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Do Koreans use too many moderate-intensity statins? Evidence from 13-years of statin utilization for new users in South Korea

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Do Koreans use too many moderate-intensity statins? Evidence from 13-years of statin utilization for new users in South Korea

Objective: Given market size of statins and a number of "me-too" drugs and generics, statin utilization has been the subject of great interest in the perspective of public health. This study analyzed utilization of statins for new statin users and assessed market dynamics of statins in Korea from 2003 to 2015.

Design: This study is a retrospective observational study focusing on the utilization of statins for new users.

Setting: The yearly claims data for statins between 2002 and 2015 were retrieved from the National Health Insurance Service-National Sample Cohort.

Main outcome measure: This study examine characteristics of new statin users and prescribed statin drugs over the last thirteen years, investigate the association between medical history of patients and intensity of statins, and analyze market dynamics of statins using interrupted time series analysis.

Results: This 13-year longitudinal study of a sample cohort provided by the NHIS found that the number of new statin users has increased from 8,205 in 2003 to 15,514 in 2015. Most new users were initiated on a monotherapy that was prescribed at primary healthcare institutions. Use of

moderate-intensity statins increased, notably at primary healthcare institutions from 48% in 2003 to 95% in 2015. We could not observe substantial differences in prescription of statins in groups with selected diseases history through the study period. Lastly, we found market invasion or switch of statins among new statin users in the market, specifically at primary healthcare institutions. In addition, we noted that the marketing of generics immediately expand markets particularly in primary healthcare institutions in the interrupted time series model.

Conclusion: Fierce market competition among statins is closely related with expansion of market of new statin users, particularly in primary healthcare institutions. Furthermore, the pricing and marketing strategies of manufacturers might encourage physicians to prescribe moderate-intensity statins in Korea.

Strengths and limitations of this study

This study notably analyzed utilization of statins for new statin users and assessed market dynamics of statins in Korea from 2003 to 2015.

The yearly claims data for statins between 2002 and 2015 were retrieved from the National Health Insurance Service-National Sample Cohort that is composed of approximately 1 million individuals (around 2% of the population).

The market of statins in Korea was dynamic. We noted that the marketing of generics immediately expand markets particularly in primary healthcare institutions in the interrupted time series model.

It seems that fierce market competition among statins, including price competition, is closely related with the expansion of markets of new statin users, particularly in primary healthcare institutions. Further investigation is needed to assess market dynamics in Korea.

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Non-financial and any similar financial associations that may be relevant to the submitted manuscript.

Introduction

Cardiovascular diseases (CVDs) account for 31% of all global deaths, taking the lives of 17.7 million people annually [1]. Similarly, CVDs are among the leading causes of death in South Korea (hereafter Korea) [2,3]. Hypercholesterolemia is a well-established, but modifiable risk factor for CVDs [4-8]. Lifestyle changes and several types of medications have been recommended to control blood lipid levels. Among the medications, statins are a major drug class that functions in reducing low-density lipoprotein cholesterol (LDL-C) [9-12]. Specifically, statins are recommended by several clinical guidelines, including the American College of Cardiology/American Heart Association (ACC/AHA) Guideline and the European Society of Cardiology (ESC) and the UK's National Institute for Health and Care Excellence Guideline, as the drug of choice for reduction of blood lipids to prevent CVDs.

In recent decades, statins have been the most commonly prescribed drugs in the world, and their global market sales reached approximately 28.5 billion dollars in 2014 [13]. Studies from the United States reported substantial increases in prescription rates of statins, including increased prescribed daily doses of statins [14]. Furthermore, ACC/AHA Guidelines recommend that patients with a CVD history or with CVD risk factors, such as high LDL-C and diabetes, receive moderate- to high-intensity statins [10]. Based on the guidelines, use of statins for patients with a disease history or

risk factors would be increased. Likewise, drug expenditure for statins has increased from 496 billion won in 2010 to 786 billion won in 2016 in Korea [2,3]. It should be noted that there are many "me-too" drugs, including generics or follow on drugs, under the statin category [12]. For example, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin, as well as a number of generics, are now available for hypercholesterolemia patients in the Korean market.

Given the market size of statins and a number of "me-too" drugs and generic statins, statin utilization, including switching drugs, in health systems has been the subject of considerable interest in the perspective of clinical pharmacy and public health [15-21]. However, notably few studies have dealt empirically with the issue or include real-world data with statin users, especially in Korea. Meanwhile, it was reported that drug switching among statin users is low in Korea [2]. Therefore, we selected new statin users to understand statin utilization and market dynamics of statins in Korea. Given the limited drug switching among statin users, analysing statin utilization of new users could be used as an important resource to evaluate the use of statins and to assess market dynamics of statins in Korea.

This study analysed the utilization of statins for new statin users and assessed the market dynamics of statins. Specifically, this study examined characteristics of new statin users and the

prescribing of statin drugs over the last thirteen years, investigated the association between medical history of patients and intensity of statins, and analysed market dynamics of statins, including market penetration and switching among new statin users.

Methods

This study used a real-world sample cohort dataset, for the period of 2002 to 2015. Therefore, we could examine trends in the prescription of statins over the long term in Korea. We also added information on the characteristics of new statin users, statin drugs, and healthcare institutions to understand statin utilization. Furthermore, we added information on statin drugs, specifically the entry of generics and price fluctuations of new medicines, to analyse market penetration and market switching among new statin users.

Data source

This study used a population-based cohort dataset provided by the National Health Insurance Service-National Sample Cohort (NHIS-NSC) [22]. The dataset is comprised of approximately 1 million individuals (approximately 2% of the population) selected randomly from South Koreans, which total 45 million people, with national claims data for the period from January 1, 2002, to

December 31, 2015. The cohort dataset consists of four databases on participants' insurance eligibility, medical treatments, medical care institutions, and general health examinations [22]. Specifically, the dataset provides information on demographic characteristics, disease diagnosis, treatments and related medical expenditure, and prescription data.

Study design

This study is interested in new statin users. New statin users were defined as those who had not been prescribed any statin in the year prior to the date of the first statin prescription observed in the cohort dataset [23]. Therefore, new statin users in each year from 2003 to 2015 were included in the study population of each year. Specifically, the first prescription for outpatients that included any statin was set as an index date and analysed in the study.

The studied drugs include the statins atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. The doses of the individual drugs marketed in Korea are as follows: atorvastatin 10 mg, 20 mg, 40 mg, and 80 mg; pravastatin 5 mg, 10 mg, 20 mg, and 40 mg; rosuvastatin 5 mg, 10 mg, and 20 mg; and simvastatin 10 mg, 20 mg, 40 mg, and 80 mg (drug code, Appendix 1). In this study, we defined mono-therapy as only one statin prescription, while we defined combination therapy as prescription for a statin plus other lipid-lowering drugs,

including fibrates or ezetimibe.

Statins were grouped into three levels of intensity [10,24]: high-intensity statins; moderate-intensity statins; and low-intensity statins. High-intensity statins include atorvastatin ≧40 mg/day, rosuvastatin ≧20 mg/day and simvastatin ≧80 mg/day. Low-intensity statins include atorvastatin <10 mg/day, rosuvastatin <5 mg/day, simvastatin <20 mg/day, pravastatin <40 mg/day, lovastatin <40 mg/day and fluvastatin <80 mg/day. Lastly, moderate-intensity statins include 10 mg/day ≦ atorvastatin <40 mg/day, 5 mg/day ≦ rosuvastatin <20 mg/day, 20 mg/day ≦ simvastatin <80 mg/ day, pravastatin ≧ 40 mg/day, lovastatin ≧40 mg/ day and fluvastatin ≧80 mg/day. Daily doses can be calculated from the prescription data.

All new statin users were classified based on their disease history, including hypertension (I10-I15), diabetes (E10-E14), diseases of arteries, arterioles and capillaries (I70-I79), ischaemic heart disease (I20-I25), cerebrovascular diseases (I60-I69), chronic obstructive pulmonary disease (J44), heart failure (I50), chronic kidney diseases (N17-N19), and atrial fibrillation (I48). Disease history was identified by the International Classification of Disease, 10th edition (ICD-10). Among these diseases, diabetes, diseases of arteries, arterioles and capillaries, cerebrovascular diseases, and heart failure are related to the use of statins for CVD prevention [25-27]. Individuals were identified

as having a disease history of the specific disease if they had a primary diagnosis that corresponded to each diagnosis within three years prior to the first prescription date [27,28]. In addition, we searched the market of statins in Korea, including price information and the entry of new drugs and follow on drugs, on the website of the Ministry of Food and Drug Safety (MFDS) and the Health Insurance Review and Assessment Service (HIRA).

Data analysis

This study used descriptive statistics to examine characteristics of new statin users and prescribed statin drugs, employed the χ^2 test to investigate the associations between certain disease history and prescription of moderate- or high-intensity statins, and applied interrupted time series analysis to understand the market dynamics of statins. In time series analysis, we added the year of marketing of generics to estimate the effect of marketing generics on the market, specifically newly prescribed statin users [29]. We presented the result of simple linear regression before and after the marketing of generics. Data management and analysis were performed using the R statistical software (version 3.4.1). P-values under 0.05 were considered to be significance.

Ethical statement

This study used a de-identified secondary dataset. Therefore, it was exempted from review by the

Institutional Review Board (IRB) of Ewha Womans University (IRB No. 158-10).

Results

Table 1 presents characteristics of new statin users over time. The number of new statin users increases from 8,205 in 2003 to 15,514 in 2015. There have been more female new users than male new users, while the portion of female new statin users steadily declined from 56.5% in 2003 to 50.4% in 2015. During this period, the average age of new statin users remained steady (54.31 – 56.52 years old). We also sorted new statin users by their income quintile. The portion of the first quintile (the lowest income) increased from 13% in 2003 to 16% in 2015, while the portion of the fifth quintile (the highest income) decreased from 33% in 2003 to 30% in 2015. In 2003, hypertension accounted for the highest portion of comorbidities (55%), followed by diabetes (37%), ischaemic heart disease (21%), diseases of arteries, arterioles and capillaries (14%), and cerebrovascular diseases (12%). These trends remained steady in 2015. However, it is noteworthy that the proportion of disease of arteries, arterioles and capillaries increased, while that of hypertension and ischaemic heart disease decreased.

Table 2 shows characteristics of prescribed statin drugs among new statin users. The majority of patients were prescribed with a single statin (monotherapy) when they started

hypercholesterolemia treatment, while few new statin users were prescribed combination therapy during the study period.

The market for monotherapy statins is dynamic. In 2003, simvastatin (37%) was the most prescribed statin, followed by lovastatin (30%) and atorvastatin (18%). The market share of simvastatin had been the highest in the market from 2003 (37%) to 2007 (50%). During this period, the market share of atorvastatin was steady (18-20%), while the market share of lovastatin decreased from 30% in 2003 to 4% in 2007. Similarly, the market share of simvastatin decreased after 2008, while the market share of atorvastatin increased and maintained the highest from 46% in 2008 to 66% in 2013. Lastly, the market share of rosuvastatin increased from 8% in 2013 to 36% in 2015, while that of atorvastatin decreased from 66% to 49% during the same period. In 2015, statins for new users were an oligopoly market: atorvastatin (49%) was the most prescribed statin, followed by rosuvastatin (36%).

In 2003, the prescription rates of low-intensity and moderate-intensity statins were 43% and 57%, respectively. However, the prescription rate of moderate-intensity statins consistently increased to 92% in 2015, while the prescription rate of low-intensity statins decreased to 3% in 2015. In addition, the use of high-intensity statins steadily increased during the study period. We also

examined health care institutions that prescribed statins. In 2003, 63% of new statin users were prescribed at primary healthcare institutions followed by secondary- (20%) and tertiary care institutions (14%). During the study period, the portion of new users prescribed at primary and tertiary healthcare institutions decreased, while the portion of new users prescribed at secondary healthcare institutions increased. In 2015, 58% of new statin users were prescribed at primary healthcare institutions followed by secondary- (29%) and tertiary healthcare institutions (11%).

Figure 1 shows statin prescription by health care institutions and the intensity of prescribed statins. The first graph in Figure 1 presents overall patterns of the prescription rates of low-, moderate-, and high-intensity statins in all institution types. The remaining graphs indicate patterns of prescription rates in primary-, secondary-, and tertiary healthcare institutions. We found that prescription rates of moderate-intensity statins were high in primary healthcare institutions, while those of high-intensity statins were high in tertiary care institutions. It is interesting to note that prescription rates of moderate-intensity statins in primary-, secondary-, and tertiary healthcare institutions in 2003 was 48%, 69%, and 78%, respectively. However, prescription rates of moderate-intensity statins changed in primary, secondary, and tertiary healthcare institutions in 2015: 95%, 90%, and 84%, respectively.

Figure 2 presents prescription rates of selected statins, including atorvastatin, rosuvastatin, and simvastatin, during the study period. The first graph in Figure 2 shows market shares of selected statins among new statin users. We noted two points in the perspective of market dynamics. The first market dynamic occurred during 2007-2009 and consisted of the market invasion of atorvastatin. Specifically, atorvastatin penetrated the market of simvastatin in this period. Similarly, the second market dynamic occurred during 2013-2015 and consisted of the market invasion of rosuvastatin. Rosuvastatin penetrated market of atorvastatin in this period. The remaining graphs present new statin users of selected statins by primary, secondary, and tertiary healthcare institutions. In this figure, we conclude that the majority of market switching of statins among new statin users occurred immediately at primary healthcare institutions.

Table 3 indicates the associations between certain disease histories and the prescription of moderate- or high-intensity statins. Interestingly, no substantial differences in the prescription of statins were observed through the study period in groups with histories of diseases of arteries, arterioles and capillaries. Furthermore, patients with diabetes and cerebrovascular diseases were less likely to be prescribed moderate- or high-intensity statins in several selected years. For instance, odds ratios were calculated at 0.78 and ranged from 0.67 to 0.91 with 95% confidence interval in 2012 for patients with diabetes.

Discussions

This 13-year longitudinal study of a sample cohort provided by the NHIS found that the number of new statin users has increased over time from 8,205 in 2003 to 15,514 in 2015. Most new users were initiated on a monotherapy that was prescribed at primary healthcare institutions. In addition, the use of moderate-intensity statins increased, notably at primary healthcare institutions, during the study period. Specifically, the prescription rate of moderate-intensity statins at primary healthcare institutions was low (48%) in 2003. However, the figure was doubled in 2015 (95%). Lastly, the market of statins was dynamic. For instance, we found market invasion or switching of statins among new statin users in the market, specifically at primary healthcare institutions.

The characteristics of new statin users and health care institutions that prescribed statins were similar to other studies that investigated prescription patterns of all statin users in Korea [2,3]. In addition, this finding is consistent with other countries [23,30-33]. It is noteworthy to compare the results of statin prescription for new users with those of Taiwan [23]. First, the intensity of prescribed statin therapy was higher in Korea. For instance, the portion of moderate-intensity statins among new statin users in Taiwan has remained at 70% since 2007. However, the portion of moderate-

intensity statins in Korea was above 90% since 2007. In addition, the market in Korea was more dynamic than that of Taiwan during the study period. Furthermore, we found no substantial differences in the prescription of moderate- or high-intensity statins in groups with histories of hypertension, diabetes, diseases of arteries, arterioles and capillaries, cerebrovascular diseases, and ischaemic heart disease in Korea.

Second, the most commonly used statin changed during the study period in Korea, while atorvastatin has been the most prescribed statin during 2002-2011 in Taiwan [23]. For instance, simvastatin had the highest prescription rate until 2007, while atorvastatin had the highest prescription rate after 2008. It should be noted that generics of atorvastatin were available with discounted prices compared to the originals of the previous year (approximately 68%) in 2008, and the price of the originals was discounted approximately 20% compared to the previous year. We could find similar results in the case of rosuvastatin. Generics of rosuvastatin were available in 2010 and the prices of generics were 451 won, 676 won, and 890 won for 5 mg, and 10 mg, and 20 mg, respectively, which account for approximately 68% of the original counterparts. In such a case of the introduction of generics, the prices of originals would be decreased to 80% compared to the previous year. However, price reduction was deferred until 2014 in this case. In the end, the price of original rosuvastatin decreased to approximately 80% compared to that of the previous

year. It is interesting to note the prescription rates of rosuvastatin: the market share of rosuvastatin in 2009 was 7% and slightly increased 9% in 2010 when generics with discounted prices (approximately 32%) were marketed, and later increased 33% in 2014 when prices of generics were discounted (approximately 20%).

These comparisons reveal that there is room for investigating the rational use of statins in Korea. Given these cases of atorvastatin and rosuvastatin, we might conclude that fierce market competition among statins, including price competition, is closely related to the expansion of markets by the addition of new statin users. Table 4 presents results of segmented regression analysis using the interrupted time series method: β_0 is the pre period intercept; β_1 is the pre period slope (baseline time trend); β_2 is the immediate effect of the event on the intercept; and β_3 is the slope change after the event. In the case of atorvastatin, the immediate effect of marketing generics was 3,236 new users ($p < 0.001$), and the growth rate was increased by 2,687 new users per year ($p < 0.005$) compared with previous trends. Similar trends were found in the case of rosuvastatin.

