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## The Use of High Intensity Statin Therapy with Simvastatin 80mg and Atorvastatin 80mg in Primary Care

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**The Use of High Intensity Statin Therapy with Simvastatin  
80mg and Atorvastatin 80mg in Primary Care**

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3 **The Use of High Intensity Statin Therapy with Simvastatin 80mg and**  
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5 **Atorvastatin 80mg in Primary Care**  
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2  
3 Disclosures  
4

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9

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11 on lipid guidelines.  
12

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14 declare.  
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27 Ethical Approval  
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29 The study was approved by the audit department of our department. The  
30 local research ethics committee is aware of the study.  
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### Abstract

Aims: Cardiovascular disease (CVD) is the most common cause of death worldwide. Pharmaceutical risk reduction with high-intensity statin therapy is advisable for high risk patients. Clinicians face a conflict between prescribing for cost (simvastatin 80mg) or for efficacy (atorvastatin 80mg). The aim of this audit was to examine the use, efficacy and tolerability of high intensity statin treatment (simvastatin 80mg; atorvastatin 80mg) in primary care.

Method: Electronic medical records were examined from two general practitioners' surgeries. Analysis involved Mann-Whitney U and Chi-squared tests.

Results: 116 patients had taken simvastatin 80mg or atorvastatin 80mg. Patients were similar between treatment groups: mostly male (62.9%), over 60 years old (68.1%) non-smokers (81.0%) taking statins for secondary prevention (56.9%). More patients on simvastatin withdrew from treatment due to inefficacy (49.3% versus 23.2%,  $p=0.025$ ) compared to the atorvastatin group. Furthermore, patients on simvastatin were more likely to be failing conventional targets of lipid control, compared with patients on atorvastatin 80mg (43.5% versus 21.3%,  $p=0.006$ ). Tolerability was similar between the two groups.

Discussion: UK guidelines recommend simvastatin 80mg as an economic choice, despite scant evidence at this dose and recent safety concerns. Conversely, robust evidence exists for atorvastatin 80mg. Head-to-head

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3 clinical trials or clinical studies comparing these agents are lacking. The  
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5 present study suggests that atorvastatin 80mg compares favourably to  
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7 simvastatin in terms of efficacy and has a similar tolerability profile.  
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12 Conclusion: This retrospective observational study suggests that despite  
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14 national guidelines, atorvastatin 80mg is used in clinical practice and is more  
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16 effective and at least as well tolerated as simvastatin 80mg.  
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3 What is already known about this topic?  
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6 The reduction of LDL-cholesterol with statins is well established in the  
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8 prevention of cardiovascular events. For high risk patients, national guidelines  
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10 recommend high intensity therapy with simvastatin 80mg but this regimen has  
11  
12 been the subject of recent safety concerns. Atorvastatin 80mg is an  
13  
14 alternative high intensity regimen with a robust evidence base. The tolerability  
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16 of high intensity statin therapy is limited by side effects such as muscle aches  
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18 and rarely myopathy and rhabdomyolysis.  
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24 What does this article add?  
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27 This study demonstrates the conflict prescribers face between prescribing  
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29 according to cost and guidelines (simvastatin) and prescribing for proven  
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31 efficacy (atorvastatin). This study shows that atorvastatin 80mg is being used  
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33 in general practice for primary prevention. We present the first retrospective  
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35 observational study comparing these agents and examining their use,  
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37 tolerability and efficacy in clinical practice in primary care.  
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43 Prior Publication  
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46 An earlier form of this study was submitted in abstract form to the HEART UK  
47  
48 conference and was presented in poster form at the conference on 9/7/2010.  
49  
50 The data was presented to a group of general practitioners locally on  
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52 21/4/2010.  
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## Introduction

Cardiovascular disease (CVD) which manifests primarily as coronary heart disease and stroke is the leading cause of illness and death in the UK and worldwide [1,2]. The most extensively researched of the pharmaceutically modifiable risk factors is cholesterol; in particular, the lowering of low-density lipoprotein cholesterol (LDL-C) forms the primary target of focus in CVD risk prevention [3,4]. Statins form the cornerstone of pharmaceutical CVD prevention and their efficacy in reducing mortality in both primary and secondary prevention settings is beyond dispute [5]. Clinical guidelines including those from the National Cholesterol Education Program (NCEP)[3] Joint British Societies (JBS) [4] and European[6] guidelines have recommended progressively lower LDL-C targets based on the evidence of the superiority of more intensive treatments.

