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Hsing-Chun Hsieh,[1,2] Jason C Hsu,[1] Christine Y Lu[3]

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[1]School of Pharmacy and Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[2]Department of Pharmacy, Chi Mei Medical Center, Tainan, Taiwan
[3]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA

Correspondence to
Dr Jason C Hsu;
jasonhsuharvard@gmail.com

ABSTRACT

Objective Statins have been commonly used to treat patients with hypercholesterolaemia and to prevent cardiovascular disease (CVD) worldwide. This study examined trends in use of statins in Taiwan from 2002 to 2011.

Design This is a retrospective observational study focusing on the utilisation of statins.

Setting The monthly claims data for statins between 2002 and 2011 were retrieved from Taiwan's National Health Insurance Research Database.

Main outcome measures We calculated the yearly prescription rate per new user for each statin. Products were classified as high-intensity/moderate-intensity/low-intensity statins by type of statin and dosage. Users were also classified based on disease histories.

Results The number of statin users increased from 10 299 (~1.4% of adults) in 2002 to 50 687 (~6.3% of adults) in 2011. Atorvastatin was the most commonly used agent (28.4%–36.7%) during the study period. After 2007, simvastatin ranked second with 21.7% market share, followed by rosuvastatin, a newer agent that exhibited a substantial growth in prescription rates (3.4% in 2005 and 19.5% in 2011). In 2011, 94.0% of new statin users used statin monotherapies, and 6.0% used combination therapies. Use of moderate-intensity statins increased from 49.0% in 2002 to 71.0% in 2011, while high-intensity statins remained low. Patients with history of coronary events or cerebrovascular events were more likely to be prescribed higher intensity statins compared with those without. Prescribing of higher intensity statins was not greater among people with diabetes compared with those without during 2007–2011. Selection of statins did not differ between people with versus without history of myopathy or liver injury.

Conclusion Atorvastatin was the most commonly used statin in Taiwan during 2002–2011. While patients with history of CVD were more likely to be prescribed higher intensity statins compared with those without, this difference was not found comparing those with and without diabetes.

Strengths and limitations of this study

- This is the first study to investigate 2002–2011 trends in prescribing patterns of statins among new statin users in Taiwan.
- Data were retrieved from Taiwan's National Health Insurance Research Database with nearly 99% of the Taiwanese population (around 23 million residents) enrolled and 97% of hospitals and clinics throughout the country.
- While patients with history of cardiovascular disease were more likely to be prescribed higher intensity statins compared with those without, this difference was not found comparing those with and without diabetes. Appropriateness of statin use among diabetes needs further investigation.

INTRODUCTION

Coronary heart disease accounts for approximately one-third of global deaths in recent years.[1] Similarly, cardiovascular diseases (CVD) are leading causes of death in Taiwan.[2] Low-density lipoprotein cholesterol (LDL-C) has been identified as one of the major modifiable risk factors of CVD.[3–6] Fundamental lifestyle changes and several medications have been recommended to control blood cholesterol. Among all medicines, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, or statins, are a major drug class given their efficacy in reducing LDL-C.[7–9] On average, administration of statins helps to lower LDL-C by 20% to 60%.[6 10–12] In addition to lowering cholesterol, statins are shown to decrease risk of coronary events by 18%, myocardial infarction by 24% and heart failure by 35%.[13]

Statins are recommended by major clinical guidelines as the drug of choice for reduction of blood lipids to prevent CVD globally.[7–9] In the USA, the 2013 'American College of Cardiology/American Heart Association (ACC/AHA)' Guideline[7] recommends that patients with CVD history or with CVD risk factors, such as high LDL-C and diabetes, receive moderate-to-high-intensity statins.[7] The European Society of Cardiology (ESC) and

UK's National Institute for Health and Care Excellence guidelines suggest prescribing statins with the highest recommended dose in order to reach target cholesterol level.[8 9] In Taiwan, prescribing of statins generally follows drug coverage requirements under the National Health Insurance (NHI), which recommends the use of statins in patients with CVD risk factors or with high cholesterol level.[14] It is reasonable for patients to be prescribed with a statin plus another lipid-lowering agent if triglyceride level is also high.

Statins have been the most commonly prescribed drugs in the world in recent decades; their global market sales reached around $28.5 billion in 2014.[15 16] Previous studies from the USA and Europe showed substantial increases in statin users, prescription rates and prescribed daily doses of statins over time.[17–19] Likewise in Taiwan statin users grew from 190 000 in 2000 to nearly 600 000 in 2004, and drug expenditures and prescription doses escalated over 200% and 400%, respectively.[20 21] Based on the updated clinical guidelines and related evidence, use of the more intense statin therapy for secondary prevention and initiation of statins for primary prevention among patients who are at a higher risk of CVD has increased.[7 22]

While statins have been the mainstay of cholesterol control and heart attack and stroke prevention for the past 20 years, the treatment paradigm may change with the availability of new drugs that target an enzyme called PCSK9 (PCSK9 inhibitors) in 2015.[23] However, little is known about recent statin use in Taiwan.[24] The aims of this study were to examine the prescribing patterns of statins over the last decade and to investigate the association between patients' medical history and drug selection of statin. Our study results can be used to improve rational use of statins in light of clinical recommendations. At present, PCSK9 inhibitors are not yet reimbursed by Taiwan's National Health Insurance (NHI). Our findings also provide baseline trends that can be used to examine how new PCSK9 inhibitors, once become available under the NHI, impact the market of cholesterol medications.

METHODS

This study used claims data from the 2010 Longitudinal Health Insurance Database (LHID2010) derived from Taiwan's National Health Insurance Research Database (NHIRD), which compiles data of over 99% of people (around 23 million residents) in Taiwan.[25] LHID2010 contains all the original claims data of 1 million beneficiaries randomly sampled in year 2010 from the NHIRD. LHID2010 data are overall representative of all beneficiaries as no significant differences were found in the distributions of age, gender and average premium rate between individuals in the LHID2010 and the original NHIRD data sets.[26] The data set provides information on demographic characteristics, diseases diagnosis, treatment and related medical expenditures, and orders of ambulatory and inpatient care.

New statin users in each year during 2002–2011 were included and formed the study population of each year. New statin users were defined as those who had not taken any statin in the previous years prior to the index date. The index date of every patient in each study year was defined as the date of the first statin prescription in the year. For patients in every study year, only the first prescription that contained any statins was examined in this study. We used the Anatomical Therapeutic Chemical (ATC) codes[27] to identify patients who were prescribed any statins, including atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin. Monotherapy was defined as only one statin prescription on the index date, while combination therapy was defined by prescriptions for a statin plus other lipid-lowering drugs (such as fibrates) on the index date.

