of a 25% reduction from baseline[39]. Baseline LDL-C levels above 4.13 mmol/l were considered high[40].

**Statistical analysis**

Clean data were imported and analysed using Stata Version 14(Stata Corp, College Station, TX). Categorical variables are presented as percentages and continuous variables as a mean(standard deviation[SD]) or median [first–third quartiles]. Comparison of clinical and demographic factors by gender and statin use was made using Chi-square or Fisher’s exact tests for categorical variables, and independent student’s t-tests or Wilcoxon rank-sum test for continuous variables as appropriate. A 2-sided p-value < 0.05 was considered as statistically significant. To assess for independent predictors for statin prescribing, generalised linear models for the binomial family were used, and a log link was specified to obtain relative risks and 95% confidence intervals. All factors with p < 0.2 on univariate analysis were added to the multivariable model. We used a backward selection modelling method, with probabilities set at 0.05 and 0.1 for inclusion and exclusion; respectively. We report adjusted risk ratios (RRs), 95% CIs, and p-values. We required a sample size of 477 to produce a two-sided 95% confidence interval with a width equal to 3.01% based on the assumptions of approximately 13% statin use among patients with type 2 diabetes in Botswana[22].
Results
Of the 500 patients in the dataset, the mean(SD) age was 58.9(12.2) years, 330 (66%) were females. Table 1 summarises the patients' characteristics by gender. The majority(96.7%) of participants aged ≥ 40 years and women were significantly older than men. Approximately a third (34.4%) of participants had a diabetes duration of over ten years. Hypertension(84.7%) and obesity(51.6%) were prevalent, especially in female participants. Overall, CKD(11.3%), proteinuria(10.7%), CVD (8.8%), and smoking(3.4%) were uncommon. The mean(SD) baseline LDL-C was 3.1(1.2) mmol/L, significantly higher in female than male participants.

[Table 1: Demographic and clinical characteristics of patients with type 2 diabetes at a specialised Diabetes clinic in Gaborone (N= 477)]

Statin eligibility and prescribing rates
Of the 500 participants, 477(95.4%) were eligible for a statin prescription. Clinicians prescribed statins (exclusively atorvastatin) in 217(45.5%; 95%CI:41.1%-50.0%) of statin-eligible participants, and only one(4.4%;95%CI:5.1%-28.4%) ineligible participants. Seven(1.5%) of all participants received prescriptions of other lipid-lowering medications alone or in combinations with statins. Of those who were eligible for statins, statin-prescribed individuals differed from those without prescriptions in several parameters on univariate analysis(Table 2). Relative to the statin-non-prescribed group, the statin-prescribed group had a longer duration of diabetes(8.9 years vs. 6.0 years; p < 0.001); were older (61.5 years vs 59.2 years ; p = 0.018), and had a a higher proportion of hypertensive patients(85.5% vs 81.5%; p<0.036), a higher proportion of those on antihypertensive(85.7% vs 78.1%, p<0.032), a higher proportion of participants with CKD(17.2% vs 6.6%; p= 0.006), and a higher baseline LDL-C(3.3 vs 2.9 mmol/L; p <0.003). The two groups did not differ significantly in the presence of CVD, proteinuria and gender.

[Table 2: Factors associated with statin prescription among statin-eligible patients with type 2 diabetes at a specialised Diabetes clinic in Gaborone (N= 477)].

Multivariable analysis
In the multivariable model which examined adjusted associations between statin prescription and various factors, the best fit had the following covariates: age, the duration of diabetes, BMI, hypertension a high baseline LDL-C, CKD, CVD, and proteinuria. Increasing diabetes duration was associated with an increased likelihood (RR: 1.01; 95%CI 1.00 - 1.03) of receiving a statin prescription (Table 3), as was the presence of CKD (RR: 1.35; 95%CI: 1.06 – 1.74) and a high baseline LDL-C (RR: 1.49; 95%CI: 1.17 - 1.89). Patients’ age, BMI, history of CVD, and a diagnosis of hypertension were not associated with statin prescribing after adjustment for the other variables in the model.

