TITLE OF THE PAPER: Has cost inhibited the uptake of more potent statins in England?

RUNNING HEAD- Impact of generics on statins utilisation

NAMES OF AUTHORS: Stephen R. Chapman, Raymond W. Fitzpatrick, Mohammed I. Aladul

NAME OF INSTITUTION: School of Pharmacy, Keele University

CORRESPONDENCE: Stephen R. Chapman

School of Pharmacy, Keele University, Hornbeam Building 3.06, Newcastle-under-Lyme, Staffordshire, ST5 5BG, United Kingdom.

Tel: +44 (0)1782 734131

Fax: +44 (0)1782 733326

E-mail: [s.r.chapman@keele.ac.uk](mailto:s.r.chapman@keele.ac.uk)

KEY WORDS: simvastatin; atorvastatin; rosuvastatin; generics; prescribing pattern, drug utilization.

BULLET POINTS

* Simvastatin and atorvastatin are the most commonly prescribed statins since 1998.
* Statins had a significant budget impact on the UK national health system.
* Generic simvastatin and atorvastatin have reduced overall expenditure on these medicines in England.

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**ABSTRACT**

**Background:**The utilisation of statins has increased substantially over the last two decades in England and represents a significant cost burden to the NHS. Therefore, it is important to understand what influences prescribers choice.

**Objectives:** This study examines the changes in utilisation pattern of all statins in England (1998 – 2015). The study focuses on the utilisation of simvastatin and atorvastatin before and after their patent expiry and rosuvastatin, to investigate the impact of the reduced acquisition costs on prescribing.

**Methods:**Interrupted time series analysis of primary care utilisation data from thehealth and social care information centre database from 1998 to 2015.

**Results:**Primary care expenditure on statins increased by 125% during the period 1998 to 2004 driven by branded simvastatin and atorvastatin. Before 2003, the rate of utilisation of more potent branded atorvastatin exceeds branded simvastatin. Between 2004 and 2011 the less potent but less expensive agent generic simvastatin has the higher utilisation rate (66%). Since 2012, the more potent agent but less expensive generic atorvastatin has the higher utilisation rate (50%). The more potent branded, rosuvastatin failed to make a significant impact on the English statins market.

**Conclusion:**The availability of generic statins has reduced overall expenditure significantly. When there is a significant price difference, acquisition cost appears to be the main influencing factor in prescribing statins, but, when costs are similar potency is a key factor. This suggests that English prescribers are cost sensitive and appear to be prepared to trade marginal benefit for savings.

**INTRODUCTION**

During the last two decades, compelling clinical evidence has emerged for the use of statins in the primary and secondary prevention of cardiovascular events.[1-4] The clinical effectiveness, safety profile and long duration of action that allows single daily dosing have all resulted in a substantial increase in the use of statins in England.[5]Studies have shown that the utilisation of statins has increased since their introduction in 1990s, but, this utilisation varies considerably across the different European markets, with the highest use in the UK and lowest in France.[6-9] In the UK, statins dominate the lipid lowering market, and accounted for more than 90% of the overall expenditure on lipid lowering medicines in 2004 representing the largest annual drug cost to the NHS at £738 million.[5, 10] This has had a significant budget impact on the UK national health system (NHS).

The combination of the pivotal Scandinavian Simvastatin Survival Study (4S)[1] and the Heart Protection Study (HPS)[11]and the patent expiry of UK branded simvastatin in 2003[12]led the National Institute for Health and Clinical Excellence (NICE) guidelines to recommend using statins for secondary prevention (post myocardial infarction) and in primary prevention of cardiovascular diseases for adults with ≤ 20% ten years risk using the Framingham risk score.[13]

Studies have shown that rosuvastatin is more potent than atorvastatin, which is, in turn, is more potent than simvastatin in reducing total cholesterol, LDL-cholesterol, and triglycerides.[14-18] Intensive lipid lowering with potent statins (e.g. atorvastatin) has demonstrated beneficial effects in lowering mortality and morbidity after acute coronary syndrome, post myocardial infarction and coronary atherosclerosis.[19-21]

Since the patent expiry of branded simvastatin (Zocor) in 2003, branded statins, faced increasing competition from less expensive generic versions of these medicines. Generic statins were expected to continue to dominate this market since they were considered first line treatment for hyperlipidaemia when used as monotherapy.[22]

A number of studies have suggested the overall increase in statin utilisation may be due to a number of different factors including population ageing, health authority programs, outcome of clinical trials, guidelines and pharmaceutical industry marketing.[23-25, 9] Table 1 summarises the significant events and UK policy recommendations since the introduction of statins in the UK in the late 1980’s.

This study examines the changes in utilisation pattern of all statins in England between 1998 and 2015. The study focuses on the utilisation of simvastatin and atorvastatin (the UK market leaders) before and after patent expiry and the more potent agent rosuvastatin, to investigate the impact of the reduced acquisition costs on prescribing.

