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Trends in statin prescription prevalence, initiation, and dosing—Hong Kong, 2004–2015

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Highlights

- Prevalence of statin prescriptions was almost five times higher in 2015 versus 2004.
- Greater initiation of statins for primary prevention, especially since 2007.
- Initiation of high-intensity statins is uncommon in Hong Kong.
- Patients aged 70–84 had the highest annual statin initiation rates.

Abstract

Background and aims

Clinical practice guidelines recommend specific statin doses for the primary and secondary prevention of cardiovascular disease. Little is known about how statin utilization and dosing has evolved over time in Hong Kong. The aim of this study was to describe trends in statin prevalence, initiation, and dosing, from 2004 to 2015.

Methods

Patients receiving public health services, who were prescribed a statin, were included if they received a lipid test at a single center (n = 58 672). Using the territory-wide electronic health record, prescribed daily statin dose, nondaily dose frequency, and statin dose intensity were determined for statin prescriptions from 2004 to 2015. Statin prescription prevalence and initiation rates were estimated using the appropriate at-risk population in the hospital catchment area as the denominator. Prescribed daily doses were stratified by primary or secondary cardiovascular prevention status to assess changes in statin dosing over time.

Results

The prescription prevalence of statins was higher in 2015 (8.68%; 95% CI, 8.60% to 8.75%) as compared with 2004 (1.82%; 95% confidence interval [CI], 1.78% to 1.86%). Initiation rates for new statin users increased from 2004 to 2013. High-intensity statins were infrequently prescribed. New users generally had higher statin initiation rates for primary prevention. There

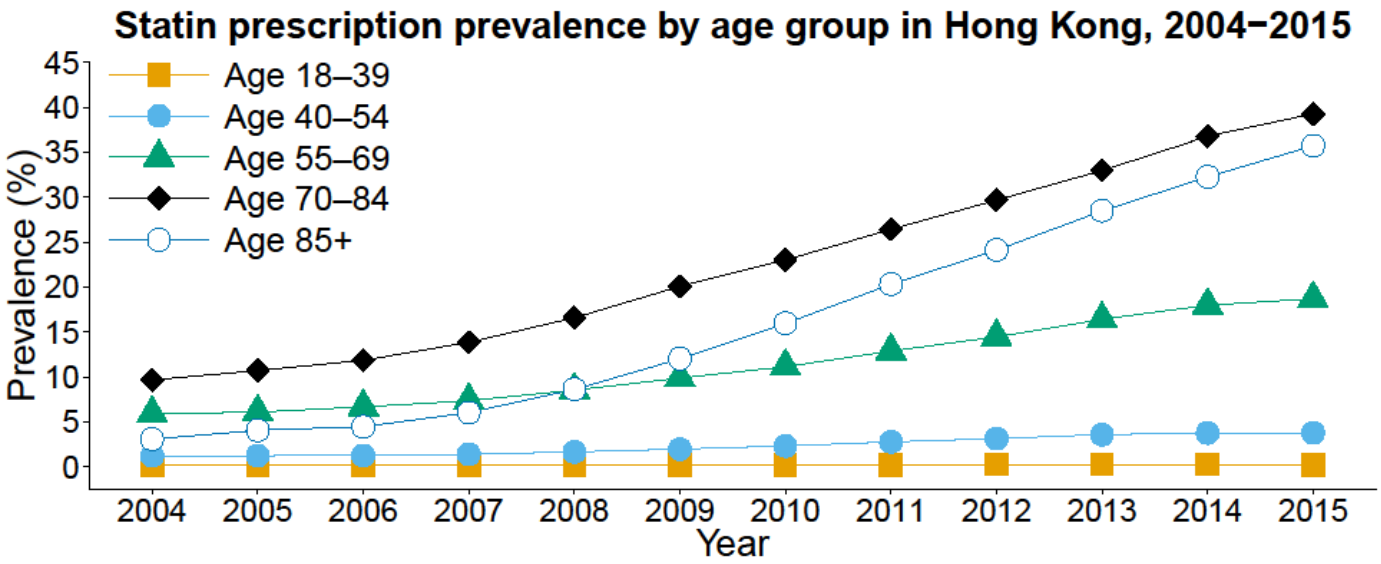
were small increases in the prescribed daily doses of statins. Nondaily statin dosing was infrequent (0.42% of all prescriptions).

Conclusions

The prevalence and initiation of statin prescriptions increased in Hong Kong, and was in part driven by low-intensity statins for the primary prevention of cardiovascular disease.

Keywords

Statin; Prescribing; Prevalence; Initiation; Dosing; Primary Prevention; Secondary Prevention



Introduction

Statins are effective for primary and secondary prevention of cardiovascular disease.[1,2] In China, cardiovascular disease is the top cause of death,[3] while in Hong Kong, heart diseases and cerebrovascular diseases together comprised 1 in 5 of all registered deaths in 2016.[4] However, scant data are available on the trends in statin prescribing in Hong Kong.

The potential pharmacokinetic differences in Asian populations frequently necessitate a lower statin dose to achieve a comparable cholesterol reduction, as compared with Western populations.[5] In clinical trials,[6,7] high-intensity statins caused an increased frequency of adverse effects versus lower intensities. Even moderate doses of simvastatin (40 mg/day) resulted in higher rates of myopathy in Chinese patients in the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial,[8] which led to the new regulatory authority recommendations that the lowest dose of simvastatin should be used in Chinese patients.[9]

There is also controversy as to whether high-intensity statins provide additional benefits in Asians. In an observational study of 14 866 Japanese patients who underwent their first coronary revascularization,[10] the incidence of major adverse cardiovascular events, did not differ between patients prescribed standard statins and “strong” statins. Similarly, 1 355 Chinese patients hospitalized for acute coronary syndrome, were randomized to receive a moderate-intensity statin or a high-intensity.[11] After two years of follow-up, there was no statistically significant difference between the two treatment groups. These results suggest that there may not be further clinical benefits to high-intensity statin therapy in most Asians.