[Table 3 Adjusted relative risks for associations between various factors and statin prescription among statin eligible patients with diabetes at a specialised diabetes clinic in Botswana]
Discussion

Among patients with type 2 diabetes at a specialised diabetes clinic in Botswana, less than half of the statin-eligible patients received a statin prescription. The longer duration of diabetes, a higher baseline LDL-C and the presence of chronic kidney disease were independently associated with the tendency to prescribe statins.

The under-prescription of statins in our cohort is a concern since the use of statins appreciably reduces cardiovascular events and mortality in patients with diabetes irrespective of their LDL-C levels[7, 9-13]. Although the proportion of patients with diabetes who are prescribed statins varies substantially worldwide, there is a low prescribing of statins both in developing and developed countries[18, 19, 21-23, 41-44]. The percentage of patients with diabetes who received statins(45.5%) in our cohort is consistent with findings from developed countries where 25% to 73% of patients with diabetes are prescribed statins despite recommendations from the guidelines[18, 19, 41-43]. The proportion of participants with a statin prescription in our cohort was higher than those reported in some cohorts in developed countries, such as Germany (25%) and Great Britain (33%)[18, 41]. While the finding of a comparatively higher statin prescription in our setting than some other settings in developed countries is encouraging, there is no reason for complacency as more than half of our patients were without CVD protection by statins. Similar to developed countries, one potential explanation for low statin prescribing rates among our patients with diabetes is poor adherence to guidelines[22, 44-46]. While there may be a fear of the association of statin therapy with a slightly increased risk of developing diabetes, the benefits of statins in reducing cardiovascular morbidity and mortality among patients with established diabetes should dispel these concerns[7-9, 47]. Several epidemiological studies have observed a lower proportion of statin prescription in patients with diabetes in Africa (3% to 13%) than in our cohort[21-23]. In addition to poor adherence to guidelines, the main reasons for low statin prescribing in Africa include limited access to these medicines due to their high cost, lack of facilities for monitoring lipid profiles while patients are on treatment, and unavailability of guidelines[22]. The availability of free consultations, tests and medications in Botswana might explain our higher
statin prescribing rates than those in other African settings without universal health access. Irrespective of the reasons, it is imperative that statins are routinely prescribed to reduce the risk of CVD events in patients with type 2 diabetes[7-13, 15, 48].

Our results of increasing statin prescribing with increasing diabetes duration also agree with previous research findings[49]. This is reassuring as a longer duration of diabetes leads to an increased risk of CVD. For this reason, guidelines recommend statins for patients with diabetes for more than ten years[5, 6]. Although this finding may suggest that clinicians correctly recognise a longer duration of diabetes as an indication for statin therapy, the results tend to agree with the fact that transmission of information between clinicians and patients about new medications requires time[50].

Another finding in our study was that the presence of chronic kidney disease increased the likelihood of statin prescribing. This finding is also encouraging as statins reduce mortality by up to 36% in patients with kidney failure[5, 6, 51, 52]. Besides, this finding is consistent with SEMDSA guideline recommendations of a statin for every patient with diabetes and CKD[6]. While the presence of any albuminuria is another marker of renal kidney disease used as an indication of statin use in people with diabetes, dipstick proteinuria was not associated with statin prescribing in our cohort. We can postulate that clinicians do not recognise proteinuria as a predictor of CVD and an indication for statins in patients with diabetes. We will investigate this further as it contrasts with Berthold et al. who reported increased odds of statin prescribing in type 2 diabetes patients with proteinuria in Germany[18]

Our findings that a high baseline LDL-C increased the likelihood of statin prescribing agreed with those of Berthold at al. that showed an 11% increase in statin prescribing rates for every 0.26 mmol/L increase in LDL-C[18]. Besides, this finding confirms the observation from previous studies that prescribers tend to respond more to the pre-treatment LDL-C value than to the patients’ overall CVD risk profile as described in clinical guidelines [9, 45]. Although there is a lack of local guidelines, the clinic adopted the SEMDSA guidelines which recommend statins along with lifestyle changes regardless of cholesterol levels for all patients with diabetes aged > 40 with or without CVD[6]. Our findings that there is approximately a 50% increased likelihood
of statin prescription in our cohort may suggest a need for deliberate efforts for improving the understanding and implementation of the adopted guidelines, and we will be taking this further.