**METHODS**

**Data source**

The study was a retrospective analysis of primary care utilisation of statins in England. Primary care data on the annual volume and net ingredient cost of medicines was derived from the health and social care information centre (HSCIC) prescribing database.[32] This database captured information on all medicines dispensed by community pharmacies against prescriptions issued by general medical practitioners and non-medical prescribers (nurses, pharmacists) in England. Data was available from 1998 to 2015. The volume comparator was the defined daily dose (DDD), used by the World Health Organisation (WHO) and defined as the mean maintenance daily dose of a medicine for its principal indication in adults.[33] Primary care data were number of items issued and amount of drug in units. An item was defined as the drug name, dose and quantity prescribed on a UK FP10 prescription form.This was converted into defined daily doses using the following formula:

Drug usage (DDDs) =

Analyses in the study used the 2009 DDD indexes across the entire study period. The DDD index for atorvastatin is 20mg, rosuvastatin 10mg, and simvastatin 30mg. Prices of the individual preparations were expressed in sterling pounds. Primary care prices were the basic price of a drug excluding value-added tax (VAT) (the price listed in the national Drug Tariff or in standard price lists) and did not include any dispensing costs or fees.

**Statistical analysis**

Segmented regression analysis of interrupted time series data was used to examine the effects of the major changes in utilisation of the statins market leaders’ simvastatin, atorvastatin and the more potent agent rosuvastatin using Wagner et al’s method.[34] The effect was assessed by two parameters, level (β2 andβ4) and trend (β3 andβ5). The following segmented regression analysis equation was applied to each individual study outcome measure:

Yt = β0 + β1 X time + β2 X launch of generic simvastatin and rosuvastatin (2003) + β3 X time after launch of generic simvastatin and rosuvastatin + β4 X launch of generic atorvastatin (2012)+ β5 X time after launch of generic atorvastatin + et (Figure 3)

Yt is the annual outcome measure. Time was a continuous variable referring to time, in year, from the start of the observation period, ranging from 1 to 18 from the start to the end of the study period. The launch of generic simvastatin and rosuvastatin was a dichotomous variable (0 before 2003; 1 since 2003). Time after launch of generic simvastatin and rosuvastatin was a continuous variable beginning in 2003. Launch of generic atorvastatin was a dichotomous variable (0 before 2012; 1 since 2012). Time after launch of generic atorvastatin was a continuous variable beginning in 2012. β0 and β1 represent the intercept and trend over time during the pre-intervention period respectively. β2 represents the change in the level at the time of launch of generic simvastatin and rosuvastatin and β3 represents the trend change in the slope after launch of generic simvastatin and rosuvastatin, both compared to those in the pre-intervention period and β4 represent the change in level at the time of launch of generic atorvastatin. β5 represent the change in slope after launch of generic atorvastatin. et represents the error term.

For branded simvastatin and atorvastatin (Zocor® and Lipitor®), the effects of two interventions were assessed (with the respective coefficients β4 and β5): (1) marketing of generic simvastatin and (2) marketing of generic atorvastatin. For branded rosuvastatin and generic simvastatin, the effect of one intervention was studied (marketing of generic atorvastatin). Finally, for generic atorvastatin, only the effect of generic atorvastatin itself was studied.

Average strength per prescription for each statin was calculated by using the formula:

Average strength =

Paired t-test was used to compare the mean average strength between branded and generic statins where *p*<0.05 was considered statistically significant. All calculations were performed using Microsoft Excel 2013 and STATA MP 13

**RESULTS**

**Statins prices**

Table 2 shows that the prices of branded simvastatin (Zocor)®, branded rosuvastatin (Crestor)®, branded cervistatin (Lipobay)® and branded fluvastatin (Lescol)® were not changed significantly during the study period, which gave a relatively flat pricing structure regardless of dose. Generic simvastatin, atorvastatin, fluvastatin and pravastatin prices gradually decreased since their introduction. In contrast, branded atorvastatin (Lipitor)® and branded pravastatin (Lipostat)® 40mg prices reduced sharply from 2003, thereafter, prices reduced gradually.

**Expenditure of statins in primary care**

Primary care expenditure on statins increased steadily by 125% during the period 1998 to 2004 from £170,388,500 to £738,114,800. This was driven by Zocor®, generic simvastatin, and Lipitor® (Figure 1). Between 2004 and 2011, the higher unit cost of Lipitor® made it cost dominant, whilst overall expenditure on statins decreased gradually to £433,297,000 in 2011 following the price reduction of generic simvastatin (Table 2 and Figure 1). Post 2012, expenditure on statins declined sharply as a result of the decreased expenditure on Lipitor® following the introduction of generic atorvastatin. Expenditure on Crestor®, increased following its launch in 2003, but, has remained relatively flat since 2007 (Figure 1).