Previous local studies show that low- or moderate-intensity statins are commonly prescribed rather than high-intensity statins.[12-14] In light of the evolution of clinical practice

guidelines and statin safety concerns, whether there have been changes over time in statin prevalence and initiation has not been investigated in Hong Kong. The objectives of this study were to characterize statin prescription prevalence, statin treatment initiation rates, statin prescription dosing and the cardiovascular prevention status (primary or secondary) of statin users, in a cohort of Hong Kong patients who received a lipid test, between 2004 and 2015.

Patients and methods

Data source

We used the data of patients accessing health services within the Hong Kong Hospital Authority: the statutory body that manages all publicly funded hospitals and ambulatory clinics in Hong Kong.[15] The Hospital Authority currently delivers primary, secondary, and tertiary care to the 7.3 million residents of Hong Kong through services at 42 public hospitals, 47 specialist clinics, and 73 general outpatient clinics. Electronic health records, including demographics, inpatient and outpatient data, drug prescribing and dispensing records, diagnoses, procedures, and laboratory tests are centralized in the Clinical Data Analysis and Reporting System (CDARS) for practice, research, and audit purposes. All patient records are anonymized to safeguard privacy. Hospital diagnosis and procedure data are coded according to the International Classification of Diseases-9th revision-Clinical Modification (ICD-9-CM). CDARS has been used extensively to conduct high quality epidemiological studies. As reported previously,[16-19] there is a high degree of data validity and accuracy. The Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster approved the study, which waived the requirement for informed patient consent.

Study participants

There is no widely adopted clinical practice guideline for the management of blood cholesterol in Hong Kong, thus clinicians routinely order lipid tests as a component of overall cardiovascular risk assessment in patients with cardiovascular risk factors according to various international guidelines. Our cohort included patients from any care setting who underwent at least one lipid test (total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], or triglycerides [TG]) at the Queen Mary Hospital, Hong Kong West Cluster, from January 1, 2004, to March 3, 2014. Patients were followed from January 1, 2004 to December 31, 2015.

The index date was defined as the date of the first statin prescription that occurred during the observation period. Patients aged 18 years or above on the index date were included in the study. We excluded patients with an unknown date of birth or sex.

The nearest lipid tests preceding the index date were described. Diagnoses and procedures recorded at any time prior to the index date plus 7 days were described and categorized based on ICD-9-CM codes (Supplemental Table 1). This 7-day period after the index date was applied to allow for sufficient time for application of diagnosis codes and to better distinguish patients prescribed a statin for secondary prevention.

Statin prescriptions and dose intensity analysis

All prescriptions were retrieved for the identification of statin prescriptions amongst the cohort. A statin prescription was defined as any dispensation of a drug product containing atorvastatin, fluvastatin, lovastatin, rosuvastatin, pravastatin, or simvastatin. Statin prescription data was analyzed to determine drug name, strength, dose, and frequency. Prescriptions with a missing dose, frequency, or drug strength were classified as missing and excluded from the dose

intensity and daily prescribed dose analyses (Supplemental Table 2). Nondaily frequency was defined as having a statin prescription with a dosing frequency longer than the usual once daily dosing (e.g. every two days).

Statin dose intensity was defined as per the American College of Cardiology/American Heart Association 2013 guidelines.[20] High-intensity was defined as atorvastatin ≥40mg/day, rosuvastatin ≥20mg/day, or simvastatin ≥80mg/day. Simvastatin ≥80mg/day was classified as high-intensity as it reduces LDL-C by approximately 50% in Asians.[21] Moderate-intensity was defined as atorvastatin <40 mg/day, rosuvastatin <20mg/day, simvastatin 11-79mg/day, pravastatin ≥40mg/day, lovastatin ≥40mg/day, or fluvastatin ≥80mg/day. Low-intensity was defined as simvastatin ≤10mg/day, pravastatin <40mg/day, lovastatin <40 mg/day**,** or fluvastatin <80mg/day.

Statin prescription prevalence and initiation

The catchment area for the Queen Mary Hospital includes the Central and Western, and Southern districts of Hong Kong Island, which accounts for roughly 7% of Hong Kong's population. We obtained the land-based non-institutional annual population estimates, stratified by age and sex, for these two districts from the Census and Statistics Department of the Hong Kong Special Administrative Region. The pre-specified age bands in the district dataset did not match the age groups selected for our study, so we estimated the number of residents in each age group in the hospital catchment area by using the age distribution of the mid-year Hong Kong resident population by single age band (0 to 85+).

A statin user had at least one statin prescription dispensing date occurring during a given calendar year. The statin prescription period prevalence was calculated by taking the total

number of patients with any statin prescription during each calendar year, divided by the annual total population in the hospital catchment area.[22] Prevalence stratified by statin dose intensity was calculated with the numerator defined as the total number of patients exposed to a statin dose intensity, divided by the annual total population in the hospital catchment area. We used the annual estimated catchment area population age groups as the denominator, to estimate the age-specific prescription prevalence, and the catchment area population by sex as the denominator, to estimate sex-specific prevalence.