In most clinical guidelines, the presence of CVD, CKD, patients age, diabetes and presence of CVD risk factors such as hypertension, albuminuria and cigarette smoking are indicators of prescribing statins among patients with type 2 diabetes[5, 6]. The recommendations are based mainly on the rationale that the presence of any of the above factors is associated with an increased risk of CVD. Except for CKD and duration of diabetes, none of the other indications was a predictor of statin prescriptions in our cohort. Given the high prevalence of hypertension and other indications in our cohort, most participants would have qualified for statins if guideline recommendations were adhered to. As our clinic has adopted the SEMDSA guidelines, this finding is a concern and a call for efforts to improve its implementation for the benefit of this high-risk population. We will be following this up.

We are mindful of the limitations of our study. We estimated the baseline LDL-C levels by a 25% adjustment of measured LDL. There was a risk of either overestimation or underestimation of the baseline LDL-C in case of significant errors in our assumptions of the dosage and the adherence of atorvastatin. Although measured LDL-C results were available for all the included participants, HDL cholesterol results were mostly missing. Guidelines consider HDL as one of the factors for statin prescriptions in patients with diabetes. However, all other indications for statin prescriptions were available in our cohort. We did not document the dosage of statin used in our cohort; hence, we are unable to determine whether moderate to high-intensity statins were prescribed as recommended by the guidelines. The study was also performed in one leading clinic, hence limiting the generalizability of the study findings to other facilities in the country. However, being one of the few specialised diabetes clinics in the country, our results likely represent the ‘best’ quality of diabetes care in Botswana. Consequently, highlighted concerns are likely to be higher in non-specialist healthcare facilities treating patients with type 2 diabetes in Botswana.
Conclusion

In conclusion, we believe this study provides a useful and reliable picture of current statin prescribing behaviour in Botswana despite the limitations mentioned above. There is under-prescribing of statins in this high-risk population. The presence of CKD, high baseline LDL, and an increased duration of diabetes strongly influence statin prescriptions in patients with diabetes. Clinicians did not consider most guideline-recommended indications for statin prescription. By identifying gaps in the prescription of statins to patients with diabetes, the study provides a substantial opportunity for improvement in diabetes quality of care. Furthermore, the study findings suggest a need for further studies to investigate the reasons for statin under-prescription in our setting. We are following this up to provide future guidance for clinicians in Botswana treating patients with type 2 diabetes, with the results likely to be of interest to other sub-Saharan African countries with high rates of type 2 diabetes.

Abbreviations

ASCVD: atherosclerotic cardiovascular disease; BMI: Body mass index; CAD: coronary artery disease; CKD: chronic kidney disease; CVD: Cardiovascular disease; eGFR: estimated glomerular filtration rate; HDL-C: HbA1c: Haemoglobin A1c; HDL-C: High density lipoprotein cholesterol; HRDC: Health Research Development Committee; LDL-C: Low density lipoprotein cholesterol; MDRD: Modification of Diet in Renal Disease PAD: peripheral artery disease; SEMDSA: Society for Endocrinology, Metabolism, and Diabetes of South Africa WHR: Waist-Hip ratio.

Declarations

Ethics approval and consent to participate

The Health Research Development Committee(HRDC) of the Botswana Ministry of Health and Wellness(HPDME:13/18/1) and Stellenbosch University Health Research Ethics Committee (X19/01/001) approved the study. The participating patients provided written, informed consent in the primary study.

Consent for publication

Not applicable
Availability of data and material
The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request and with permission of the HRDC of Botswana Ministry of Health and Wellness.

Competing interests
The authors declare that they have no competing interests.

Funding
No funding was received.

Authors' contributions
JCM, BG and EMT conceptualized the study. JCM analysed data and drafted the initial draft. ETM and BG critically reviewed data and reviewed the manuscripts. All the authors read and approved the final manuscript.