**Volume of utilisation**

Statins utilisation in primary care in England increased dramatically by 185% from 110,785,000 DDDs in 1998 to 2,691,077,000 DDDs in 2015. Zocor® and Lipitor® represented 75% - 85% of utilised statins between 1998 and 2003 (Figure 2). Following the patent expiry of Zocor® in 2003, generic simvastatin completely replaced Zocor® achieving 66% of the statins market share by 2011. Following the patent expiry of Lipitor® in 2012, and the availability of a generic version, the volume of utilisation of atorvastatin started to increase again and by 2015 reached 50% of the market share in primary care (Figure 2). The utilisation of other statins was relatively small compared to simvastatin and atorvastatin throughout the study period.

**Segmented regression of interrupted time series**

*Pre-generic market phase (1998–2002)*

The trend of interrupted time series analyses (Table 3) indicates that the annual utilisation of all strengths of Zocor® and Lipitor® rose before 2003 as shown by the change in slope β1. This annual increase was statistically significant for all strengths with the exception of Lipitor® 40mg and 80mg. During this period Lipitor® showed increased annual utilisation compared with Zocor® as demonstrated in β2 value (Table 3).

*Post-generic simvastatin market phase (2003-2011)*

The change in trend (β3) showed a significant increase in utilisation of generic simvastatin (Table 3) (with the exception of generic simvastatin 10mg). There was also a significant negative impact on the level (β2) and trend (β3) of utilisation of all strengths of Zocor® and low doses of Lipitor® (10mg and 20mg). The trend for high dose Lipitor® (40mg and 80mg) increased during this phase together with the newly marketed Crestor®.

*Post-generic atorvastatin market phase (2012-2015)*

Once generic atorvastatin, was available, there was a significant increase in the utilisation trend (β5) (with exception of generic atorvastatin 10mg) which had a significant negative impact on the level of utilisation (β4) of all strengths of Lipitor®, Crestor® and low dose generic simvastatin with a negative impact on the trend of utilisation (β5) of Lipitor®, Crestor® and generic simvastatin. There was a negligible positive effect on Zocor® as a result of the very low volume of utilisation at that period (Table 3 and Figure 3).

Table 4 shows the average strength of statins prescribed by year since 1998. The annual average strengths of prescribed simvastatin increased following the introduction of generic simvastatin. The annual average strengths of prescribed generic simvastatin were significantly higher than branded simvastatin (*p*<0.005). Similarly, the annual average strengths of prescribed atorvastatin increased following the introduction of generic atorvastatin and the annual strengths of generic atorvastatin were significantly higher than branded atorvastatin (*p*<0.05). The annual average strengths of Crestor® have remained stable since its introduction (Table 4).

**DISCUSSION**

Expenditure on statins has been a significant contributor to the increasing burden on the NHS budget exceeding £600 million in 2004. The main drivers of increased expenditure were: (i) increased utilisation of statins overall between 1998 and 2015 (Figures 1 and 2) and (ii) utilisation of more expensive branded agents (Zocor®, Lipitor® and Crestor®) (Figure 2). Increased statins utilisation has been reported in many studies across Europe, Australia, and China in recent years.[6, 35-38] This increase was attributed to the aggressive utilisation of statins for primary and secondary prevention of coronary heart disease.[39-41] The impact of branded statins on expenditure in our study is similar to the findings from a Swedish study i .[42] The price of generic simvastatin fell sharply during the study period as a result of the competition between generic manufacturers. This was in line with Cook et al’s work describing the large number of competitors producing generics after the patent expiry of 11 out of 13 blockbuster agents just two months after patent expiry.[43] The availability of less expensive generic simvastatin reduced expenditure as it replaced branded simvastatin (Table 2 and Figure 1). Expenditure on statins was reduced further with the availability of generic atorvastatin (Figure 1). Although the utilisation of statins continued to increase during the post generic atorvastatin phase, the overall expenditure decreased dramatically as a result of genericisation of simvastatin and atorvastatin in the market (Figure 2).

Segmented regression was used to identify the effect of the availability of generic simvastatin and atorvastatin (the market leaders) and the more potent rosuvastatin on the utilisation of different doses of these medicines. This analysis compared the pattern (trend) and level of utilisation before and after each patent expiry and drug launch.

The segmented regression analysis suggests that potency and unit cost were the key influencing factors for choosing statins over the last 18 years in primary care in England. Policy changes such as NICE guidance and National Service Framework appeared not to have influenced the utilisation of statins (Figure 2).