To identify new statin users, we excluded patients with a statin prescription during a 365-day washout period preceding the index date. A washout period of one year is commonly used in statin studies to identify new users as statins are taken as chronic treatment.[23,24] Patients who had prescriptions for different statin drugs on the index date (n=67) or who had the same statin drug but different statin dose intensities (n=30) were removed from the new user analysis.

The statin prescription initiation rate was calculated with the numerator being the total number of new statin users in each year and the denominator representing the appropriate annual population at risk, as was described previously. Statin initiation was further stratified by sex, age, and statin intensity. Proportions for prevalence and initiation rate were rescaled to percentages.

Primary and secondary prevention of cardiovascular disease

We classified statin users based on the potential reason of statin use into either primary or secondary prevention of cardiovascular disease. Secondary prevention was defined by the occurrence of at least one prior diagnosis code for atherosclerotic cardiovascular disease, defined as coronary artery disease, cerebrovascular disease, or peripheral artery disease; or a procedure code for percutaneous coronary intervention, coronary artery bypass graft surgery, or other

coronary revascularization (Supplemental Table 1).[25] Statin users not classified into the secondary prevention category, were classified into the primary prevention category.

Statistical analysis

Summary statistics were calculated using frequencies and proportions for categorical data. We calculated the medians and interquartile ranges or means with standard deviation for continuous variables. We calculated 95% confidence intervals for the observed prevalence and initiation rates. Chi-square test for trend in proportions was used to test for a linear trend in overall statin prescription prevalence. Linear regression was used to test for trend in prescribed statin doses. A p value <0.05 was considered statistically significant for all analyses. Analyses were performed in RStudio (version 1.1.453; RStudio Team, Boston, MA) using R version 3.5.0 (R Core Team, Vienna, Austria).

Results

Patient characteristics

A total of 145 875 patients who underwent at least one lipid test between January 2004 and March 2014 were identified. After analyzing their prescription records, 40.2% of adult patients received at least one statin prescription during the observation period, and the majority were classified as primary prevention (Table 1). Most patients (77%) had a recorded lipid test prior to initiating a statin. There were slightly more males than females in the cohort and most patients were aged ≥40 years at the time of the first statin prescription.

Prevalence of statin prescriptions

There was an increased trend in statin prescription prevalence (test for trend in proportions, $p<0.001$), and the prevalence of statin prescriptions increased nearly fivefold from 2004 (prevalence rate, 1.82%; 95% confidence interval [CI], 1.78% to 1.86%) to 2015 (prevalence rate, 8.68%; 95% CI, 8.60% to 8.75%) as shown in Supplemental Table 3.

Figure 1 shows statin prescription prevalence stratified by sex, age, and statin intensity. Males tended to have a higher prevalence of statin treatment than women, and reached a peak statin prevalence rate in 2015 (prevalence rate, 10.17%; 95% CI, 10.05% to 10.29%). When stratified by age group [Figure 1(C)], the 70–84 year age group had the highest statin prescription prevalence in every year of the study, and had the highest prevalence rate in 2015 (prevalence rate, 39.27%; 95% CI, 38.8% to 39.74%).

Over time, the prescription prevalence of all statin intensities increased [Figure 1(D)]. The prevalence of moderate-intensity (2004 prevalence rate, 1.17%; 95% CI, 1.14% to 1.20%) and low-intensity statins (2004 prevalence rate, 0.67%; 95% CI, 0.65% to 0.70%) grew steadily until 2015, during which the prevalence of low-intensity statins (prevalence rate, 4.20%; 95% CI, 4.14% to 4.25%) was similar to the prevalence of moderate-intensity statins (prevalence rate, 4.60%; 95% CI, 4.54% to 4.65%). There was a small increase in the prescription prevalence of high-intensity statins between 2004 (prevalence rate, 0.05%; 95% CI, 0.05% to 0.06%) and 2015 (prevalence rate, 0.42%; 95% CI, 0.40% to 0.44%).

Simvastatin was consistently the most prescribed statin, and had a 31.9% increase in its share of statin users between 2004 and 2015 (Supplemental Table 4). Atorvastatin and rosuvastatin were the second and third most commonly prescribed statins. Lovastatin, fluvastatin and pravastatin together accounted for less than 8% of statin users in 2004, and their combined total of statin users declined to less than 1% in 2015. There was rapid annual growth in the

proportion of rosuvastatin users at the beginning of the study period, corresponding with its introduction to the Hong Kong market in 2004.

Statin initiation rates

There were 51 610 statin users who met the definition of new user. Statin initiation rates consistently increased from 0.44% (95% CI, 0.42% to 0.46%) in 2004 to 1.23% (95% CI, 1.20% to 1.26%) in 2013 (Supplemental Table 5). A decrease in initiation rates occurred in 2014 and 2015, likely because our cohort did not continue to enroll patients with a lipid test after March 2014. When stratified according to age [Figure 2(C)], there was a consistent initiation rate for new users under the age of 40. In contrast, there were increases in initiation rates for the other age groups, especially in those aged 85+. This age group experienced a rapid increase in statin therapy initiation between 2004 (initiation rate, 0.99%; 95% CI, 0.77% to 1.29%) and 2013 (initiation rate, 3.92%; 95% CI, 3.57% to 4.31%). New users aged 70–84 had the highest overall statin therapy initiation rates in each year of the study.