When faced with a treatment decision clinicians have to weigh the relative benefits and risks of treatment. This decision is further confounded when the relative drug costs need to be taken into account. Up to a two fold difference in LDL-C lowering ability exists between some statins [7], however the differences between other statins are more subtle. The two most commonly prescribed statins in the United Kingdom (UK) and most other countries are atorvastatin and simvastatin [8], with the market leader, atorvastatin demonstrating superior efficacy. The patent for simvastatin expired in 2004 (UK) and 2006 (USA) making it a vastly cheaper treatment option compared to atorvastatin. This cost merit has been incorporated into the national guideline from the United Kingdom (UK) National Institute of Clinical



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3 Effectiveness (NICE) which recommends high intensity statin therapy with  
4 simvastatin 80mg for secondary prevention of CVD [9].  
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10 Atorvastatin 80 mg is a well-established treatment option for high risk  
11 individuals following the demonstration of its superior efficacy in the PROVE-  
12 IT (compared to pravastatin 40 mg) [10] and TNT (compared to atorvastatin  
13 10 mg) [11] studies. In contrast to this, data from the SEARCH trial which  
14 compared simvastatin 20mg to 80mg have raised concerns about the risk-  
15 benefit ratio of simvastatin 80 mg [12, 13]. Most recently, the United States  
16 (US) Food and Drug Administration (FDA) issued a warning about increased  
17 incidence of myopathy and rhabdomyolysis with simvastatin 80 mg compared  
18 with the 20mg dose [14]. In the United Kingdom, the Medicines and  
19 Healthcare products Regulatory Authority (MHRA) have advised a similarly  
20 cautious approach: "There is an increased risk of myopathy associated with  
21 high-dose (80 mg) The 80-mg dose should be considered only in patients with  
22 severe hypercholesterolaemia and high risk of cardiovascular complications  
23 who have not achieved their treatment goals on lower doses, when the  
24 benefits are expected to outweigh the potential risks" [15]. Subsequently,  
25 uncertainty prevails as clinicians who attempt to choose a safe, economic and  
26 effective statin medication for their patients are faced with conflicting evidence  
27 and guidelines. There is a lack of clinical evidence to guide statin use in  
28 current practice. Furthermore, no large-scale studies have compared the  
29 highest licensed doses for these two drugs, namely atorvastatin 80 mg and  
30 simvastatin 80 mg, although there has been a comparison in familial  
31 hypercholesterolaemia [16]. The aim of this audit was to examine the use,  
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3 efficacy and tolerability of high intensity statin treatment with simvastatin  
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6 80mg and atorvastatin 80mg in patients in primary care.  
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### Methods & Statistical Analysis

Patients who had ever been treated with atorvastatin 80 mg or simvastatin 80 mg were identified at two local general practitioners' surgeries in Hertfordshire, UK. The first surgery is a semi-rural practice of 16,000 patients based in an affluent village with 7 partners. It is a dispensing practice which is also involved in training. The second practice is based in a large town with 5 partners and is non-dispensing. The practice serves 9,300 patients in a lower demographic group and has a slightly larger proportion than average of patients who are elderly or with ischaemic heart disease or diabetes. Data was obtained through computer-based medical records and use of the hospital pathology database.

The Caldicott guardians for each of the surgeries were aware of the study and were satisfied with the methodology. According to the guidelines of the local ethics committee, this study was an audit and did not require formal research ethics approval. This methodology follows the audit cycle [17, 18]. This is a first cycle audit.

1: Identify audit topic or the problem to be addressed

The audit question was, 'Does local prescribing in primary care follow the NICE guidance?'

