Original Research

Quality and efficiency of statin prescribing in South Africa

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Abstract

Introduction: Statins are recommended first-line treatment for hyperlipidaemia, with published studies suggesting limited differences between them. However, there are reports of under-dosing. South Africa has introduced measures to enhance generic utilisation. Part one documents prescribed doses of statins in 2011. Part two determines the extent of generics versus originator and patented statins in 2011 and their costs. Results: Underdosing of simvastatin in 2011 with average prescribed dose of 23.7mg; however, not for atorvastatin (20.91mg) or rosuvastatin (15.02mg). High utilisation of generics versus originators at 93% to 99% for atorvastatin and simvastatin, with limited utilisation of single sourced statins (22% of total statins - defined daily dose basis), mirroring Netherlands, Sweden and UK. Generics priced 33% to 51% below originator prices. Discussion: Opportunity to increase simvastatin dosing through education, prescribing targets and incentives. Opportunity to lower generic prices with generic simvastatin 96% to 98% below patented prices in some European countries.

Introduction

Statins (HMG CoA reductase inhibitors) are recommended as first-line treatment in patients with hypercholesterolaemia and are used extensively to reduce morbidity and mortality, especially in high risk patients and for secondary prevention (1-12). This follows the publication of outcome studies such as the 4S study and the heart protection study, both with simvastatin, as well as corresponding studies with other statins (5, 8, 9). Overall, statins lower blood cholesterol levels and reduce the relative risk of coronary events by approximately 30% in both primary and secondary prevention (4, 13).

Studies have suggested that there is little difference in effectiveness between the various statins at appropriate doses (14-18). This has resulted in initiatives among health authorities across countries to encourage the prescribing of low cost generic statins compared with single-sourced (patented) statins to

conserve resources without compromising care. Measures that have been instigated include educating physicians through academic detailing, formularies and guidelines, prescribing targets, therapeutic switching programmes, restricting the prescribing of patented statins to patients failing to reach target lipid levels with generic statins as well as delisting single-sourced statins from the current reimbursement list once generics became available. The latter happened in Germany as there was no demonstrable difference in outcomes between patented and multiple sourced statins (1, 12, 16-26).

Published studies such as the Heart Protection study have led respected guideline groups such as the Scottish Intercollegiate Guidelines Network (SIGN) group in Scotland to just recommend 40mg simvastatin for the prevention of cardiovascular disease as well as for primary prevention in patients with Type 1 diabetes. In addition, recommend 40mg simvastatin or 10mg atorvastatin for the prevention of cardiovascular disease in patients with Type 2 diabetes, irrespective of their starting lipid levels (9, 11, 12, 20). However, prescribed doses of statins have varied considerably across countries. For instance, a recent analysis of a cohort of patients aged 18 years or older in Finland showed that patients prescribed statins for the first time were typically initiated with either 10mg or 20mg simvastatin (94% of the cohort). In addition, a considerable proportion of patients initiated on statin therapy with less potent doses remained at the initial dose after 1 year (27). This suggested potential underdosing was common, even among patients with high cardiovascular risk (27). Similar findings were seen in Ireland, the Netherlands and the Stockholm Healthcare Region, Sweden, with the average dose of simvastatin for secondary prevention in patients in Ireland at 22mg (22, 28). In the Netherlands, many patients were prescribed starting doses at just over 15mg (mean dose 1.02 +/- 0.39 defined daily doses) (29). In the Stockholm healthcare region, the average prescribed dose of simvastatin was 20.4mg, with an appreciable proportion of patients prescribed only 10mg simvastatin (20, 22). There was also variable dosing of statins among the different regions in Norway. The authors found that patients in the high statin consumption regions in Norway had the highest prescribed daily dose (PDD) for simvastatin across all patients at 25.9 mg; similarly for atorvastatin at 21.9 mg. In addition, more users in the high consumption statin regions received statin tablets in the upper range of available strengths compared with the low consuming regions (30). There was also variable prescribed doses of statins in South Africa in the study of Raal et al (2) (Table 1), with low doses of simvastatin prescribed compared with recommended doses of 40mg in high risk patient groups such as those with diabetes (12, 31). However, higher doses of atorvastatin were prescribed (Table 1) (2).