When stratified according to dose intensity [Figure 2(D)], there was a consistent annual increase in the initiation rate of low-intensity statins. The initiation rate for moderate- and high-intensity statins remained stable throughout the study. New user age-specific initiation rates, grouped by cardiovascular prevention status and age group, are shown in Figure 3. New users in each age group generally had higher annual statin initiation rates for primary prevention of cardiovascular disease, except for patients 70 years or greater. Patients age 85+ initiated statins for secondary prevention at a similar or higher rate than primary prevention in each study year. This age group had increased initiation rates of statins for primary prevention up until 2012. The overall initiation rates for the three most prescribed statin drugs are presented in Supplemental Figure 1. There were shifts in the initiation rates of atorvastatin and simvastatin. Simvastatin

initiation rates for primary prevention increased over time until 2014. However, the initiation of simvastatin for secondary prevention stabilized in 2009 then declined in 2012. A decline in the use of atorvastatin for secondary prevention occurred in the early years of our study.

The number of new users represented between 10% and 23% of total statin users in each year (Supplemental Table 6). New users primarily initiated treatment with simvastatin: over 80% of new users initiated simvastatin between 2010 and 2015.

Use of combination statin products and statin prescription dosing

During the study period, there were 1 523 330 statin prescriptions dispensed, and two combination products containing a statin were available in Hong Kong: Vytorin (ezetimibe and simvastatin; Merck Sharp & Dohme Ltd) and Caduet (amlodipine and atorvastatin; Pfizer Inc). Overall, very few prescriptions (<0.2%) for a combination drug product containing a statin were dispensed and the number of prescriptions remained stable over time (Supplemental Table 7).

For prescriptions with ascertainable dosing information, only a small number of statin prescriptions (n = 6 352; 0.42%) were for a nondaily dosing frequency. The proportion of prescriptions with nondaily dosing seemed to decline slightly over time (Supplemental Table 2).

Table 2 shows bi-yearly mean prescribed daily doses of statin prescriptions. For each statin, the mean prescribed daily doses for secondary prevention were generally higher than the doses prescribed for primary prevention of cardiovascular disease. There was a trend towards modestly higher doses of all statins (except fluvastatin) for secondary prevention of cardiovascular disease. The prescribed doses of simvastatin for the secondary prevention of cardiovascular disease peaked in 2010–2011 then stabilized thereafter. For primary prevention of

cardiovascular disease, the prescribed doses of atorvastatin and rosuvastatin increased over time while the doses of simvastatin decreased.

Discussion

To our knowledge, this is the first study to report statin prescription prevalence, initiation, and dosing trends in Hong Kong. In 2015, the statin prescription prevalence was nearly five times greater than in 2004, while the statin prescription initiation rate doubled during the 12-year study period. There were also changes in statin drug choices and dosages. The most significant finding is that increases in statin prescribing have been driven by greater use of low- and moderate-intensity statins for the primary prevention of cardiovascular disease.

The prevalence of statin use is lower in Hong Kong as compared with the United States (US), but appears similar to Taiwan. Kantor et al. reported on the prevalence of use of statins within 30 days from 1999 to 2012 in the US, using data from the National Health and Nutrition Examination Survey.[26] The prevalence of statin use was estimated at 11% (95% CI, 9.6% to 12%) in 2003–2004 and increased to 17% (95% CI, 15% to 19%) in 2011–2012. This contrasts with our results, which show that statin prevalence reached its highest point at about 9% in 2015, still lower than the 2003-2004 prevalence estimate from the US. A lower prevalence of heart disease in Hong Kong (2.1%)[27] than in the US (6%) explains some of the different in statin prevalence.[28] Since many East Asian populations have a low prevalence of heart disease, it is not surprising that our results more closely correspond with those from Taiwan. Hsieh et al., using a representative sample from Taiwan's National Health Insurance Research Database, estimated the prevalence of statin use at 6.3% in 2011.[23] This is similar to our 2011 estimate of 5.4%. Thus the increased prevalence of statin treatment in Hong Kong, seems to be influenced by global guideline recommendations; such as the 2001 Adult Treatment Panel III in the US[29]

and the 2003 European Guidelines on Cardiovascular Disease Prevention;[30] pharmaceutical company marketing; and the increased evidence base for statins. While the increase in statin prescription prevalence is similar to Taiwan, the timing of the increased uptake of statins in Hong Kong contrasts with several regions.

The peak in statin therapy initiation rates in Hong Kong occurred several years later than other regional studies of statin utilization.[23,31,32] In a Danish cohort, the incidence of statin treatment peaked in 2008 and started to decline in 2009.[31] A study from the United Kingdom, of statin use in primary prevention, found that the peak statin initiation rate occurred in 2006, followed by a decline then stabilization in 2011.[32] In Taiwan, the statin initiation rate in the final year of study (2011), was 1.8%.[23] Hong Kong deviates from this pattern with a peak initiation rate occurring in 2013 (1.2%). This gap may be a result of the lack of Hong Kong specific clinical practice guidelines for the management of dyslipidemia associated with hypertension or diabetes, prior to 2011, delays in funding new drug treatments, concerns about statin adverse effects, and the limited evidence about the risks and benefits of statins in Asian populations.

The development of the Hong Kong primary care reference frameworks for lipid management in patients with diabetes and hypertension in 2011, likely contributed to increased statin initiation rates, particularly for low-intensity statins for the primary prevention of cardiovascular disease.[33] These reference frameworks recommend initiating statin therapy with low- or moderate-intensity statins (e.g. simvastatin 10mg/day, atorvastatin 10mg/day, rosuvastatin 5mg/day), based on the patient's cardiovascular risk.[34,35] Greater awareness of cardiovascular risk assessment and guidance to prescribe statins has supported prescribers to initiate statins for primary prevention.