It is interesting to analyse market expansion by health care institutions. In both cases, the immediate effect of the event was large in primary healthcare institutions. For instance, the

immediate effect of marketing generics of rosuvastatin was 3,163 users (p <0.0000) and 517 users (p <0.005) in primary- and secondary- healthcare institutions, respectively. However, the immediate effect of generics in tertiary care institutions was marginal and insignificant: 16.2 (p =0.78) for atorvastatin and 7.1 (0.95) for rosuvastatin. These results demonstrate that the marketing of generics immediately expands markets, particularly in primary healthcare institutions. In addition, the growth rates, sorted by health care institutions, after the introduction of generics vary according to drugs. For instance, the growth rate of atorvastatin was in the order of primary-, secondary-, and tertiary healthcare institutions, 1,597 (p <0.0001), 736 (p <0.05), and 352 (p <0.001), respectively, while that of simvastatin was in the order of secondary-, primary-, and tertiary healthcare institutions, 2,243 (p <0.0001), 178 (p <0.05), and 33 (p =0.80), respectively,

In addition, we found the pricing and marketing strategies of manufacturers might encourage physicians to prescribe moderate-intensity statins. For instance, the manufacturer discounted the price of simvastatin 40 mg (approximately 34%), and the price was the same as simvastatin 20 mg. Likewise, the other manufacturer that produce atorvastatin utilized the same strategy. Specifically, the manufacturer discounted the price of atorvastatin 40 mg (35%), and the price was the same as atorvastatin 20 mg in 2003. In addition, the manufacturer discounted the price of atorvastatin 20 mg (30%), which was the same price as atorvastatin atorvastatin 10 mg. In addition, the

manufacturer marketed atorvastatin 80 mg in the market to preempt the high-strength statins market.

This study notably analysed the utilization of statins for new statin users and assessed the market dynamics of statins over the last thirteen years with a real-world dataset provided by the NHIS. However, this study has several limitations. First, this study used claims data that does not contain information on biochemical test data of patients, such as LDL cholesterol level. This finding means that we could not assess prescription patterns by disease severity. In addition, the claims data does not contain information on whether the prescribed drugs were originals or generics. Therefore, further research is needed to assess the impact of generics on the market, including the contribution to market expansion by originals and generics, respectively. Second, this study only used the first prescription that included any statins. Therefore, switches among statins were not included in the study. However, it would be reasonable to assume that switches among statins would be low in the Korean market [2].

Conclusions

This 13-year longitudinal study of a sample cohort provided by the NHIS found that the number

of new statin users has increased over time from 8,205 in 2003 to 15,514 in 2015, and the market of statins for new statin users has been dynamic for the same period. Furthermore, it is noteworthy that the portion of new statin users that were prescribed moderate- or high-intensity statins has increased from 57% in 2003 to 95% in 2015. In addition, no substantial differences in the prescriptions of statins were observed through the study period in groups with selected disease histories. These interesting findings reveal that there is room to investigating the rational use of statins in Korea. It seems that fierce market competition among statins, including price competition, is closely related with the expansion of markets of new statin users, particularly in primary healthcare institutions. Furthermore, the pricing and marketing strategies of manufacturers might encourage physicians to prescribe moderate-intensity statins for new statin users.

Author's contribution

KS designed the study, collected and analyzed data, and wrote the manuscript.

SB revised the paper for important intellectual content.

All authors read and approved the final manuscript.

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Table 1. Characteristics of new statin users over time

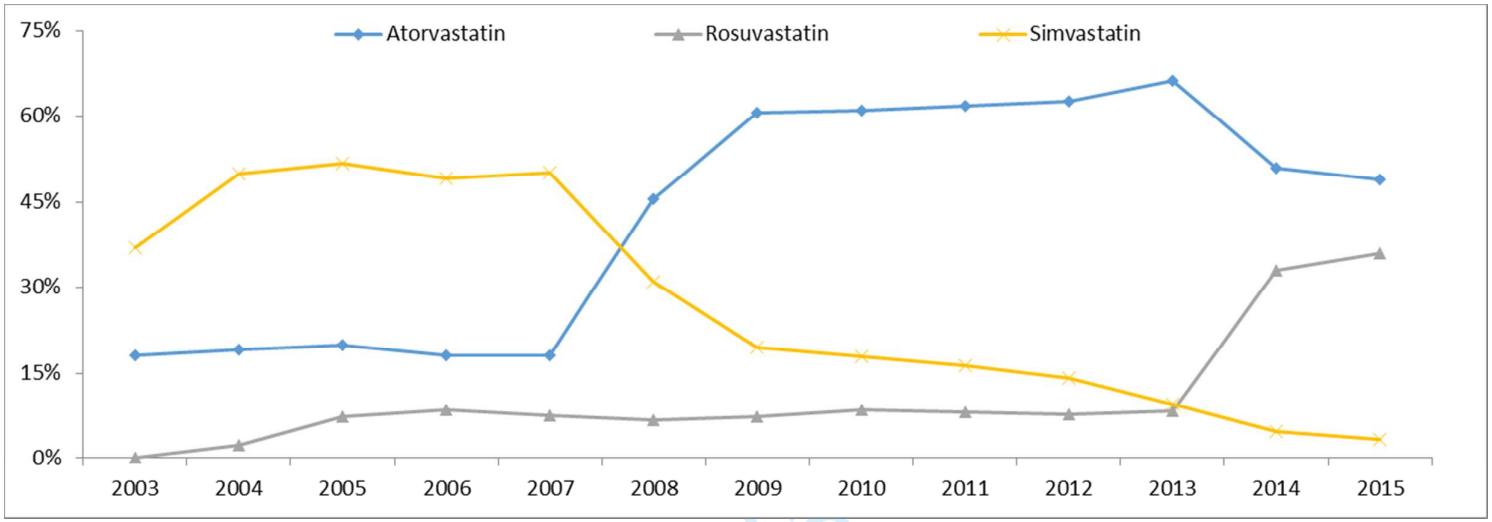
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Number of new statin users	8,205	8,835	11,181	12,564	12,774	13,333	15,139	14,713	14,374	14,639	14,117	15,731	15,514
Sex													
Female	56.5%	55.0%	56.8%	55.8%	54.8%	54.3%	55.2%	54.6%	53.2%	53.1%	52.0%	50.7%	50.4%
Age													
Mean	54.40	54.31	55.15	55.61	55.62	55.48	55.61	55.71	55.58	55.65	55.57	56.52	55.90
SD	11.82	12.00	12.15	12.47	12.68	12.52	12.51	12.39	12.46	12.71	12.89	12.79	12.75
Income level (the quintile)													
The first	13%	14%	15%	15%	15%	14%	15%	15%	15%	15%	16%	16%	16%
The second	13%	13%	12%	14%	13%	14%	14%	15%	15%	15%	14%	15%	15%
The third	17%	17%	18%	16%	18%	18%	18%	17%	18%	17%	17%	17%	17%
The fourth	24%	23%	22%	23%	23%	23%	23%	23%	22%	22%	23%	22%	22%
The fifth	33%	32%	33%	32%	32%	31%	30%	31%	30%	30%	30%	30%	30%
Comorbidities													
Hypertension	N/A		55%	59%	58%	58%	56%	54%	53%	53%	52%	52%	48%
Diabetes			37%	39%	40%	39%	37%	36%	36%	37%	38%	41%	39%
DoA			14%	17%	20%	24%	25%	25%	23%	22%	21%	22%	20%
IHD			21%	22%	22%	21%	19%	19%	19%	18%	17%	18%	16%
CeVD			12%	13%	15%	15%	15%	15%	14%	15%	15%	14%	14%
COPD			5%	6%	6%	6%	5%	5%	5%	5%	5%	5%	4%
Heart failure			5%	4%	4%	4%	3%	4%	4%	4%	4%	4%	4%
CKD			2%	2%	2%	2%	2%	2%	2%	2%	3%	3%	3%
Afib			2%	2%	2%	3%	2%	2%	2%	2%	2%	3%	2%

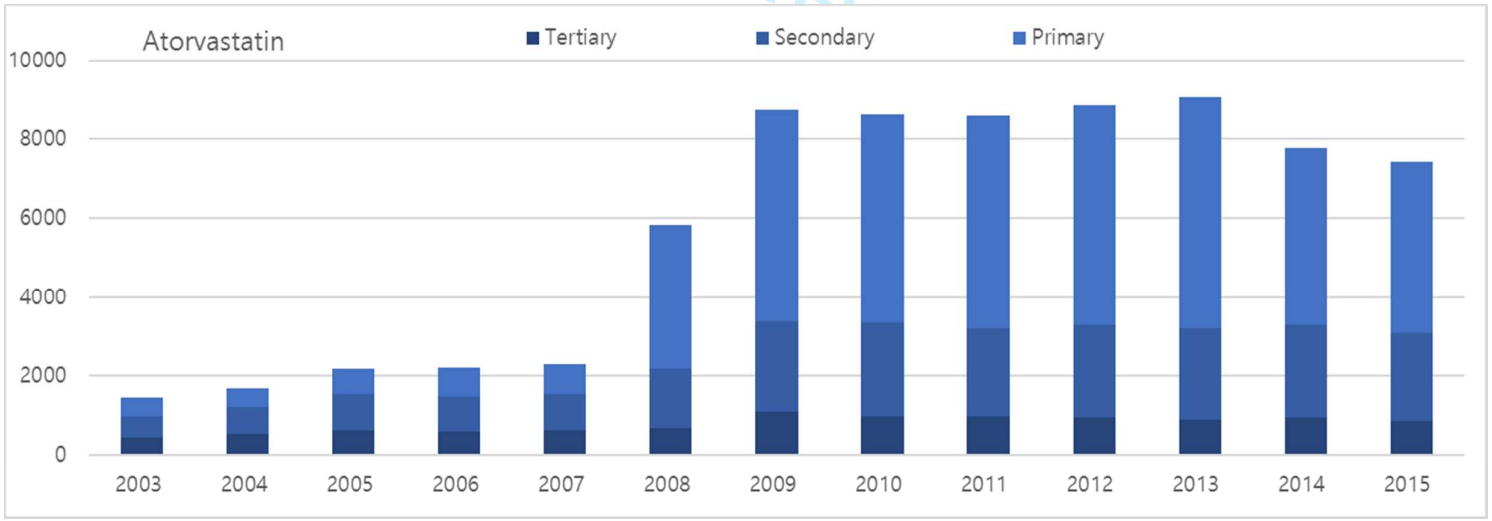
Notes: DoA: diseases of arteries, arterioles and capillaries; IHD: ischemic heart disease; CeVD: cerebrovascular diseases; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney diseases; and Afib: atrial fibrillation

Table 2. Characteristics of prescribed statin drugs among new statin users

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Number of new statin users	8,205	8,835	11,181	12,564	12,774	13,333	15,139	14,713	14,374	14,639	14,117	15,731	15,514
Monotherapy	**100%**	**100%**	**99%**	**98%**	**97%**	**98%**	**97%**	**97%**	**95%**	**94%**	**95%**	**96%**	**95%**
Atorvastatin	18%	19%	20%	18%	18%	46%	61%	61%	62%	63%	66%	51%	49%
Fluvastatin	4%	2%	2%	4%	4%	2%	1%	1%	1%	1%	1%	1%	0%
Lovastatin	30%	18%	12%	6%	4%	2%	1%	1%	1%	0%	0%	0%	0%
Pitavastatin	0%	0%	1%	7%	9%	7%	4%	4%	4%	4%	6%	5%	5%
Pravastatin	11%	8%	6%	5%	4%	4%	3%	3%	3%	2%	2%	2%	1%
Rosuvastatin	0%	2%	7%	9%	8%	7%	7%	9%	8%	8%	8%	33%	36%
Simvastatin	37%	50%	52%	49%	50%	31%	20%	18%	16%	14%	9%	5%	3%
Combination	**0%**	**0%**	**1%**	**2%**	**3%**	**2%**	**3%**	**3%**	**5%**	**6%**	**5%**	**4%**	**5%**
Intensity													
Low	43%	25%	17%	11%	9%	6%	5%	5%	5%	5%	5%	3%	3%
Moderate	57%	75%	83%	88%	90%	94%	94%	94%	93%	93%	93%	92%	92%
High	0%	0%	0%	0%	1%	1%	1%	2%	2%	2%	2%	4%	5%
Institution													
Primary	63%	61%	59%	59%	58%	58%	56%	56%	56%	57%	56%	58%	58%
Secondary	20%	23%	25%	26%	26%	25%	27%	28%	28%	28%	29%	29%	29%
Tertiary	14%	13%	13%	14%	14%	13%	14%	13%	14%	13%	12%	11%	11%
Others	3%	2%	2%	2%	3%	3%	4%	3%	3%	2%	2%	2%	2%

Figure 1. Statin prescriptions by institution and intensity a) all; b) primary-; c) secondary-; and d) tertiary healthcare institutions





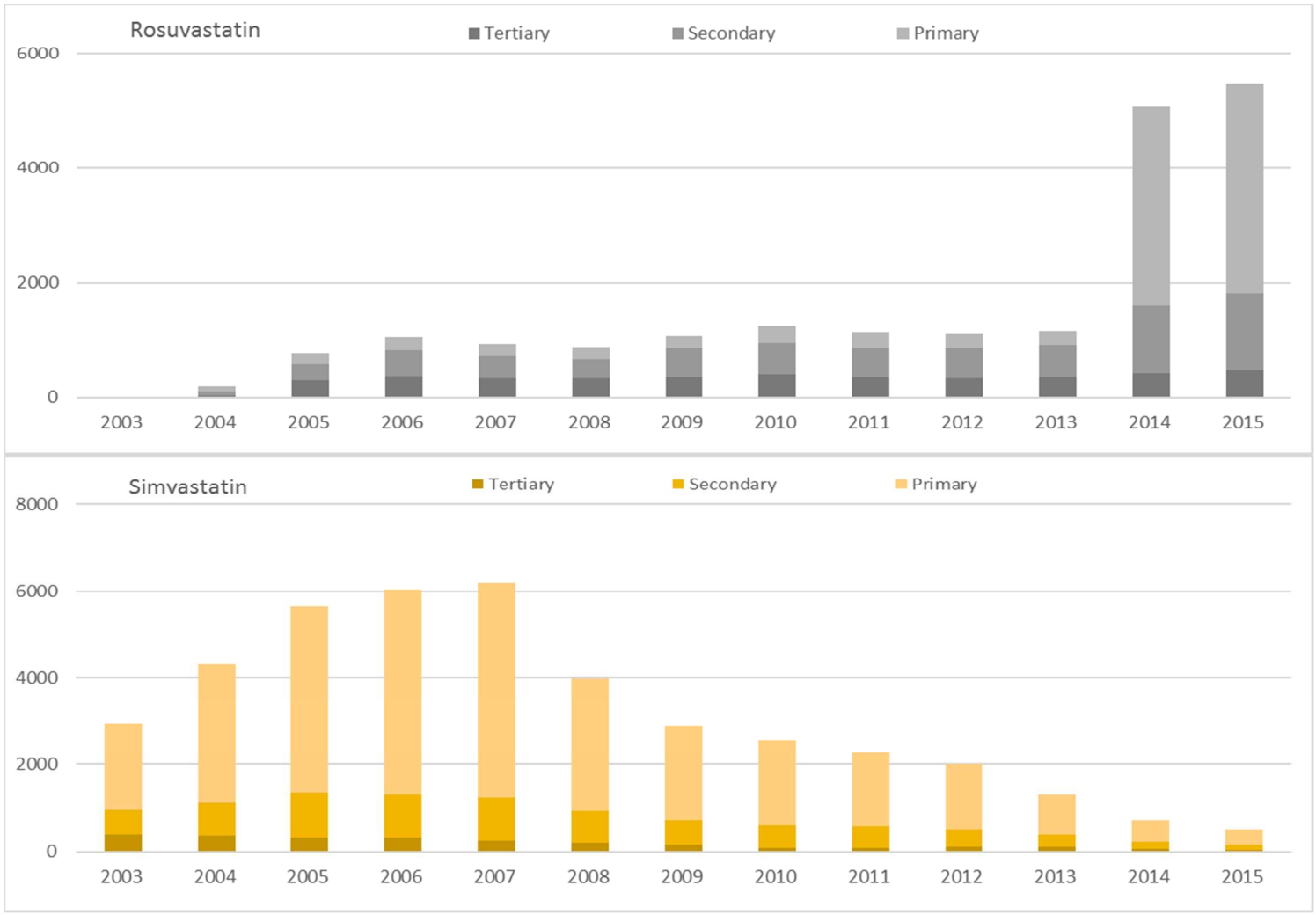


Figure 2. Prescribing rates of selected statins among new statin users

Table 3. Associations between disease history and prescription of moderated- or high-intensity statins