During the pre-generic phase, when prices were similar, the annual growth of branded atorvastatin (the more potent agent) exceeded branded simvastatin, suggesting that prescribing decisions were based on potency (Figure 3 and Table 3). In the post-generic simvastatin market phase, the availability of the less expensive generic simvastatin reduced the utilisation trend of all strengths of Zocor® and low doses Lipitor® (Table 3). Internationally, financial incentives result in governments promoting prescribing of medicines by international non-proprietary name to encourage utilisation of generics.[44-48] In England NICE guidance recommended prescribing statins with the lowest acquisition cost and the availability of the lower price generic simvastatin compared to other statins, resulted in the complete substitution of branded simvastatin, and to a lesser extent, low dose of branded atorvastatin with generic simvastatin (Figure 2). This reflects the findings from utilisation studies of statins in Scotland and Sweden where simvastatin had the majority of market share (63% and 83% respectively).[35, 42] The growth in utilisation of generic simvastatin 40mg (Figure 3 and Table 3) prior to the availability of generic atorvastatin is in line with NICE technology appraisal guidance TA94 (2006) that recommended statins for primary prevention of cardiovascular disease and guideline CG67 (in 2008) that recommend simvastatin 40 as a first line treatment.[27, 13] Interestingly changes in the utilisation of low cost generic simvastatin occurred before the publication of these policies (Table 1 and Figure 2). This suggests that the prescribing decisions during this phase were based on price rather than potency. Interestingly, the growth of high dose branded atorvastatin (40mg and 80) also increased (Table 3), as the price of these doses reduced (Table 2). Despite the fact that rosuvastatin was more potent than other statins,[49] with a modestly lower price than branded atorvastatin, its utilisation was limited (Figure 2). This implies that either cost reductions were not sufficient or that the perceived lack of safety data on long-term use inhibited prescribers.[50]

In the post-generic atorvastatin market phase from 2012 and following the availability of generic atorvastatin at prices similar to generic simvastatin, the statins market reverted to the pattern seen in the pre-generic phase. Generic atorvastatin entirely replaced branded atorvastatin (Lipitor)® and to a lesser extent generic simvastatin, to became market dominant in 2015 (Figures 2, 3 and Table 3). This result was also in line with revised NICE guideline CG 181 (in 2014) [31] that recommended the use of atorvastatin in primary and secondary prevention of cardiovascular diseases and key clinical trials, IDEAL [51] TNT [52] and PROVE-IT-TIMI22 [53] which all identified an effect of high-dose atorvastatin in secondary care prevention. Similarly to generic simvastatin the utilisation of generic atorvastatin started to increase before the publication of this guidance. This suggests that when price was not a factor, potency was influencing prescribing decisions (Figure 2).

Interestingly, the segmented regression analysis also showed that with the availability of generic versions of statins, the utilisation of higher doses increased. Before 2003, Zocor 20mg had the highest annual growth, but with the availability of generic simvastatin, 40mg doses had the highest growth (Table 3). This is confirmed in Table 4 which shows the average strength of statins prescribed following the marketing of generic simvastatin and atorvastatin increased significantly. This elevation of the average strength of prescribed statins indicates that higher doses with increased potency were chosen. This finding reinforces the hypothesis that potency and unit cost were the key influencing factors for choosing statins.

The strengths of this study were that we were able to analyse utilisation of statins over a long period of time which allowed analysis by Interrupted Time Series.. We were able to access actual amounts of statins prescribed in primary care which was then converted into DDD’s which avoids the inherent problems when accessing data in DDD’s. A potential limitation was that data was derived from prescriptions dispensed rather than prescriptions written so can take no account of prescriptions obtained by a patient but never presented for dispensing – which is one crude measure of adherence.

**CONCLUSION**

In England, the availability of generic simvastatin and atorvastatin has reduced overall expenditure on statins significantly. This study has shown that when there is a significant price difference, acquisition cost appears to be the main influencing factor in the utilisation of statins, but, when costs are similar potency is the key factor. Furthermore, when less expensive generic statins became available, prescribers used higher doses, presumably to elicit the extra clinical benefit. This suggests that English prescribers are cost sensitive and appear to be prepared to trade marginal benefit for savings.