The main measure was yearly prescription rate of each statin among new statin users. Yearly prescription rate of a specific statin agent was calculated by the number of patients prescribed with the specific statin agent divided by the total number of new statin users in the year. We also calculated the yearly prescription rates of monotherapy/combined statin therapy and of different levels of intensity.

Statins were grouped into three levels of intensity according to their ability to lower LDL-C based on the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol[7] and Rosenson *et al*[28]: (1) high-intensity statins: atorvastatin ≧40 mg/day, rosuvastatin ≧20 mg/day and simvastatin ≧80 mg/day; (2) moderate-intensity statins: 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; and (3) low-intensity statins: 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. Daily dose can be calculated from the information of what statin has been prescribed, its dosage form, frequency and number of pills within a certain period.

All new statin users were also classified based on whether they have disease histories of interest (including coronary events, cerebrovascular events, myopathy, liver injury and diabetes) or not. Disease histories were identified by the International Classification of Diseases, 9th edition diagnosis codes for major coronary artery disease (410, 411), major cerebrovascular (430, 431, 433–436), diabetes (250),[29] myopathy (792.1, 359.4, 359.8, 359.9) and liver injury (155.0, 155.1, 155.2, 197.7, 230.8, 570, 571.1, 572.2, 572.4, 572.8, 573.3, 573.8, 573.9, 574.0, 574.1, 574.9, 646.7).[30] The first three diagnoses relate to use of statin for CVD prevention and the latter two diagnoses related to the potential adverse effects of statins. We anticipate a higher percentage use of higher intensity statins among patients with CVD or diabetes. Myopathy[31 32] and liver toxicity[32 33] (increasing the enzymes aspartate transaminase and alanine transaminase) are two of the main dose-dependent side effects associated with statin use.[34 35]

Therefore, it was anticipated that a higher percentage of patients with a history of these diseases would use low-intensity statins. Individuals were defined as having a history of the following diseases if they have a diagnosis within certain years prior to the given year: coronary event (3 years), cerebrovascular event (5 years), diabetes (1 year), myopathy (3 years) and liver injury (3 years).[30 36–38]

This study applied descriptive statistics to report the prescription rates of each statin and used χ^2 test to investigate the associations between patients' disease history and statin drug selection. All analyses were carried out with SAS V.9.3 software and Excel 2013.

RESULTS

In 2002, 10 299 (~1.4% of adults aged 18 and over) statin users were identified among the 1 million cohort from LHID2010 dataset (table 1). Among statin users, more than half (n=5956; 57.8%) were new users. Statins users grew from 10 299 (~1.4% of adults) in 2002 to 50 687 (~6.3% of adults) in 2011, while the proportion of new statin users declined from 57.8% to 35.0%. More women used statins than men (52.3% vs 47.7% in 2011). The average age of new statin users remained steady (58–60 years old) during the study period. Three quarters of new statin users were diagnosed with dyslipidemia. Hypertension accounted for the highest proportion of comorbidities (60.9% in 2011), followed by diabetes (35.3% in 2011); their rates remained steady during the study period. On the contrary, the proportions of other comorbidities, including ischaemic heart disease and chronic liver diseases, slightly declined over time.

Table 2 presents the statin choices among new statin users. Atorvastatin was the most commonly prescribed statin among new statin users throughout the study (33.8% in 2002 and 35.8% in 2011). Lovastatin had the second highest prescription rates from 24.7% in 2002 to 24.2% in 2006, but it declined after 2007 to 5.8% in 2011. On the other hand, simvastatin became the second commonly used statin since 2007 (21.7%), and its prescription rate peaked in 2009 (27.1%). Rosuvastatin entered the market in 2005, and its prescription rate rapidly increased to 19.5% in 2011. Prescription rates of other statins remained relatively low. Figure 1 shows the prescribing trends of statins over time.

During the study period, almost all patients were prescribed with a single statin when they first started (98.6% in 2002 and 94.0% in 2011). Only 1.4% of patients were prescribed with combination therapy in 2002, with fibrates accounting for 83.3% of the combination therapies. Use of combination therapy increased to 6.0% in 2011, with ezetimibe accounting for 66.2% of combined lipid-lowering drugs.

In 2002, prescription rates of low-intensity and moderate-intensity statins were similar (51.0% and 49.0%). However, prescription rates of moderate-intensity statins gradually increased to 71.0% in 2011, while prescription rates of low-intensity statins gradually decreased to 27.3% in 2011. In comparison, use of high-intensity statins remained low (under 2.1%) during the study period (figure 2).

Table 3 and figure 3 show the prescription rates of statins among new statin users with/without history of specific diseases. Compared with those without CVD, higher percentages of people with history of coronary events or cerebrovascular events were prescribed atorvastatin (51.4% vs 35.6% and 42.7% vs 35.4%, respectively, in 2011) or rosuvastatin (32.5% vs 19.3% and 27.5% vs 19.1%, respectively, in 2011). In patients with myopathy or liver injury history, prescription rates of different statins did not vary greatly through the study period compared with those without history of the diseases. Similarly, prescription rates of different statins did not vary greatly between people with and without diabetes.

Table 4 indicates the findings of the associations between certain disease history and prescription of high- or moderate-intensity statins. Patients with CVD history were more likely to be prescribed moderate-intensity or high-intensity statins (OR ranged from 1.52 to 2.83 during the study period, $p<0.05$). Similar results were found in patients with cerebrovascular events history compared with those without (OR ranged from 1.17 to 1.88 during 2006–2011, $p<0.05$). However, patients with diabetes history were less likely to be prescribed moderate-intensity or high-intensity statins compared with patients without diabetes history (OR ranged from 0.83 to 0.90 during 2007–2011, $p<0.05$). No substantial differences in prescribing patterns of statins were observed throughout the study period in groups with versus without history of myopathy or liver injury (table 4).

DISCUSSION

This longitudinal study of a national cohort found that more than half statin users were initiated on a single statin, with atorvastatin being the most commonly prescribed statin over the last decade in Taiwan. Use of moderate-intensity statins increased by 22.0% between 2002 and 2011, while use of high-intensity statins remained low. Lastly, patients with history of coronary events or cerebrovascular events were more likely to be prescribed higher intensity statins compared with those without. Prescribing of higher intensity statins was not greater among people with diabetes compared with those without during 2007–2011. This difference was also not seen in people with versus without history of myopathy or liver injury.