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
History of hypertension	1.04	1.16	1.04	0.92	1.01	0.98	1.09	1.04	1.02	1.05	1.20
	0.94-1.15	1.03-1.29	0.92-1.18	0.80-1.07	0.87-1.18	0.84-1.14	0.94-1.26	0.90-1.20	0.87-1.19	0.88-1.24	1.00-1.44
History of diabetes	1.12	1.15	0.99	0.94	0.75	0.82	0.78	0.78	0.92	0.83	0.92
	1.01-1.24	1.03-1.29	0.88-1.12	0.81-1.09	0.64-0.87	0.70-0.96	0.68-0.91	0.67-0.91	0.78-1.08	0.69-0.99	0.76-1.11
History of DoA	1.00	0.99	1.01	1.01	1.02	1.08	0.98	1.08	1.10	1.02	1.03
	0.87-1.15	0.86-1.14	0.87-1.18	0.85-1.20	0.85-1.21	0.91-1.30	0.83-1.17	0.91-1.31	0.91-1.34	0.82-1.25	0.82-1.30
History of CeVD	1.18	1.20	0.84	0.83	0.69	0.88	0.70	0.85	0.80	0.72	0.77
	1.00-1.38	1.01-1.42	0.71-0.99	0.69-1.01	0.57-0.83	0.71-1.08	0.58-0.84	0.70-1.04	0.65-0.98	0.58-0.90	0.60-0.98
History of IHD	1.41	1.26	1.04	1.02	0.76	0.75	0.94	0.88	1.01	1.06	0.92
	1.24-1.60	1.09-1.44	0.90-1.21	0.85-1.22	0.64-0.91	0.63-0.90	0.78-1.13	0.73-1.06	0.82-1.23	0.85-1.33	0.72-1.18

Table 4. Results of segmented regression analysis of interrupted time series method

	Total			Primary care			Secondary care			Tertiary care		
	Coefficient	Standard error	p-value	Coefficient	Standard error	p-value	Coefficient	Standard error	p-value	Coefficient	Standard error	p-value
Atorvastatin (2003-2009)												
β_0 :Intercept	2611.9	168.5	< 0.001	850.3	46.4	< 0.001	1109.8	102.7	< 0.005	651.8	38.7	< 0.001
β_1 :Time	221.5	50.8	< 0.05	75.1	14.0	< 0.05	108.2	32.5	< 0.05	38.2	11.7	< 0.05
β_2 :Generic	3236.1	232.8	< 0.001	2846.7	64.1	< 0.0001	373.2	148.8	0.087	16.2	53.5	0.78
β_3 :Time:Generic	2687.5	232.8	< 0.05	1597.9	64.1	< 0.0001	736.8	148.8	< 0.05	352.8	53.5	< 0.01
Rosuvastatin (2004-2015)												
β_0 :Intercept	1376.5	141.9	< 0.001	295.7	29.1	< 0.001	655.9	59.0	< 0.001	424.9	61.8	< 0.0001
β_1 :Time	76.1	22.9	< 0.05	13.5	4.7	< 0.05	42.8	9.5	< 0.005	19.8	10.0	0.08
β_2 :Generic	3687.5	251.6	< 0.0001	3163.3	51.6	< 0.0001	517.1	104.5	< 0.0051	7.1	109.6	0.95
β_3 :Time:Generic	2453.9	294.7	< 0.0001	177.5	60.4	< 0.05	2243.2	122.4	< 0.0001	33.2	128.4	0.80

Notes: β0 is the pre period intercept; β1 is the pre period slope (baseline time trend); β2 is the immediate effect of the event on the intercept; β3 is the slope change after the event;

Appendix 1. Drug code of statins in Korea

Drug Names	ATC code	National Code system (Strength (mg) and code)	
Atorvastatin	C10AA05	10	111501ATB
		20	111502ATB
		40	111503ATB
		80	111504ATB
Fluvastatin	C10AA04	20	162401ACH
		40	162402ACH
		80	162403ATR
Lovastatin	C10AA02	20	185801ATB
Pitavastatin	C10AA08	1	470902ATB
		2	470901ATB
		4	470903ATB
Pravastatin	C10AA03	5	216602ATB
		10	216601ATB
		20	216603ATB
		40	216604ATB
Rosuvastatin	C10AA07	5	454003ATB
		10	454001ATB
		20	454002ATB
Simvastatin	C10AA01	5	227805ATB
		10	227803ATB
		20	227801ATB, 227801ATR
		40	227802ATB
		80	227806ATB
Ezetimibe and atorvastatin	C10BA05	10 + 10	633800ATB
		10 + 20	633900ATB
		10 + 40	634800ATB
Ezetimibe and rosuvastatin	C10BA06	10 + 5	640700ATB
		10 + 10	640800ATB
		10 + 20	640900ATB
Ezetimibe and simvastatin	C10BA02	10 + 10	471000ATB
		10 + 20	471100ATB
Fenofibrate and simvastatin	C10BA04	145 + 20	631400ATB
		145 + 40	631500ATB

ATC: anatomical therapeutic chemical

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Patterns of statin utilization for new users and market dynamics in South Korea: A 13-year Retrospective Cohort Study

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Patterns of statin utilization for new users and market dynamics in South Korea: A 13-year Retrospective Cohort Study

Objective: This study analyzed utilization of statins for new statin users and assessed market dynamics of statins in South Korea.

Design: This study is a retrospective cohort study.

Setting: The yearly claims data for statins were retrieved from the National Health Insurance Service-National Sample Cohort.

Main outcome measure: We are interested in new statin users during 2003-2015 in Korea. Information on prescribed statins, including intensity of statins and entry of new and follow-on statins in the market, and health care institutions that prescribed the statins were also collected. In time series analysis, we estimated the effect of introduction of generics in the market, specifically for newly prescribed statin users.

Results: This 13-year longitudinal study of a sample cohort provided by the NHIS found that the incidence of new statin user increase from 838.1/100,000 persons in 2003 to 1626.9/100,000 persons in 2015. Most new users were initiated on a monotherapy that was prescribed at primary healthcare

institutions. However, the statin market for new users were quite dynamic in Korea. Firstly, the most commonly prescribed statin changed several times during the study period. Secondly, the use of moderate-intensity statins increased from 57% in 2003 to 92% in 2015. In line with this result, we could not observe substantial differences in prescription of statins in groups having selected diseases history. Lastly, we found market invasion or switch of statins among new statin users, specifically at primary healthcare institutions.

Conclusion: Similar to other countries, the incidence of new statin users has been increased in Korea. However, the statin market in Korea is quite dynamic compared to other countries. Interestingly, discounted price of originals after the introduction of generics immediately expand markets or substitute the market particularly in primary healthcare institutions in Korea.

Strengths and limitations of this study

Given the market size of statins and a number of "me-too" drugs and generic statins, statin utilization, including switching drugs, in health systems has been the subject of considerable interest.

The National Health Insurance Service-National Sample Cohort (NHIS-NSC), a population-based cohort, provides public health researchers useful information regarding utilization of health services.

This 13-year longitudinal study of a sample cohort presented that the incidence of new statin user increase from 838.1/100,000 persons in 2003 to 1626.9/100,000 persons in 2015.

Patterns of prescription and market dynamics of statins found in this study is quite different from other studies in different regions.

Interestingly, discounted price of originals after the introduction of generics immediately expand markets or substitute the market particularly in primary healthcare institutions in Korea.

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A competing interests statement

Non-financial and any similar financial associations that may be relevant to the submitted manuscript.

Introduction

Cardiovascular diseases (CVDs) account for 31% of all global deaths, taking the lives of 17.7 million people annually [1]. Similarly, CVDs are among the leading causes of death in South Korea (hereafter Korea) [2,3]. Hypercholesterolemia is a well-established, but modifiable risk factor for CVDs [4-8]. Lifestyle changes and several types of medications have been recommended to control blood lipid levels. Among the medications, statins are a major drug class that functions in reducing low-density lipoprotein cholesterol (LDL-C) [9-16]. Specifically, statins are recommended by several clinical guidelines, including the American College of Cardiology/American Heart Association (ACC/AHA) Guideline [10] , the European Society of Cardiology (ESC) [16], and the UK's National Institute for Health and Care Excellence Guideline [11], as the drug of choice for reduction of blood lipids to prevent CVDs.

In recent decades, statins have been the most commonly prescribed drugs in the world, and their global market sales reached approximately 28.5 billion dollars in 2014 [17]. Studies from several countries reported substantial increases in prescription rates of statins, including increased daily doses of statins [18-22]. Likewise, drug expenditure for statins has increased from 496 billion won in 2010 to 786 billion won in 2016 in Korea [2,3]. It should also be noted that there are many "me-too" drugs, including generics or follow on drugs, under the statin category [12]. For example, atorvastatin,

fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin, as well as a number of generics, are now available for hypercholesterolemia patients in the Korean market.

Given the market size of statins and a number of "me-too" drugs and generic statins, statin utilization, including switching drugs, in health systems has been the subject of considerable interest in the perspective of clinical pharmacy and public health [23-29]. For instance, several European countries have restricted the prescribing of patented statins when generic statins became available at a much lower cost [30,31]. However, notably few studies have dealt empirically with the issue or included real-world data with statin users, especially in Korea. Meanwhile, it was reported that drug switching among statin users is low in Korea [2]. Therefore, we selected new statin users to understand statin utilization and market dynamics of statins in Korea. Given the limited drug switching among statin users, analysing statin utilization of new users could be used as an important resource to evaluate the use of statins and to assess market dynamics of statins in Korea.

This study analysed the utilization of statins for new statin users and assessed the market dynamics of statins. Specifically, this study examined characteristics of new statin users and the prescribing of statin drugs over the last thirteen years, investigated the association between medical history of patients and intensity of statins, and analysed market dynamics of statins, including market

penetration and switching among new statin users.

Methods

Data source

This study used the National Health Insurance Service-National Sample Cohort (NHIS-NSC), a population-based cohort established by the National Health Insurance Service [32]. The dataset is comprised of approximately 1 million individuals (approximately 2% of the population) selected randomly from South Koreans. The NHIS built a target population of 46,605,433 individuals in 2002, and then 1,025,340 participants was randomly selected from the target population. Specifically, systematic stratified random sampling with proportional allocation within each stratum was conducted to construct the cohort [32].

The cohort dataset consists of four databases on participants' insurance eligibility, medical treatments, health care institutions, and general health examinations for the period from January 1, 2002, to December 31, 2015 [32]. The dataset provides information on demographic and socioeconomic characteristics, such as age, gender, and level of income. Income level was calculated based on the insurance premium that participant pays. Also, patients' disease diagnosis was coded based on the International Classification of Diseases-10th Revision (ICD-10), and the corresponding

medical expenditure such as medical and prescription information are available. The prescription information covers the date and duration of the prescription, the prescribed drugs' international nonproprietary names (INN), dosage, the route of administration, prescribers' specialty and the types of the healthcare institution.

Study design

This study is interested in new statin users. New statin users were defined as those who had not been prescribed any statin in the year prior to the date of the first statin prescription observed in the cohort dataset [33]. Therefore, new statin users in each year from 2003 to 2015 were included in the study population of each year. Specifically, the first prescription for outpatients that included any statin was set as an index date and analysed in the study.

The studied drugs include the statins atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. The information of individual drugs marketed in Korea are stated in Appendix 1. In this study, we defined mono-therapy as only one statin prescription, while we defined combination therapy as prescription for a statin plus other lipid-lowering drugs, including fibrates or ezetimibe. In addition, we searched the market of statins in Korea, including the entry of new drugs and follow on drugs and their pricing information on the website of the Ministry of Food and

Drug Safety (MFDS)[1] and the Health Insurance Review and Assessment Service (HIRA)[2], respectively. In Korea, co-payment for medicines that prescribed for outpatients are 30% of total expenditure, including pharmacy preparation charge, thus financial burden is less likely to influence the statin adherence, unlike previous study [34].

Statins were grouped into three levels of intensity [10,35]: high-intensity statins; moderate-intensity statins; and low-intensity statins. Daily doses can be calculated from the prescription data. High-intensity statins include atorvastatin ≧40 mg/day, rosuvastatin ≧20 mg/day and simvastatin ≧80 mg/day. Low-intensity statins include atorvastatin <10 mg/day, rosuvastatin <5 mg/day, simvastatin <20 mg/day, pravastatin <40 mg/day, lovastatin <40 mg/day, pitavastatin <2mg/day and fluvastatin <80 mg/day. Lastly, moderate-intensity statins include 10 mg/day ≦ atorvastatin <40 mg/day, 5 mg/day ≦ rosuvastatin <20 mg/day, 20 mg/day ≦ simvastatin <80 mg/ day, pravastatin ≧40 mg/day, lovastatin ≧40 mg/ day, pitavastatin ≧2 mg/ day and fluvastatin ≧80 mg/day.

All new statin users were classified based on their disease history, including hypertension (I10-I15),

[1] available at http://drug.mfds.go.kr/html/search_total_download_itemPermit.jsp

[2] available at https://biz.hira.or.kr/popup.ndo?formname=qya_bizcom%3A%3AInfoBank.xfdl&framename=InfoBank

diabetes (E10-E14), diseases of arteries, arterioles and capillaries (I70-I79), ischemic heart disease (I20-I25), cerebrovascular diseases (I60-I69), chronic obstructive pulmonary disease (J44), heart failure (I50), chronic kidney diseases (N17-N19), and atrial fibrillation (I48). Disease history was identified by the ICD-10 codes. Among these diseases, diabetes, diseases of arteries, arterioles and capillaries, cerebrovascular diseases, and heart failure are related to the use of statins for CVD prevention [14,15,36-38]. Individuals were identified as having a disease history of the specific disease if they had a primary diagnosis that corresponded to each diagnosis within three years prior to the first prescription date [38,39].

Lastly, to investigate the association between the providers' characteristics and the intensity of the statin prescribed, we sorted medical institutions by primary-, secondary-, and tertiary institutions. Primary care institutions include clinic-level medical institutions that provide medical services to outpatients. Secondary care institutions include hospital-level medical institutions that provide health services primarily to inpatients. Tertiary care institutions include superior general hospitals, designated by the Minister of Health and Welfare, that provide medical service requiring high level of expertise for treating serious disease.

Data analysis

This study used descriptive statistics to examine characteristics of new statin users and prescribed statin drugs, employed the χ^2 test to investigate the associations between certain disease history and prescription of moderate- or high-intensity statins, and applied interrupted time series analysis to understand the market dynamics of statins. In time series analysis, we estimated the effect of the introduction of generics on the market, specifically for newly prescribed statin users [40]. We presented the result of simple linear regression before and after the introduction of generics [41]

$$Y_t = \beta_0 + \beta_1 \mathrm{T} + \beta_2 X_t + \beta_3 \mathrm{T} X_t$$

Y_t: the number of new users that prescribed the certain statin at time t

T: the time elapsed since the start of the study

X_t: a dummy variable indicating the pre-intervention period or the post-intervention period

It should be noted that we defined the intervention year as the year when the price of originals were discounted due to the entry of follow on drugs. Generally speaking, the price of originals was

discounted as soon as the entry of the follow on drugs, in case of atorvastatin that occurred in 2008. However, the price reduction of original rosuvastatin was deferred until 2014 for the reason of valid patent that original rosuvastatin has until 2014, even though the follow on drugs were available in 2008. Therefore, we used the year of 2008 and 2014 as the intervention year of the model for atorvastatin and rosuvastatin, respectively. Data management and analysis were performed using the R statistical software (version 3.4.1). P-values under 0.05 were considered to be significance.

Ethical statement

This study used a de-identified secondary dataset. Therefore, it was exempted from review by the Institutional Review Board (IRB) of Ewha Womans University (IRB No. 158-10).

Patient and public involvement

No patients were involved in developing the research question, outcome measure, and design of the study. We are unable to disseminate the results of the research directly to study participants.

Results

Characteristics of new statin users over time

Table 1 presents characteristics of new statin users over time. Incidence of new statin user increase from 838.1/100,000 persons in 2003 to 1626.9/100,000 persons in 2015. There have been more

female new users than male new users, while the portion of female new statin users steadily declined from 56.5% in 2003 to 50.4% in 2015. During this period, the average age of new statin users with standard deviation remained steady (54.31 – 56.52 years old with 11.82 – 12.89 standard deviations). We also sorted new statin users by their income quintile. The portion of the first quintile (the lowest income) increased from 13% in 2003 to 16% in 2015, while the portion of the fifth quintile (the highest income) decreased from 33% in 2003 to 30% in 2015. In 2003, hypertension accounted for the highest portion of comorbidities (55%), followed by diabetes (37%), ischemic heart disease (21%), diseases of arteries, arterioles and capillaries (14%), and cerebrovascular diseases (12%). These trends remained steady in 2015.

Characteristics of prescribed statin drugs among new statin users

Table 2 shows characteristics of prescribed statin drugs among new statin users. The majority of patients were prescribed with a single statin (monotherapy) when they started hypercholesterolemia treatment, while few new users were prescribed combination therapy during the study period.

The market for monotherapy statins is dynamic. In 2003, simvastatin (37%) was the most prescribed statin, followed by lovastatin (30%) and atorvastatin (18%). The market share of simvastatin had been the highest in the market from 2003 (37%) to 2007 (50%). During this period, the market share

of atorvastatin was steady (18-20%), while the market share of lovastatin decreased from 30% in 2003 to 4% in 2007. Similarly, the market share of simvastatin decreased after 2008, while the market share of atorvastatin increased and maintained the highest from 46% in 2008 to 66% in 2013. Lastly, the market share of rosuvastatin increased from 8% in 2013 to 36% in 2015, while that of atorvastatin decreased from 66% to 49% during the same period. In 2015, statins for new users were an oligopoly market: atorvastatin (49%) was the most prescribed statin, followed by rosuvastatin (36%).