Over time, we observed modest increases in the prescribed daily doses of most statins. As expected, the mean daily statin doses used for patients classified as secondary prevention, are higher than those used for patients classified as primary prevention. Increased prescribed daily doses of statins have been described in European studies.[36,37] Walley et al. reported increases in European prescribed daily doses of statins between 2000 and 2003.[37] When comparing our results with this study, the mean daily doses of statins were comparatively lower, and increases occurred over a 12-year period. Statin dosing in Hong Kong appears to be conservative, as we observed decreased initiation of higher potency statins (atorvastatin and rosuvastatin) and steady increases in the initiation of simvastatin for both primary and secondary prevention. It can be postulated that the gradual increase in statin doses observed in this study may have been influenced by the potential adverse effects of statins.

Prescribers have gained greater awareness of the adverse effects of statins, notably with high-intensity simvastatin. In 2011, the US Food and Drug Administration warned about the risks of rhabdomyolysis associated with simvastatin 80mg/day.[38] Interestingly, the peak in mean simvastatin doses, for both primary and secondary prevention, seems to align with the timing of the regulatory warning in 2010–2011. Furthermore, the initiation rate of moderate- and high-intensity statins remained stable after 2011.Taken together, the data in later years of our study, suggest that prescribers often balance the risks and benefits of statin treatment by initiating low-intensity statins.

Adults 70 years and older comprised just over a third of our study population and as a group have the highest statin prevalence and initiation rates. Interestingly, in patients 70–84 years, statin initiation for primary prevention overtakes initiation for secondary prevention in 2011, with continued increase then stabilization in 2014 (Figure 3). In the 85+ age group, we

observed a rapid increase in the prevalence of statin therapy from 2004 (~3%) to 2015 (~36%). In this age group, the statin initiation rate progressively increased to about 4% in 2013: around one-third to one-half of patients (depending on the year) started statins for primary prevention. Initiating statins in patients older than 75 years, for primary prevention of cardiovascular disease, remains controversial given the lack of evidence from randomized controlled trials.[39] A recent post hoc analysis from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial (ALLHAT-LLT) of pravastatin vs usual care, did not show any benefit for pravastatin when used for primary prevention in adults 65 years and older.[40] In addition, real-world data from a population-based cohort study suggests that patients over the age of 74 years without type 2 diabetes who initiate statins, obtain no reduction in the risk of atherosclerotic cardiovascular disease or total mortality.[41] The observed statin prescribing for primary prevention in the elderly in our cohort reflects the fact that as the population ages, older people are at even greater risk of experiencing a cardiovascular outcome and would, according to clinical guidelines and risk calculators, qualify for statin therapy. However, this group of patients may be less likely to benefit from statin treatment for primary prevention of cardiovascular disease. Additional research assessing the clinical outcomes of statin use in the elderly is required, since clinicians appear to be increasingly prescribing statins to a group of patients who may derive minimal benefit from treatment.

There are several limitations of this study. Certain components of electronic drug orders may be free-text entries recorded by front-line healthcare professionals. We could not ascertain dosing information for some prescriptions as this information was missing or uninterpretable. Regardless, 88% of the total prescriptions were included in the dose intensity analysis. For our selected cohort, all inpatient and outpatient prescriptions within the public health system were

included, effectively capturing statin utilization and initiation for both the primary and secondary prevention of cardiovascular disease.

Further, our results likely represent an underestimation of the "true" prevalence and initiation of statins, since our sample does not include data from the private healthcare system (most primary care and private specialist physicians). Hospital Authority formulary guidelines limit statin choices and recommend simvastatin as the first-line statin. Thus, the choice of prescribed statins in our study may not be entirely generalizable to the private healthcare sector.

Areas for additional research include patterns of use of all lipid lowering drugs (e.g. ezetimibe, fibrates) in the Hong Kong population to provide a comprehensive estimate of the population prescribing prevalence of all lipid lowering drugs. This information will better inform clinicians about the potential for over or under use of lipid lowering drugs, in various at-risk groups of patients.

Statin prescribing prevalence and initiation generally increased from 2004 to 2015, with most patients receiving low- or moderate-intensity statins. Initiation of statins for primary prevention occurred more frequently in later years. Further investigation into the patterns of use of non-statin lipid lowering drugs and the use of statins in the elderly, will further our understanding about the current approach to cardiovascular risk reduction in Hong Kong.

Conflict of interest

Esther W. Chan has received research funding from The Hong Kong Research Grants Council, The Research Fund Secretariat of the Food and Health Bureau of The Government of the Hong Kong Special Administrative Region, Narcotics Division of the Security Bureau of The Government of the Hong Kong Special Administrative Region, Bristol-Myers Squibb, Pfizer, Bayer and Janssen, a Division of Johnson & Johnson, for work unrelated to this study.

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Conception and design: Joseph E. Blais, Esther W. Chan, and Chung-Wah Siu.

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Interpretation of data: All authors.

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Supervision: Esther W. Chan and Chung-Wah Siu.

All authors have provided final approval of the submitted article.