2: Set standards for acceptable care

As a measure of the adequacy of treatment, patients were allocated to groups depending on their serum lipid concentrations. Thresholds for lipid control

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3 were based on the Joint British Society guidelines [4] for audit thresholds and  
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5 were consistent with NICE guidance [9] that many patients fail to achieve the  
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7 stricter targets of TC <4 mmol/l and LDL-C <2 mmol/l, and more lenient  
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9 targets should be employed for audit purposes. Thus, patients with total  
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11 cholesterol (TC) <5 mmol/l and LDL-C <3 mmol/l were said to be controlled  
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13 according to audit thresholds. Patients with TC  $\geq$ 5 mmol/l or LDL-C  $\geq$ 3 mmol/l  
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15 were said to be uncontrolled. For blood results to be included in the study, the  
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17 patient had to have received four weeks' treatment with the medication prior  
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19 to the test being performed.  
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### 27 3: Data collection

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29 Data was collected from the surgeries by a single investigator and was  
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31 anonymised. Encrypted devices and secure NHS-based email accounts were  
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33 used to protect the data.  
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### 38 4: Data analysis

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40 Statistical analysis was performed using STATA 11 [19; Boston College  
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42 Department of Economics]. Categorical variables were described using  
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44 number and percentage and analysed for significance using Pearson's Chi  
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46 ( $X^2$ ) test. Continuous variables were described using medians and  
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48 lower/upper quartiles, and were analysed for significance using the Mann-  
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Whitney U test.

In order to ensure treatment effect estimates were not biased because  
of differences in the demographic and clinical makeup of the treatment

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3 groups, propensity score matching was employed to adjust for  
4 pre-treatment differences between the groups. Propensity score  
5 matching based on Mahalanobis distances was undertaken using the  
6 psmatch2 [19] command in STATA 11. The propensity score was derived  
7 using logistic regression, with the propensity score representing the  
8 conditional probability that they had received simvastatin given their age, sex,  
9 the surgery they were treated in, and whether they were taking the drug for  
10 primary or secondary prevention.  
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25 5: Implement change

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27 **We have sought to disseminate the information through a series of**  
28 **educational seminars for prescribers to encourage increased discussion**  
29 **of safe prescribing practices for hyperlipidaemia and cardiovascular**  
30 **risk. This information was also presented as a poster at the HEART UK**  
31 **conference annual conference of 2010.**  
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## Results

116 patients were identified who had ever been treated with simvastatin 80mg or atorvastatin 80mg. 47 patients had been treated with atorvastatin 80mg and 69 had received simvastatin 80mg. No major adverse cardiovascular events, such as myocardial infarction or stroke, had been recorded during treatment with atorvastatin 80mg or simvastatin 80mg.

### I: All patients ever receiving treatment (Table 1): atorvastatin 80mg versus simvastatin 80mg

Characteristics of all patients ever treated with atorvastatin 80mg and simvastatin 80mg are described in table 1. The treatment groups were similar in age, sex, body mass index (BMI), diabetes status and smoking status. Most patients were male (62.9%) non-smokers (77.3%), over 60 years old (68.1%) and taking a statin for secondary prevention (56.9%).

There was evidence that prescribers were using atorvastatin 80mg in primary prevention patients, contrary to recent guidelines. Indeed the proportion of patients on atorvastatin 80mg for primary prevention (34.0%) was statistically similar to the proportion on simvastatin (49.3%;  $p>0.1$ ). This highlights the value of clinical data and reflects the conflict clinicians face between prescribing according to cost and guidelines, or to superior efficacy.

Patients generally discontinued a medication due to intolerance or a lack of efficacy. The majority of patients discontinuing the medication due to intolerance reported mild muscle aches, fatigue or malaise (n=5 out of 8