In 2003, the prescription rates of low-intensity and moderate-intensity statins were 43% and 57%, respectively. However, the prescription rate of moderate-intensity statins consistently increased to 92% in 2015, while the prescription rate of low-intensity statins decreased to 3% in 2015. In addition, the use of high-intensity statins steadily increased during the study period. We also examined health care institutions that prescribed statins. In 2003, 63% of new statin users were prescribed at primary healthcare institutions followed by secondary- (20%) and tertiary care institutions (14%). During the study period, the portion of new users prescribed at primary and tertiary healthcare institutions decreased, while the portion of new users prescribed at secondary healthcare institutions increased. In 2015, 58% of new statin users were prescribed at primary healthcare institutions followed by secondary- (29%) and tertiary healthcare institutions (11%).

Figure 1 shows statin prescription by health care institutions and the intensity of prescribed statins. The first graph in Figure 1 presents overall patterns of the prescription rates of low-, moderate-, and high-intensity statins in all institution types. The remaining graphs indicate patterns of prescription rates in primary-, secondary-, and tertiary healthcare institutions. We found that prescription rates of moderate-intensity statins were high in primary healthcare institutions, while those of high-intensity statins were high in tertiary care institutions. It is interesting to note that prescription rates of moderate-intensity statins in primary-, secondary-, and tertiary healthcare institutions in 2003 was 48%, 69%, and 78%, respectively. However, prescription rates of moderate-intensity statins reversed in primary, secondary, and tertiary healthcare institutions in 2015: 95%, 90%, and 84%, respectively.

Figure 2 presents prescription rates of selected statins, including atorvastatin, rosuvastatin, and simvastatin, during the study period. The first graph in Figure 2 shows market shares of selected statins among new statin users. Two points are noteworthy in the perspective of market dynamics. The first market dynamic occurred during 2007-2009. Specifically, atorvastatin penetrated the market of simvastatin in this period. Similarly, the second market dynamic occurred during 2013-2015. Rosuvastatin penetrated market of atorvastatin in this period. The remaining graphs present new

statin users of selected statins by primary-, secondary-, and tertiary- healthcare institutions. In this figure, we conclude that the majority of market switching of statins among new statin users occurred immediately at primary healthcare institutions.

Table 3 indicates the associations between certain disease histories and the prescription of moderate- or high-intensity statins. Interestingly, no substantial differences in the prescription of statins were observed through the study period in groups with histories of diseases of arteries, arterioles and capillaries. Furthermore, patients with history of diabetes, cerebrovascular diseases, and ischemic heart disease were less likely to be prescribed moderate- or high-intensity statins in several selected years. For instance, odds ratios were calculated at 0.78 and ranged from 0.67 to 0.91 with 95% confidence interval in 2012 for patients with diabetes.

Interrupted time series analysis

Table 4 presents results of segmented regression analysis using the interrupted time series method: β_0 is the pre period intercept; β_1 is the pre period slope (baseline time trend); β_2 is the immediate effect of the event on the intercept; and β_3 is the slope change after the event. In the case of atorvastatin, the immediate effect of marketing generics was 3,236 new users ($p < 0.001$), and the growth rate was increased by 2,687 new users per year ($p < 0.005$) compared with previous trends.

Similar trends were found in the case of rosuvastatin.

Discussions

This 13-year longitudinal study of a sample cohort provided by the NHIS found that incidence of new statin user increase from 838.1/100,000 persons in 2003 to 1626.9/100,000 persons in 2015. Most new users were initiated on a monotherapy that was prescribed at primary healthcare institutions. In addition, the use of moderate-intensity statins increased, notably at primary healthcare institutions. Specifically, the prescription rate of moderate-intensity statins at primary healthcare institutions was low (48%) in 2003. However, the figure was doubled in 2015 (95%).

The characteristics of new statin users and health care institutions that prescribed statins were similar to other studies that investigated prescription patterns of all statin users in Korea [2,3]. It is noteworthy to compare the results of statin prescription for new users with other countries [33,42-45]: statin market for new users is quite dynamic in Korea.

First, the most commonly used statin changed several times during the study period in Korea, while atorvastatin has been the most prescribed statin during 2002-2011 in Taiwan [33]. For instance,

simvastatin had the highest prescription rate until 2007, while atorvastatin had the highest prescription rate after 2008. It should be noted that generics of atorvastatin were available with discounted prices compared to the originals of the previous year (approximately 68%) in 2008, and the price of the originals was discounted approximately 20% compared to the previous year. We could find similar results in the case of rosuvastatin. Generics of rosuvastatin were available in 2010 and the prices of generics were 0.41 $[3], 0.61 $, and 0.81 $ for a single tablet of 5 mg, and 10 mg, and 20 mg, respectively, which account for approximately 68% of the original counterparts. In such a case of the introduction of generics, the prices of originals would be decreased to 80% compared to the previous year. However, price reduction was deferred until 2014 in this case for the reason of valid patent that original rosuvastatin has until 2014. In the end, the price of original rosuvastatin decreased to approximately 80% compared to that of the previous year in 2014. It is interesting to note the prescription rates of rosuvastatin: the market share of rosuvastatin in 2009 was 7% and slightly increased 9% in 2010 when generics with discounted prices (approximately 32%) were marketed, and later increased 33% in 2014 when prices of the original were discounted (approximately 20%). It means that the sole introduction of generics is not quite effective in expanding the market in Korea. However, discounted price of the original after the introduction of generics was related with the market expansion.

[3] Exchange rate is 1,100 won / dollar

Interestingly, patterns of prescription found in this study is quite different from other studies in different regions. For instance, the incidence of new treatments decreased for atorvastatin and increased for simvastatin in Italia, Denmark, and Spain [46-48]. Specifically, the market share of statin for new users in Southern Italian primary care was in the order of simvastatin (34%), atorvastatin (26.6%), and rosuvastatin (15.4%) [48]. Furthermore, the vast majority of new users were started treatments with simvastatin in Northern Denmark from 2004 to 2010 [47]. However, in Korea simvastatin has been losing market share since 2008 and the current market share of simvastatin is marginal (3%) in 2015.

Second, the portion of moderate-intensity statins was high in Korea. For instance, the portion of low-, moderate-, and high-intensity statins among new statin users in Korea was 5%, 93%, and 2% in 2011. However, the portion of low-, moderate-, and high-intensity statins in Taiwan was 27%, 71%, and 2% in the same year. Lastly, the portion of low-, moderate-, and high-intensity statins in Spain was 4%, 72%, and 24% from 2006 to 2010. Given these findings, we could conclude that Korean general practitioners or specialists frequently prescribes moderate-intensity statins. In line with this result, we found no substantial differences in the prescription of moderate- or high-intensity statins in groups with histories of hypertension, diabetes, diseases of arteries, arterioles

and capillaries, cerebrovascular diseases, and ischemic heart disease in Korea.

Korean guidelines for the management of dyslipidemia states that the first goal is LDL-C [49]. Statin is the first-choice drug for the treatment of hypercholesterolemia (class of recommendation I, level of evidence A) because it has a relatively low risk profile and proven effects of decreasing CVD by lowering LDL-C. *"Statins should be prescribed"* and the dose adjusted to reach the LDL-C target level for high-risk and very high-risk groups (I, A), whereas *"statin use should be considered"* if LDL-C is not reduced to the first target even after lifestyle modification for weeks or months (IIa, B). The guidelines also provide dosage and administration of statins: lovastatin 20-80 mg/day, pravastatin 10-40 mg/day, simvastatin 20-40 mg/day, fluvastatin 20-80 mg/day, atorvastatin 10-80 mg/day, rosuvastatin 5-20mg/day, and pitavastatin 1-4 mg/day. Interestingly, atorvastatin and rosuvastatin, the top-2 best-selling statins in Korea, was recommended as moderate- and high-intensity dosage.

In addition, we found that the pricing and marketing strategies of manufacturers might encourage physicians to prescribe moderate- and high-intensity statins. For instance, the manufacturer discounted the price of simvastatin 40 mg (approximately 34%) in 2003, and the price was the same as simvastatin 20 mg. Likewise, the other manufacturer that produce atorvastatin utilized the same

strategy: the manufacturer discounted the price of atorvastatin 40 mg (35%) in 2003, and the price was the same as atorvastatin 20 mg; and the manufacturer discounted the price of atorvastatin 20 mg (30%) in 2007, which was the same price as atorvastatin 10 mg. In addition, the manufacturer marketed atorvastatin 80 mg in the market to preempt the high-strength statins market in 2008.

Third, we found market expansion when price of original statins were discounted. It is interesting to analyse market expansion by health care institutions. In cases of atorvastatin and rosuvastatin, the immediate effect of the event was large in primary healthcare institutions. For instance, the immediate effect of marketing generics of rosuvastatin was 3,163 users ($p < 0.0000$) and 517 users ($p < 0.005$) in primary- and secondary- healthcare institutions, respectively. However, the immediate effect of the event in tertiary care institutions was marginal and insignificant: 16.2 ($p = 0.78$) for atorvastatin and 7.1 ($p = 0.95$) for rosuvastatin. These results demonstrate that the discounted price of originals after the introduction of generics immediately expands markets, particularly in primary healthcare institutions. However, the growth rates, sorted by health care institutions, after the event vary according to drugs. For instance, the growth rate of atorvastatin was in the order of primary-, secondary-, and tertiary healthcare institutions, 1,597 ($p < 0.0001$), 736 ($p < 0.05$), and 352 ($p < 0.001$), respectively, while that of simvastatin was in the order of secondary-, primary-, and tertiary healthcare institutions, 2,243 ($p < 0.0001$), 178 ($p < 0.05$), and 33 ($p = 0.80$), respectively,

This study notably analysed the utilization of statins for new statin users and assessed the market dynamics of statins over the last thirteen years with a real-world dataset provided by the NHIS. However, this study has several limitations. First, this study used claims data that does not contain information on biochemical test data of patients, such as LDL cholesterol level. It means that we could not assess prescription patterns by disease severity. In addition, the claims data does not contain information on whether the prescribed drugs were originals or generics. Therefore, further research is needed to assess the impact of generics on the market, including the contribution to market expansion by originals and generics, respectively. Second, this study used sample data and assumed that the data is to be representative, yet attention should be paid when generalize our results. Lastly, this study only used the first prescription that included any statins. Therefore, switches among statins were not included in the study. However, it would be reasonable to assume that switches among statins would be low in the Korean market [2].

Conclusions

Similar to other countries, the incidence of new statin users has been increased in Korea. However, the statin market in Korea is quite dynamic compared to other countries. It is noteworthy that the portion of new statin users that were prescribed moderate intensity statins has increased during

the study period. In addition, no substantial differences in the prescriptions of statins were observed in groups with selected disease histories. Interestingly, discounted price of originals after the introduction of generics immediately expand markets or substitute the market particularly in primary healthcare institutions in Korea.

Contributors KS designed the study, collected and analyzed data, wrote, and revised the manuscript. SB wrote the draft and revised the paper for important intellectual content. All authors read and approved the final manuscript.

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Table 1. Characteristics of new statin users over time

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Incidence (100,000 person)	838.1	893.2	1118.2	1256.4	1277.4	1341.7	1532.3	1497.8	1472.4	1508.4	1463.5	1640.3	1626.9
Sex													
Female	56.5%	55.0%	56.8%	55.8%	54.8%	54.3%	55.2%	54.6%	53.2%	53.1%	52.0%	50.7%	50.4%
Age													
Mean	54.40	54.31	55.15	55.61	55.62	55.48	55.61	55.71	55.58	55.65	55.57	56.52	55.90
SD	11.82	12.00	12.15	12.47	12.68	12.52	12.51	12.39	12.46	12.71	12.89	12.79	12.75
Income level (the quintile)													
The first	13%	14%	15%	15%	15%	14%	15%	15%	15%	15%	16%	16%	16%
The second	13%	13%	12%	14%	13%	14%	14%	15%	15%	15%	14%	15%	15%
The third	17%	17%	18%	16%	18%	18%	18%	17%	18%	17%	17%	17%	17%
The fourth	24%	23%	22%	23%	23%	23%	23%	23%	22%	22%	23%	22%	22%
The fifth	33%	32%	33%	32%	32%	31%	30%	31%	30%	30%	30%	30%	30%
Comorbidities													
Hypertension	N/A		55%	59%	58%	58%	56%	54%	53%	53%	52%	52%	48%
Diabetes			37%	39%	40%	39%	37%	36%	36%	37%	38%	41%	39%
DoA			14%	17%	20%	24%	25%	25%	23%	22%	21%	22%	20%
IHD			21%	22%	22%	21%	19%	19%	19%	18%	17%	18%	16%
CeVD			12%	13%	15%	15%	15%	15%	14%	15%	15%	14%	14%
COPD			5%	6%	6%	6%	5%	5%	5%	5%	5%	5%	4%
Heart failure			5%	4%	4%	4%	3%	4%	4%	4%	4%	4%	4%
CKD			2%	2%	2%	2%	2%	2%	2%	2%	3%	3%	3%
Afib			2%	2%	2%	3%	2%	2%	2%	2%	2%	3%	2%

Notes: DoA: diseases of arteries, arterioles and capillaries; IHD: ischemic heart disease; CeVD: cerebrovascular diseases; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney diseases; and Afib: atrial fibrillation

Table 2. Characteristics of prescribed statin drugs among new statin users

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Number of new statin users	8,205	8,835	11,181	12,564	12,774	13,333	15,139	14,713	14,374	14,639	14,117	15,731	15,514
Monotherapy	**100%**	**100%**	**99%**	**98%**	**97%**	**98%**	**97%**	**97%**	**95%**	**94%**	**95%**	**96%**	**95%**
Atorvastatin	18%	19%	20%	18%	18%	46%	61%	61%	62%	63%	66%	51%	49%
Fluvastatin	4%	2%	2%	4%	4%	2%	1%	1%	1%	1%	1%	1%	0%
Lovastatin	30%	18%	12%	6%	4%	2%	1%	1%	1%	0%	0%	0%	0%
Pitavastatin	0%	0%	1%	7%	9%	7%	4%	4%	4%	4%	6%	5%	5%
Pravastatin	11%	8%	6%	5%	4%	4%	3%	3%	3%	2%	2%	2%	1%
Rosuvastatin	0%	2%	7%	9%	8%	7%	7%	9%	8%	8%	8%	33%	36%
Simvastatin	37%	50%	52%	49%	50%	31%	20%	18%	16%	14%	9%	5%	3%
Combination	**0%**	**0%**	**1%**	**2%**	**3%**	**2%**	**3%**	**3%**	**5%**	**6%**	**5%**	**4%**	**5%**
Intensity													
Low	43%	25%	17%	11%	9%	6%	5%	5%	5%	5%	5%	3%	3%
Moderate	57%	75%	83%	88%	90%	94%	94%	94%	93%	93%	93%	92%	92%
High	0%	0%	0%	0%	1%	1%	1%	2%	2%	2%	2%	4%	5%
Institution													
Primary	63%	61%	59%	59%	58%	58%	56%	56%	56%	57%	56%	58%	58%
Secondary	20%	23%	25%	26%	26%	25%	27%	28%	28%	28%	29%	29%	29%
Tertiary	14%	13%	13%	14%	14%	13%	14%	13%	14%	13%	12%	11%	11%
Others	3%	2%	2%	2%	3%	3%	4%	3%	3%	2%	2%	2%	2%

Table 3. Associations between disease history and prescription of moderated- or high-intensity statins

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
History of hypertension	1.04	1.16	1.04	0.92	1.01	0.98	1.09	1.04	1.02	1.05	1.20
	0.94-1.15	1.03-1.29	0.92-1.18	0.80-1.07	0.87-1.18	0.84-1.14	0.94-1.26	0.90-1.20	0.87-1.19	0.88-1.24	1.00-1.44
History of diabetes	1.12	1.15	0.99	0.94	0.75	0.82	0.78	0.78	0.92	0.83	0.92
	1.01-1.24	1.03-1.29	0.88-1.12	0.81-1.09	0.64-0.87	0.70-0.96	0.68-0.91	0.67-0.91	0.78-1.08	0.69-0.99	0.76-1.11
History of DoA	1.00	0.99	1.01	1.01	1.02	1.08	0.98	1.08	1.10	1.02	1.03
	0.87-1.15	0.86-1.14	0.87-1.18	0.85-1.20	0.85-1.21	0.91-1.30	0.83-1.17	0.91-1.31	0.91-1.34	0.82-1.25	0.82-1.30
History of CeVD	1.18	1.20	0.84	0.83	0.69	0.88	0.70	0.85	0.80	0.72	0.77
	1.00-1.38	1.01-1.42	0.71-0.99	0.69-1.01	0.57-0.83	0.71-1.08	0.58-0.84	0.70-1.04	0.65-0.98	0.58-0.90	0.60-0.98
History of IHD	1.41	1.26	1.04	1.02	0.76	0.75	0.94	0.88	1.01	1.06	0.92
	1.24-1.60	1.09-1.44	0.90-1.21	0.85-1.22	0.64-0.91	0.63-0.90	0.78-1.13	0.73-1.06	0.82-1.23	0.85-1.33	0.72-1.18

Notes: DoA: diseases of arteries, arterioles and capillaries; IHD: ischemic heart disease; CeVD: cerebrovascular diseases;

Table 4. Results of segmented regression analysis of interrupted time series method