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References


28. IDF Diabetes Atlas [https://diabetesatlas.org/IDF_Diabetes_Atlas_8e_interactive_EN/]


### Table 1: Demographic and clinical characteristics of patients with type 2 diabetes at a specialised Diabetes clinic in Gaborone (N= 477)

<table>
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<tr>
<th>Characteristics</th>
<th>All (N=477)</th>
<th>Males (n= 160)</th>
<th>Females (n= 317)</th>
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<tr>
<td><strong>Age, mean(SD), years</strong></td>
<td>60.3(10.8)</td>
<td>56.8(11.5)</td>
<td>62.0(10.1)</td>
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<tr>
<td><strong>Age &gt; 40 years n(%)</strong></td>
<td>461(96.7)</td>
<td>150(93.8)</td>
<td>311(98.1)</td>
</tr>
<tr>
<td><strong>Diabetes duration, median, IQR, years</strong></td>
<td>7(3-13)</td>
<td>8.9(3-14)</td>
<td>7 (3-13)</td>
</tr>
<tr>
<td><strong>Diabetes duration &gt; 10 years</strong></td>
<td>164 (34.4)</td>
<td>63(39.4)</td>
<td>101(31.9)</td>
</tr>
<tr>
<td><strong>BMI, mean (SD) kg/m²</strong></td>
<td>30.7(6.0)</td>
<td>29.0(5.2)</td>
<td>31.6(6.1)</td>
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<td>Normal weight n(%)</td>
<td>85(17.8)</td>
<td>39(24.4)</td>
<td>46(14.5)</td>
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<tr>
<td>Overweight n(%)</td>
<td>146(30.6)</td>
<td>59(36.7)</td>
<td>87(27.4)</td>
</tr>
<tr>
<td>Obese n(%)</td>
<td>246(51.6)</td>
<td>62(38.8)</td>
<td>184(58.0)</td>
</tr>
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<td><strong>Marital status</strong></td>
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<tr>
<td>Living alone n(%)</td>
<td>247(51.8)</td>
<td>47(29.4)</td>
<td>200(63.1)</td>
</tr>
<tr>
<td>Living with a partner n(%)</td>
<td>230(48.2)</td>
<td>113(70.6)</td>
<td>117(36.9)</td>
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<td><strong>Education status</strong></td>
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<tr>
<td>≤ Primary education, n(%)</td>
<td>306(64.1)</td>
<td>82(51.3)</td>
<td>224(70.7)</td>
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<tr>
<td>≥ Secondary or tertiary, n(%)</td>
<td>171(35.9)</td>
<td>78(48.7)</td>
<td>93(29.3)</td>
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<tr>
<td><strong>WHR, mean (SD)</strong></td>
<td>0.94(0.10)</td>
<td>0.97(0.08)</td>
<td>0.93(0.09)</td>
</tr>
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<td>Low WHR n (%)</td>
<td>79(16.6)</td>
<td>67(41.9)</td>
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<tr>
<td>High WHR n (%)</td>
<td>398(83.4)</td>
<td>93(58.1)</td>
<td>305(96.2)</td>
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<td><strong>Hypertension n (%)</strong></td>
<td>404(84.7)</td>
<td>120(75.0)</td>
<td>284(89.6)</td>
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<td><strong>Use of antihypertensive n (%)</strong></td>
<td>389(81.6)</td>
<td>110(68.8)</td>
<td>279(88.0)</td>
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<td><strong>Smoking n (%)</strong></td>
<td>16(3.4)</td>
<td>12(7.5)</td>
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<td><strong>Lipid-lowering medications n (%)</strong></td>
<td>224(47.0)</td>
<td>70(43.8)</td>
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<td>Statins n (%)</td>
<td>217(45.5)</td>
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<td>PAD n (%)</td>
<td>11(2.3)</td>
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<td>Coronary artery disease n (%)</td>
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<td>22(4.6)</td>
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<td><strong>CKD n (%)</strong></td>
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</tr>
<tr>
<td>Proteinuria n (%)</td>
<td>51(10.7)</td>
<td>27(16.9)</td>
<td>24(7.6)</td>
</tr>
<tr>
<td><strong>HbA1c mean (SD), %</strong></td>
<td>8.4(2.4)</td>
<td>8.5(2.6)</td>
<td>8.3(2.3)</td>
</tr>
<tr>
<td>Baseline LDL-C, mean (SD), mmol/L</td>
<td>3.1(1.2)</td>
<td>2.8(1.1)</td>
<td>3.3(1.2)</td>
</tr>
<tr>
<td>Normal</td>
<td>315(66.0)</td>
<td>113(70.6)</td>
<td>202(63.7)</td>
</tr>
<tr>
<td>High</td>
<td>59(12.4)</td>
<td>9(5.6)</td>
<td>50(15.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>103(21.6)</td>
<td>38(23.8)</td>
<td>65(20.5)</td>
</tr>
</tbody>
</table>