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Figures

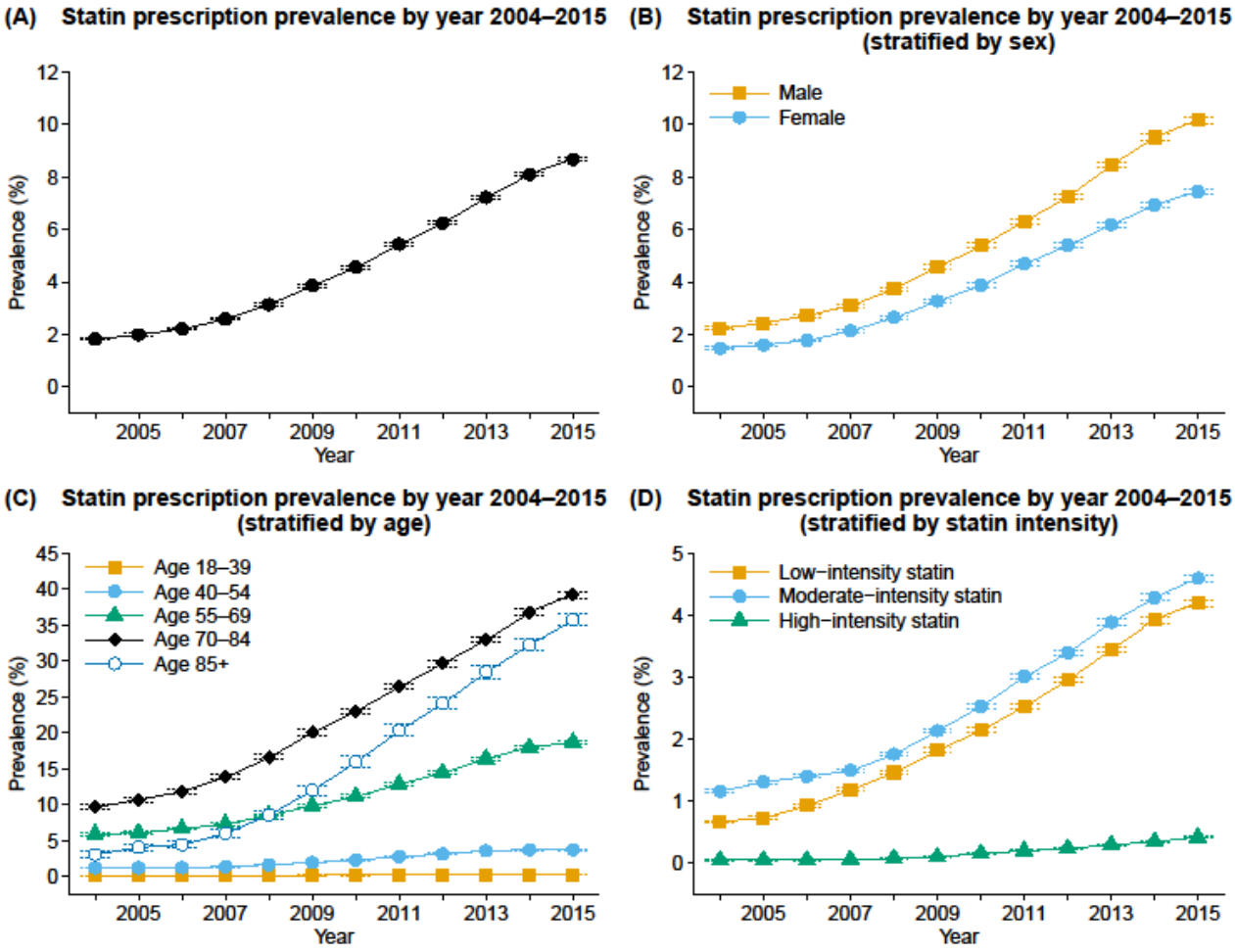


Figure 1 Plots showing the estimated statin prescription prevalence rates from 2004 to 2015. Dashed lines represent the upper and lower bounds of the 95% confidence intervals. (A) Overall prevalence rate for the cohort, (B) prevalence rate stratified according to sex, (C) prevalence rate stratified according to age, and (D) prevalence rate stratified according to statin dose intensity. Prescriptions with missing dose are excluded from panel (D).