	Total			Primary care			Secondary care			Tertiary care		
	Coefficient	**Standard error**	**p-value**	**Coefficient**	**Standard error**	**p-value**	**Coefficient**	**Standard error**	**p-value**	**Coefficient**	**Standard error**	**p-value**
Atorvastatin (2003-2009)												
β_0 :Intercept	2611.9	168.5	< 0.001	850.3	46.4	< 0.001	1109.8	102.7	< 0.005	651.8	38.7	< 0.001
β_1 :Time	221.5	50.8	< 0.05	75.1	14.0	< 0.05	108.2	32.5	< 0.05	38.2	11.7	< 0.05
β_2 :Generic	3236.1	232.8	< 0.001	2846.7	64.1	< 0.0001	373.2	148.8	0.087	16.2	53.5	0.78
β_3 :Time:Generic	2687.5	232.8	< 0.05	1597.9	64.1	< 0.0001	736.8	148.8	< 0.05	352.8	53.5	< 0.01
Rosuvastatin (2004-2015)												
β_0 :Intercept	1376.5	141.9	< 0.001	295.7	29.1	< 0.001	655.9	59.0	< 0.001	424.9	61.8	< 0.0001
β_1 :Time	76.1	22.9	< 0.05	13.5	4.7	< 0.05	42.8	9.5	< 0.005	19.8	10.0	0.08
β_2 :Generic	3687.5	251.6	< 0.0001	3163.3	51.6	< 0.0001	517.1	104.5	< 0.0051	7.1	109.6	0.95
β_3 :Time:Generic	2453.9	294.7	< 0.0001	177.5	60.4	< 0.05	2243.2	122.4	< 0.0001	33.2	128.4	0.80

Notes: β0 is the pre period intercept; β1 is the pre period slope (baseline time trend); β2 is the immediate effect of the event on the intercept; β3 is the slope change after the event;

Figure 1. Statin prescriptions by institution and intensity a) all; b) primary-; c) secondary-; and d) tertiary healthcare institutions

Figure 2. Prescribing rates of selected statins among new statin users

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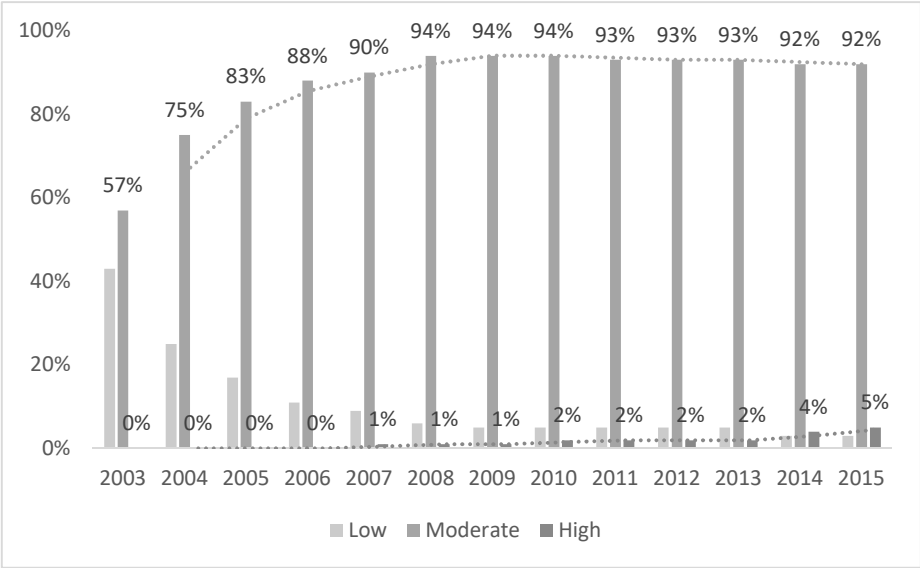
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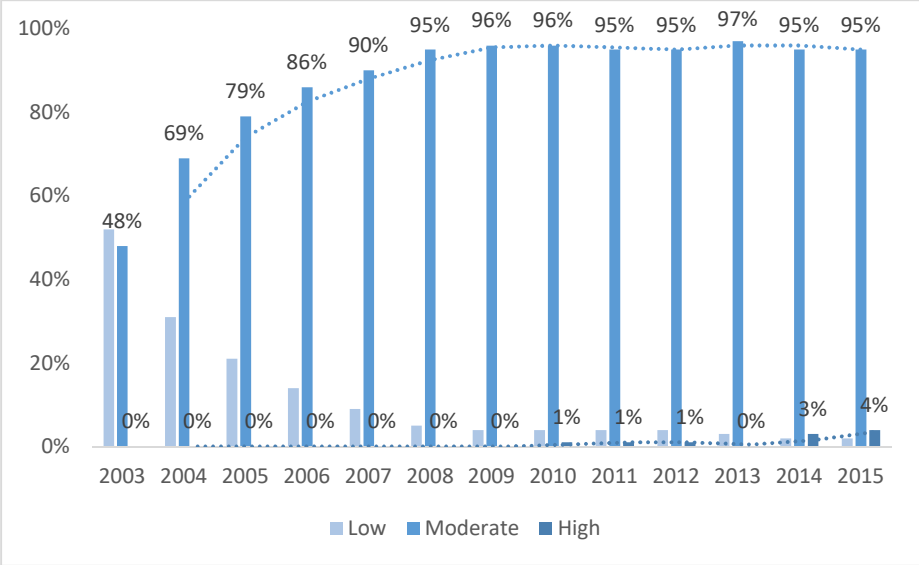
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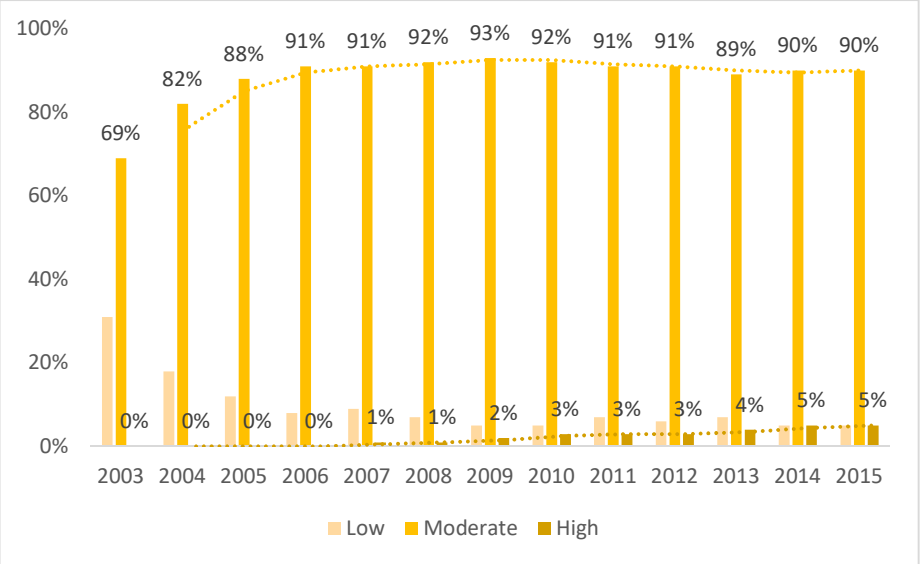
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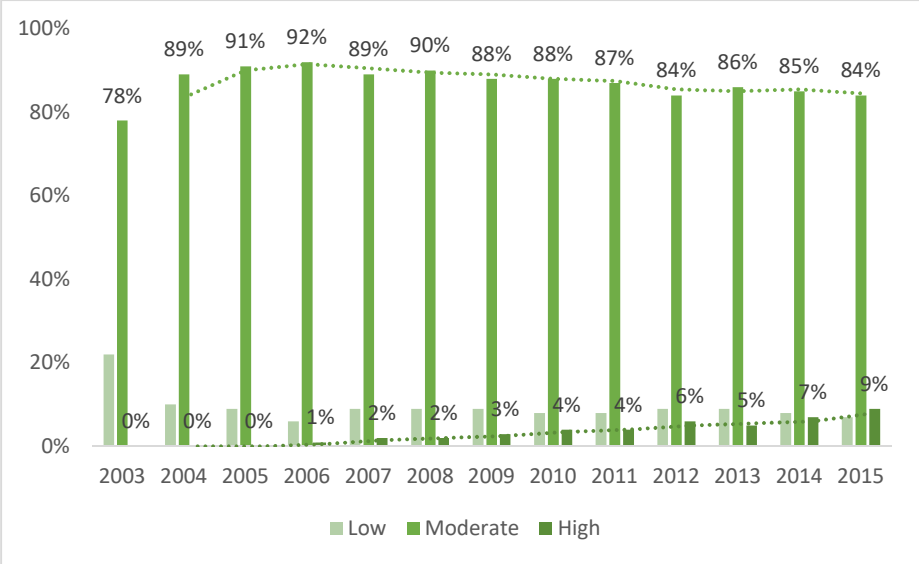
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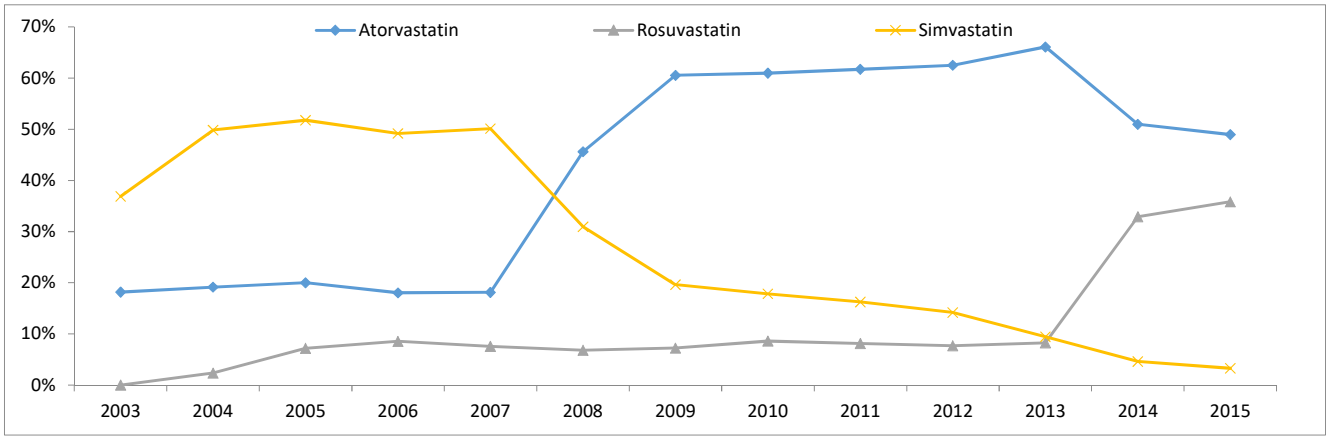
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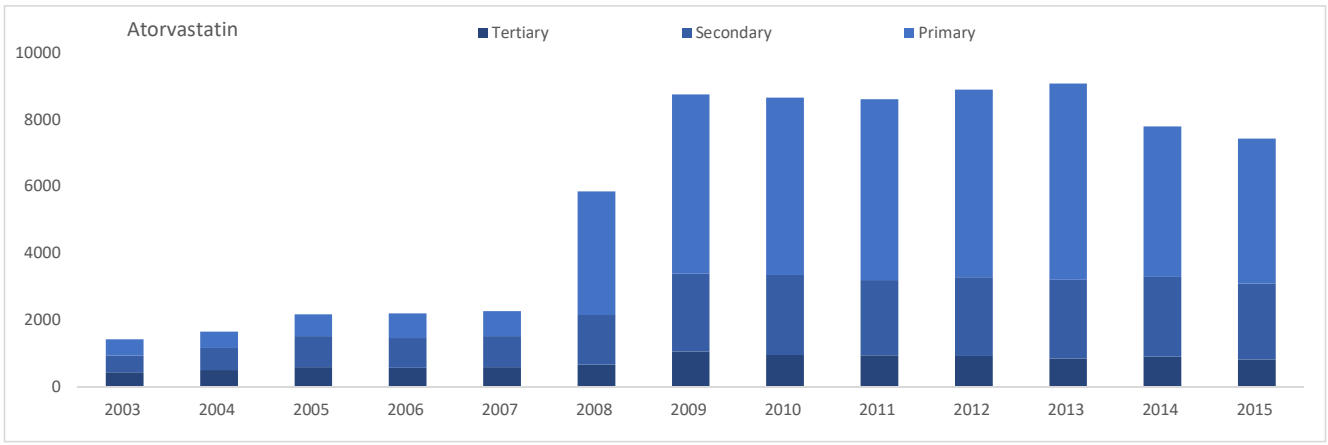
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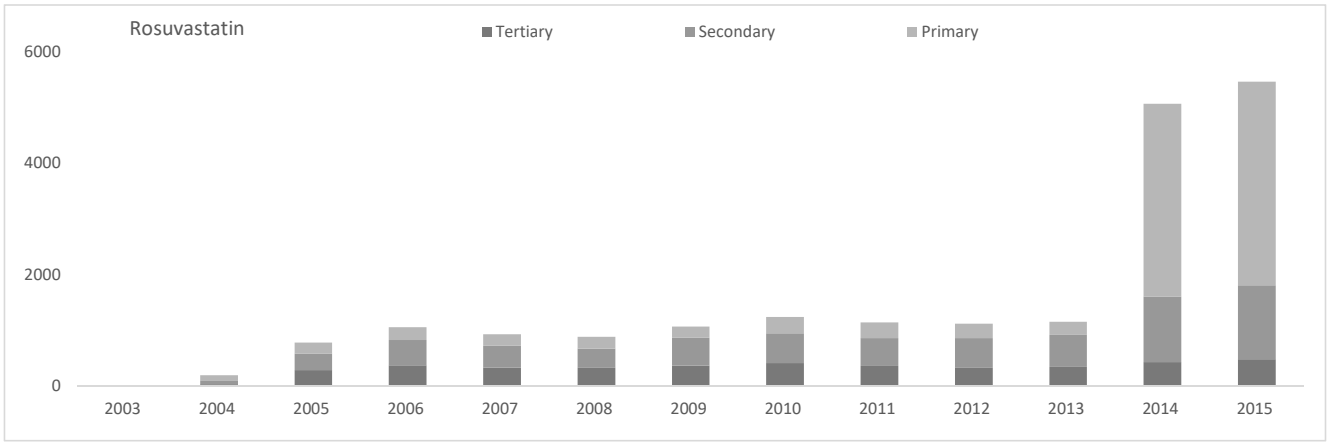
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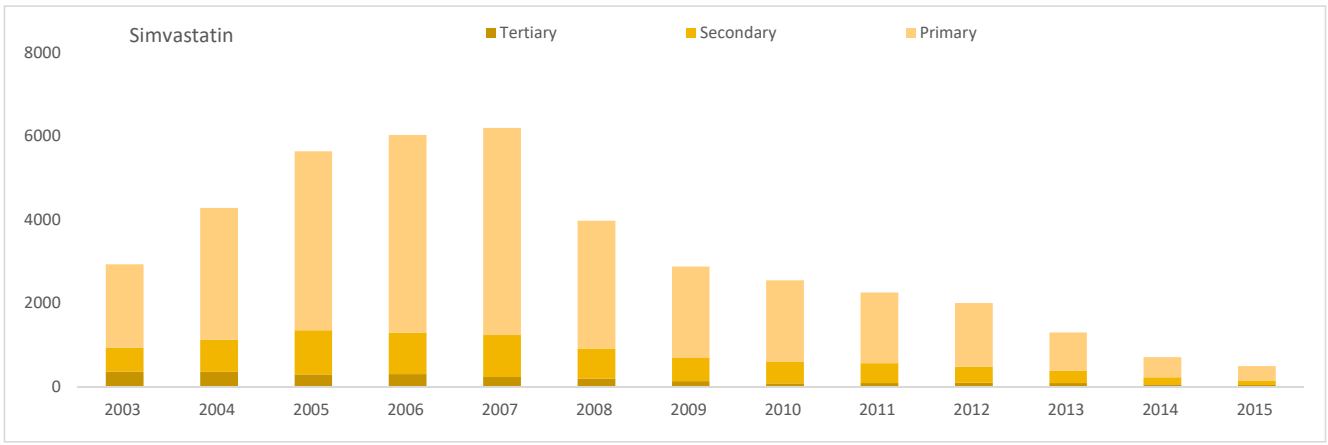
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Appendix 1. Drug code of statins in Korea

Drug Names	ATC code	National Code System (Strength and code)		The date of drug entry	
				New drug	First follow on drug
Atorvastatin	C10AA05	10	111501ATB	1999.08.01	2007.01.17
		20	111502ATB		
		40	111503ATB		
		80	111504ATB		
Fluvastatin	C10AA04	20	162401ACH	1994.10.10	N/A
		40	162402ACH		
		80	162403ATR		
Lovastatin	C10AA02	20	185801ATB	1997.08.06	1997.12.11
Pitavastatin	C10AA08	1	470902ATB	2005.01.06	2011.05.24
		2	470901ATB		
		4	470903ATB		
Pravastatin	C10AA03	5	216602ATB	1990.04.10	1994.05.17
		10	216601ATB		
		20	216603ATB		
		40	216604ATB		
Rosuvastatin	C10AA07	5	454003ATB	2002.01.15	2008.11.07
		10	454001ATB		
		20	454002ATB		
Simvastatin	C10AA01	5	227805ATB	1996.08.01	2002.07.09
		10	227803ATB		
		20	227801ATB, 227801ATR		
		40	227802ATB		
		80	227806ATB		
Ezetimibe and atorvastatin	C10BA05	10 + 10	633800ATB		
		10 + 20	633900ATB		
		10 + 40	634800ATB		
Ezetimibe and rosuvastatin	C10BA06	10 + 5	640700ATB		
		10 + 10	640800ATB		
		10 + 20	640900ATB		
Ezetimibe and simvastatin	C10BA02	10 + 10	471000ATB		
		10 + 20	471100ATB		
Fenofibrate and simvastatin	C10BA04	145 + 20	631400ATB		
		145 + 40	631500ATB		

ATC: anatomical therapeutic chemical

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Page #	Recommendation
Title and abstract	1	2	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		2	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	2	7	Explain the scientific background and rationale for the investigation being reported
Objectives	3	7	State specific objectives, including any prespecified hypotheses
Methods			
Study design	4	9-11	Present key elements of study design early in the paper
Setting	5	8-9	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	9-11	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		N/A	(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	9-13	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	9-11	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	N/A	Describe any efforts to address potential sources of bias
Study size	10	N/A	Explain how the study size was arrived at
Quantitative variables	11	9-13	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	9-13	(*a*) Describe all statistical methods, including those used to control for confounding
		N/A	(*b*) Describe any methods used to examine subgroups and interactions
		N/A	(*c*) Explain how missing data were addressed
		N/A	(*d*) If applicable, explain how loss to follow-up was addressed
		N/A	(*e*) Describe any sensitivity analyses
Results			
Participants	13*	13-14	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		13-14	(b) Give reasons for non-participation at each stage

		N/A	(c) Consider use of a flow diagram
Descriptive data	14*	14-17	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		N/A	(b) Indicate number of participants with missing data for each variable of interest
		N/A	(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	13-14	Report numbers of outcome events or summary measures over time
Main results	16	13-17	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		N/A	(*b*) Report category boundaries when continuous variables were categorized
		N/A	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	N/A	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18	18	Summarise key results with reference to study objectives
Limitations	19	22-23	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	18-23	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	22-23	Discuss the generalisability (external validity) of the study results
Other information			
Funding	22	24	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Patterns of statin utilization for new users and market dynamics in South Korea: A 13-year Retrospective Cohort Study

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Keywords:	statins, statin utilization, a retrospective study, South Korea

Patterns of statin utilization for new users and market dynamics in South Korea: A 13-year Retrospective Cohort Study

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Patterns of statin utilization for new users and market dynamics in South Korea: A 13-year Retrospective Cohort Study

Objective: This study analyzed utilization of statins for new statin users and assessed market dynamics of statins in South Korea.