Table 1 – Prescribed daily doses of simvastatin and atorvastatin in the study of Raal et al (2)

Statin	Number of patients	%
Simvastatin		
10mg	11	21.6
20mg	11	21.6
40mg	22	43.1
80mg	3	5.9
Atorvastatin		
10mg	13	7.7
20mg	53	31.4
40mg	79	46.7
80mg	16	9.5
other	8	4.7

In a more recent study conducted in South Africa by Raal and colleagues, 48% of patients did not reach target low-density lipoprotein cholesterol (LDL-C) levels (32). Any underdosing needs to be addressed as this significantly increases patients' risk of developing or progressing their cardiovascular disease with reduced cardioprotection (33). In addition, it puts them at risk for heart attack or stroke (4). Consequently, dyslipidaemia appears to remain a major cardiovascular risk factor in the South African population.

The next key issue for health authorities is to enhance the prescribing of low cost generics once they are available versus originators and single-sourced (patented) products in a class if all products in the class are seen as therapeutically similar at appropriate doses. This applies to the statins (14, 24). South Africa implemented mandatory generic substitution in May 2003, making it a legal requirement according to the Medicines and Related Substances Act (Act 101 of 1965) (34) to inform patients of the availability of alternative generic medicines to allow them to make informed choices. Alongside this, many medical aid schemes in South Africa will only reimburse the cost of the generic product with medicine selection for high volume low cost medicines generally based on price (35), and a co-payment is required from patients if they want to be prescribed and dispensed the more expensive originator product.

This paper will be divided into two parts. The first part will summarise published studies , regarding prescribed doses of statins including more recent findings in South Africa (36). This will be compared with countries that have increased doses of statins prescribed to provide future direction. The second part, which is an original study, will examine the extent of prescribing of generic versus originator statins as well as patented statins in the same year (2011) to determine whether further measures are needed in South Africa to enhance prescribing efficiency among patients enrolled into medical aid schemes. The authors would expect to see considerable utilisation of generic versus originator and single-sourced statins in South Africa. As a result, similar to the recent findings with the proton pump inhibitors in South Africa (37). This will also be similar to statin utilisation patterns in the Netherlands, Sweden and the UK after the introduction of generic simvastatin in these three countries with their extensive demand-side measures (1, 20, 21). The authors will also examine the utilisation of ezetimibe given current concerns and ongoing studies evaluating whether there is increased reduction in cardiovascular events with ezetimibide versus 40mg simvastatin (18, 38-42).

Part 1 - Published studies of statin dosing

The aim of the South African study published in 2014 was to analyse the prescribed doses of statins following an increase in the defined daily doses of statins (DDDs – the average maintenance dose per day for a medicine used for its main indication in adults (43, 44)), where the DDDs of five of the six statins were increased to reflect current dosing recommendations in January 2009 (36). This included atorvastatin, increased from 10mg to 20mg, and simvastatin, increased from 15mg to 30mg (36, 43).

This published study involved a retrospective, cross-sectional pharmacoepidemiological study on claims data from a medical insurance (medical aid) administrator in 2011 (36). The study covered patients whose medical records are administered by one of the medical aid scheme administrators (private insurance) in South Africa, with the database containing 2,298,312 records for medicine, medical devices and procedures. Each medication record contained information on the age and gender of the patient, with a unique number to identify each patient, the date of the prescription, detailed information on the dispensed drug, e.g. name, package size, formulation, strength and quantity, as well as the amount claimed and paid. A total of 4 805 patients (57% males) were prescribed 38 373 hypolipidaemic agents (Table 2). Statins constituted 94% of all prescriptions for lipid lowering drugs, with simvastatin contributing 67% of all statin prescriptions (Table 2). The findings can be considered representational of the South African private health care system with the database including patients from the different provinces.

Table 2 – Prescribing frequency (based on the total number of prescriptions) of hyperlipidaemic drugs in 2011 in South Africa (adapted from (36))

HYPOLIPIDAEMIC CLASSES	Number of patients	%
Fibrates	1 387	3.6
HMG CoA Reductase Inhibitors (statins). The breakdown of their prescribing was: • Atorvastatin – 16.2% • Fluvastatin – 0.9% • Lovastatin – 1.0% • Pravastatin – 0.8% • Rosuvastatin – 12.4% • Simvastatin – 66.7%	36 014	93.9
*Cholesterol Absorption Inhibitors (Ezetimibe alone or in combination with simvastatin)	818	2.1
Hypolipidaemic Agents (Others – including cholestyramine)	342	0.4
TOTAL	38 373	100

*NB Some of these patients are included in the simvastatin group as well

The average prescribed daily dose (PDD) of the statins was generally lower or in agreement with the revised respective DDD (Table 3). The exception was rosuvastatin whose average PDD was higher (Table 3). The average PDD of three most prescribed statins (Table 2) was simvastatin 23.7mg, atorvastatin 20.9mg, and rosuvastatin 15.0mg (Table 3). PDDs are defined as the average dose prescribed according to a representative sample of prescriptions, i.e. the average amount of a medicine actually prescribed in routine clinical practice.