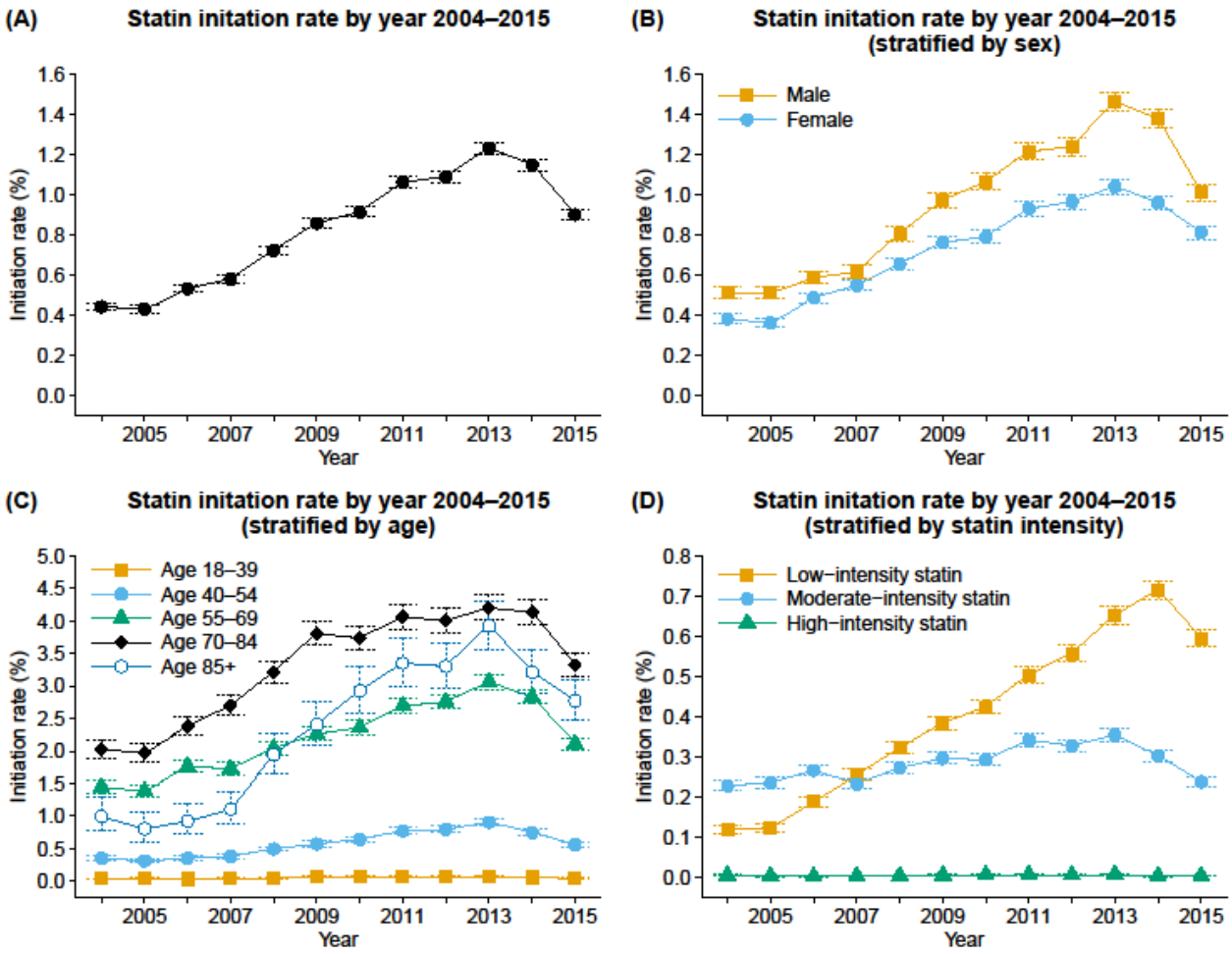


Figure 2 Plots showing the estimated statin prescription initiation rates for new statin users, from 2004 to 2015. Dashed lines represent the upper and lower bounds of the 95% confidence intervals. (A) Overall initiation rate for the cohort, (B) initiation rate stratified according to sex, (C) initiation rate stratified according to age, and (D) initiation rate stratified according to statin dose intensity. Prescriptions with missing dose are excluded from panel (D).

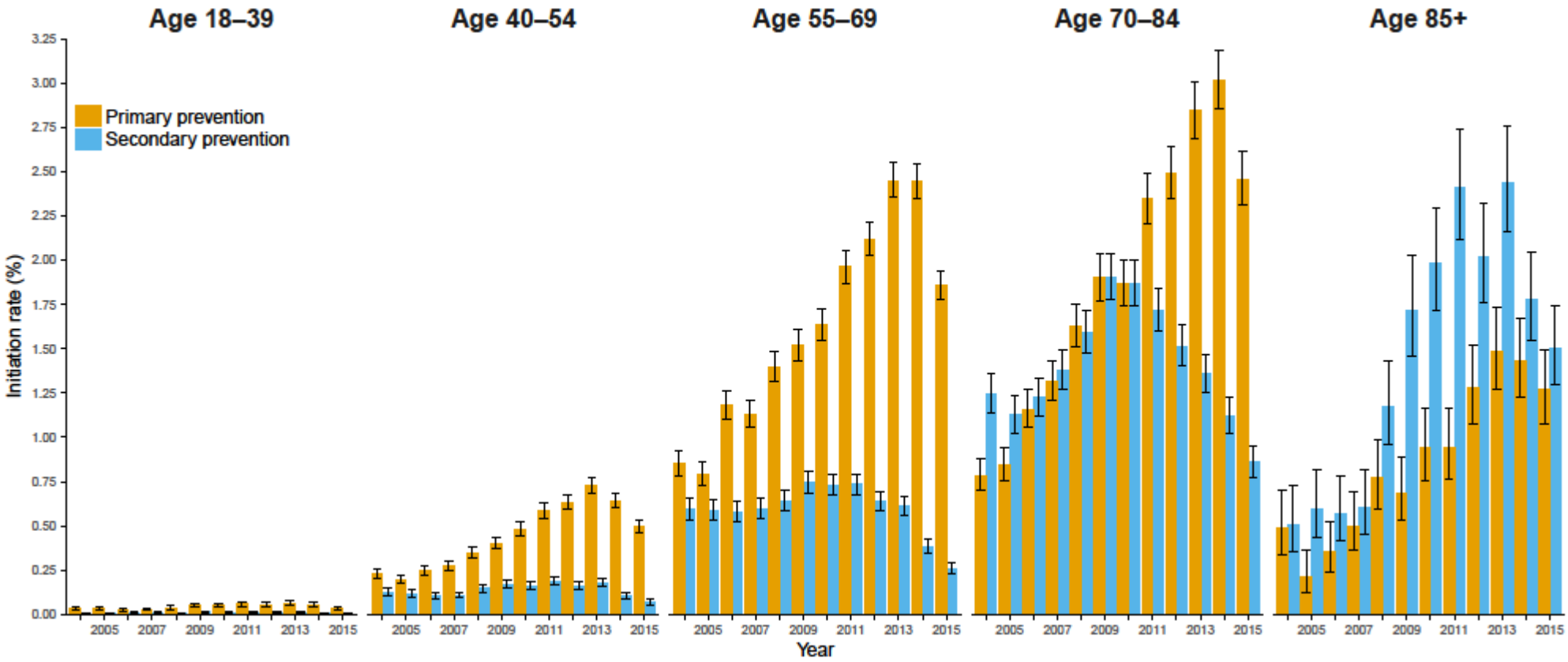


Figure 3 The estimated age-specific initiation rates for new statin users, stratified by cardiovascular prevention status and age group, from 2004 to 2015. Solid error bars represent the upper and lower bounds of the 95% confidence intervals.