From 2002 to 2011, initiation of statins increased over time, similar to studies from other countries.[18 39–41] Initiation of statins in Taiwan has grown from 0.6% in 2002 to 1.8% in 2011. Our findings are similar to studies from other countries that found similar utilisation rates and increasing trend over time. For instance, a study used data of Italian local pharmacies and demonstrated incidence of statin exposure growing from 0.36% in 1994 to 0.74% in 2003.[42] Another study, which was also conducted in Italy, exhibited yearly incidence of statin

Table 1 Characteristics of new statin users over time

Year	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011	
Number of new statin users	5956	57.8%	9056	57.6%	10924	52.4%	10253	45.9%	12178	47.0%	13535	44.4%	15233	42.7%	16499	40.3%	17509	37.8%	17755	35.0%
All statin users	10299	100.0%	15724	100.0%	20848	100.0%	22317	100.0%	25924	100.0%	30491	100.0%	35674	100.0%	40989	100.0%	46323	100.0%	50687	100.0%
Sex:																				
F	3232	54.3%	4925	54.4%	5913	54.1%	5523	53.9%	6391	52.5%	7180	53.0%	8043	52.8%	8519	51.6%	9185	52.5%	9278	52.3%
M	2724	45.7%	4131	45.6%	5011	45.9%	4730	46.1%	5787	47.5%	6355	47.0%	7190	47.2%	7980	48.4%	8324	47.5%	8477	47.7%
Age: mean (SD)	58.41	(11.84)	58.22	(12.19)	57.98	(12.40)	58.44	(12.45)	59.01	(12.51)	59.13	(12.45)	59.35	(12.59)	59.28	(12.68)	59.77	(12.73)	59.76	(12.70)
Indication and comorbidities																				
Dyslipidemia (indication)	4457	74.8%	6815	75.3%	8357	76.5%	7844	76.5%	9352	76.8%	10 281	76.0%	11 594	76.1%	12 655	76.7%	13 431	76.7%	13 723	77.3%
Hypertension	3564	59.8%	5214	57.6%	6192	56.7%	6005	58.6%	7290	59.9%	8031	59.3%	9122	59.9%	9859	59.8%	10726	61.3%	10816	60.9%
Diabetes	2092	35.1%	3168	35.0%	3632	33.2%	3639	35.5%	4336	35.6%	4897	36.2%	5378	35.3%	6011	36.4%	6412	36.6%	6262	35.3%
IHD	1561	26.2%	2266	25.0%	2530	23.2%	2431	23.7%	2851	23.4%	3078	22.7%	3357	22.0%	3513	21.3%	3680	21.0%	3536	19.9%
Heart failure	217	3.6%	326	3.6%	367	3.4%	384	3.7%	462	3.8%	486	3.6%	562	3.7%	590	3.6%	644	3.7%	637	3.6%
Afib	36	0.6%	69	0.8%	74	0.7%	91	0.9%	120	1.0%	141	1.0%	173	1.1%	220	1.3%	188	1.1%	239	1.3%
CeVD	749	12.6%	1121	12.4%	1245	11.4%	1216	11.9%	1472	12.1%	1626	12.0%	1822	12.0%	1879	11.4%	2090	11.9%	2019	11.4%
PVD	228	3.8%	344	3.8%	414	3.8%	377	3.7%	478	3.9%	455	3.4%	566	3.7%	591	3.6%	671	3.8%	654	3.7%
CKD	384	6.4%	497	5.5%	540	4.9%	521	5.1%	608	5.0%	689	5.1%	777	5.1%	839	5.1%	878	5.0%	1027	5.8%
CLD	1301	21.8%	1867	20.6%	2107	19.3%	1984	19.4%	2142	17.6%	2288	16.9%	2409	15.8%	2585	15.7%	2758	15.8%	2689	15.1%
COPD	576	9.7%	817	9.0%	977	8.9%	871	8.5%	919	7.5%	996	7.4%	1017	6.7%	1106	6.7%	1141	6.5%	1065	6.0%
Dementia	49	0.8%	72	0.8%	82	0.8%	83	0.8%	110	0.9%	158	1.2%	199	1.3%	226	1.4%	315	1.8%	298	1.7%
Malignancy	165	2.8%	255	2.8%	325	3.0%	305	3.0%	397	3.3%	479	3.5%	546	3.6%	655	4.0%	702	4.0%	752	4.2%

Unit: number of patient.
Afib, atrial fibrillation; CeVD, cerebrovascular diseases; CKD, chronic kidney diseases; CLD, chronic liver diseases; COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; PVD, peripheral vascular diseases.