Design: This study is a retrospective cohort study.

Setting: The yearly claims data for statins were retrieved from the National Health Insurance Service-National Sample Cohort.

Main outcome measure: We are interested in new statin users during 2003-2015 in Korea. Information on prescribed statins, including intensity of statins and entry of new and follow-on statins in the market, and health care institutions that prescribed the statins were also collected. In time series analysis, we estimated the effect of introduction of generics in the market, specifically for newly prescribed statin users.

Results: This 13-year longitudinal study of a sample cohort provided by the NHIS found that the incidence of new statin user increase from 838.1/100,000 persons in 2003 to 1626.9/100,000 persons in 2015. Most new users were initiated on a monotherapy that was prescribed at primary healthcare

institutions. However, the statin market for new users were quite dynamic in Korea. Firstly, the most commonly prescribed statin changed several times during the study period. Secondly, the use of moderate-intensity statins increased from 57% in 2003 to 92% in 2015. In line with this result, we could not observe substantial differences in prescription of statins in groups having selected diseases history. Lastly, we found market invasion or switch of statins among new statin users, specifically at primary healthcare institutions.

Conclusion: Similar to other countries, the incidence of new statin users has been increased in Korea. However, the statin market in Korea is quite dynamic compared to other countries. Interestingly, discounted price of originals after the introduction of generics immediately expand markets or substitute the market particularly in primary healthcare institutions in Korea.

Strengths and limitations of this study

Given the market size of statins and a number of "me-too" drugs and generic statins, statin utilization, including switching drugs, in health systems has been the subject of considerable interest.

The National Health Insurance Service-National Sample Cohort (NHIS-NSC), a population-based cohort, provides public health researchers useful information regarding utilization of health services.

This 13-year longitudinal study of a sample cohort presented that the incidence of new statin user increase from 838.1/100,000 persons in 2003 to 1626.9/100,000 persons in 2015.

Patterns of prescription and market dynamics of statins found in this study is quite different from other studies in different regions.

Interestingly, discounted price of originals after the introduction of generics immediately expand markets or substitute the market particularly in primary healthcare institutions in Korea.

A funding statement:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

A competing interests statement

Non-financial and any similar financial associations that may be relevant to the submitted manuscript.

Introduction

Cardiovascular diseases (CVDs) account for 31% of all global deaths, taking the lives of 17.7 million people annually [1]. Similarly, CVDs are among the leading causes of death in South Korea (hereafter Korea) [2,3]. Hypercholesterolemia is a well-established, but modifiable risk factor for CVDs [4-8]. Lifestyle changes and several types of medications have been recommended to control blood lipid levels. Among the medications, statins are a major drug class that functions in reducing low-density lipoprotein cholesterol (LDL-C) [9-16]. Specifically, statins are recommended by several clinical guidelines, including the American College of Cardiology/American Heart Association (ACC/AHA) Guideline [10] , the European Society of Cardiology (ESC) [16], and the UK's National Institute for Health and Care Excellence Guideline [11], as the drug of choice for reduction of blood lipids to prevent CVDs.

In recent decades, statins have been the most commonly prescribed drugs in the world, and their global market sales reached approximately 28.5 billion dollars in 2014 [17]. Studies from several countries reported substantial increases in prescription rates of statins, including increased daily doses of statins [18-22]. Likewise, drug expenditure for statins has increased from 496 billion won in 2010 to 786 billion won in 2016 in Korea [2,3]. It should also be noted that there are many "me-too" drugs, including generics or follow on drugs, under the statin category [12]. For example, atorvastatin,

fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin, as well as a number of generics, are now available for hypercholesterolemia patients in the Korean market.

Given the market size of statins and a number of "me-too" drugs and generic statins, statin utilization, including switching drugs, in health systems has been the subject of considerable interest in the perspective of clinical pharmacy and public health [23-29]. For instance, several European countries have restricted the prescribing of patented statins when generic statins became available at a much lower cost [30,31]. However, notably few studies have dealt empirically with the issue or included real-world data with statin users, especially in Korea. Meanwhile, it was reported that drug switching among statin users is low in Korea [2]. Therefore, we selected new statin users to understand statin utilization and market dynamics of statins in Korea. Given the limited drug switching among statin users, analysing statin utilization of new users could be used as an important resource to evaluate the use of statins and to assess market dynamics of statins in Korea.

This study analysed the utilization of statins for new statin users and assessed the market dynamics of statins. Specifically, this study examined characteristics of new statin users and the prescribing of statin drugs over the last thirteen years, investigated the association between medical history of patients and intensity of statins, and analysed market dynamics of statins, including market

penetration and switching among new statin users.

Methods

Data source

This study used the National Health Insurance Service-National Sample Cohort (NHIS-NSC), a population-based cohort established by the National Health Insurance Service [32]. The dataset is comprised of approximately 1 million individuals (approximately 2% of the population) selected randomly from South Koreans. The NHIS built a target population of 46,605,433 individuals in 2002, and then 1,025,340 participants was randomly selected from the target population. Specifically, systematic stratified random sampling with proportional allocation within each stratum was conducted to construct the cohort [32].

The cohort dataset consists of four databases on participants' insurance eligibility, medical treatments, health care institutions, and general health examinations for the period from January 1, 2002, to December 31, 2015 [32]. The dataset provides information on demographic and socioeconomic characteristics, such as age, gender, and level of income. Income level was calculated based on the insurance premium that participant pays. Also, patients' disease diagnosis was coded based on the International Classification of Diseases-10th Revision (ICD-10), and the corresponding

medical expenditure such as medical and prescription information are available. The prescription information covers the date and duration of the prescription, the prescribed drugs' international nonproprietary names (INN), dosage, the route of administration, prescribers' specialty and the types of the healthcare institution.

Study design

This study is interested in new statin users. New statin users were defined as those who had not been prescribed any statin in the year prior to the date of the first statin prescription observed in the cohort dataset [33]. Therefore, new statin users in each year from 2003 to 2015 were included in the study population of each year. Specifically, the first prescription for outpatients that included any statin was set as an index date and analysed in the study.

The studied drugs include the statins atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. The information of individual drugs marketed in Korea are stated in Appendix 1. In this study, we defined mono-therapy as only one statin prescription, while we defined combination therapy as prescription for a statin plus other lipid-lowering drugs, including fibrates or ezetimibe. In addition, we searched the market of statins in Korea, including the entry of new drugs and follow on drugs and their pricing information on the website of the Ministry of Food and

Drug Safety (MFDS)[1] and the Health Insurance Review and Assessment Service (HIRA)[2], respectively. In Korea, co-payment for medicines that prescribed for outpatients are 30% of total expenditure, including pharmacy preparation charge, thus financial burden is less likely to influence the statin adherence, unlike previous study [34].

Statins were grouped into three levels of intensity [10,35]: high-intensity statins; moderate-intensity statins; and low-intensity statins. Daily doses can be calculated from the prescription data. High-intensity statins include atorvastatin 40–80 mg/day, rosuvastatin 20–40 mg/day and simvastatin 80 mg/day. Low-intensity statins include simvastatin 10 mg/day, pravastatin 10–20 mg/day, lovastatin 20 mg/day, pitavastatin 1mg/day and fluvastatin 20–40 mg/day. Lastly, moderate-intensity statins include atorvastatin 10–20 mg/day, rosuvastatin 5–10 mg/day, simvastatin 20–40 mg/ day, pravastatin 40–80 mg/day, lovastatin 40 mg/day, pitavastatin 2–4 mg/day and fluvastatin 80 mg/day.

All new statin users were classified based on their disease history, including hypertension (I10-I15),

[1] available at http://drug.mfds.go.kr/html/search_total_download_itemPermit.jsp

[2] available at https://biz.hira.or.kr/popup.ndo?formname=qya_bizcom%3A%3AInfoBank.xfdl&framename=InfoBank

diabetes (E10-E14), diseases of arteries, arterioles and capillaries (I70-I79), ischemic heart disease (I20-I25), cerebrovascular diseases (I60-I69), chronic obstructive pulmonary disease (J44), heart failure (I50), chronic kidney diseases (N17-N19), and atrial fibrillation (I48). Disease history was identified by the ICD-10 codes. Among these diseases, diabetes, diseases of arteries, arterioles and capillaries, cerebrovascular diseases, and heart failure are related to the use of statins for CVD prevention [14,15,36-38]. Individuals were identified as having a disease history of the specific disease if they had a primary diagnosis that corresponded to each diagnosis within three years prior to the first prescription date [38,39].

Lastly, to investigate the association between the providers' characteristics and the intensity of the statin prescribed, we sorted medical institutions by primary-, secondary-, and tertiary institutions. Primary care institutions include clinic-level medical institutions that provide medical services to outpatients. Secondary care institutions include hospital-level medical institutions that provide health services primarily to inpatients. Tertiary care institutions include superior general hospitals, designated by the Minister of Health and Welfare, that provide medical service requiring high level of expertise for treating serious disease.

Data analysis

This study used descriptive statistics to examine characteristics of new statin users and prescribed statin drugs, employed the χ^2 test to investigate the associations between certain disease history and prescription of moderate- or high-intensity statins, and applied interrupted time series analysis to understand the market dynamics of statins. In time series analysis, we estimated the effect of the introduction of generics on the market, specifically for newly prescribed statin users [40]. We presented the result of simple linear regression before and after the introduction of generics [41]

$$Y_t = \beta_0 + \beta_1 \mathrm{T} + \beta_2 X_t + \beta_3 \mathrm{T} X_t$$

Y_t: the number of new users that prescribed the certain statin at time t

T: the time elapsed since the start of the study

X_t: a dummy variable indicating the pre-intervention period or the post-intervention period

It should be noted that we defined the intervention year as the year when the price of originals were discounted due to the entry of follow on drugs. Generally speaking, the price of originals was

discounted as soon as the entry of the follow on drugs, in case of atorvastatin that occurred in 2008. However, the price reduction of original rosuvastatin was deferred until 2014 for the reason of valid patent that original rosuvastatin has until 2014, even though the follow on drugs were available in 2008. Therefore, we used the year of 2008 and 2014 as the intervention year of the model for atorvastatin and rosuvastatin, respectively. Data management and analysis were performed using the R statistical software (version 3.4.1). P-values under 0.05 were considered to be significance.

Ethical statement

This study used a de-identified secondary dataset. Therefore, it was exempted from review by the Institutional Review Board (IRB) of Ewha Womans University (IRB No. 158-10).

Patient and public involvement

No patients were involved in developing the research question, outcome measure, and design of the study. We are unable to disseminate the results of the research directly to study participants.

Results

Characteristics of new statin users over time

Table 1 presents characteristics of new statin users over time. Incidence of new statin user increase from 838.1/100,000 persons in 2003 to 1626.9/100,000 persons in 2015. There have been more

female new users than male new users, while the portion of female new statin users steadily declined from 56.5% in 2003 to 50.4% in 2015. During this period, the average age of new statin users with standard deviation remained steady (54.31 – 56.52 years old with 11.82 – 12.89 standard deviations). We also sorted new statin users by their income quintile. The portion of the first quintile (the lowest income) increased from 13% in 2003 to 16% in 2015, while the portion of the fifth quintile (the highest income) decreased from 33% in 2003 to 30% in 2015. In 2003, hypertension accounted for the highest portion of comorbidities (55%), followed by diabetes (37%), ischemic heart disease (21%), diseases of arteries, arterioles and capillaries (14%), and cerebrovascular diseases (12%). These trends remained steady in 2015.

Characteristics of prescribed statin drugs among new statin users

Table 2 shows characteristics of prescribed statin drugs among new statin users. The majority of patients were prescribed with a single statin (monotherapy) when they started hypercholesterolemia treatment, while few new users were prescribed combination therapy during the study period.

The market for monotherapy statins is dynamic. In 2003, simvastatin (37%) was the most prescribed statin, followed by lovastatin (30%) and atorvastatin (18%). The market share of simvastatin had been the highest in the market from 2003 (37%) to 2007 (50%). During this period, the market share

of atorvastatin was steady (18-20%), while the market share of lovastatin decreased from 30% in 2003 to 4% in 2007. Similarly, the market share of simvastatin decreased after 2008, while the market share of atorvastatin increased and maintained the highest from 46% in 2008 to 66% in 2013. Lastly, the market share of rosuvastatin increased from 8% in 2013 to 36% in 2015, while that of atorvastatin decreased from 66% to 49% during the same period. In 2015, statins for new users were an oligopoly market: atorvastatin (49%) was the most prescribed statin, followed by rosuvastatin (36%).

In 2003, the prescription rates of low-intensity and moderate-intensity statins were 43% and 57%, respectively. However, the prescription rate of moderate-intensity statins consistently increased to 92% in 2015, while the prescription rate of low-intensity statins decreased to 3% in 2015. In addition, the use of high-intensity statins steadily increased during the study period. We also examined health care institutions that prescribed statins. In 2003, 63% of new statin users were prescribed at primary healthcare institutions followed by secondary- (20%) and tertiary care institutions (14%). During the study period, the portion of new users prescribed at primary and tertiary healthcare institutions decreased, while the portion of new users prescribed at secondary healthcare institutions increased. In 2015, 58% of new statin users were prescribed at primary healthcare institutions followed by secondary- (29%) and tertiary healthcare institutions (11%).

Figure 1 shows statin prescription by health care institutions and the intensity of prescribed statins. The first graph in Figure 1 presents overall patterns of the prescription rates of low-, moderate-, and high-intensity statins in all institution types. The remaining graphs indicate patterns of prescription rates in primary-, secondary-, and tertiary healthcare institutions. We found that prescription rates of moderate-intensity statins were high in primary healthcare institutions, while those of high-intensity statins were high in tertiary care institutions. It is interesting to note that prescription rates of moderate-intensity statins in primary-, secondary-, and tertiary healthcare institutions in 2003 was 48%, 69%, and 78%, respectively. However, prescription rates of moderate-intensity statins reversed in primary, secondary, and tertiary healthcare institutions in 2015: 95%, 90%, and 84%, respectively.

Figure 2 presents prescription rates of selected statins, including atorvastatin, rosuvastatin, and simvastatin, during the study period. The first graph in Figure 2 shows market shares of selected statins among new statin users. Two points are noteworthy in the perspective of market dynamics. The first market dynamic occurred during 2007-2009. Specifically, atorvastatin penetrated the market of simvastatin in this period. Similarly, the second market dynamic occurred during 2013-2015. Rosuvastatin penetrated market of atorvastatin in this period. The remaining graphs present new

statin users of selected statins by primary-, secondary-, and tertiary- healthcare institutions. In this figure, we conclude that the majority of market switching of statins among new statin users occurred immediately at primary healthcare institutions.

Table 3 indicates the associations between certain disease histories and the prescription of moderate- or high-intensity statins. Interestingly, no substantial differences in the prescription of statins were observed through the study period in groups with histories of diseases of arteries, arterioles and capillaries. Furthermore, patients with history of diabetes, cerebrovascular diseases, and ischemic heart disease were less likely to be prescribed moderate- or high-intensity statins in several selected years. For instance, odds ratios were calculated at 0.78 and ranged from 0.67 to 0.91 with 95% confidence interval in 2012 for patients with diabetes.