**References**

1. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4,444 patients with coronary heart disease. *Lancet* 1994; 344(8934): 1383-1388.
2. Sacks FM, Pfeffer MA, Moye LA, *et al*. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; 335(14): 1001-1009.
3. Sever PS, Dahlof B, Poulter NR, *et al*. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; 361(9364): 1149-1158.
4. Heart Protection Study Collaborative Group. MRC/ BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals. *Lancet* 2002; 360(9326): 7-22.
5. Moon JC and Bogle RG. Switching statins. *BMJ* 2006; 332(7554): 1344-1345.
6. Walley T, Folino‐Gallo P, Stephens P, *et al.* Trends in prescribing and utilization of statins and other lipid lowering drugs across Europe 1997–2003. *Br J Clin Pharmacol* 2005; 60(5): 543-551.
7. Kotseva K, Wood D, De Backer G, *et al*. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *Lancet* 2009; 373(9667): 929-940.
8. ‏ Godman B, Wettermark B, van Woerkom M, *et al.* Multiple policies to enhance prescribing efficiency for established medicines in Europe with a particular focus on demand-side measures: findings and future implications. *Front Pharmacol* 2014; 5: 106.‏
9. Vancheri F, Backlund L, Strender LE, *et al.* Time trends in statin utilisation and coronary mortality in Western European countries. *BMJ open* 2016; 6(3): e010500.‏
10. Department of health. Prescription Cost Analysis: England 2004. 2005. <http://webarchive.nationalarchives.gov.uk/20120503222906/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4107626.pdf> (Accessed February 16, 2017).
11. Collins R, Armitage J, Parish S, et al. Heart Protection Study. *Lancet* 2003; 361(9356): 529-530.
12. Duerden MG and Hughes DA. Generic and therapeutic substitutions in the UK: Are they a good thing? *Br J Clin Pharmacol* 2010; 70(3): 335-341.
13. Cooper A, Nherera L, Calvert N, et al. Clinical guidelines and evidence review for lipid modification: Cardiovascular risk assessment and the primary and secondary prevention of cardiovascular disease. National Collaborating Centre for Primary Care and Royal College of General Practitioners, pp. 3. London: Hyde Park; 2008.
14. Rogers SL, Magliano DJ, Levison DB, *et al*. A dose-specific meta-analysis of lipid changes in randomized controlled trials of atorvastatin and simvastatin. *Clin Ther* 2007; 29(2): 242-252.
15. Branchi A, Fiorenza AM, Rovellini A, *et al*. Lowering effects of four different statins on serum triglyceride level. *Eur J Clin Pharmacol* 1999; 55(7): 499-502.
16. Gentile S, Turco S, Guarino G, *et al*. Comparative efficacy study of atorvastatin vs. simvastatin, pravastatin, lovastatin and placebo in type 2 diabetic patients with hypercholesterolaemia. *Diabetes Obes Metab* 2000; 2(6): 355-362.
17. McTaggart F, Buckett L, Davidson R, *et al*. Preclinical and clinical pharmacology of rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. *Am J Cardiol* 2001; 87(5): 28-32.
18. Holdgate GA, Ward WH, McTaggart F. Molecular mechanism for inhibition of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase by rosuvastatin. *Biochem Soc Trans* 2003; 31(3): 528-531.
19. Cannon CP, Braunwald E, McCabe CH, *et al*. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; 350(15): 1495-1504.
20. Schwartz GG, Olsson AG, Ezekowitz MD, *et al.* Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001; 285(13): 1711-1718.
21. Nissen SE, Tuzcu EM, Brown BG, *et al*. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 2004; 291(9): 1071-1080.
22. Hudson V. The dyslipidaemia market. *Nat Rev Drug Discov* 2014; 13(11): 807-808.‏
23. Mamdani MM, and Tu JV. Did the major clinical trials of statins affect prescribing behaviour?. *CMAJ* 2001; 164(12): 1695-1696.‏
24. Teeling M, Bennett K, and Feely J. The influence of guidelines on the use of statins: analysis of prescribing trends 1998–2002. *Br J Clin Pharmacol* 2005; 59(2): 227-232.‏
25. O’Keeffe AG, Nazareth I, and Petersen I. Time trends in the prescription of statins for the primary prevention of cardiovascular disease in the United Kingdom: a cohort study using The Health Improvement Network primary care data. *J Clin Epidemiol* 2016; 8: 123.‏
26. Tobert JA. Lovastatin and beyond: the history of the HMG-CoA reductase inhibitors. *Nat Rev Drug Discov* 2003; 2(7): 517-526.‏
27. Chaplin S. NICE statins guidance: Prevention of cardiovascular events. *Prescriber* 2006; 17(4): 58-60.
