

Prescribing trends of statins in Scotland: A drug utilization study

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Abstract

Statins are highly effective in managing hypercholesterolaemia in patients with or without chronic heart disease due to extensive evidence for safety, efficacy and cost effectiveness. Observational cross sectional retrospective cohort study was done in approximately 200 primary care practices in Scotland. Frequency, rates and time trends for statin prescriptions together with demographic data and the prescribing patterns for high dose simvastatin and newer statins in its place was measured. 63, 27, 5, 4 and 1% patients were prescribed simvastatin, atorvastatin, pravastatin, rosuvastatin and fluvastatin respectively (n = 1,91370). Prevalence for individual statin as well as for all statin prescriptions, significantly increased (p<0.05). Except rosuvastatin the incidence of other statins prescription significantly decreased (p<0.05). The highest number of patients, 884 (24%) switched to atorvastatin from high dose simvastatin. Increase in prevalent use and decrease in incident use of statins, implies the diminished cardiovascular disease related mortality and subsequent increased life expectancy of patients with cardiovascular disease.

Introduction

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality throughout the world. Approximately 17 million people die of CVDs each year, particularly heart attacks and strokes in both developed and developing countries. In 2007, in Scotland, 10,300 patients died from coronary heart disease (CHD) and 5,800 from cerebrovascular disease, from a combined 72,000 hospital admissions (SIGN, Management of coronary heart disease, 2010).

Lipid lowering agent, statins are the most used drugs in the UK and other part of the globe for the wide evidence of safety, cost effectiveness, potency in decreasing CHD and stroke risk both in primary and secondary cases (Mason et al., 2009; Mcelduff et al., 2006).

The daily dose of 40 mg simvastatin was suggested by NICE as the first-line treatment option for reducing the

CVD incidence. According to the NCEP ATP III guidelines 2004 (National Cholesterol Education Programme/Adult Treatment Panel III guidelines) (Grundy et al., 2004), in addition to the current goal of 100 mg/dL, the new goal for LDL-C has been recommended as 70 mg/dL for the patients with increased risk of CVD events. Multiple studies have demonstrated the incremental benefits with aggressive statin treatment over moderate statin therapy in high risk patients (Pedersen et al., 2005; Rosa et al., 2005). On the contrary high dose simvastatin (80 mg) may not be suitable for prescribing due to the risk of developing rhabdomyolysis (Lemos et al., 2004; Bruckert et al., 2005; SEARCH, 2010; Davidson et al., 2007)

The aims of this study were using a routinely collected prescribing database to assess the prescribing trends of statins in primary care throughout Scotland, together with demographic data and also the prescribed pattern



for high dose simvastatin and newer statins in its place.

Material and Methods

Using primary care data from the Primary Care Clinical Informatics Unit (PCCIU) database, we assessed patients' age in years (date was counted from the first date of prescribed statins) and sex of individual patients prescribed any statin, number of patients prescribed individual statin (simvastatin, atorvastatin, rosuvastatin, pravastatin and fluvastatin), percentages of patients prescribed high dose (80 mg) simvastatin and the patients those switched from high dose simvastatin to other statin within the study period. Patient's age was categorized into 6 categories; ≤ 40 years, 41-50, 51-60, 61-70, 71-80 years and >80 years. Age categorization was done due to age-standardized prevalence and incidence of CVD related diagnosis such as, angina, MI, heart failure, stroke frequently occurs within these age groups in the UK (Davis et al., 2007) and thereby individuals of this age range are commonly prescribed chronic medicine like statin. The PCCIU database contains prescribing information for approximately 1 million patients registered with 200 primary care practices and it covers around 20% of the Scottish population (The official gateway to Scotland, 2010) with regard to age, gender, deprivation, and urban/rural ratio mix. Currently PCCIU data is used by the Scottish Government, NHS Boards, charities, researchers and many others associated with the primary health care, Scotland (Primary Care Clinical Information Units, 2010).