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3 (62.5%) intolerant of atorvastatin; n=9 out of 11 (81.8%) intolerant of  
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6 simvastatin). Other adverse effects on atorvastatin 80mg included diarrhoea  
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8 (n=1), low mood (n=1) and gastric ulceration (n=1) in a patient with a history  
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10 of ulceration predating statin treatment. Among those patients treated with  
11  
12 simvastatin 80mg, other reasons for intolerance included abnormal liver  
13  
14 function tests (n=2) and gastrointestinal disturbance (also present in 2  
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16 patients with muscle aches). Levels of creatine kinase (CK) were checked in a  
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18 minority of patients (n=16) and none were significantly elevated to five times  
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20 the upper reference limit (Median 125.5, range 56-340 U/l; local reference  
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22 interval 24-195 U/l). Patients on simvastatin 80mg were significantly more  
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24 likely to discontinue therapy for any reason (p=0.025). Patients receiving  
25  
26 simvastatin 80mg were significantly more likely to be failing targets for  
27  
28 management, and were more likely to have to discontinue the medication due  
29  
30 to lack of efficacy compared with patients receiving atorvastatin (p=0.020).  
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32 There was no significant difference in treatment choice or statin performance  
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34 between the two general practitioners' surgeries.  
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44 Several patients discontinued medications for reasons other than intolerance  
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46 or inefficacy. Three patients discontinued simvastatin due to renal impairment  
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48 (n=1), interactions with other medications (n=1) and because the patient was  
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50 exceeding treatment targets (n=1). In the atorvastatin group, one patient  
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52 discontinued the medication due to renal failure and another due to poor  
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54 compliance.  
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3 Two logistic regression models were then constructed, one predicting whether  
4 patients were more likely to discontinue their medication for any reason, and  
5 another for whether they discontinued medication due to failing to meet  
6 cholesterol control targets, dependent on which medication they had been  
7 taking and their propensity score. According to the first model (table 2), the  
8 odds of a patient stopping therapy for any reason were significantly higher for  
9 patients taking simvastatin compared to atorvastatin when treatment was  
10 taken as an individual predictor ( $p=0.025$ ), but not in the model as a whole  
11 factoring in propensity scores ( $X^2 = 5.33$   $p=0.070$ ). According to the second  
12 model (table 3), the odds of a patient stopping therapy due to failing to meet  
13 cholesterol targets were significantly higher for patients taking simvastatin,  
14 both as an individual predictor ( $p=0.006$ ) and in the model as a whole once  
15 propensity scores were factored into the model ( $X^2 = 8.77$   $p=0.013$ ). The odds  
16 ratio of patients stopping therapy on simvastatin versus atorvastatin due to  
17 failing targets was 3.274 (95% CI: 1.395 – 7.683).  
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#### 41 II: Current treatment (Table 4): atorvastatin 80mg versus simvastatin 80mg

42 Patients currently receiving atorvastatin 80mg and simvastatin 80mg are  
43 described in table 2. The median duration of current treatment was 33 months  
44 (range 1-109 months). Patients in the two treatment groups were similar in  
45 terms of age, sex, BMI, diabetes status and smoking status. The atorvastatin  
46 group had a higher amount of patients taking other lipid-lowering therapies  
47 particularly Ezetimibe (n=13 on ezetimibe, n=1 on fenofibrate). Treatment  
48 groups had similar concentrations of total cholesterol, triglycerides, LDL-C,  
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HDL-C, ALT and GGT. There were no significant differences between level of control in treatment groups.

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## Discussion

In the UK, NICE seeks to guide clinicians towards clinically effective and economic choices for patient management. **The NICE guidance (May 2008) on lipid modification recommends simvastatin 80mg for secondary prevention and highlights the cost difference between a year's treatment with simvastatin 80mg (£64.53) compared with atorvastatin 80mg (£364.67) [9]. According to the September 2010 British National Formulary the cost difference has remained relatively unchanged, with a year's treatment with simvastatin 80mg now costing £35.28 compared with £338.52 for atorvastatin 80mg.** However, atorvastatin is supported by more robust evidence at this dosage, particularly for secondary prevention [10, 11]. When atorvastatin comes off patent in the next few years the cost difference between these medications will be significantly reduced. Until then, clinicians are faced with a conflict between prescribing for cost or for proven efficacy. This is particularly challenging for clinicians treating high risk patients, for whom the results of further cardiovascular events, loss of earnings and potential disability also have significant adverse economic effects which may justify using a more expensive preventative agent. Unfortunately, there are no head-to-head randomised controlled studies comparing high intensity atorvastatin and simvastatin. Additionally, there is little evidence about the relative merits of these agents in the setting of current clinical practice.