28. Furberg CD, and Pitt B. Withdrawal of cerivastatin from the world market. Trials 2001; 2(5): 1.‏
29. Fox KF. A critical evaluation of the NICE guidelines for post-myocardial infarction prophylaxis. *Expert Opin Pharmacother* 2001; 2(12): 2079-2084.‏
30. McGuire T, and Bauhoff S. Adoption of a cost-saving innovation: Germany, UK and Simvastatin. England and Germany in Europe–What lessons can we learn from each other, 2011; 11-26.‏
31. NICE. Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. 2008. http://www.salforddiabetescare.co.uk/admin/resources/uploaded/NICE%20guidance%20on%20lipids209.pdf (Accessed 21 May 2016).
32. Health and social care information centre. The national provider of information, data and IT systems for health and social care. <http://www.hscic.gov.uk/>. (Accessed March 2, 2016).
33. WHOCC. Definition and general considerations. 2016. <http://www.whocc.no/ddd/definition_and_general_considera/>. (Accessed July 26, 2015).
34. Wagner AK, Soumerai SB, Zhang F, *et al*. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002; 27(4): 299-309.‏
35. Bennie M, Godman B, Bishop I, *et al*. Multiple initiatives continue to enhance the prescribing efficiency for the proton pump inhibitors and statins in Scotland. *Expert Rev Pharmacoecon Outcomes Res* 2012; 12(1): 125-130.
36. Woerkom MV, Piepenbrink H, Godman B, et al. Ongoing measures to enhance the efficiency of prescribing of proton pump inhibitors and statins in The Netherlands: influence and future implications. *J Comp Eff Res* 2012; 1(6): 527-538.
37. Thai LP, Moss JR, Godman B, et al. Cost driver analysis of statin expenditure on Australia’s Pharmaceutical Benefits Scheme. *Expert Rev Pharmacoecon Outcomes Res* 2016; 1: 1-15.
38. Finlayson AE, Godman B, Xi H, et al. Ongoing initiatives to improve prescribing efficiency in China; statins as a case history. *GaBI J* 2014; 3(3): 122-132.
39. Smith J. Appropriate primary prevention of cardiovascular disease: does this mean more or less statin use? *Aust Prescr* 2011; 34(6): 169-172.
40. Lazar LD, Pletcher MJ, Coxson PG, et al. Cost-effectiveness of statin therapy for primary prevention in a low-cost statin era. *Circulation* 2011; 124(2): 146-153.
41. Ward S, Lloyd Jones M, Pandor A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. In: NIHR Health Technology Assessment programme: Executive Summaries. Southampton (UK): NIHR Journals Library. 2007. http://www.ncbi.nlm.nih.gov/books/NBK62291/. (Accessed March 2, 2016).
42. Pettersson B, Hoffmann M, Wändell P, et al. Utilization and costs of lipid modifying therapies following health technology assessment for the new reimbursement scheme in Sweden. *Health policy* 2012; 104(1): 84-91.
43. Cook A, Acton P, Schwartz E. Congressional Budget Office: How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry. Washington: US Government Printing Office; 1998.
44. Mrazek MF, Mossialos EA. Regulating pharmaceutical prices in the European Union (Chapter 6). In: Mossialos EA, Mrazek MF, Walley T, editors. Regulating pharmaceuticals in Europe: striving for efficiency, equity and quality. Buckingham: Open University Press; 2004.
45. King DR, Kanavos P. Encouraging the use of generic medicines: implications for transition economies. *Croatian Med J* 2002; 43: 462-469.
46. Kanavos P. International generic pharmaceutical policies. Richmond: PJB Publications Ltd; 2004
47. Soumerai SB. Benefits and risks of increasing restrictions on access to costly drugs in Medicaid. *Health Aff* 2004; 23: 135-146.
48. Grabowski H, Vernon J. Longer patents for lower imitation barriers: the 1984 Drug Act. *American Econ Rev Papers Proc* 1986; 76: 195-198
49. Davidson MH. Rosuvastatin: a highly efficacious statin for the treatment of dyslipidaemia. *Expert Opin Investig Drugs* 2002; 11(1): 125-141.‏
50. Armitage J. (2007). The safety of statins in clinical practice. *Lancet* 2007; 370(9601): 1781-1790.‏
51. Pedersen R, Faergeman O, Kastelein J, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: The IDEAL study: A randomized controlled trial. *JAMA* 2005; 294(19): 2437-2445.
52. Shepherd J, Kastelein J, Bittner V, et al. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: The TNT (treating to new targets) study. *J Am Coll Cardiol* 2008; 51(15): 1448-1454.
53. Ray K, Cannon P, McCabe H, et al. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol* 2005; 46(8): 1405-1410.