Prescribing data for patients prescribed any statin and selective information regarding patient contacts with their primary care physicians for the 5 years, from March 1, 2005, to February 28, 2010, were extracted. This is the most current 5 years data available from the PCCIU database. To determine accurate prevalence of patients prescribed statins in the Scottish population, the periods between March 1, 2005, and August 31, 2005, and another period between September 1, 2009, and February 28, 2010 were assigned as wash out periods. Whereas, for determining the incidence, the period between March 1, 2005 and August 31, 2006 was framed as wash out periods. The actual study period for prevalence and incidence of the patients prescribed statin were from September 2005 to September 2009 and from September 2006 to February 2010 respectively. A switching period of 180 days was used to identify patients that switched from high dose (80 mg) simvastatin to low dose statins. Patients, those switched or did not switch to low dose within the 180 days switching period from the date of discontinuing high dose simvastatin were assigned as 'switched' or 'not switched'. Subgroup analysis was performed on patients (September 2005- August 2009), for whom data on

switching to low dose statin, their age group and gender was available. Another subgroup analysis was executed on patients (September 2005 - August 2009), for whom data on using of usual dose or high dose simvastatin, age group and gender was available. Number of patients prescribed high dose simvastatin and usual doses were described as 80 mg or low dose.

Patients started on the medicines of interest between September 1, 2005, and August 31, 2009, were identified and then tracked as an exposed cohort. The time between the first and last prescription for the specific statin was then determined. Patients' characteristics were summarized as means (SD), median and percentages.

Test of significance included the chi-square (χ^2 test), continuity correction, Fisher's exact test, pearson chi-square test. Curve estimation of linear regression analysis was also used to determine the significance value. A two tailed $p < 0.05$ value was considered significant. All statistical analysis was carried out using the SPSS version 17.0 software. Any records for a patient, dead or moved from the practice following discontinuation of the drug were excluded from the analysis. The study did not require ethical approval but it was reviewed and approved by the Primary Care Clinical Information Unit (PCCIU) advisory group.

Results

Interrogation of the PCCIU electronic prescribing database identified 191370 patients prescribed statins between March 2005 to February 2010, in which 120,278 (63%) patients were prescribed simvastatin, 52125 (27%) patients prescribed atorvastatin, 10247 (5%) patients prescribed pravastatin, 8005 (4%) patients prescribed rosuvastatin and 715 (1%) patients prescribed fluvastatin. 52% patients were males and 48% were female. The highest proportion of patients 30% were in 61-70 year age group and the lowest proportion 2% were in ≤ 40 year age group. The mean, median age and standard deviation of patients those were prescribed statins in the study period are detailed in Table I.

Patients those were prescribed simvastatin and atorvastatin, 48% (57,720) and 49% (25,652) were females respectively with the highest proportion lies in the 71-80 years age group, while 52% (62,558) and 51% (26,473) were males accordingly with the highest proportion in the 61-70 years group for both the drugs. For rosuvastatin, pravastatin and fluvastatin 49% female and 51% male were prescribed individual drugs, with the highest proportion lies in the 71-80 years age group in both the gender (Table I).

Prescriptions for simvastatin, atorvastatin, rosuvastatin increased gradually from 01/09/2005 to 01/09/2009

(Figure 1). This changes in the prevalence rate for the above three prescribed statins was significantly higher ($p<0.05$) at all the time points over the five year study period, while the prevalence rate of pravastatin and fluvastatin prescriptions significantly dropped ($p<0.05$). However, the cumulative changes in the prevalence rate for all the statin prescriptions was significantly higher ($p<0.05$) in the observed period. (Figure 1).

New prescriptions for individual statin reduced over the study period. This shifting in the incidence rate for the individual statin except rosuvastatin was significantly lower ($p<0.05$) at all the time points in the study frame. However, the cumulative changes in the incidence rate for all the statin prescriptions was significantly lower ($p<0.05$) in our study period (Figure 2).

An overall decrease in the percentages of patients prescribed high dose (80 mg) simvastatin is visible. However, this downward trend in the percentages of the patients was not significant ($p>0.05$) in our study period (Figure 3).

Among 3712 patients prescribed high dose (80 mg) simvastatin, 30% (1097) switched to other statin and of them maximum number 884 (24%) switched to ator-

vastatin (Table II).

Female patients and particularly 61-70 years age band were significantly more prescribed high dose simvastatin than males ($p<0.05$) (Table III).