This study offers some comparison of high intensity atorvastatin with simvastatin in current clinical practice. Prescribers may find this 'real-life'

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3 approach useful when large-scale clinical evidence is lacking and clinical  
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5 guidelines are conflicting. This audit suggests that high intensity atorvastatin  
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7 is used in primary care, despite national guidelines which specifically  
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9 recommend simvastatin use [9]. In this study, patients on atorvastatin were  
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11 less likely to fail to meet targets of cholesterol and LDL-C control when  
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13 compared with simvastatin. This is consistent with other evidence supporting  
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15 the efficacy of atorvastatin [7, 10-11].  
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22 There are several limitations to this study. Importantly, it is a retrospective  
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24 study with no blinding or randomisation of treatment groups. There were very  
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26 few baseline lipid results available which limits any comparison of relative  
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28 efficacy of these medications on the basis of current lipid values. This is  
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30 because many patients had received statin treatment in some form for over a  
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32 decade, predating notation in current records. However, the comparison of  
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34 these agents, based on the need to discontinue therapy due to target failure  
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36 remains valid, although may be affected by differences of prescribing  
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38 behaviour and risk perception among prescribers. On data analysis, no  
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40 statistically significant differences among prescribing behaviour and treatment  
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42 effects were detected between the two general practitioners' surgeries.  
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51 **A further limitation to this study involves the significantly increased**  
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53 **usage of other lipid-lowering treatments in the atorvastatin group**  
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55 **(p=0.002). One must interpret the lipid concentrations with caution in**  
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57 **light of this confounding factor, and regarding the absence of pre-**  
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59 **treatment lipid values.**  
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3 There has been recent concern about increased incidence of myositis and  
4 rhabdomyolysis in patients receiving simvastatin 80mg [13-14]. This study did  
5 not identify any patients with myositis or rhabdomyolysis in either treatment  
6 group. Interestingly, creatine kinase (CK) was checked in a minority of  
7 patients only. There were no statistically significant differences in tolerability  
8 between the two treatment groups. Current guidance suggests that patients  
9 with muscle-related symptoms on a statin should have a CK checked [9].  
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22 In summary, this retrospective observational study describes routine clinical  
23 practice and highlights the conflict prescribers face with regard to high  
24 intensity statin use. Clinical trial evidence favours atorvastatin while  
25 simvastatin remains the economic option and is favoured by national  
26 guidelines. Patients receiving atorvastatin 80mg were significantly more likely  
27 to remain on the medication, achieving adequate cholesterol and LDL-C  
28 control, with no increase in intolerance when compared with patients treated  
29 with simvastatin 80mg.  
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Table 1: Characteristics of all patients ever treated with atorvastatin 80mg compared with simvastatin 80mg.

	Atorvastatin 80mg N=47 (%)	Simvastatin 80 mg N=69 (%)	Significance
Age			
<60 years	16 (34.0)	21 (30.4)	-
≥60 years	31 (66.0)	48 (69.6)	
Sex - Male	29 (61.7)	44 (63.8)	-
Primary Prevention	16 (34.0)	34 (49.3)	-
Secondary Prevention	31 (66.0)	35 (50.7)	
Diabetic	12 (25.5)	21 (30.4)	-
BMI			
<25	6 (12.8)	7 (10.1)	-
≥25	32 (68.1)	53 (76.8)	
Current smoker	9 (19.1)	13 (18.8)	-
Positive family history of IHD	27 (57.4)	31 (44.9)	-
Stopping therapy for any reason	11 (23.4)	34 (49.3)	$X^2(1, N=116)=4.9907, p=0.025$
Intolerant	8 (17.0)	11 (15.9)	$X^2(1, N=116)=0.0238, p=0.887$
Failed targets	1 (2.1)	20 (28.9)	$X^2(1, N=116)=5.3949, p=0.020$
Other reasons	2 (4.3)	3 (4.3)	-
Failing targets (previous and on-going treatment)	10 (21.3)	30 (43.5)	$X^2(1, N=114)=7.4916, p=0.006$
Surgery 1	21 (44.7)	40 (58.0)	$X^2(1, N=116)=1.9805, p=0.159$
Surgery 2	26 (55.3)	29 (42.0)	