*Table 1 Summary of significant events and UK policy recommendations since the introduction of statins*

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| --- | --- |
| **Date** | **Event** |
| 1987 | Lovastatin was first statin introduced. [26] |
| 1988 | Simvastatin introduced. [26] |
| 1991 | Pravastatin introduced. [26] |
| 1994 | Fluvastatin introduced. [26] |
| 1997 | Atorvastatin introduced. [26] |
| 1998 | Cerivastatin introduced. [26] |
| 2000 | The Coronary Heart Disease National Service Framework recommended statins for secondary prevention of cardiovascular events in all patients with a history of cardio-vascular disease.[27] |
| 2001 | Cerivastatin was withdrawn due to reported drug related rhabdomyolysis leading to renal failure. [28] |
| 2001 | NICE guideline “Prophylaxis for patients who have experienced a myocardial infarction.  Recommended statins for patients with hypercholesterolaemia and advocate their use in patient without heart failure post myocardial infarction.[29] |
| 2003 | Rosuvastatin introduced. [26] |
| 2003 | Patent expiry of branded simvastatin (Zocor).[12] |
| 2006 | NICE Technology Appraisal Guidance “Statins for the prevention of cardiovascular events” endorsed a criteria for secondary prevention but lowers the threshold of risk for primary prevention.[27] |
| 2008 | NICE guideline “Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease”.  Recommended simvastatin 40 mg (statins with a low acquisition cost) for primary and secondary prevention of cardiovascular disease.[13] |
| 2012 | Patent expiry of branded atorvastatin (Lipitor).[30] |
| 2014 | NICE guideline “Cardiovascular disease: risk assessment and reduction, including lipid modification”. Recommended atorvastatin 20mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD, people 85 years or older, people with type 2 diabetes and people with CKD. Atorvastatin 80 mg for secondary prevention of cardiovascular disease.[31] |

*Table 2 Costs of different statins in England between 1998 and 2015 in sterling pounds*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **1998** | **2000** | **2003** | **2006** | **2009** | **2012** | **2015** |
| **Zocor**® | **10mg** | 26.86 | 27 | 26.2 | 25.99 | 26.86 | 25.72 | 25.38 |
| **40mg** | 43 | 43.6 | 40.6 | 37.81 | 40.79 | 40.13 | 39.96 |
| **Generic simvastatin** | **10mg** | - | - | 22.49 | 2.43 | 1.15 | 1.02 | 1.02 |
| **40mg** | - | - | 36.01 | 5.2 | 1.74 | 1.4 | 1.32 |
| **Lipitor**® | **10mg** | 28.37 | 26.72 | 25.1 | 24.32 | 22.9 | 16.48 | 18.44 |
| **40mg** | 70.67 | 71.67 | 41.9 | 37.52 | 31.74 | 29.47 | 34.89 |
| **Generic atorvastatin** | **10mg** | - | - | - | - | - | 4.13 | 1.46 |
| **40mg** | - | - | - | - | - | 7.21 | 1.85 |
| **Crestor**® | **5mg** | - | - | - | 22.74 | 22.91 | 22.48 | 21.97 |
| **20mg** | - | - | 39.31 | 38.21 | 32.35 | 31.66 | 31.18 |
| **Lipobay**® | **100mcg** | 18.01 | 17.8 | - | - | - | - | - |
| **300mcg** | 25.85 | 24.85 | - | - | - | - | - |
| **Lescol**® | **20mg** | 22.44 | 18.67 | 17.61 | 18.37 | 20.38 | 20.09 | 20.61 |
| **40mg** | 24.98 | 18.97 | 17.24 | 18.52 | 20.62 | 20.71 | 21.87 |
| **Generic fluvastatin** | **20mg** | - | - | - | - | 17.69 | 4.05 | 3.26 |
| **40mg** | - | - | - | - | 18.71 | 4.28 | 3.96 |
| **Lipostat**® | **10mg** | 24.3 | 23.48 | 22.24 | 17.91 | 19.89 | 20.46 | 20.38 |
| **40mg** | 49.11 | 39.03 | 37.37 | 31.53 | 34.69 | 33.53 | 32.97 |
| **Generic pravastatin** | **10mg** | - | - | - | 2.75 | 2.27 | 1.8 | 1.54 |
| **40mg** | - | - | - | 4.25 | 3.42 | 2.69 | 2.21 |

*Table 3 interrupted time series regression analysis of change in the utilisation of different doses of statins*