Greater portion (52%) of the patients switched from high dose were female ($p>0.05$). Patients in the age group of 61-70 years, significantly more switched to low dose ($p<0.05$) (Table IV).

Discussion

CVD is a major cause of mortality and morbidity worldwide as well as in the UK. In the year 2000, death from CVD accounted for approximately 125000 in the UK (Wilson et al., 2003). Although coronary heart disease mortality rates have dropped in recent years in the UK, they remain still higher than the rest of the world. Incidence of CVD events is more frequent in younger male than female due to total cholesterol level increases steadily in males after the onset of puberty till the age of 50, then remains static until 70 years (Arnlov et al., 2006). Indeed, sex hormones accompanied with hypercholesterolemia and the genetic deficiency of

Drug	Age category						Mean/ Median age
	≤ 40	41-50	51-60	61-70	71-80	> 80	
<i>Simvastatin</i>							
Female	810 (0.7)	3,347 (2.8)	9,239 (7.7)	15,767 (13.1)	16,893 (14.0)	11,664 (9.7)	69.4 (12.3)
Male	1416 (1.2)	5710 (4.7)	13259 (11.0)	18981 (15.8)	15858 (13.2)	7334 (6.1)	65.8 (12.2)
<i>Atorvastatin</i>							
Female	320 (0.6)	1424 (2.7)	4234 (8.1)	7672 (14.7)	7880 (15.1)	4122 (7.9)	70.0
Male	613 (1.2)	2548 (4.9)	6155 (11.8)	8485 (16.3)	6458 (12.4)	2214 (4.2)	65.0
<i>Rosuvastatin</i>							
Female	60 (0.7)	253 (3.2)	754 (9.4)	754 (9.4)	1341 (16.8)	429 (5.4)	66.8 (11.2)
Male	124 (1.5)	485 (6.1)	1121 (14.0)	1121 (14.0)	1290 (16.1)	208 (2.6)	62.4 (11.4)
<i>Pravastatin</i>							
Female	40 (0.4)	170 (1.7)	623 (6.1)	623 (6.1)	1331 (13.0)	1142 (11.1)	73.0
Male	71 (0.7)	312 (3.0)	849 (8.3)	849 (8.3)	1568 (15.3)	740 (7.2)	71.0
<i>Fluvastatin</i>							
Female	4 (0.6)	17 (2.4)	45 (6.3)	45 (6.3)	105 (14.7)	61 (8.5)	71.0
Male	6 (0.8)	32 (4.5)	60 (8.4)	60 (8.4)	113 (15.8)	50 (7.0)	69.0