Table 2 Prescription rates of statins among new statin users

Year	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011	
Yearly cohort size	5956		9056		10 924		10 253		12 178		13 535		15 233		16 499		17 509		17 755	
Overall																				
Atorvastatin	2014	33.8%	3320	36.7%	3926	35.9%	3610	35.2%	3883	31.9%	4101	30.3%	4322	28.4%	4912	29.8%	5841	33.4%	6357	35.8%
Fluvastatin	710	11.9%	855	9.4%	1063	9.7%	1159	11.3%	1109	9.1%	1214	9.0%	1284	8.4%	1193	7.2%	1186	6.8%	1063	6.0%
Lovastatin	1473	24.7%	2829	31.2%	3595	32.9%	3112	30.4%	2951	24.2%	2298	17.0%	1965	12.9%	1724	10.4%	1242	7.1%	1025	5.8%
Pravastatin	654	11.0%	791	8.7%	813	7.4%	687	6.7%	766	6.3%	776	5.7%	1005	6.6%	1122	6.8%	1438	8.2%	1676	9.4%
Rosuvastatin	NA		NA		NA		348	3.4%	1690	13.9%	2216	16.4%	2739	18.0%	3082	18.7%	3396	19.4%	3464	19.5%
Simvastatin	1106	18.6%	1262	13.9%	1529	14.0%	1339	13.1%	1786	14.7%	2940	21.7%	3920	25.7%	4478	27.1%	4412	25.2%	4190	23.6%
Monotherapy	**5872**	**98.6%**	**8908**	**98.4%**	**10 765**	**98.5%**	**10 137**	**98.9%**	**12 011**	**98.6%**	**13 055**	**96.5%**	**14 590**	**95.8%**	**15 594**	**94.5%**	**16 540**	**94.5%**	**16 695**	**94.0%**
Atorvastatin	1984	33.8%	3276	36.8%	3861	35.9%	3572	35.2%	3829	31.9%	4042	31.0%	4266	29.2%	4826	30.9%	5727	34.6%	6224	37.3%
Fluvastatin	701	11.9%	840	9.4%	1045	9.7%	1145	11.3%	1093	9.1%	1197	9.2%	1268	8.7%	1163	7.5%	1168	7.1%	1034	6.2%
Lovastatin	1457	24.8%	2777	31.2%	3556	33.0%	3089	30.5%	2915	24.3%	2264	17.3%	1948	13.4%	1691	10.8%	1224	7.4%	1006	6.0%
Pravastatin	637	10.8%	772	8.7%	799	7.4%	671	6.6%	745	6.2%	758	5.8%	992	6.8%	1108	7.1%	1400	8.5%	1628	9.8%
Rosuvastatin	NA	NA	NA	NA	NA	NA	343	3.4%	1665	13.9%	2164	16.6%	2680	18.4%	3016	19.3%	3316	20.0%	3386	20.3%
Simvastatin	1093	18.6%	1243	14.0%	1504	14.0%	1317	13.0%	1764	14.7%	2630	20.1%	3436	23.6%	3790	24.3%	3705	22.4%	3417	20.5%
Combination	**84**	**1.4%**	**148**	**1.6%**	**159**	**1.5%**	**116**	**1.1%**	**167**	**1.4%**	**480**	**3.5%**	**643**	**4.2%**	**905**	**5.5%**	**969**	**5.5%**	**1060**	**6.0%**
Statin + fibrate	70	83.3%	94	63.5%	132	83.0%	95	81.9%	124	74.3%	160	33.3%	161	25.0%	210	23.2%	226	23.3%	249	23.5%
Statin + ezetimibe	0	0.0%	0	0.0%	0	0.0%	0	0.0%	7	4.2%	280	58.3%	454	70.6%	638	70.5%	652	67.3%	702	66.2%
Statin + others	14	16.7%	58	39.2%	28	17.6%	22	19.0%	36	21.6%	47	9.8%	30	4.7%	60	6.6%	95	9.8%	114	10.8%
Different intensity of statin therapy																				
Low	3039	51.0%	4490	49.6%	5112	46.8%	4518	44.1%	4477	36.8%	4100	30.3%	4065	26.7%	4602	27.9%	4954	28.3%	4852	27.3%
Moderate	2918	49.0%	4564	50.4%	5785	53.0%	5688	55.5%	7591	62.3%	9261	68.4%	10 903	71.6%	11 634	70.5%	12 200	69.7%	12 599	71.0%
High	1	0.0%	6	0.1%	32	0.3%	49	0.5%	118	1.0%	187	1.4%	272	1.8%	279	1.7%	365	2.1%	333	1.9%

Statins were grouped into three levels of intensity according to its ability of lowering LDL-C based on the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol[7] and Rosenson et al[28]: (1) high-intensity statins: atorvastatin ≧40 mg/day, rosuvastatin ≧20 mg/day and simvastatin ≧80 mg/day; (2) moderate-intensity statins: 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; and (3) low-intensity statins: 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. Combinations, statin + other lipid-modifying agents.

ACC/AHA, American College of Cardiology/American Heart Association; LDL-C, low-density lipoprotein cholesterol; NA, not applicable.

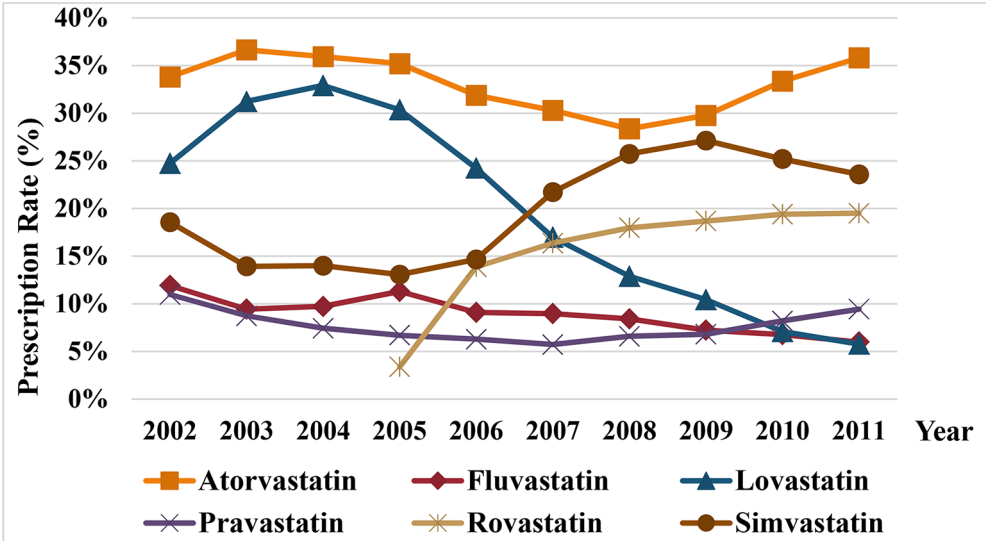

Figure 1 Prescribing rates of statins among new statin users from 2002 to 2011. All values were calculated in patient number. Yearly prescription rate = number of patients prescribed with the specific statin agent / total number of new statin users in the year.

use increasing from 13.3/1000 inhabitants in 2005 to 19.5/1000 inhabitants in 2010 among people aged 15 and over.[39] A study by Svensson *et al* aligned with the previous results showing annual rates of new statin use ranging from 14 to 20/1000 person-years.[40]

Our study found that atorvastatin had the highest prescription rate in Taiwan throughout the entire study. It was first introduced into Taiwan's market in 2000 and its market share surged to surpass other agents of the same drug class since the first study year.[21] In other countries, atorvastatin has also been one of the most commonly used statins.[39 40 43] The popularity of atorvastatin might be attributed to favourable research results suggesting its clinical benefits in preventing major coronary events[44] as well as marketing strategies of the pharmaceutical company.[45] When examining trends of different statins, it was noted that trends of atorvastatin and simvastatin exhibited opposite directions (figure 1). Since both statins were moderate-to-high potency agents, their similar potency may be a reason for the substitution observed.[12 46]