Table 2: Logistic regression analysis of patients stopping therapy

Predictor	X <sup>2</sup>	df	p	Odds Ratio	95% CI
Constant	-	1	0.687	-	-
Treatment	-	1	0.025	2.397	1.118 - 5.142
Propensity	-	1	0.583	-	-
Test					
Hosmer & Lemeshow	8.79	8	0.360	-	-
Model X <sup>2</sup> (2, N=116) = 5.33, p = 0.070					

Table 3: Logistic regression analysis of patients stopping therapy due to failing targets

Predictor	X <sup>2</sup>	df	p	Odds Ratio	95% CI
Constant	-	1	0.545	-	-
Treatment	-	1	0.006	3.274	1.395 – 7.683
Propensity	-	1	0.321	-	-
Test					
Hosmer & Lemeshow	9.99	8	0.266	-	-
Model X <sup>2</sup> (2, N=116) = 8.77, p = 0.013					

Table 4: Characteristics of patients currently treated with atorvastatin 80mg and simvastatin 80mg.

	Current Atorvastatin 80mg n=43 (%)	Current Simvastatin 80mg n=35 (%)	Significance
Age <60 years	18 (40.9)	11 (31.4)	-
≥60 years	26 (59.1)	24 (68.6)	
Sex -male	28 (63.6)	23 (65.7)	-
Primary prevention	16 (36.4)	18 (51.4)	-
Secondary prevention	28 (63.6)	17 (48.9)	
BMI kg/m <sup>2</sup>			
<25	8 (18.2)	2 (5.7)	-
≥25	29 (66.0)	27 (77.1)	
Current smoker	8 (18.2)	10 (28.6)	-
Family history of IHD	26 (59.1)	15 (42.8)	-
Diabetic (Type 2 DM)	10 (22.7)	11 (31.4)	-
Lipids mmol/l	Median(LQ-UQ)	Median(LQ-UQ)	
Total cholesterol (TC)	4.4 (3.6-5)	4.4 (3.5-5.5)	Z(1, N=76)=0.540, p=0.589
Triglycerides	1.45 (1.11-2.11)	1.55 (1.08-2.27)	Z(1, N=66)=0.168, p=0.867
LDL-C	2.37 (1.78-3.19)	1.98 (1.48-2.58)	Z(1, N=43)=-0.869, p=0.385
HDL-C	1.35 (1.10-1.72)	1.31 (1.05-1.78)	Z(1, N=74)=-0.191, p=0.849
Chol/HDL ratio	3.3 (2.7-3.8)	3.3 (2.6-3.8)	Z(1, N=74)=0.131, p=0.896
Liver function			
ALT	30 (20-40)	23 (17-37)	Z(1, N=65)=-0.159, p=0.247
GGT	29 (24-68)	37 (22-62)	Z(1, N=42)=0.202, p=0.840
Alcohol consumption units/wk	2 (0-11.5)	7 (0-16)	Z(1, N=69)=1.114, p=0.265
Level of lipid control			
Controlled (TC <5, LDL-C <3)	31 (70.5)	22 (62.9)	X <sup>2</sup> (1, N=79)=0.8914, p=0.640
Uncontrolled (TC ≥5, LDL-C ≥3)	12 (27.3)	11 (31.4)	
Unknown	1 (2.3)	2 (5.7)	
On Ezetimibe	13 (29.5)	1 (2.9)	X <sup>2</sup> (1, N=79)=9.5224, p=0.002
On Fenofibrate	1 (2.3)	0 (0)	-

### Author Contributions

Claire Meek contributed to study design, collected and collated the data and wrote the final paper. Jonathan Reston did the statistical analysis for the data, helped with interpretation and reviewed the final paper. Hari Pathmanathan contributed to study concept and design, data collection and reviewed the final paper. Tim Ramsbottom contributed to data collection and reviewed the final paper. Adie Viljoen was primarily responsible for study concept and design and made significant contributions to writing and reviewing the final manuscript.

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