Data within parenthesis is percentage

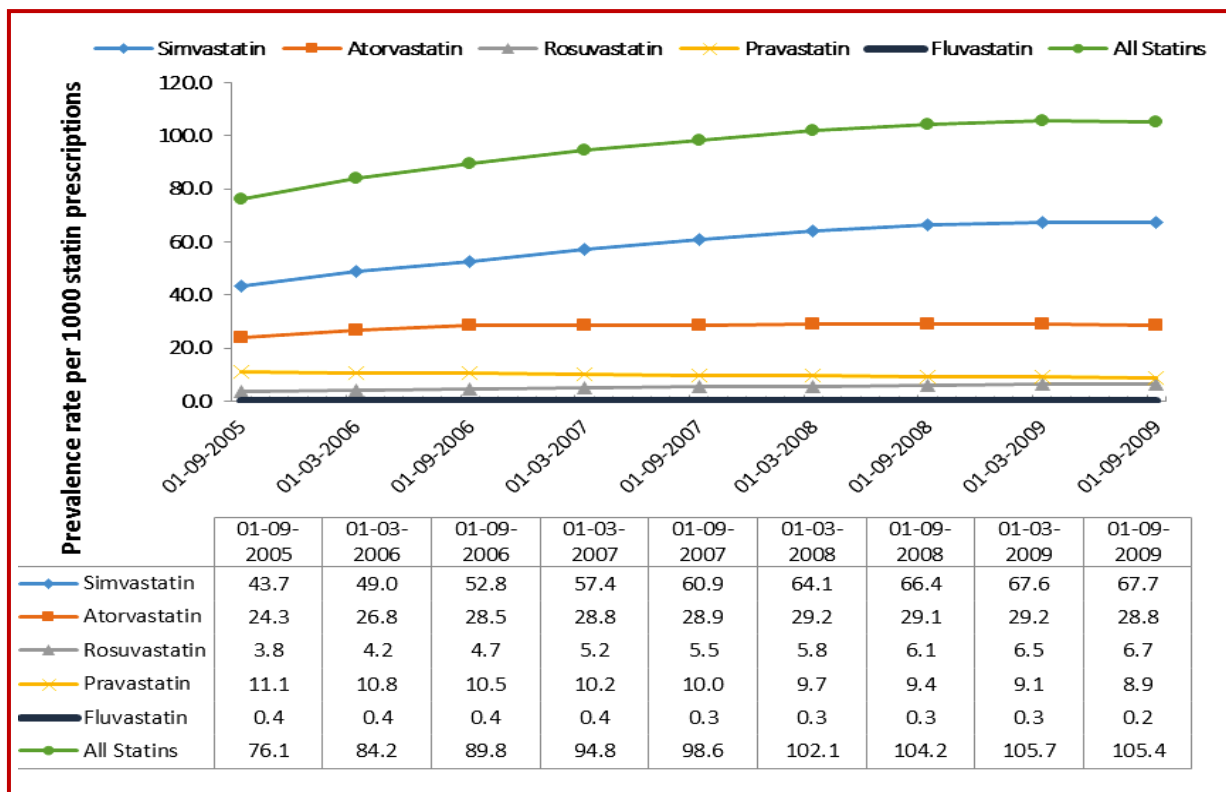


Figure 1: Prevalence rate per thousand statin prescriptions in Scotland from 2005 to 2010