Table 3 – DDDs and PDDs in mgs for the various statins in South Africa in 2011 (adapted from (36))

	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
DDD (mg)	20	60	45	30	10	30
Average PDD (mg)	20.91	57.29	26.31	25.35	15.02	23.7
PDD (Males) (mg)	21.6	55.59	28.33	25.74	15.97	23.8
PDD (Females) (mg)	19.84	55.59	28.33	25.74	15.97	23.8

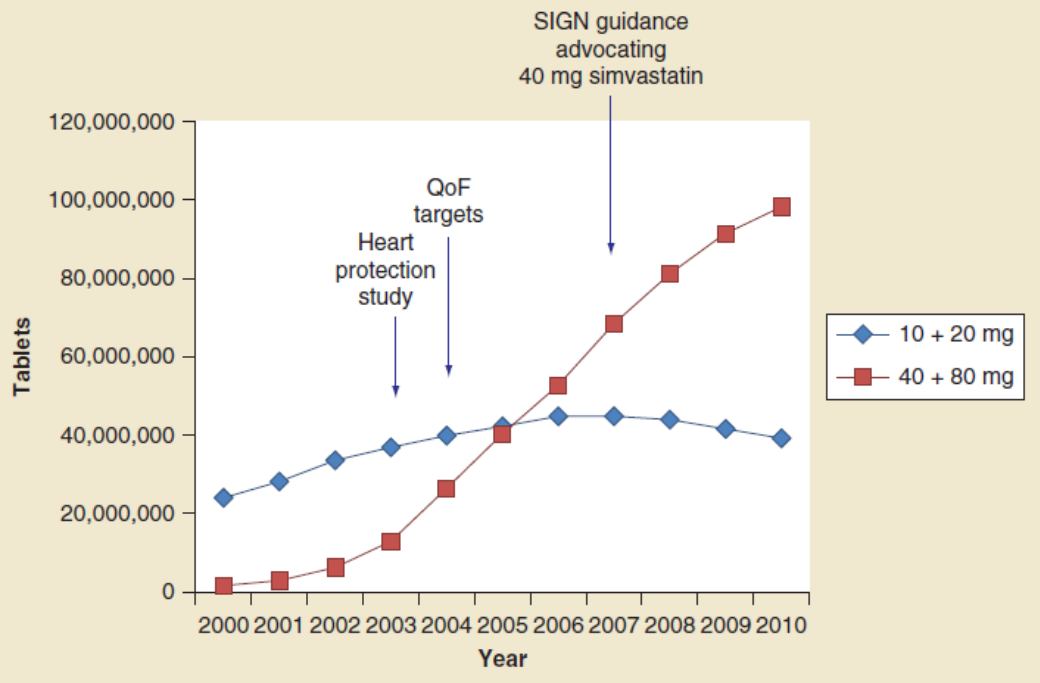
Table 3 shows that the PDDs of statins have increased in South Africa in recent years compared with a previous study conducted in the early to mid 1990s (45). In this study, the average PDD for simvastatin was 12.6 mg and for pravastatin was 12.5 mg. However, seemingly there has been limited change from the findings of Raal and colleagues in 2007 described in Table 1.

The limited utilisation of fibrates (Table 2) is welcomed with bezafibrate (accounting for 91% of total fibrates) showing no significant difference in five-year coronary event rates compared with placebo (9.4% reduction, $p = 0.26$) when used for secondary prevention (46).

Potential ways forward in South Africa to increase the prescribing of higher strength statins could include additional education initiatives including prescribing guidance encouraging the prescribing of higher doses of simvastatin as there appears to be limited problems with PDDs of atorvastatin or rosuvastatin, which are the next two most prescribed statins (Table 2). This advice builds on the findings in Scotland following the publication of the Heart Protection Study (9, 11, 12, 20). In addition, potential prescribing indicators for statins especially in secondary prevention (47). These initiatives could be combined with financial incentives for physicians to encourage them to treat patients to agreed target cholesterol levels. This is

the situation in the United Kingdom with the introduction of the Quality and Outcomes Framework (QoF), which includes patients with diabetes, hypertension and coronary vascular disease (1, 20, 23, 48). These combined factors enhanced the prescribing of higher strength simvastatin in Scotland (Figure 1), with similar findings for atorvastatin (20). These were similar to the findings in one English primary care group (23).