Table 2: Factors associated with statin prescription among statin-eligible patients with type 2 diabetes at a specialised Diabetes clinic in Gaborone (N = 477)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Statin not prescribed (n= 260)</th>
<th>Statin prescribed (n= 217)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>92(35.4)</td>
<td>68(31.3)</td>
<td>0.351</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>168(64.6)</td>
<td>149(68.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes duration, median, IQR, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration ≤ 10 years</td>
<td>179(68.9)</td>
<td>134(61.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration &gt; 10 years</td>
<td>81(31.1)</td>
<td>83(38.2)</td>
<td>0.104</td>
</tr>
<tr>
<td><strong>Age, mean (SD), years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤ 40 years, n (%)</td>
<td>12(4.6)</td>
<td>4(1.8)</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 40 years n (%)</td>
<td>248(95.4)</td>
<td>213(98.2)</td>
<td>&lt;0.094</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living alone n (%)</td>
<td>135(51.9)</td>
<td>112(51.6)</td>
<td>0.946</td>
</tr>
<tr>
<td>Living with a partner n (%)</td>
<td>125(48.1)</td>
<td>105(48.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Education status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Primary education, n (%)</td>
<td>166(63.9)</td>
<td>140(64.2)</td>
<td>0.879</td>
</tr>
<tr>
<td>≥ Secondary or tertiary, n (%)</td>
<td>94(36.1)</td>
<td>77(35.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension n (%)</strong></td>
<td>212(81.5)</td>
<td>192(88.5)</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>Antihypertensive use n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD, n (%)</td>
<td>20(7.7)</td>
<td>22(10.1)</td>
<td>0.538</td>
</tr>
<tr>
<td>PAD, n (%)</td>
<td>7(2.7)</td>
<td>4(1.8)</td>
<td>0.625</td>
</tr>
<tr>
<td>Coronary artery disease n (%)</td>
<td>6(2.3)</td>
<td>6(2.8)</td>
<td>0.751</td>
</tr>
<tr>
<td>Cerebrovascular diseases n (%)</td>
<td>9(3.5)</td>
<td>13(6.0)</td>
<td>0.190</td>
</tr>
<tr>
<td><strong>BMI, mean (SD) kg/m²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight n (%)</td>
<td>50(19.2)</td>
<td>35(16.1)</td>
<td></td>
</tr>
<tr>
<td>Overweight n (%)</td>
<td>79(30.4)</td>
<td>67(30.9)</td>
<td>0.669</td>
</tr>
<tr>
<td>Obese n (%)</td>
<td>135(47.9)</td>
<td>115(52.8)</td>
<td></td>
</tr>
<tr>
<td><strong>WHR, mean (SD) kg/m²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low WHR n (%)</td>
<td>46(17.7)</td>
<td>33(15.2)</td>
<td>0.467</td>
</tr>
<tr>
<td>High WHR n (%)</td>
<td>214(82.3)</td>
<td>184(84.8)</td>
<td></td>
</tr>
<tr>
<td><strong>CKD, n (%)</strong></td>
<td>20(7.7)</td>
<td>34(15.7)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Proteinuria, n (%)</strong></td>
<td>30(11.5)</td>
<td>21(9.7)</td>
<td>0.512</td>
</tr>
<tr>
<td><strong>HbA1c mean (SD), %</strong></td>
<td>8.4(2.6)</td>
<td>8.4(2.2)</td>
<td>0.948</td>
</tr>
<tr>
<td><strong>Baseline LDL-C mean (SD), mmol/L</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>2.9(0.9)</td>
<td>3.3(1.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>High</td>
<td>177(68.1)</td>
<td>120(55.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missing</td>
<td>66(25.4)</td>
<td>55(25.3)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Adjusted relative risks for associations between various factors and statin prescription among statin eligible patients with diabetes at a specialised diabetes clinic in Botswana