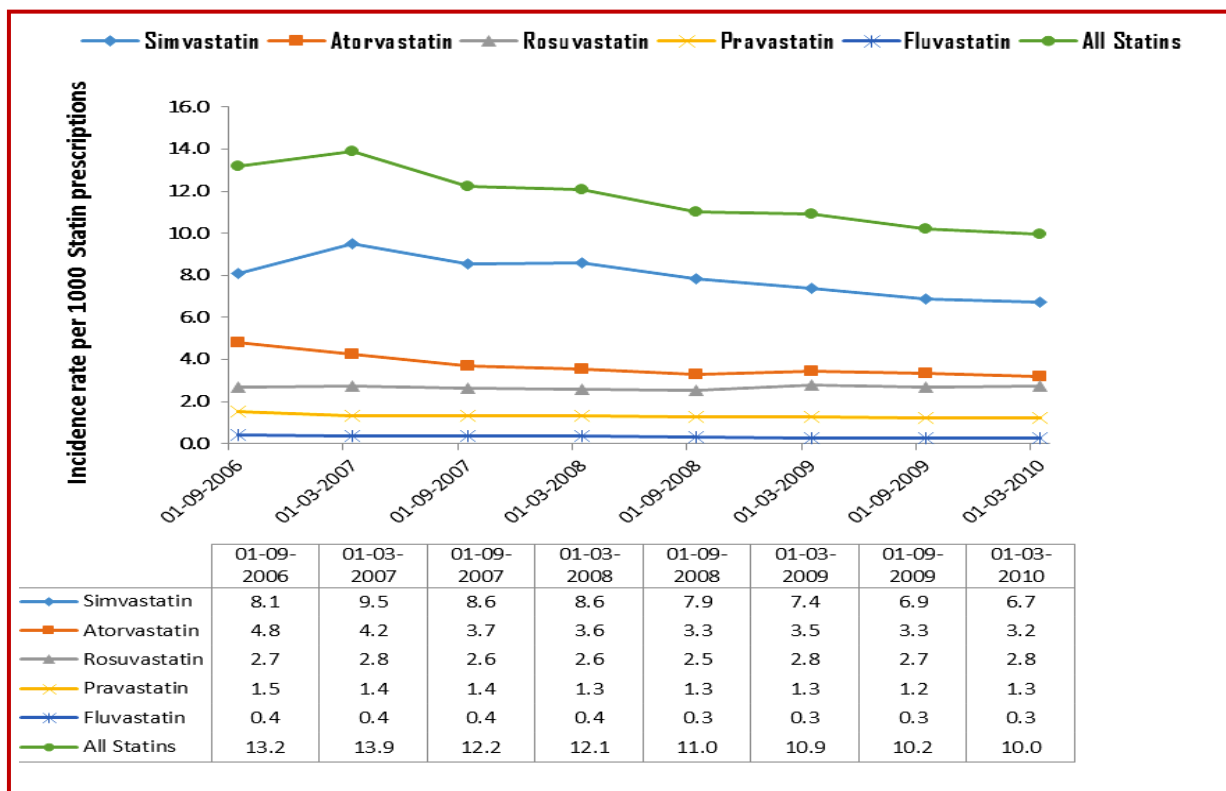


Figure 2: Incidence rate per thousand statin prescriptions in Scotland from 2005 to 2010

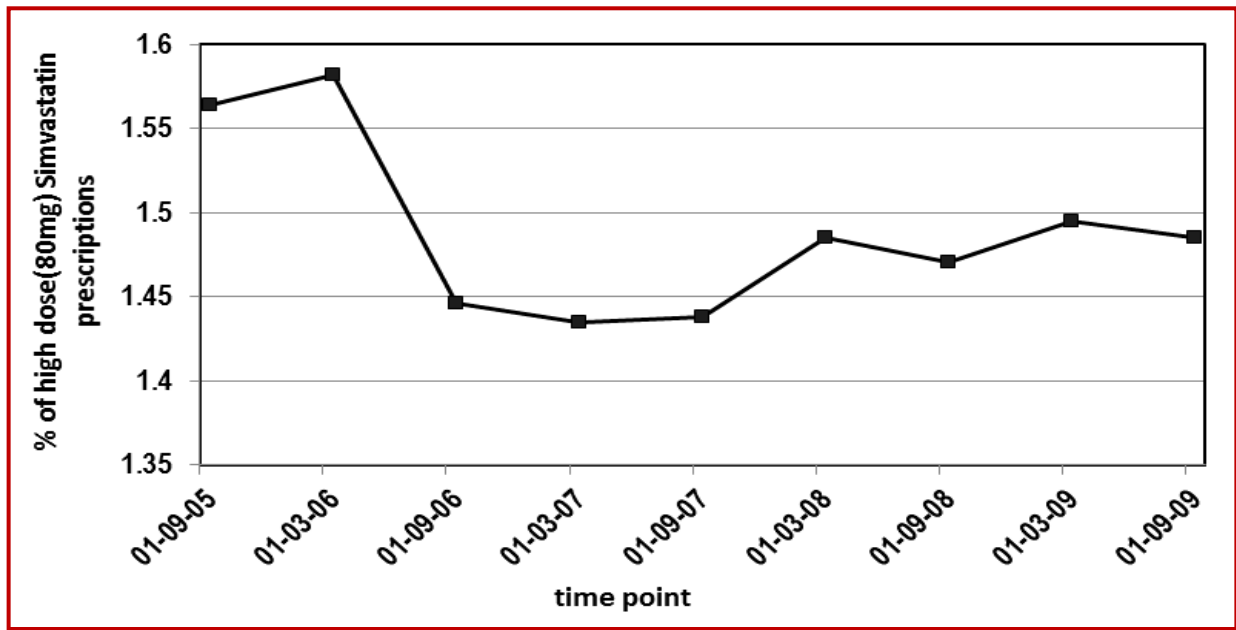


Figure 3: Percentages of high dose (80 mg) simvastatin prescriptions in Scotland on different time point

Table II

Frequency and percentage of patients switched to low dose statin from high dose (80 mg) simvastatin