Figure 1 – Number of different strength simvastatin tablets dispensed in Scotland 2000 – 2010 (Reproduced with kind permission of the journal) (20)



Part 2 - Original research study

The same datasets used in the 2014 publication (36) were used to determine the extent of prescribing of the different statins, including both generic and originator statins, broken down by DDDs (43). Reimbursed expenditure/ DDD was also calculated in South African Rand (ZAR) to calculate price reductions between the originator and the generics and to compare with findings with price reductions seen in the Netherlands, Sweden and the UK. These three countries were chosen as aggressive pricing policies in these three countries have resulted in the prices of generic statins as low as 2% to 4% of the originator price prior to patent loss, i.e. prior to multiple sources becoming available (20-22).

Only data from chronic prescriptions, i.e. 28 or 30 days medicine supply per prescription, were used in the analysis to give an accurate picture of their long term use in the prevention of cardiac events in patients with cardiovascular disease.

Simvastatin dominated statin utilisation when prescriptions were converted to DDDs at 56% of total statins followed by 21% for atorvastatin and 20% for rosuvastatin. This is similar to the situation when prescription data was analysed (Table 2). Typically, statins were prescribed as the generic once they became available (Table 4), greatest for simvastatin at 99% of total simvastatin, with single sourced (patented) statins (rosuvastatin, pravastatin and lovastatin) accounting for 22% of total statin utilisation in 2011 (DDD basis).

Table 4 – Prescribing of generic versus originator statins (DDD basis) in 2011 in South Africa

Statin	% generic
Atorvastatin (4 branded generics)	93
Pravastatin (3 branded generics)	82
Simvastatin (15 branded generics)	99

There was also variability in expenditure/ DDD for originator and generic statins (Table 5). Price reductions for the generics varied between 33% and 51%, i.e. 67% to 49% of the originator prices.

Table 5 – Reimbursed expenditure/ DDD (ZAR) of the various statins in South Africa in 2011

STATIN	TYPE	Expenditure/DDD (ZAR)	% Reduction
Atorvastatin	ALL	3.92	
	ORIGINATOR	6.20	
	GENERICS	3.74	40
Fluvastatin	ALL	8.51	No generics
Lovastatin	ALL	8.00	No generics
Pravastatin	ALL	9.09	
	ORIGINATOR	12.46	
	GENERICS	8.34	33
Rosuvastatin	ALL	5.68	No generics
Simvastatin	ALL	2.09	
	ORIGINATOR	4.23	
	GENERICS	2.06	51

The appreciable prescribing of generic simvastatin at 99% of total simvastatin in 2011 (Table 4) is similar to the findings with generic lansoprazole and omeprazole at 98% to 99% of total prescriptions for these two PPIs in South Africa in 2010 (37). In addition, the low utilisation of singled sourced statins at 22% of total statins is similar to the low utilisation of esomeprazole (principal single sourced PPI) at 20% of total PPIs in 2010 (37) The high utilisation of generic simvastatin is similar to the situation in the England (97% of total simvastatin in 2007), Netherlands (98% of total simvastatin in 2010), Scotland (98% in 2010) and Sweden (98% of total simvastatin in 2007) (1, 20, 21). In the Netherlands, Sweden and the UK, there was also a reduction in the utilisation of patented (single-sourced) statins following the availability of generic simvastatin as a result of the instigation of multiple demand-side measures (1, 20, 21). This compares with France and Ireland where there was an increase in the utilisation of patented statins following generic simvastatin with their limited demand-side measures to combat the influence of the pharmaceutical companies (1). As a result, reimbursed expenditure on the statins in Ireland in 2007 with its limited demand-side measures and high prices for generics was over ten times that seen in Sweden when adjusted for population size. However, the population in Ireland had higher morbidity (1). This suggests that the reforms in South Africa to encourage the prescribing of low cost generics when available appear to be working well. This is further seen with the limited utilisation of ezetimibe alone or in combination at 2.1% of total lipid lowering drugs in 2011 (Table 2). This is welcomed given the current controversies surrounding the value of ezetimibe in clinical practice. This low rate was similar to the low utilisation of ezetimibe (alone or in combination) at 3% of total ezetimibe and statins (DDD basis) in England and Sweden in 2007 (1). This compared with France at 8% in 2007 with less demand-side measures to counter-act the marketing activities of the pharmaceutical company (1).

The appreciable prescribing of generic statins suggests there appears to be no problems with branded generic statins in South Africa. This mirrors the situation in Europe (1, 20-22, 49). The authors

acknowledge though that this cannot be said with complete confidence as no specific studies were undertaken comparing the outcomes of the different branded generic statins with their respective originators in South Africa. However, the findings suggest there should be no problems in routine clinical practice.