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Risk ratio</th>
<th>95% Conf. Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.006</td>
<td>0.994-1.017</td>
<td>0.362</td>
</tr>
<tr>
<td>CKD</td>
<td>1.354</td>
<td>1.055-1.738</td>
<td>0.017</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.336</td>
<td>0.846-2.110</td>
<td>0.213</td>
</tr>
<tr>
<td>BMI</td>
<td>1.014</td>
<td>0.994-1.034</td>
<td>0.16</td>
</tr>
<tr>
<td>High baseline LDL</td>
<td>1.488</td>
<td>1.173-1.887</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes duration, years</td>
<td>1.014</td>
<td>1.000-1.027</td>
<td>0.048</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0.979</td>
<td>0.644-1.488</td>
<td>0.922</td>
</tr>
<tr>
<td>CVD</td>
<td>0.901</td>
<td>0.623-1.303</td>
<td>0.581</td>
</tr>
</tbody>
</table>


Part B: Appendices

a. Relevant journal Instructions to Authors:

https://bmcendocrdisord.biomedcentral.com/submission-guidelines

Research article

Criteria

Research articles should report on original primary research, but may report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our editorial policies. Please note that non-commissioned pooled analyses of selected published research will not be considered.

BMC Endocrine Disorders strongly encourages that all datasets on which the conclusions of the paper rely should be available to readers. We encourage authors to ensure that their datasets are either deposited in publicly available repositories (where available and appropriate) or presented in the main manuscript or additional supporting files whenever possible. Please see Springer Nature’s information on recommended repositories. Where a widely established research community expectation for data archiving in public repositories exists, submission to a community-endorsed, public repository is mandatory. A list of data where deposition is required, with the appropriate repositories, can be found on the Editorial Policies Page.

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Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
  - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
  - or for non-clinical or non-research studies a description of what the article reports
- list the full names and institutional addresses for all authors
  - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the “Acknowledgements” section in accordance with the instructions below
- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow
the **CONSORT** extension for abstracts. The abstract must include the following separate sections:

- **Background**: the context and purpose of the study
- **Methods**: how the study was performed and statistical tests used
- **Results**: the main findings
- **Conclusions**: brief summary and potential implications
- **Trial registration**: If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our [editorial policies](#) for more information on trial registration.

**Keywords**

Three to ten keywords representing the main content of the article.

**Background**

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

**Methods**

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

**Results**

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

**Discussion**
This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text, they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and material
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was waived)
• include the name of the ethics committee that approved the study and the committee’s reference number if appropriate

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If your manuscript contains any individual person’s data in any form (including any individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.

You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication).

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All manuscripts must include an ‘Availability of data and materials’ statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):
The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

All data generated or analysed during this study are included in this published article [and its supplementary information files].

The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].

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With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]. [Reference number]
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All financial and non-financial competing interests must be declared in this section.

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**Funding**

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

**Authors’ contributions**

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Please use initials to refer to each author's contribution in this section, for example: "FC analyzed and interpreted the patient data regarding the hematological disease and the transplant. RH performed the histological examination of the kidney and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

**Acknowledgements**

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

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Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

References

Examples of the Vancouver reference style are shown below.

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Web links and URLs: All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and
the URL, as well as the date the site was accessed, in the following format: The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do. Accessed 20 May 2013. If an author or group of authors can clearly be associated with a web link, such as for weblogs, then they should be included in the reference.

**Example reference style:**

**Article within a journal**

**Article within a journal (no page numbers)**

**Article within a journal by DOI**

**Article within a journal supplement**

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**OnlineFirst chapter in a series (without a volume designation but with a DOI)**

**Complete book, authored**

**Online document**

**Online database**

**Supplementary material/private homepage**

**University site**

**FTP site**

**Organization site**

**Dataset with persistent identifier**

b. **Questionnaire/data capture instrument(s) (as prepared originally for protocol)**
   None, as this was a secondary data analysis

c. **Ethics consent form(s) (as prepared originally for protocol)**

   Attached – SU and Ministry of Health and wellness, Botswana
Approval
New Application

06/03/2019

Project ID: 8886

HREC Reference # X19/01/001

Title: Statin eligibility, and prescription among patients with Type 2 Diabetes in a specialised public clinic, Botswana.