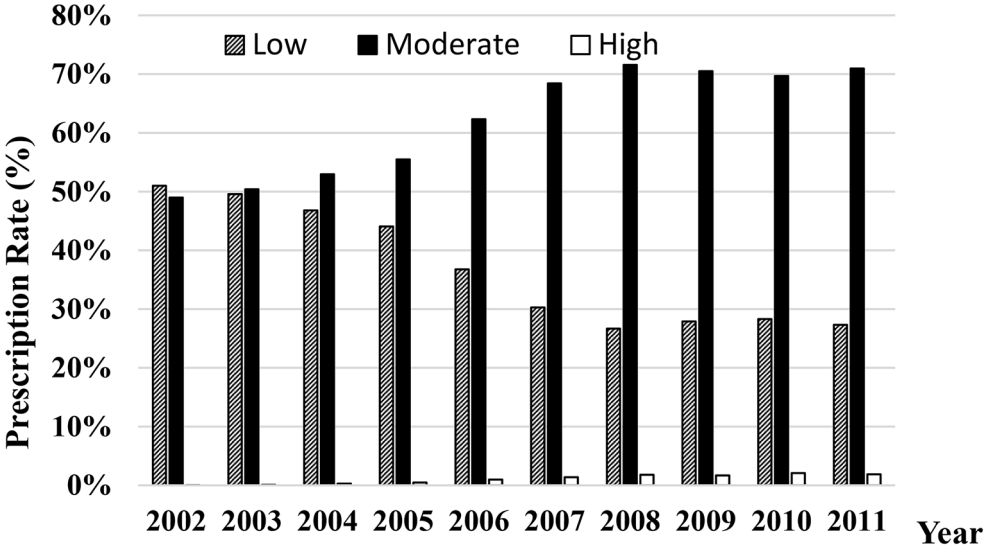

Figure 2 Prescribing rates of statins by intensity. All values were calculated in patient number. Yearly prescription rate = number of patients prescribed with the specific statin agent / total number of new statin users in the year. Statins were grouped into three levels of intensity according to their ability to lower LDL-C based on the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol[7] and Rosenson *et al*[28]: (1) high-intensity statins: atorvastatin ≧40 mg/day, rosuvastatin ≧20 mg/day and simvastatin ≧80 mg/day; (2) moderate-intensity statins: 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; and (3) low-intensity statins: 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. ACC/AHA, American College of Cardiology/American Heart Association; LDL-C, low-density lipoprotein cholesterol.

Table 3 Prescription rates of statins among new statin users with/without disease history

Year	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011	
Yearly number of new statin users	5956		9056		10924		10253		12178		13535		15233		16499		17509		17755	
With coronary events history	NA	NA	NA	NA	201	1.8%	179	1.7%	232	1.9%	219	1.6%	254	1.7%	301	1.8%	309	1.8%	286	1.6%
Atorvastatin	NA	NA	NA	NA	104	51.7%	93	52.0%	93	40.1%	94	42.9%	125	49.2%	152	50.5%	159	51.5%	147	51.4%
Fluvastatin	NA	NA	NA	NA	32	15.9%	29	16.2%	27	11.6%	24	11.0%	21	8.3%	21	7.0%	14	4.5%	7	2.5%
Lovastatin	NA	NA	NA	NA	12	6.0%	10	5.6%	11	4.7%	7	3.2%	4	1.6%	8	2.7%	4	1.3%	4	1.4%
Pravastatin	NA	NA	NA	NA	18	9.0%	10	5.6%	21	9.1%	13	5.9%	10	3.9%	15	5.0%	7	2.3%	13	4.6%
Rosuvastatin	NA	NA	NA	NA	NA	NA	6	3.4%	59	25.4%	64	29.2%	76	29.9%	85	28.2%	103	33.3%	93	32.5%
Simvastatin	NA	NA	NA	NA	35	17.4%	31	17.3%	21	9.1%	17	7.8%	18	7.1%	20	6.6%	22	7.1%	22	7.7%
Without coronary events history	NA	NA	NA	NA	10723	98.2%	10074	98.3%	11946	98.1%	13316	98.4%	14979	98.3%	16198	98.2%	17200	98.2%	17469	98.4%
Atorvastatin	NA	NA	NA	NA	3822	35.6%	3517	34.9%	3790	31.7%	4007	30.1%	4197	28.0%	4760	29.4%	5682	33.0%	6210	35.6%
Fluvastatin	NA	NA	NA	NA	1031	9.6%	1130	11.2%	1082	9.1%	1190	8.9%	1263	8.4%	1172	7.2%	1172	6.8%	1056	6.0%
Lovastatin	NA	NA	NA	NA	3583	33.4%	3102	30.8%	2940	24.6%	2291	17.2%	1961	13.1%	1716	10.6%	1238	7.2%	1021	5.8%
Pravastatin	NA	NA	NA	NA	795	7.4%	677	6.7%	745	6.2%	763	5.7%	995	6.6%	1107	6.8%	1431	8.3%	1663	9.5%
Rosuvastatin	NA	NA	NA	NA	NA	NA	342	3.4%	1631	13.7%	2153	16.2%	2663	17.8%	2997	18.5%	3293	19.2%	3371	19.3%
Simvastatin	NA	NA	NA	NA	1494	13.9%	1308	13.0%	1765	14.8%	2924	22.0%	3902	26.1%	4458	27.5%	4390	25.5%	4168	23.9%
With cerebrovascular events history	NA	NA	NA	NA	NA	NA	NA	NA	661	5.4%	735	5.4%	820	5.4%	821	5.0%	893	5.1%	878	5.0%
Atorvastatin	NA	NA	NA	NA	NA	NA	NA	NA	315	47.7%	325	44.2%	328	40.0%	321	39.1%	389	43.6%	375	42.7%
Fluvastatin	NA	NA	NA	NA	NA	NA	NA	NA	68	10.3%	71	9.7%	77	9.4%	68	8.3%	78	8.7%	63	7.2%
Lovastatin	NA	NA	NA	NA	NA	NA	NA	NA	62	9.4%	52	7.1%	61	7.4%	48	5.9%	43	4.8%	26	3.0%
Pravastatin	NA	NA	NA	NA	NA	NA	NA	NA	48	7.3%	41	5.6%	53	6.5%	39	4.8%	40	4.5%	59	6.7%
Rosuvastatin	NA	NA	NA	NA	NA	NA	NA	NA	99	15.0%	149	20.3%	173	21.1%	201	24.5%	223	25.0%	241	27.5%
Simvastatin	NA	NA	NA	NA	NA	NA	NA	NA	69	10.4%	97	13.2%	128	15.6%	146	17.8%	120	13.4%	115	13.1%
Without cerebrovascular events history	NA	NA	NA	NA	NA	NA	NA	NA	11517	94.6%	12800	94.6%	14413	94.6%	15678	95.0%	16616	94.9%	16877	95.1%
Atorvastatin	NA	NA	NA	NA	NA	NA	NA	NA	3568	31.0%	3776	29.5%	3994	27.7%	4591	29.3%	5452	32.8%	5982	35.4%
Fluvastatin	NA	NA	NA	NA	NA	NA	NA	NA	1041	9.0%	1143	8.9%	1207	8.4%	1125	7.2%	1108	6.7%	1000	5.9%
Lovastatin	NA	NA	NA	NA	NA	NA	NA	NA	2889	25.1%	2246	17.6%	1904	13.2%	1676	10.7%	1199	7.2%	999	5.9%
Pravastatin	NA	NA	NA	NA	NA	NA	NA	NA	718	6.2%	735	5.7%	952	6.6%	1083	6.9%	1398	8.4%	1617	9.6%
Rosuvastatin	NA	NA	NA	NA	NA	NA	NA	NA	1591	13.8%	2067	16.2%	2566	17.8%	2881	18.4%	3173	19.1%	3223	19.1%
Simvastatin	NA	NA	NA	NA	NA	NA	NA	NA	1717	14.9%	2843	22.2%	3792	26.3%	4332	27.6%	4292	25.8%	4075	24.2%
With diabetes history	1947	32.7%	2884	31.8%	3212	29.4%	3272	31.9%	3888	31.9%	4362	32.2%	4785	31.4%	5366	32.5%	5737	32.8%	5540	31.2%
Atorvastatin	705	36.2%	1177	40.8%	1287	40.1%	1207	36.9%	1256	32.3%	1360	31.2%	1302	27.2%	1602	29.9%	1870	32.6%	1987	35.9%
Fluvastatin	227	11.7%	273	9.5%	293	9.1%	398	12.2%	392	10.1%	366	8.4%	445	9.3%	422	7.9%	437	7.6%	343	6.2%
Lovastatin	428	22.0%	747	25.9%	919	28.6%	857	26.2%	842	21.7%	702	16.1%	572	12.0%	541	10.1%	389	6.8%	325	5.9%