The domination of simvastatin in both prescriptions (Table 2) and DDDs compared with the findings of Raal and colleagues in 2007 (Table 1) may well be due to the earlier launch of branded generic simvastatin at lower costs than patented atorvastatin, with the lower expenditure/ DDD for generic simvastatin still persisting (Table 5). Again though the authors cannot say this with certainty as this was not specifically researched.

However, there does appear to be relatively high prices for generic statins in South Africa (Table 5). As mentioned, this compares with the low prices for generic simvastatin in the Netherlands, Scotland and Sweden at between 2% to 4% of the prices or the originator before patent loss, i.e. 96% to 98% price reduction, despite strict bioequivalence criteria (20-22). Further research has shown that population size does not appear to be a barrier to countries obtaining low prices for generics as seen in Lithuania and the Republic of Srpska (50, 51). Potential ways forward for South Africa to achieve lower prices for generics could include either instigating a prescriptive pricing policy for generics as seen in Austria (60% below pre-patent loss prices by the time the third generic is launched), France (55% below initially) or Norway (maximum of 85% below pre-patent loss prices for high volume generics); alternatively instigating aggressive market forces (52-55). Aggressive market forces could include increased transparency in the pricing of generics as seen in the UK with high International non-proprietary name (INN) prescribing rates coupled with regular requests for companies to provide data on the cost of producing generics as well as any rebates or discounts given to wholesalers or pharmacists to preferentially dispense a particular generic (20, 23). Alternatively, instigating tendering systems as seen in the Netherlands and Sweden (21, 55). In Sweden there are now monthly auctions whereby the manufacturer that wins the bid for their particular generic, typically the lowest bid, is guaranteed an appreciable percentage of prescriptions the following month (55, 56). These are considerations for the future.

There can also potentially be patient confusion if different branded generics each with different names are dispensed each time. This happens in Sweden (22, 56) if patients do not receive adequate information about their medicines (22, 57). As a result, potentially leading to either duplication of medicines; alternatively, patients not taking their prescribed treatments as directed; consequently, not gaining the most benefit (58). These scenarios are exacerbated if pharmacists lack training on how to handle concerns with substitution and/ or do not receive payment for providing relevant information to patients potentially limiting the time spent with them (57, 59). INN prescribing, apart from a limited number of well-known situations, is one way to address this as well as obtain low prices for generics when combined with increased knowledge on how the prices of generics are derived as well as any rebates and discounts in the system (23, 60). This has worked well in the UK with very high INN prescribing rates of 98 to 99% across a range of molecules (60).

The authors accept that the there are several limitations to the study. These include the fact that there was no clinical information or diagnoses available in the database, and that only patients served by the private health care sector in South Africa were included in the study. We acknowledge that tenders are used in the public sector in South Africa to enhance potential savings (35), and this currently includes 10mg and 20mg simvastatin, However, there is limited access to utilisation and expenditure data in the public sector and this is not routinely collected electronically (61); patient dosing data is also not accurately recorded electronically. Consequently, we are unable to compare the findings between the two sectors. Overall, the authors believe the findings are still valid and provide guidance to all the authorities in South Africa in the future, especially given the broad provincial coverage of the medical insurance data used in the analysis.

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Executive summary

- Statins are recommended as first-line treatment in patients with hypercholesterolaemia and are used extensively to reduce morbidity and mortality, especially in high risk patients and for secondary prevention. However, there are concerns with their underdosing including South Africa
- A study published in 2011 showed that there was underdoing of prescribed doses of simvastatin (23.7mg) but not for atorvastatin (20.91mg) or rosuvastatin (15.02mg). This needs to be addressed to help reduce coronary events in these patients, with potential activities including formularies, guidelines, prescribing targets and incentives mirroring the situation in the UK
- There have been recent reforms in South Africa to increase the prescribing of generics in a class. This includes mandated generic substitution as well as additional co-payments if patients want a more expensive product than the available generic
- These measures resulted in generic atorvastatin and simvastatin at 93% to 99% of total utilisation for these molecules (defined daily dose basis) in South Africa in 2011, with similar patterns seen in the Netherlands, Sweden and the UK. The utilisation of single sourced (patented) statins was only 22% of total statin utilisation (DDD basis) in South Africa in 2011, with low utilisation of ezetimibe (2.1% of total lipid lowering medicines)
- This low utilisation of single sourced statins as well as ezetimibe mirrors patterns in the Netherlands, Sweden and the UK with their multiple demand-side measures
- Prices of generic statins were 33% to 51% below originator prices in South Africa in 2011. This could be improved through a number of initiatives with prices of generic simvastatin at 96% to 98% below prices prior to the loss of patents in the Netherlands, Sweden and the UK through a variety of initiatives

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