Interrupted time series analysis

Table 4 presents results of segmented regression analysis using the interrupted time series method: β_0 is the pre period intercept; β_1 is the pre period slope (baseline time trend); β_2 is the immediate effect of the event on the intercept; and β_3 is the slope change after the event. In the case of atorvastatin, the immediate effect of marketing generics was 3,236 new users ($p < 0.001$), and the growth rate was increased by 2,687 new users per year ($p < 0.005$) compared with previous trends.

Similar trends were found in the case of rosuvastatin.

Discussions

This 13-year longitudinal study of a sample cohort provided by the NHIS found that incidence of new statin user increase from 838.1/100,000 persons in 2003 to 1626.9/100,000 persons in 2015. Most new users were initiated on a monotherapy that was prescribed at primary healthcare institutions. In addition, the use of moderate-intensity statins increased, notably at primary healthcare institutions. Specifically, the prescription rate of moderate-intensity statins at primary healthcare institutions was low (48%) in 2003. However, the figure was doubled in 2015 (95%).

The characteristics of new statin users and health care institutions that prescribed statins were similar to other studies that investigated prescription patterns of all statin users in Korea [2,3]. It is noteworthy to compare the results of statin prescription for new users with other countries [33,42-45]: statin market for new users is quite dynamic in Korea.

First, the most commonly used statin changed several times during the study period in Korea, while atorvastatin has been the most prescribed statin during 2002-2011 in Taiwan [33]. For instance,

simvastatin had the highest prescription rate until 2007, while atorvastatin had the highest prescription rate after 2008. It should be noted that generics of atorvastatin were available with discounted prices compared to the originals of the previous year (approximately 68%) in 2008, and the price of the originals was discounted approximately 20% compared to the previous year. We could find similar results in the case of rosuvastatin. Generics of rosuvastatin were available in 2010 and the prices of generics were 0.41 $[3], 0.61 $, and 0.81 $ for a single tablet of 5 mg, and 10 mg, and 20 mg, respectively, which account for approximately 68% of the original counterparts. In such a case of the introduction of generics, the prices of originals would be decreased to 80% compared to the previous year. However, price reduction was deferred until 2014 in this case for the reason of valid patent that original rosuvastatin has until 2014. In the end, the price of original rosuvastatin decreased to approximately 80% compared to that of the previous year in 2014. It is interesting to note the prescription rates of rosuvastatin: the market share of rosuvastatin in 2009 was 7% and slightly increased 9% in 2010 when generics with discounted prices (approximately 32%) were marketed, and later increased 33% in 2014 when prices of the original were discounted (approximately 20%). It means that the sole introduction of generics is not quite effective in expanding the market in Korea. However, discounted price of the original after the introduction of generics was related with the market expansion.

[3] Exchange rate is 1,100 won / dollar

Interestingly, patterns of prescription found in this study is quite different from other studies in different regions. For instance, the incidence of new treatments decreased for atorvastatin and increased for simvastatin in Italia, Denmark, and Spain [46-48]. Specifically, the market share of statin for new users in Southern Italian primary care was in the order of simvastatin (34%), atorvastatin (26.6%), and rosuvastatin (15.4%) [48]. Furthermore, the vast majority of new users were started treatments with simvastatin in Northern Denmark from 2004 to 2010 [47]. However, in Korea simvastatin has been losing market share since 2008 and the current market share of simvastatin is marginal (3%) in 2015.

Second, the portion of moderate-intensity statins was high in Korea, which is not common in other countries. For instance, the portion of low-, moderate-, and high-intensity statins among new statin users in Korea was 5%, 93%, and 2% in 2011. However, the portion of low-, moderate-, and high-intensity statins in Taiwan was 27%, 71%, and 2% in the same year. Lastly, the portion of low-, moderate-, and high-intensity statins in Spain was 4%, 72%, and 24% from 2006 to 2010. Given these findings, we could conclude that Korean general practitioners or specialists frequently prescribes moderate-intensity statins. In line with this result, we found no substantial differences in the prescription of moderate- or high-intensity statins in groups with histories of hypertension,

diabetes, diseases of arteries, arterioles and capillaries, cerebrovascular diseases, and ischemic heart disease in Korea.

Korean guidelines for the management of dyslipidemia states that the first goal is LDL-C [49]. Statin is the first-choice drug for the treatment of hypercholesterolemia (class of recommendation I, level of evidence A) because it has a relatively low risk profile and proven effects of decreasing CVD by lowering LDL-C. *"Statins should be prescribed"* and the dose adjusted to reach the LDL-C target level for high-risk and very high-risk groups (I, A), whereas *"statin use should be considered"* if LDL-C is not reduced to the first target even after lifestyle modification for weeks or months (IIa, B). The guidelines also provide dosage and administration of statins: lovastatin 20-80 mg/day, pravastatin 10-40 mg/day, simvastatin 20-40 mg/day, fluvastatin 20-80 mg/day, atorvastatin 10-80 mg/day, rosuvastatin 5-20mg/day, and pitavastatin 1-4 mg/day. Interestingly, atorvastatin and rosuvastatin, the top-2 best-selling statins in Korea, was recommended as moderate- and high-intensity dosage.

In addition, we found that the pricing and marketing strategies of manufacturers might encourage physicians to prescribe moderate- and high-intensity statins. For instance, the manufacturer discounted the price of simvastatin 40 mg (approximately 34%) in 2003, and the price was the same

as simvastatin 20 mg. Likewise, the other manufacturer that produce atorvastatin utilized the same strategy: the manufacturer discounted the price of atorvastatin 40 mg (35%) in 2003, and the price was the same as atorvastatin 20 mg; and the manufacturer discounted the price of atorvastatin 20 mg (30%) in 2007, which was the same price as atorvastatin 10 mg. In addition, the manufacturer marketed atorvastatin 80 mg in the market to preempt the high-strength statins market in 2008.

Third, we found market expansion when price of original statins were discounted. It is interesting to analyse market expansion by health care institutions. In cases of atorvastatin and rosuvastatin, the immediate effect of the event was large in primary healthcare institutions. For instance, the immediate effect of marketing generics of rosuvastatin was 3,163 users ($p < 0.0000$) and 517 users ($p < 0.005$) in primary- and secondary- healthcare institutions, respectively. However, the immediate effect of the event in tertiary care institutions was marginal and insignificant: 16.2 ($p = 0.78$) for atorvastatin and 7.1 ($p = 0.95$) for rosuvastatin. These results demonstrate that the discounted price of originals after the introduction of generics immediately expands markets, particularly in primary healthcare institutions. However, the growth rates, sorted by health care institutions, after the event vary according to drugs. For instance, the growth rate of atorvastatin was in the order of primary-, secondary-, and tertiary healthcare institutions, 1,597 ($p < 0.0001$), 736 ($p < 0.05$), and 352 ($p < 0.001$), respectively, while that of simvastatin was in the order of secondary-, primary-, and tertiary

healthcare institutions, 2,243 ($p < 0.0001$), 178 ($p < 0.05$), and 33 ($p = 0.80$), respectively,

This study notably analysed the utilization of statins for new statin users and assessed the market dynamics of statins over the last thirteen years with a real-world dataset provided by the NHIS. However, this study has several limitations. First, this study used claims data that does not contain information on biochemical test data of patients, such as LDL cholesterol level. It means that we could not assess prescription patterns by disease severity. In addition, the claims data does not contain information on whether the prescribed drugs were originals or generics. Therefore, further research is needed to assess the impact of generics on the market, including the contribution to market expansion by originals and generics, respectively. Second, this study used sample data and assumed that the data is to be representative, yet attention should be paid when generalize our results. Third, this study only used the first prescription that included any statins. Therefore, switches among statins were not included in the study. However, it would be reasonable to assume that switches among statins would be low in the Korean market [2]. Lastly, we noted the dosing for statins increased in Korea, and partially explained this trends with the Korean guidelines for the management of dyslipidemia and the pricing and marketing strategies of manufacturers. However, further qualitative methods are needed to understand these interesting observations.

Conclusions

Similar to other countries, the incidence of new statin users has been increased in Korea. However, the statin market in Korea is quite dynamic compared to other countries. It is noteworthy that the portion of new statin users that were prescribed moderate intensity statins has increased during the study period. In addition, no substantial differences in the prescriptions of statins were observed in groups with selected disease histories. Interestingly, discounted price of originals after the introduction of generics immediately expand markets or substitute the market particularly in primary healthcare institutions in Korea.

Contributors KS designed the study, collected and analyzed data, wrote, and revised the manuscript. SB revised the paper for important intellectual content. All authors read and approved the final manuscript.

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Patient consent Not required.

Data sharing statement: No additional data are available.

Table 1. Characteristics of new statin users over time

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Incidence (100,000 person)	838.1	893.2	1118.2	1256.4	1277.4	1341.7	1532.3	1497.8	1472.4	1508.4	1463.5	1640.3	1626.9
Sex													
Female	56.5%	55.0%	56.8%	55.8%	54.8%	54.3%	55.2%	54.6%	53.2%	53.1%	52.0%	50.7%	50.4%
Age													
Mean	54.40	54.31	55.15	55.61	55.62	55.48	55.61	55.71	55.58	55.65	55.57	56.52	55.90
SD	11.82	12.00	12.15	12.47	12.68	12.52	12.51	12.39	12.46	12.71	12.89	12.79	12.75
Income level (the quintile)													
The first	13%	14%	15%	15%	15%	14%	15%	15%	15%	15%	16%	16%	16%
The second	13%	13%	12%	14%	13%	14%	14%	15%	15%	15%	14%	15%	15%
The third	17%	17%	18%	16%	18%	18%	18%	17%	18%	17%	17%	17%	17%
The fourth	24%	23%	22%	23%	23%	23%	23%	23%	22%	22%	23%	22%	22%
The fifth	33%	32%	33%	32%	32%	31%	30%	31%	30%	30%	30%	30%	30%
Comorbidities													
Hypertension	N/A		55%	59%	58%	58%	56%	54%	53%	53%	52%	52%	48%
Diabetes			37%	39%	40%	39%	37%	36%	36%	37%	38%	41%	39%
DoA			14%	17%	20%	24%	25%	25%	23%	22%	21%	22%	20%
IHD			21%	22%	22%	21%	19%	19%	19%	18%	17%	18%	16%
CeVD			12%	13%	15%	15%	15%	15%	14%	15%	15%	14%	14%
COPD			5%	6%	6%	6%	5%	5%	5%	5%	5%	5%	4%
Heart failure			5%	4%	4%	4%	3%	4%	4%	4%	4%	4%	4%
CKD			2%	2%	2%	2%	2%	2%	2%	2%	3%	3%	3%
Afib			2%	2%	2%	3%	2%	2%	2%	2%	2%	3%	2%

Notes: DoA: diseases of arteries, arterioles and capillaries; IHD: ischemic heart disease; CeVD: cerebrovascular diseases; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney diseases; and Afib: atrial fibrillation

Table 2. Characteristics of prescribed statin drugs among new statin users

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Number of new statin users	8,205	8,835	11,181	12,564	12,774	13,333	15,139	14,713	14,374	14,639	14,117	15,731	15,514
Monotherapy	**100%**	**100%**	**99%**	**98%**	**97%**	**98%**	**97%**	**97%**	**95%**	**94%**	**95%**	**96%**	**95%**
Atorvastatin	18%	19%	20%	18%	18%	46%	61%	61%	62%	63%	66%	51%	49%
Fluvastatin	4%	2%	2%	4%	4%	2%	1%	1%	1%	1%	1%	1%	0%
Lovastatin	30%	18%	12%	6%	4%	2%	1%	1%	1%	0%	0%	0%	0%
Pitavastatin	0%	0%	1%	7%	9%	7%	4%	4%	4%	4%	6%	5%	5%
Pravastatin	11%	8%	6%	5%	4%	4%	3%	3%	3%	2%	2%	2%	1%
Rosuvastatin	0%	2%	7%	9%	8%	7%	7%	9%	8%	8%	8%	33%	36%
Simvastatin	37%	50%	52%	49%	50%	31%	20%	18%	16%	14%	9%	5%	3%
Combination	**0%**	**0%**	**1%**	**2%**	**3%**	**2%**	**3%**	**3%**	**5%**	**6%**	**5%**	**4%**	**5%**
Intensity													
Low	43%	25%	17%	11%	9%	6%	5%	5%	5%	5%	5%	3%	3%
Moderate	57%	75%	83%	88%	90%	94%	94%	94%	93%	93%	93%	92%	92%
High	0%	0%	0%	0%	1%	1%	1%	2%	2%	2%	2%	4%	5%
Institution													
Primary	63%	61%	59%	59%	58%	58%	56%	56%	56%	57%	56%	58%	58%
Secondary	20%	23%	25%	26%	26%	25%	27%	28%	28%	28%	29%	29%	29%
Tertiary	14%	13%	13%	14%	14%	13%	14%	13%	14%	13%	12%	11%	11%
Others	3%	2%	2%	2%	3%	3%	4%	3%	3%	2%	2%	2%	2%

Table 3. Associations between disease history and prescription of moderated- or high-intensity statins

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
History of hypertension	1.04	1.16	1.04	0.92	1.01	0.98	1.09	1.04	1.02	1.05	1.20
	0.94-1.15	1.03-1.29	0.92-1.18	0.80-1.07	0.87-1.18	0.84-1.14	0.94-1.26	0.90-1.20	0.87-1.19	0.88-1.24	1.00-1.44
History of diabetes	1.12	1.15	0.99	0.94	0.75	0.82	0.78	0.78	0.92	0.83	0.92
	1.01-1.24	1.03-1.29	0.88-1.12	0.81-1.09	0.64-0.87	0.70-0.96	0.68-0.91	0.67-0.91	0.78-1.08	0.69-0.99	0.76-1.11
History of DoA	1.00	0.99	1.01	1.01	1.02	1.08	0.98	1.08	1.10	1.02	1.03
	0.87-1.15	0.86-1.14	0.87-1.18	0.85-1.20	0.85-1.21	0.91-1.30	0.83-1.17	0.91-1.31	0.91-1.34	0.82-1.25	0.82-1.30
History of CeVD	1.18	1.20	0.84	0.83	0.69	0.88	0.70	0.85	0.80	0.72	0.77
	1.00-1.38	1.01-1.42	0.71-0.99	0.69-1.01	0.57-0.83	0.71-1.08	0.58-0.84	0.70-1.04	0.65-0.98	0.58-0.90	0.60-0.98
History of IHD	1.41	1.26	1.04	1.02	0.76	0.75	0.94	0.88	1.01	1.06	0.92
	1.24-1.60	1.09-1.44	0.90-1.21	0.85-1.22	0.64-0.91	0.63-0.90	0.78-1.13	0.73-1.06	0.82-1.23	0.85-1.33	0.72-1.18

Notes: DoA: diseases of arteries, arterioles and capillaries; IHD: ischemic heart disease; CeVD: cerebrovascular diseases;

Table 4. Results of segmented regression analysis of interrupted time series method

	Total			Primary care			Secondary care			Tertiary care		
	Coefficient	**Standard error**	**p-value**	**Coefficient**	**Standard error**	**p-value**	**Coefficient**	**Standard error**	**p-value**	**Coefficient**	**Standard error**	**p-value**
Atorvastatin (2003-2009)												
β_0 :Intercept	2611.9	168.5	< 0.001	850.3	46.4	< 0.001	1109.8	102.7	< 0.005	651.8	38.7	< 0.001
β_1 :Time	221.5	50.8	< 0.05	75.1	14.0	< 0.05	108.2	32.5	< 0.05	38.2	11.7	< 0.05
β_2 :Generic	3236.1	232.8	< 0.001	2846.7	64.1	< 0.0001	373.2	148.8	0.087	16.2	53.5	0.78
β_3 :Time:Generic	2687.5	232.8	< 0.05	1597.9	64.1	< 0.0001	736.8	148.8	< 0.05	352.8	53.5	< 0.01
Rosuvastatin (2004-2015)												
β_0 :Intercept	1376.5	141.9	< 0.001	295.7	29.1	< 0.001	655.9	59.0	< 0.001	424.9	61.8	< 0.0001
β_1 :Time	76.1	22.9	< 0.05	13.5	4.7	< 0.05	42.8	9.5	< 0.005	19.8	10.0	0.08
β_2 :Generic	3687.5	251.6	< 0.0001	3163.3	51.6	< 0.0001	517.1	104.5	< 0.0051	7.1	109.6	0.95
β_3 :Time:Generic	2453.9	294.7	< 0.0001	177.5	60.4	< 0.05	2243.2	122.4	< 0.0001	33.2	128.4	0.80

Notes: β0 is the pre period intercept; β1 is the pre period slope (baseline time trend); β2 is the immediate effect of the event on the intercept; β3 is the slope change after the event;

Figure 1. Statin prescriptions by institution and intensity a) all; b) primary-; c) secondary-; and d) tertiary healthcare institutions