Continued

Table 3 Continued

Year	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011	
Pravastatin	237	12.2%	287	10.0%	232	7.2%	233	7.1%	276	7.1%	259	5.9%	332	6.9%	365	6.8%	496	8.7%	531	9.6%
Rosuvastatin	NA	NA	NA	NA	NA	NA	140	4.3%	595	15.3%	754	17.3%	941	19.7%	1024	19.1%	1126	19.6%	1042	18.8%
Simvastatin	350	18.0%	400	13.9%	481	15.0%	437	13.4%	528	13.6%	923	21.2%	1194	25.0%	1414	26.4%	1421	24.8%	1317	23.8%
Without diabetes history	4009	67.3%	6172	68.2%	7712	70.6%	6981	68.1%	8290	68.1%	9173	67.8%	10448	68.6%	11133	67.5%	11772	67.2%	12215	68.8%
Atorvastatin	1309	32.7%	2143	34.7%	2639	34.2%	2403	34.4%	2627	31.7%	2741	29.9%	3020	28.9%	3310	29.7%	3971	33.7%	4370	35.8%
Fluvastatin	483	12.1%	582	9.4%	770	10.0%	761	10.9%	717	8.7%	848	9.2%	839	8.0%	771	6.9%	749	6.4%	720	5.9%
Lovastatin	1045	26.1%	2082	33.7%	2676	34.7%	2255	32.3%	2109	25.4%	1596	17.4%	1393	13.3%	1183	10.6%	853	7.3%	700	5.7%
Pravastatin	417	10.4%	504	8.2%	581	7.5%	454	6.5%	490	5.9%	517	5.6%	673	6.4%	757	6.8%	942	8.0%	1145	9.4%
Rosuvastatin	NA	NA	NA	NA	NA	NA	208	3.0%	1095	13.2%	1462	15.9%	1798	17.2%	2058	18.5%	2270	19.3%	2422	19.8%
Simvastatin	756	18.9%	862	14.0%	1048	13.6%	902	12.9%	1258	15.2%	2018	22.0%	2726	26.1%	3064	27.5%	2991	25.4%	2873	23.5%
With myopathy history	NA	NA	NA	NA	2924	26.8%	2806	27.4%	3342	27.4%	3816	28.2%	4202	27.6%	4502	27.3%	4068	23.2%	5061	28.5%
Atorvastatin	NA	NA	NA	NA	1036	35.4%	949	33.8%	1016	30.4%	1135	29.7%	1102	26.2%	1308	29.1%	1616	39.7%	1769	35.0%
Fluvastatin	NA	NA	NA	NA	289	9.9%	314	11.2%	299	9.0%	332	8.7%	355	8.5%	319	7.1%	335	8.2%	279	5.5%
Lovastatin	NA	NA	NA	NA	979	33.5%	895	31.9%	880	26.3%	671	17.6%	581	13.8%	486	10.8%	364	9.0%	291	5.8%
Pravastatin	NA	NA	NA	NA	214	7.3%	190	6.8%	200	6.0%	199	5.2%	281	6.7%	302	6.7%	448	11.0%	470	9.3%
Rosuvastatin	NA	NA	NA	NA	NA	NA	110	3.9%	479	14.3%	595	15.6%	713	17.0%	814	18.1%	923	22.7%	924	18.3%
Simvastatin	NA	NA	NA	NA	407	13.9%	348	12.4%	472	14.1%	888	23.3%	1170	27.8%	1277	28.4%	1283	31.5%	1331	26.3%
Without myopathy history	NA	NA	NA	NA	8000	73.2%	7447	72.6%	8836	72.6%	9719	71.8%	11031	72.4%	11997	72.7%	12541	71.6%	12694	71.5%
Atorvastatin	NA	NA	NA	NA	2890	36.1%	2661	35.7%	2867	32.5%	2966	30.5%	3220	29.2%	3604	30.0%	4225	33.7%	4588	36.1%
Fluvastatin	NA	NA	NA	NA	774	9.7%	845	11.4%	810	9.2%	882	9.1%	929	8.4%	874	7.3%	851	6.8%	784	6.2%
Lovastatin	NA	NA	NA	NA	2616	32.7%	2217	29.8%	2071	23.4%	1627	16.7%	1384	12.6%	1238	10.3%	878	7.0%	734	5.8%
Pravastatin	NA	NA	NA	NA	599	7.5%	497	6.7%	566	6.4%	577	5.9%	724	6.6%	820	6.8%	990	7.9%	1206	9.5%
Rosuvastatin	NA	NA	NA	NA	NA	NA	238	3.2%	1211	13.7%	1622	16.7%	2026	18.4%	2268	18.9%	2473	19.7%	2540	20.0%
Simvastatin	NA	NA	NA	NA	1122	14.0%	991	13.3%	1314	14.9%	2053	21.1%	2750	24.9%	3201	26.7%	3129	25.0%	2859	22.5%
With liver injury history	NA	NA	NA	NA	856	7.8%	798	7.8%	907	7.4%	1040	7.7%	1075	7.1%	1187	7.2%	1375	7.9%	1403	7.9%
Atorvastatin	NA	NA	NA	NA	369	43.1%	304	38.1%	294	32.4%	301	28.9%	324	30.1%	367	30.9%	429	31.2%	519	37.0%
Fluvastatin	NA	NA	NA	NA	69	8.1%	86	10.8%	90	9.9%	91	8.8%	79	7.4%	79	6.7%	94	6.8%	84	6.0%
Lovastatin	NA	NA	NA	NA	255	29.8%	219	27.4%	211	23.3%	183	17.6%	123	11.4%	88	7.4%	79	5.8%	75	5.4%
Pravastatin	NA	NA	NA	NA	51	6.0%	45	5.6%	65	7.2%	65	6.3%	68	6.3%	86	7.3%	134	9.8%	147	10.5%
Rosuvastatin	NA	NA	NA	NA	NA	NA	31	3.9%	121	13.3%	169	16.3%	198	18.4%	221	18.6%	258	18.8%	246	17.5%
Simvastatin	NA	NA	NA	NA	112	13.1%	113	14.2%	127	14.0%	232	22.3%	284	26.4%	346	29.2%	381	27.7%	332	23.7%
Without liver injury history	NA	NA	NA	NA	10068	92.2%	9455	92.2%	11271	92.6%	12495	92.3%	14158	92.9%	15312	92.8%	16134	92.1%	16352	92.1%
Atorvastatin	NA	NA	NA	NA	3557	35.3%	3306	35.0%	3589	31.8%	3800	30.4%	3998	28.2%	4545	29.7%	5412	33.5%	5838	35.7%
Fluvastatin	NA	NA	NA	NA	994	9.9%	1073	11.4%	1019	9.0%	1123	9.0%	1205	8.5%	1114	7.3%	1092	6.8%	979	6.0%