Time period	Patients prescribed high dose (80 mg) simvastatin	Patients switched to low dose statin from high dose simvastatin (80 mg)							
		Atorvastatin		Rosuvastatin		Pravastatin		Fluvastatin	
		Frequen- cy	%	Frequen- cy	%	Frequen- cy	%	Frequen- cy	%
(01/09/2005-31/08/2006)	2170	249	11	23	1	9	0.4	-	-
(01/09/2006-31/08/2007)	561	269	48	44	8	3	0.5	2	0.4
(01/09/2007-31/08/2008)	493	197	40	41	8	2	0.4	-	-
(1/09/2008 - 31/08/2009)	488	169	35	42	9	3	0.6	-	-
Total patients (01/09/2005 - 31/08/2009)	3712	884	24	150	4	17	0.5	2	0.05

estrogens synthesis in male is substantially associated with the premature development of atherosclerosis and eventually CVD (Arnlov et al., 2006; Connor et al., 1990; Millias et al., 2006; Toth et al., 2007). In our study male patients were more prescribed statins than female (52 and 48% respectively) which can be explained by the above findings. A similar trend in the UK and in Scotland being also observed by Cappuccio et al. (2005) and Simpson et al. (2005).

The patent for simvastatin and pravastatin expired in 2003 and 2004 respectively in the UK and rest of the statins is only available as the branded version (Petty et al., 2008). Consequently, simvastatin and pravastatin are relatively inexpensive compared to other statins. NICE recommended physicians to prescribe these

drugs due to have similar efficacy as more expensive alternatives in achieving national cholesterol targets.

The UK government has also provided strong inducement for generic prescribing and usage through guidance (Kanavos et al., 2007). In the current study, in a total of 191,370 starting prescription, simvastatin stands for 63%, followed by atorvastatin 27%, pravastatin 5%, rosuvastatin 4% and fluvastatin is the least 1% only. These observations are in line with the recommendation of Department of Health in England and the NICE Guideline 67, (2008) for statin usage in primary care (Petty et al., 2008). However, the superior efficacy in low dose (Stein et al., 1998) and also for the cost effectiveness compared to the other branded version, atorvastatin may be the second most prescribed statin by the UK

Table III	
Proportion of female and male patients and their age group in Scotland those were prescribed simvastatin from 01/03/2005 to 28/02/2010	
80 mg simvastatin (n = 4,128)	Frequency (%)
<i>Age group</i>	
<=40 Years	46 (1)
41-50 Years	327 (8)
51-60 Years	929 (23)
61-70 Years	1,405 (34)
71-80 Years	1,054 (26)
>80 Years	367 (9)
<i>Gender</i>	
Male	2,011 (49)
Female	2,117 (51)
Low dose simvastatin (n = 116,150)	
<i>Age group</i>	
<=40 Years	2,180 (2)
41-50 Years	8,730 (8)
51-60 Years	21,569 (19)
61-70 Years	33,343 (29)
71-80 Years	31,697 (27)
>80 Years	18,631 (16)
<i>Gender</i>	
Male	60,547 (52)
Female	55,603 (48)

Table IV	
Proportion of female and male patients and their age group in Scotland those were Switched to other statins from high dose simvastatin from 01/03/2005 to 28/02/2009	
Patients switched from 80 mg simvastatin (n = 1053)	Frequency (%)
<i>Age group</i>	
<=40 Years	15 (1)
41-50 Years	107 (10)
51-60 Years	270 (26)
61-70 Years	364 (35)
71-80 Years	250 (24)
>80 Years	47 (5)
<i>Gender</i>	
Male	500 (48)
Female	553 (52)
Patients continued 80 mg simvastatin (n = 2,659)	
<i>Age group</i>	
<=40 Years	23 (1)
41-50 Years	164 (6)
51-60 Years	543 (20)
61-70 Years	912 (34)
71-80 Years	727 (27)
>80 Years	290 (11)
<i>Gender</i>	
Male	1,310 (49)
Female	1,349 (51)

general practitioners. Fluvastatin was the least preferred due to its lower efficacy and more costly than other (McDonald et al., 2008).

30 and 28% of the patients prescribed statins were in the 61-70 and 71-80 years age group; figures similar to the previously reported study by Maycock et al. (2002). Patients' mean ages were 65 ± 12 years, a figure similar to previously published data where adults aged ≥ 65 are the most susceptible for CVD; about 80% of cardiovascular deaths occur in these age groups and statin therapy effectively decreased CVD risk in this age group (Shepherd et al., 2002; Deedwania et al., 2007; 4S Study group, 1994). Patients aged >80 years were prescribed pravastatin more frequently close to the PROSPER trial (Shepherd et al., 2002).