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Zocor10** | **Zocor20** | **Zocor40** | **Zocor80** | **Lipitor10** | **Lipitor20** | **Lipitor40** | **Lipitor80** | **Crestor5** | **Crestor10** |
| Trend (β1) | 81.59  (0.004) | 333 (0.000) | 239 (0.003) | 109  (0.000) | 452  (0.002) | 350  (0.045) | 248  (0.191) | 220  (0.727) | - | - |
| Level  (β2) | -817  (0.000) | -1469 (0.000) | -540 (0.026) | -170  (0.000) | 1465  (0.002) | 1870  (0.004) | 625  (0.320) | -472  (0.400) | - | - |
| Trend (β3) | -103  (0.001) | -389  (0.000) | -290 (0.001) | -117  (0.000) | -717  (0.000) | -380  (0.044) | 534  (0.017) | 433  (0.499) | 35.90  (0.000) | 84.37  (0.023) |
| Level  (β4) | 50.58  (0.625) | 127  (0.680) | 111  (0.693) | 17.18  (0.663) | -126  (0.891) | -2037  (0.011) | -5826  (0.000) | -3481  (0.000) | -12.73  (0.305) | -397  (0.258) |
| Trend (β5) | 22.10  (0.530) | 55.38  (0.598) | 49.56  (0.605) | 7.52  (0.575) | -15.06 (0.930) | -270  (0.263) | -1623  (0.000) | -1310  (0.000) | -10.46  (0.034) | -149  (0.214) |
|  | **Crestor**  **20** | **Crestor**  **40** | **G.Simva**  **10** | **G.Simva**  **20** | **G.Simva**  **40** | **G.Simva**  **80** | **G.Atorva**  **10** | **G.Atorva**  **20** | **G.Atorva**  **40** | **G.Atorva**  **80** |
| Trend (β1) | - | - | - | - | - | - | - | - | - | - |
| Level  (β2) | - | - | - | - | - | - | - | - | - | - |
| Trend (β3) | 117  (0.000) | 37.64  (0.434) | 1.85  (0.914) | 659  (0.000) | 4656  (0.000) | 144  (0.000) | - | - | - | - |
| Level  (β4) | -79.71  (0.740) | -137  (0.785) | -105  (0.566) | -802  (0.525) | 2564  (0.239) | 202  (0.340) | - | - | - | - |
| Trend (β5) | -152  (0.086) | -24.95  (0.884) | -49  (0.430) | -368  (0.393) | -8405  (0.000) | -343  (0.001) | 647  (0.057) | 2207  (0.010) | 3253  (0.027) | 2293  (0.015) |

β1 refers to the effect of time before launch of generic simvastatin; β2 and β3 refer to launch of generic simvastatin; β4 and β5 refer to launch of generic atorvastatin. DDD is the unit of utilisation.

*Table 4 Average strength of statins in mg/prescription in England between 1998 and 2015*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Phase** | **Year** | **Zocor** | **Generic simvastatin** | **Difference** | **Lipitor** | **Generic atorvastatin** | **Difference** | **Crestor** |
| **Pre-generic market phase** | 1998 | 13.87 |  |  | 14.07 |  |  |  |
| 1999 | 14.45 |  |  | 14.24 |  |  |  |
| 2000 | 15.24 |  |  | 14.47 |  |  |  |
| 2001 | 16.41 |  |  | 14.96 |  |  |  |
| 2002 | 18.46 |  |  | 15.82 |  |  |  |
| **Post-generic simvastatin market phase** | 2003 | 20.54 | 22.34 | 1.8 | 16.98 |  |  | 12.54 |
| 2004 | 21.07 | 25.51 | 4.44 | 18.40 |  |  | 12.76 |
| 2005 | 22.57 | 26.90 | 4.33 | 20.16 |  |  | 12.29 |
| 2006 | 24.23 | 28.47 | 4.24 | 22.74 |  |  | 12.28 |
| 2007 | 24.03 | 30.23 | 6.2 | 26.25 |  |  | 15.73 |
| 2008 | 24.48 | 31.20 | 6.72 | 28.11 |  |  | 12.68 |
| 2009 | 25.94 | 32.27 | 6.33 | 29.66 |  |  | 12.70 |
| 2010 | 26.55 | 33.04 | 6.49 | 31.36 |  |  | 12.67 |
| 2011 | 26.67 | 33.54 | 7.04 | 32.89 |  |  | 12.69 |
| **Post-generic atorvastatin market phase** | 2012 | 25.04 | 33.71 | 8.67 | 33.56 | 33.18 | -0.53 | 12.71 |
| 2013 | 24.90 | 32.18 | 7.28 | 23.43 | 30.96 | 7.53 | 12.64 |
| 2014 | 24.10 | 31.76 | 7.66 | 22.38 | 30.62 | 8.24 | 12.47 |
| 2015 | 26.65 | 31.56 | 4.91 | 20.21 | 30.75 | 10.54 | 12.31 |

Figure 1 Expenditure on statins in primary care in England 1998-2015 in sterling pounds.

Zocor®: branded simvastatin. Lipitor®: branded atorvastatin. Crestor®: branded rosuvastatin. Lipobay®: branded cervistatin. Lescol®: branded fluvastatin. Lipostat®: branded pravastatin.

Lipitor patent expiration

Crestor launch

Zocor patent expiration

Figure 2 Statins utilisation in primary care in England 1998-2015 in DDDs.

Zocor®: branded simvastatin. Lipitor®: branded atorvastatin. Crestor®: branded rosuvastatin. Lipobay®: branded cervistatin. Lescol®: branded fluvastatin. Lipostat®: branded pravastatin.

2008 NICE Guidance

2001 NICE Guidance

2014 NICE Guidance

2012 Marketing of generic atorvastatin

2003 Marketing of generic simvastatin and Crestor

Figure 3 Utilisation of different doses of statins in primary care between 1998 and 2015.

Zocor®: branded simvastatin. Lipitor®: branded atorvastatin. Crestor®: branded rosuvastatin.