Continued

Table 3 Continued

Year	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011	
Lovastatin	NA	NA	NA	NA	3340	33.2%	2893	30.6%	2740	24.3%	2115	16.9%	1842	13.0%	1636	10.7%	1163	7.2%	950	5.8%
Pravastatin	NA	NA	NA	NA	762	7.6%	642	6.8%	701	6.2%	711	5.7%	937	6.6%	1036	6.8%	1304	8.1%	1529	9.4%
Rosuvastatin	NA	NA	NA	NA	NA	NA	317	3.4%	1569	13.9%	2048	16.4%	2541	18.0%	2861	18.7%	3138	19.5%	3218	19.7%
Simvastatin	NA	NA	NA	NA	1417	14.1%	1226	13.0%	1659	14.7%	2709	21.7%	3636	25.7%	4132	27.0%	4031	25.0%	3858	23.6%

Individuals were defined as having a history of the following diseases if they have a diagnosis within certain years prior to the given year: coronary event (3 years), cerebrovascular event (5 years), diabetes (1 year), myopathy (3 years) and liver injury (3 years).
NA, not available.

Another high-potency statin—rosuvastatin—manifested an increase in prescription rates since its market entry at 2005. The growth in use of atorvastatin, simvastatin (+/- ezetimibe) and rosuvastatin suggests treatment trending towards use of high-potency or moderate-to-high-intensity statin therapy, which is aligned with major clinical guidelines.[7–9]

The majority of statin regimen stayed within the moderate-intensity range rather than high-intensity therapy, which remained less than 5% during the study period. In a study from USA, relatively lower percentage (approximately 20% of total statin use) of high-intensity statin therapy was reported among adults ≧40 years old during 2002–2013.[47] In comparison, our study reveals substantially low use of high-intensity statin, suggesting that there is room for improving rational use of statins in Taiwan.

Few statin users initiated with combination therapy overall. Use of combined lipid-lowering agents shifted from fibrates (83.3% in 2002) to ezetimibe (66.2% in 2011). Ezetimibe entered Taiwan's market under the National Insurance coverage in 2006 as a combination drug with simvastatin (tradename Vytorin). High uptake of ezetimibe products might be associated with the evidence that ezetimibe plus simvastatin is more effective in lowering LDL-C than simvastatin alone.[48 49]

Our findings demonstrated an association between having a history of CVD and high-intensity or moderate-intensity statin use. Similarly other studies have reported that patients with CVD histories were prescribed statins with higher intensity or doses.[19 50] Use of statins among these individuals might have been appropriately influenced by clinical guidelines and related evidence suggesting more intensive statin therapy reduces cardiovascular events in patients with prior CVD.[22] While diabetes has been viewed as a coronary risk equivalent,[51] we did not find greater use of higher intensity statins among those with diabetes. A possible explanation might include the accumulating evidence suggesting the association between statin use and increasing risk of diabetes[52 53] and the deterioration of glucose control in patients receiving higher intensity statin regimens.[54] Appropriateness of statin use among diabetes needs further investigation. Interestingly, we did not find different patterns of statin use between those with and without history of myopathy or liver diseases. This finding suggests that these side effects might not be of a primary concern when prescribing statin therapy in Taiwan.

This study contributes to the literature by examining the prescribing patterns of statins during 2002–2011 in Taiwan, including statin choices among patients with certain medical histories. Despite these strengths, it does have limitations. First, our analysis was based on claims data, which do not contain patients' biochemical test data (such as level of LDL-C), so we could not assess prescription patterns by disease severity. Second, this study only examined statin use among new users; we did not assess switches between statins. Further research is needed to