Figure 2. Prescribing rates of selected statins among new statin users

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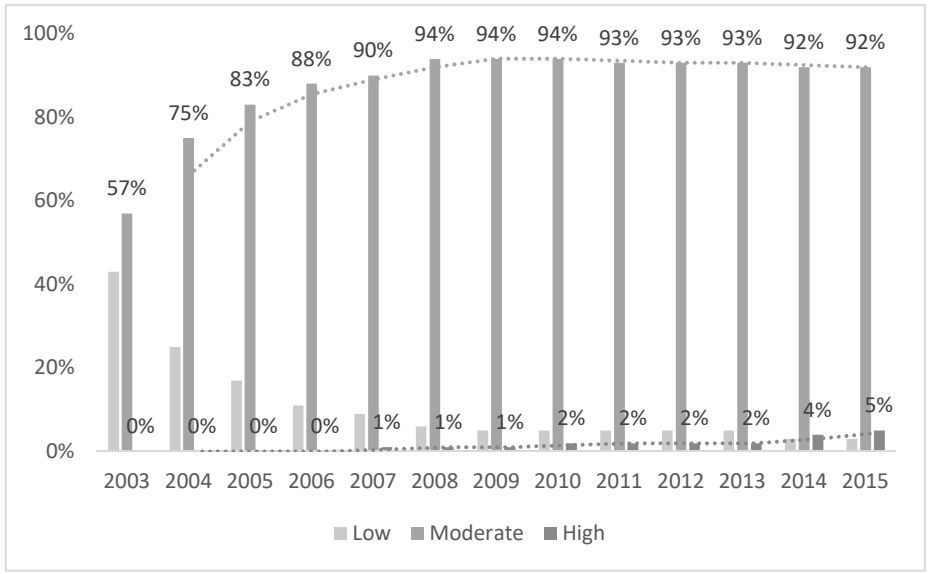
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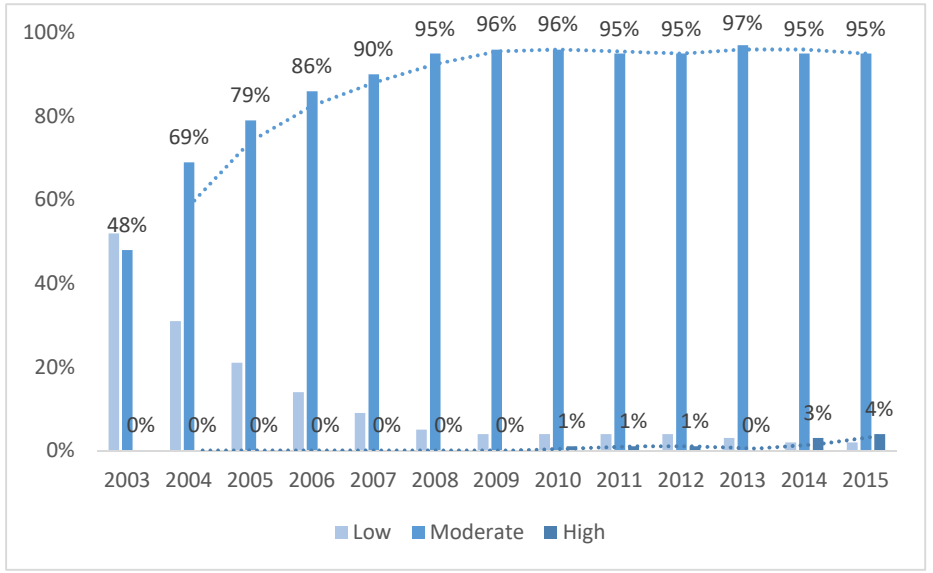
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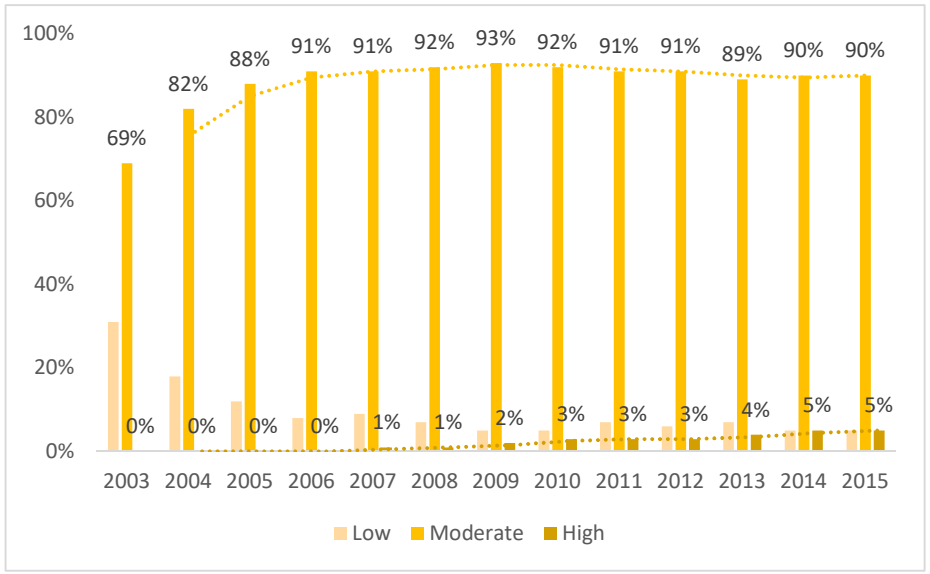
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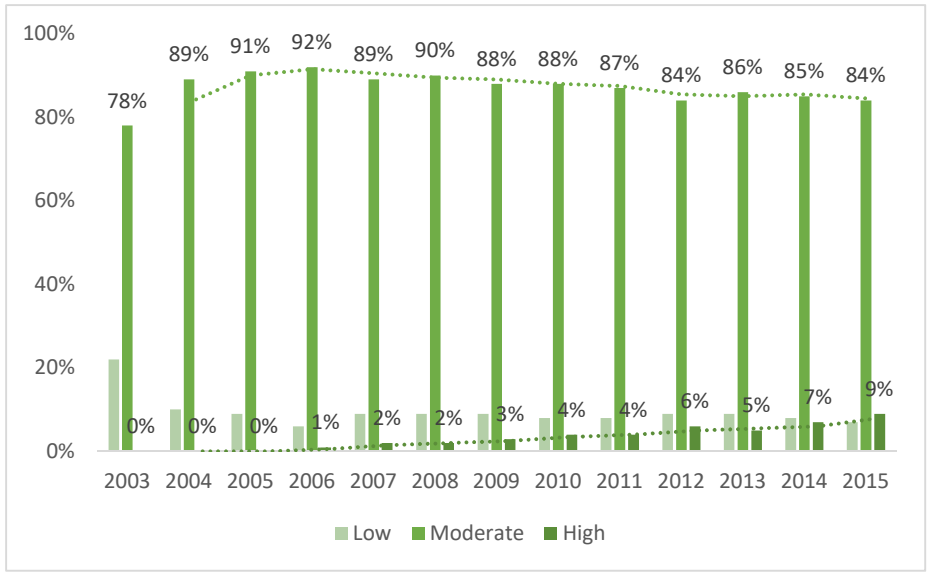
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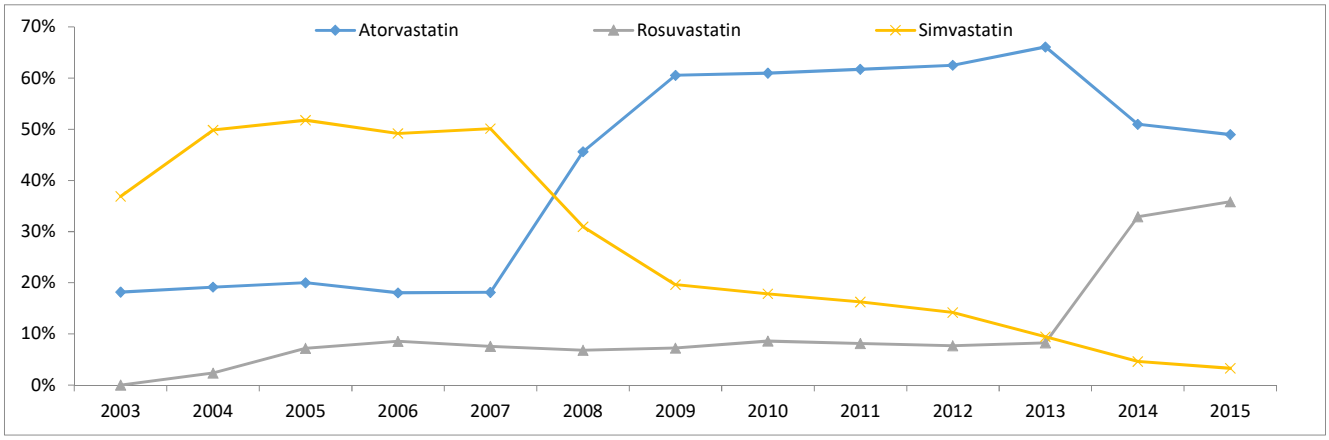
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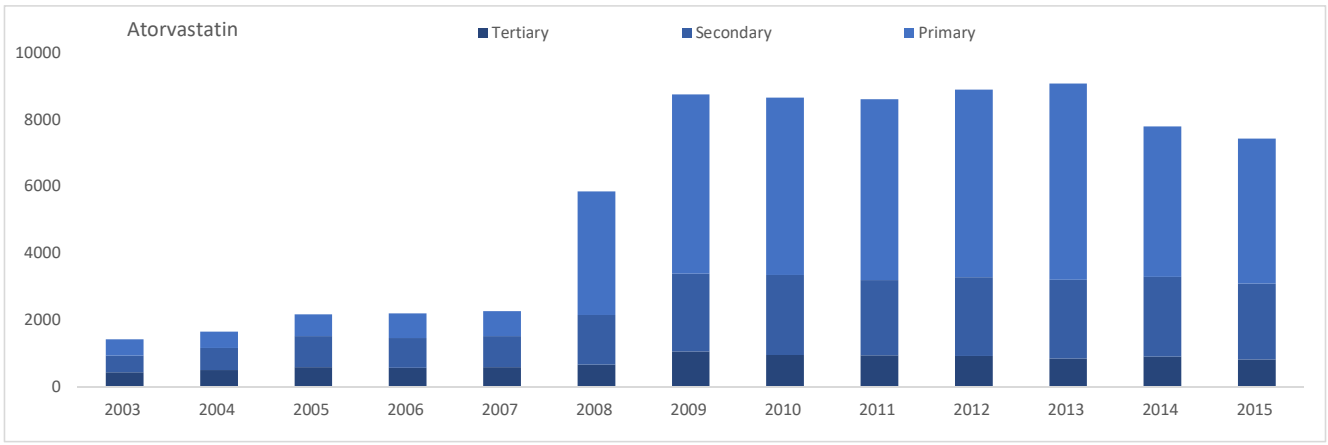
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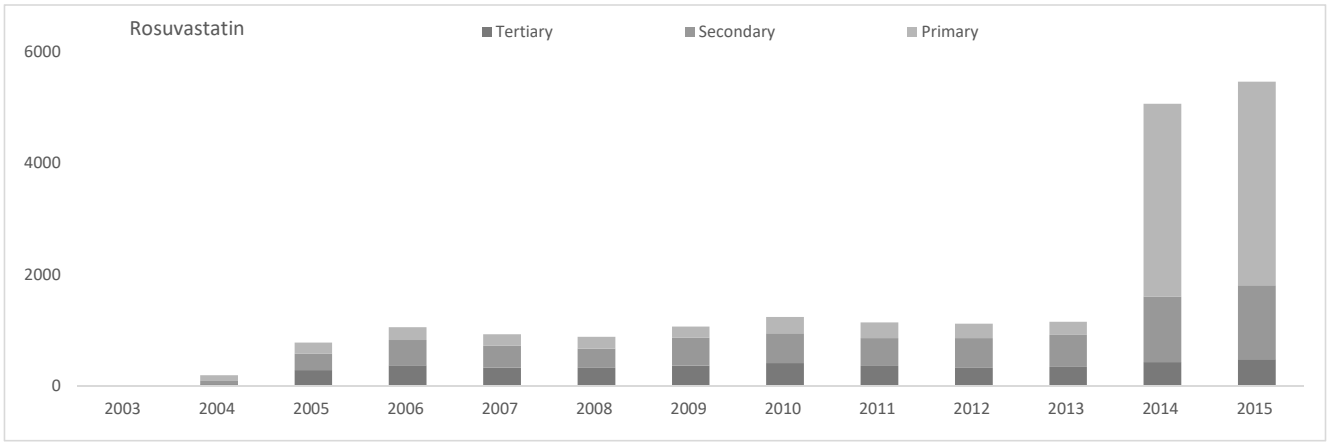
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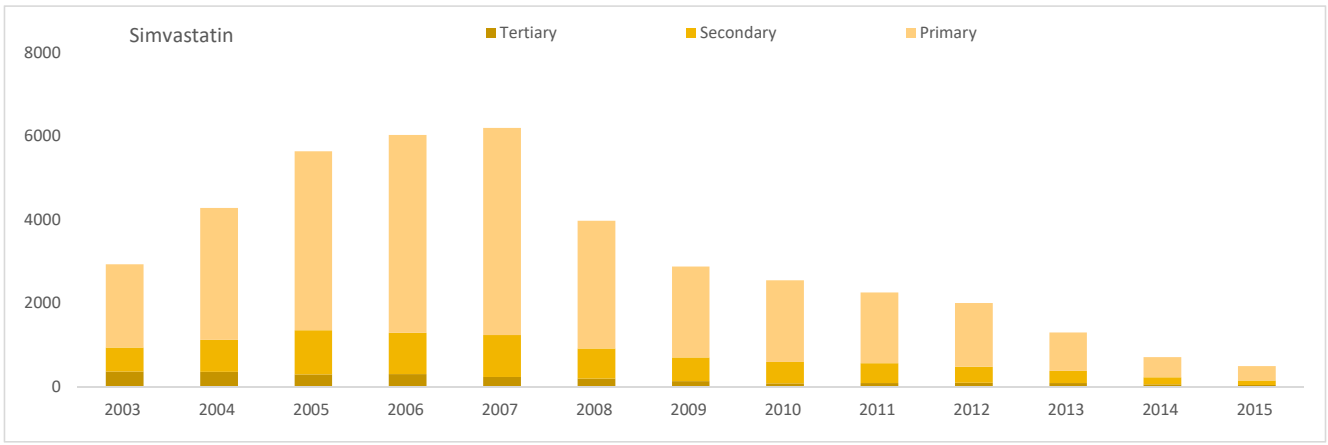
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Appendix 1. Drug code of statins in Korea

Drug Names	ATC code	National Code System (Strength and code)		The date of drug entry	
				New drug	First follow on drug
Atorvastatin	C10AA05	10	111501ATB	1999.08.01	2007.01.17
		20	111502ATB		
		40	111503ATB		
		80	111504ATB		
Fluvastatin	C10AA04	20	162401ACH	1994.10.10	N/A
		40	162402ACH		
		80	162403ATR		
Lovastatin	C10AA02	20	185801ATB	1997.08.06	1997.12.11
Pitavastatin	C10AA08	1	470902ATB	2005.01.06	2011.05.24
		2	470901ATB		
		4	470903ATB		
Pravastatin	C10AA03	5	216602ATB	1990.04.10	1994.05.17
		10	216601ATB		
		20	216603ATB		
		40	216604ATB		
Rosuvastatin	C10AA07	5	454003ATB	2002.01.15	2008.11.07
		10	454001ATB		
		20	454002ATB		
Simvastatin	C10AA01	5	227805ATB	1996.08.01	2002.07.09
		10	227803ATB		
		20	227801ATB, 227801ATR		
		40	227802ATB		
		80	227806ATB		
Ezetimibe and atorvastatin	C10BA05	10 + 10	633800ATB		
		10 + 20	633900ATB		
		10 + 40	634800ATB		
Ezetimibe and rosuvastatin	C10BA06	10 + 5	640700ATB		
		10 + 10	640800ATB		
		10 + 20	640900ATB		
Ezetimibe and simvastatin	C10BA02	10 + 10	471000ATB		
		10 + 20	471100ATB		
Fenofibrate and simvastatin	C10BA04	145 + 20	631400ATB		
		145 + 40	631500ATB		

ATC: anatomical therapeutic chemical

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Page #	Recommendation
Title and abstract	1	2	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		2	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	2	7	Explain the scientific background and rationale for the investigation being reported
Objectives	3	7	State specific objectives, including any prespecified hypotheses
Methods			
Study design	4	9-11	Present key elements of study design early in the paper
Setting	5	8-9	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	9-11	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		N/A	(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	9-13	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	9-11	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	N/A	Describe any efforts to address potential sources of bias
Study size	10	N/A	Explain how the study size was arrived at
Quantitative variables	11	9-13	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	9-13	(*a*) Describe all statistical methods, including those used to control for confounding
		N/A	(*b*) Describe any methods used to examine subgroups and interactions
		N/A	(*c*) Explain how missing data were addressed
		N/A	(*d*) If applicable, explain how loss to follow-up was addressed
		N/A	(*e*) Describe any sensitivity analyses
Results			
Participants	13*	13-14	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		13-14	(b) Give reasons for non-participation at each stage

		N/A	(c) Consider use of a flow diagram
Descriptive data	14*	14-17	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		N/A	(b) Indicate number of participants with missing data for each variable of interest
		N/A	(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	13-14	Report numbers of outcome events or summary measures over time
Main results	16	13-17	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		N/A	(*b*) Report category boundaries when continuous variables were categorized
		N/A	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	N/A	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18	18	Summarise key results with reference to study objectives
Limitations	19	22-23	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	18-23	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	22-23	Discuss the generalisability (external validity) of the study results
Other information			
Funding	22	24	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.