Dear Dr Julius Mwita,

The New Application received on 28/02/2019 11:25 was reviewed by members of Health Research Ethics Committee via expedited review procedures on 06/03/2019 and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Period: 06 March 2019 to 05 March 2020

Please remember to use your project ID (8886) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review
Translation of the informed consent document(s) to the language(s) applicable to your study participants should now be submitted to the HREC.

Please note you can submit your progress report through the online ethics application process, available at: Links Application Form Direct
Link and the application should be submitted to the HREC before the year has expired. Please see Forms and Instructions on our HREC website (www.sun.ac.za/healthresearchethics) for guidance on how to submit a progress report.

The HREC will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval
Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research-approval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.
For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website https://applyethics.sun.ac.za/ProjectView/Index/8886

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,
Mrs. Melody Shana,
Coordinator,
HREC1

National Health Research Ethics Council (NHREC) Registration Number:
The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013), Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, the South African Department of Health (2006). Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition); as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.
Health Research and Development Division

Dr Julius C. Mwita
University of Botswana
Private Bag 00708
Gaborone

Dear Dr Julius C. Mwita

PERMIT: STATIN ELIGIBILITY, AND PRESCRIPTION AMONG PATIENTS WITH TYPE 2 DIABETES IN A SPECIALISED PUBLIC CLINIC, BOTSWANA

Your application for a research permit for the above stated research protocol refers. We note that your proposal has been reviewed and approved by University of Botswana Review Board.

Permission is therefore granted to conduct the above mentioned study. This approval is valid for a period of 1 year effective 23rd May 2019.

This permit does not however give you authority to collect data from the selected site(s) without prior approval from the management. Consent from the identified individuals should be obtained at all times.

The research should be conducted as outlined in the approved proposal. Any changes to the approved proposal must be submitted to the Health Research and Development Division in the Ministry of Health and Wellness for consideration and approval.

Furthermore, you are requested to submit at least one hardcopy and an electronic copy of the report to the Health Research, Ministry of Health Wellness within 3 months of completion of the study. Approval is for academic fulfillment only. Copies should also be submitted to all other relevant authorities.

Thank you for your cooperation and your commitment to the protection of human subjects in research.

Yours faithfully,

Ms S. Mosekanyane
for PERMANENT SECRETARY
d. **Selected tables or figures,**
   With brief explanatory text that would be useful for the examiner to see as part of the analyses, but which could not be included in the article for reasons of space. This should not simply be a collection of analysis printouts but should be readable as an addendum with reference to the article.
   None

e. **Any technical appendices needed – for example, laboratory techniques, statistical formulae.**
   None

f. **Acknowledgements**
   Part of the manuscript. This research project has been conducted as part of the academic requirements of the MSc in Clinical Epidemiology [www.sun.ac.za/clinepi](http://www.sun.ac.za/clinepi), Stellenbosch University.

g. **Turnitin report**
   Attached
<table>
<thead>
<tr>
<th>PRIMARY SOURCES</th>
<th>INTERNET SOURCES</th>
<th>PUBLICATIONS</th>
<th>STUDENT PAPERS</th>
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<tr>
<td>1 scholar.sun.ac.za</td>
<td>Internet Source</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>2 &quot;Abstracts 2007&quot;, Diabetologia, 2007</td>
<td>Publication</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>3 Heiner K Berthold. &quot;Patterns and predictors of statin prescription in patients with type 2 diabetes&quot;, Cardiovascular Diabetology, 2009</td>
<td>Publication</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>4 &quot;Minutes of the 44th General Assembly of the European Association for the Study of Diabetes&quot;, Diabetologia, 2009</td>
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<td>6 &quot;Minutes of The 43rd General Assembly of the European Association for the Study of Diabetes&quot;, Diabetologia, 2008</td>
<td>Publication</td>
<td>1%</td>
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<td>7 Submitted to University of Glamorgan</td>
<td>Student Paper</td>
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<td></td>
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<tr>
<td>8 &quot;Abstracts of the EASD, Stockholm 2010&quot;, Diabetologia, 2010</td>
<td></td>
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