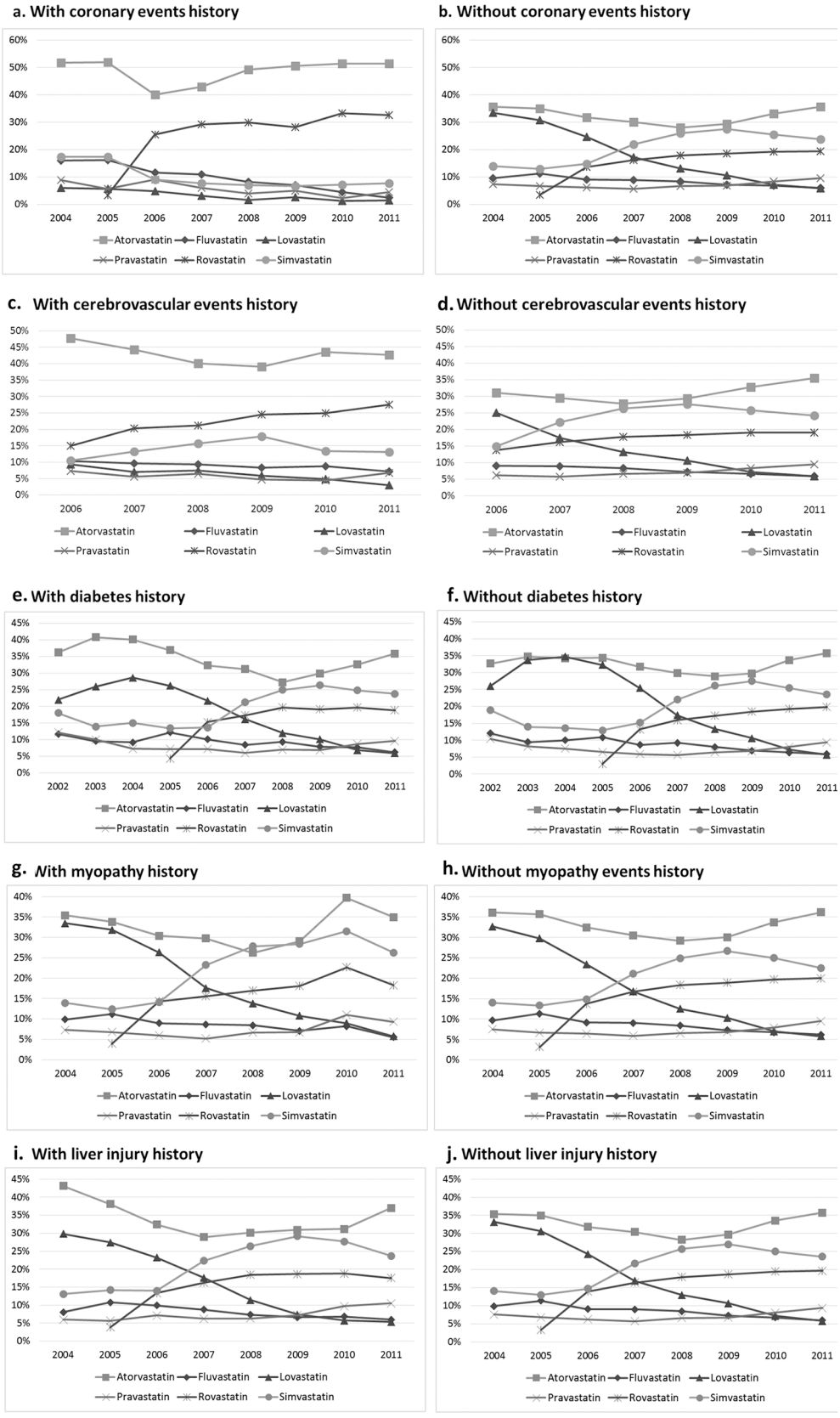

Figure 3 Prescribing rates of statins among new statin users with/without history of specific diseases.

address these gaps. As new PCSK9 inhibitors become available on Taiwan's NHI, our findings provide baseline trends that can be used in a future study to examine how new PCSK9 inhibitors impact the market of cholesterol medications.

Table 4 Associations between disease history and prescription of moderate-intensity or high-intensity statins

Year	2004	2005	2006	2007	2008	2009	2010	2011
OR† (95% CI)								
History of coronary events	2.04*	2.55*	2.83*	1.69*	2.39*	1.80*	2.06*	1.52*
	(1.51 to 2.76)	(1.80 to 3.59)	(2.01 to 3.99)	(1.22 to 2.35)	(1.66 to 3.44)	(1.34 to 2.42)	(1.52 to 2.80)	(1.13 to 2.03)
History of cerebrovascular events	–	–	1.88*	1.61*	1.17*	1.40*	1.66*	1.61*
	–	–	(1.56 to 2.25)	(1.34 to 1.93)	(0.99 to 1.38)	(1.18 to 1.65)	(1.40 to 1.96)	(1.36 to 1.91)
History of diabetes	1.17*	1.08*	1.01	0.88*	0.90*	0.83*	0.85*	0.83*
	(1.08 to 1.27)	(0.99 to 1.18)	(0.93 to 1.09)	(0.81 to 0.95)	(0.83 to 0.97)	(0.77 to 0.89)	(0.79 to 0.91)	(0.77 to 0.89)
History of myopathy	0.97	0.95	0.93	0.99	0.97	1.00	0.94	0.96
	(0.89 to 1.05)	(0.87 to 1.04)	(0.86 to 1.01)	(0.91 to 1.07)	(0.90 to 1.05)	(0.73 to 1.08)	(0.87 to 1.01)	(0.89 to 1.03)
History of liver injury	1.29*	1.19	0.96	1.04	1.10	1.15*	0.95	1.04
	(1.12 to 1.49)	(1.02 to 1.37)	(0.84 to 1.11)	(0.91 to 1.20)	(0.95 to 1.27)	(1.00 to 1.31)	(0.84 to 1.07)	(0.92 to 1.17

*Indicates significant difference in prescription rate between patient with certain medical history and those without; p value <0.05.
†OR was calculated as the odds of being prescribed high-intensity or moderate-intensity statins for those with certain disease history compared with those without.
Statins were grouped into three levels of intensity according to its ability of lowering LDL-C based on 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol[7] and Rosenson et al[28]: (1) high-intensity statins: atorvastatin 40 mg/day, rosuvastatin 20 mg/day and simvastatin 80 mg/day; (2) moderate-intensity statins: 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; and (3) low-intensity statins: 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. Individuals were defined as having a history of the following diseases if they have a diagnosis within certain years prior to the given year: coronary event (3 years), cerebrovascular event (5 years), diabetes (1 year), myopathy (3 years) and liver injury (3 years).
ACC/AHA, American College of Cardiology/American Heart Association; LDL-C, low-density lipoprotein cholesterol.

CONCLUSION

Our study with national cohorts of new statin users in each year during 2002–2011 in Taiwan found that the majority of new users initiated on statin monotherapy, and atorvastatin was the most commonly prescribed statin. While patients with history of CVD were more likely to be prescribed higher intensity statins compared with those without, which is consistent with clinical guidelines, such difference was not found comparing those with and without diabetes. Appropriateness of statin use among diabetes needs further investigation.

Contributor JCH and HCH conceptualised and designed the study. HCH collected data, performed analysis and drafted the manuscript. JCH and CYL reviewed all data and revised the manuscript critically for intellectual content. All authors approved the final version for submission.

Competing interests None declared.

Ethics approval National Cheng Kung University Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The authors have obtained nationwide, monthly claims data for lipid-lowering agents, from 2002 to 2011, from the Taiwan National Health Insurance Research Database (NHIRD). NHIRD does not permit external sharing of any of the data elements. No additional data available.

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