The rate for prevalence of simvastatin prescription increased and at the same time incidence declined. Both these changes were significant ($p < 0.05$) at all the time points over the study period. The overall prevalence for patients prescribed simvastatin increased irrespective of declining in incidence, reflecting that a reduction in new prescription of simvastatin as other statins are

being increasingly favoured. However, due to the large number of patients are already on simvastatin and also for its cost effectiveness, excellent safety and efficacy profile in lowering LDL-C and the influence of NICE guidelines, prevalence continues to increase and it is the preferred statin to be prescribed by GPs in Scotland. The prevalence rate increased ($p = 0.02$) whereas incidence declined significantly ($p = 0.003$) of atorvastatin prescription. In the UK, atorvastatin is available as a branded name in the market for its patent protection. The high cost compared to generic simvastatin and for the NICE recommendations, patients to be started on statin therapy are usually not prescribed atorvastatin by GPs. The better efficacy of 10/20 mg atorvastatin than 20/40 mg of simvastatin, in the primary prevention of CVD (Weng et al., 2010) might be the reason for the second most common prescribed statin in Scotland. Furthermore, it can be assumed that with the expiry of the patent, prescribing of atorvastatin may sharply increase. Incidence rate of rosuvastatin prescription increased markedly ($p = 0.001$). Rosuvastatin is the third generation statin that got

approval from the FDA in 2003 and till date it is the most potent of the approved statins (Crouse, 2008). Regarding the efficacy, several clinical trials and meta-analysis demonstrated the superior efficacy of rosuvastatin 10 mg as starting dose than doses of atorvastatin, simvastatin and pravastatin in reducing LDL-C in hypercholesterolaemia (Hobbs et al., 2005). Literally, rosuvastatin is the only current statin that can reduce LDL-C >50% at such a dose as 20 mg (Catapano et al., 2005).

In spite of increasing evidences of rosuvastatin efficacy than other available statins, fewer patients were prescribed rosuvastatin in Scotland. This under prescription could be due to the lack of long-term safety data and is licensed for using in primary hypercholesterolemia only in the UK. Meanwhile, other available statins have long-term mortality and morbidity data and permitted to use both in primary and secondary CVD events prevention. NICE (2010) recommended that statin therapy should usually be started with a drug with a low acquisition cost; the expenditure for 5 mg rosuvastatin is £18.03 for 28 days, 13 times more costly than 40 mg simvastatin and £5 more costly than 10 mg atorvastatin for the same duration (Prescribing Indicators, 2010). Henceforth, GPs will be less inclined to prescribe rosuvastatin except when other statins are not well tolerated by patients. Both the prevalence and incidence rate of pravastatin prescriptions decreased in the study period ($p=0.001$ and $p=0.004$ respectively). Pravastatin represents the lowest potency statin. Ideally it needs to be taken 40 mg daily to achieve a 30% decrease in LDL-C level (Shepherd et al., 2002; Shepherd et al., 1995) whereas simvastatin, atorvastatin and rosuvastatin at 40 mg dose lowers the LDL by 37, 49 and 59% respectively (Davidson et al., 2007). Ohsfeldt et al., 2008 pointed out the 7% more efficacy of generic simvastatin than pravastatin in lowering LDL-C. Hence, pravastatin will be the less preferred statin as a first line drug for preventing primary or secondary CVD events. A downward trend was noted both in the prevalence ($p=0.001$) and incidence ($p=0.02$) rate of fluvastatin prescriptions. Although fluvastatin is one of the first marketed statins in the world, its effective dose range is still not fully explored; thereby making it as the lowest potency statin (McDonald et al., 2008). A daily dose of 80 mg fluvastatin can reduce 30% LDL-C, a very high dose compared to other marketed statins (Weng et al., 2010).

The cumulative prevalence rate for all statins increased by 28% ($p=0.001$). While, the incidence rate reduced by 24% ($p=0.001$). Packham et al. (2000) in Nottingham, Kucera et al. (2005) in the Czech population, Magrini et al. (1997) in Australia, Finland, Italy, Norway and Sweden, Jackevicious et al. (2003) in Canada noted a similar pattern of increased prevalent statin use. Due to the better survival of patients with previously

diagnosed CHD, GPs continued renewing the treatment resulting cumulative increase in prevalence rate. Concurrently, mortality declined among people with CHD in the Scottish population. The reduction in the mortality outweighs the newly diagnosed CHD and the combined effects in turn declines the incidence rate of statin prescriptions. Davies et al. (2007) in their study also documented a similar trend in the prevalence and incidence of CHD in the UK population.

While, many clinical trials (Cannon et al., 2002; Pedersen et al., 2005; Rosa et al., 2005) evidenced the incremental benefits of high dose statin therapy in lowering the LDL-C level especially in patients with CHD or diabetes, there is also manifestation (Lemos et al., 2004; Bruckert et al., 2005; SEARCH group, 2010) of increased rate of adverse events such as myopathy, elevation of hepatic transaminases leading to patients non adherence and treatment discontinuation. Recently, FDA has issued a warning for patients on 80 mg daily dose of simvastatin for the increased risk of myopathy and in the UK, the MHRA also suggested the GPs to review their patients who are on 80 mg simvastatin therapy based on new safety concern.

In the current study, a slight decreasing trend, 1.56% in 2005 to 1.45% in 2009 is visible in the percentages high dose (80 mg) simvastatin ($p=0.151$) prescriptions. Mohamed et al. (2011), in Scotland denoted a similar trend, where patients discontinued simvastatin within 3 to 6 months of treatment initiation due to adverse drug event. As there is increased data on association of high dose simvastatin and the adverse event, it can be anticipated that most of the patients discontinued were on high dose simvastatin. However, a slight upward trend from 2008 to 2009 in the percentage of prescriptions might be due to the release of NICE clinical guideline, 67; where GPs were suggested to prescribe patients with 80 mg simvastatin for secondary prevention of CVD. The percentages further decreased in the upcoming years suggestive of raised awareness from GPs regarding the issue of dose related toxic effect of simvastatin.

Female patients aged 61-70, were significantly more prescribed high dose simvastatin than male ($p<0.001$). This finding is similar to the study population of other large clinical trials namely SAGE (Deedwania et al., 2007), TNT (Rosa et al., 2005) and PRIMO (Bruckert et al., 2005). In all these trials, patients in this age group mostly benefited from intensive statin therapy.

Both in cumulative and individual year data analysis we found that most of the patients switched to atorvastatin from 80 mg simvastatin. Atorvastatin has long standing excellent safety and efficacy profile both in moderate to high dose in all age groups of patients. Many clinical trials (Rosa et al., 2005; Deedwania et al., 2007) and meta-analysis noted that 10-80 mg

atorvastatin can reduce LDL-C by 37-55% while 40-80 mg simvastatin reduces 37-42% LDL-C (Weng et al., 2010). Accordingly atorvastatin is the preferred switch drug for GPs, despite the high cost.

Analysing the switching data from high dose simvastatin we found that switching to rosuvastatin slowly increased, from 1% patients in 2006 to 9% in 2009. Jones et al. (2003) demonstrated that rosuvastatin provides 8% additional reduction of LDL-C at the same dose of atorvastatin. MERCURY I and II trial (Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapy) (Schuster et al., 2004; Izzat et al., 2006) illustrated that rosuvastatin is safe and effective to achieve the NCEP/ATP-III LDL-C targets for high risk patients with hypercholesterolemia even though switched from atorvastatin or simvastatin. Since unavailability of long-term safety or cardiovascular event data and the higher acquisition cost, made it less preferred by the GPs in Scotland as an alternative statin for switching. 61-70 years age group patient mostly switched to other statin ($p < 0.001$) which might be due to the association of drug related adverse effect and elderly physiological changes.

Conclusion

Increasing prevalence rate with the simultaneous reduction in the incidence rate for statin prescriptions being observed in Scotland, likely to be attributed to the decline in CHD mortality and subsequent increased survival of patients with CHD as well as the high efficacy and good safety profile of statins.

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