Table 1 Characteristics of statin users (n = 58 672)

Characteristic	**Value**[a]
Sex	
Female	27 611 (47.1)
Age	
18–39 years old	1 207 (2.1)
40–54 years old	10 615 (18.1)
55–69 years old	24 890 (42.4)
70–84 years old	19 266 (32.8)
85 years old or greater	2 694 (4.6)
Median, (IQR) — yr	65 (18)
Lipid test, mean (SD) — mmol/L[b]	
Total cholesterol	5.51 (1.19)
LDL-C	3.51 (1.02)
HDL-C	1.28 (0.37)
Triglycerides	1.61 (1.32)
Cardiovascular prevention status	
Primary prevention	37 869 (64.5)
Secondary prevention	20 803 (35.5)
Medical history	
Coronary artery disease	13 186 (22.5)
Cerebrovascular disease	9 014 (15.4)
Peripheral artery disease	387 (0.7)

Percutaneous coronary intervention	3 740 (6.4)
Coronary artery bypass graft	291 (0.5)
Other revascularization	46 (0.1)
Heart failure	3 031 (5.2)
Diabetes	11 516 (19.6)
Hypertension	16 783 (28.6)
Hyperlipidemia	6 667 (11.4)
Obesity	430 (0.7)
Renal disease	3 187 (5.4)
Rheumatoid arthritis	359 (0.6)
COPD	884 (1.5)
Liver disease	1 442 (2.5)

[a]Data are presented as number (percentage) of patients unless otherwise indicated.

[b]Lipid test data prior to the index date available for the following number of patients: total cholesterol, 45 636; LDL-C, 45 161; HDL-C, 45 300; and triglycerides 45 595.

Abbreviations: COPD, chronic obstructive pulmonary disease; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.

Table 2 Mean prescribed daily doses of statin prescriptions stratified by cardiovascular prevention status 2004–2015

Years	Atorvastatin				Fluvastatin				Lovastatin				Pravastatin				Rosuvastatin				Simvastatin			
	Primary		Secondary		Primary		Secondary		Primary		Secondary		Primary		Secondary		Primary		Secondary		Primary		Secondary	
	Mean (SD)	*p* for trend	Mean (SD)	*p* for trend	Mean (SD)	*p* for trend	Mean (SD)	*p* for trend[a]	Mean (SD)	*p* for trend	Mean (SD)	*p* for trend	Mean (SD)	*p* for trend	Mean (SD)	*p* for trend	Mean (SD)	*p* for trend	Mean (SD)	*p* for trend	Mean (SD)	*p* for trend[a]	Mean (SD)	*p* for trend
2004–05	12.3 (8.3)		13.9 (10.9)		37.3 (20.8)		39.5 (23.0)		20.0 (0.0)		20.0 (0.0)		19.3 (9.7)		19.3 (9.6)		9.4 (4.1)		8.2 (3.6)		12.1 (7.1)		13.4 (8.0)	
2006–07	11.7 (8.1)		13.4 (10.8)		38.1 (22.8)		35.2 (21.7)		20.0 (0.0)		24.0 (8.9)		16.7 (9.3)		22.2 (10.2)		9.4 (5.0)		8.4 (4.5)		13.9 (8.7)		13.8 (9.1)	
2008–09	11.7 (8.0)		14.5 (11.6)		35.3 (20.7)		28.0 (16.2)		19.0 (3.0)		33.1 (13.3)		16.8 (9.9)		22.0 (9.0)		10.2 (5.7)		11.2 (6.4)		14.5 (9.0)		15.4 (10.2)	
		<0.001		<0.001		0.180		<0.001		0.998		<0.001		0.151		<0.001		<0.001		<0.001		<0.001		<0.001
2010–11	12.2 (8.9)		16.2 (12.9)		40.8 (22.3)		30.3 (17.1)		18.3 (3.8)		36.4 (8.1)		19.1 (17.8)		34.2 (11.7)		10.8 (5.8)		12.7 (6.4)		14.6 (8.7)		16.6 (10.2)	
2012–13	13.2 (9.2)		17.1 (11.6)		37.7 (17.1)		31.7 (15.1)		19.6 (3.3)		40.0 (0.0)		18.2 (6.1)		50.0 (0.0)		11.3 (6.1)		13.1 (6.3)		13.9 (7.5)		16.6 (9.2)	
2014–15	14.1 (9.2)		18.4 (10.9)		38.5 (19.2)		38.2 (22.1)		19.6 (2.5)		40.0 (0.0)		17.6 (6.5)		44.0 (12.3)		11.8 (6.2)		13.7 (6.5)		13.6 (7.0)		16.1 (8.6)	

[a]Decreasing trend as indicated by a negative coefficient in linear regression model.
Unless indicated, trends refers to increasing doses of statin prescriptions. Prescribed daily doses of each statin in milligrams of statin per day. Prescriptions with missing dose information were removed. Patients were stratified into either primary or secondary prevention of cardiovascular disease on the date of their first statin prescription.
Abbreviations: SD, standard deviation.

Trends in statin prescription prevalence, initiation, and dosing—Hong Kong, 2004–2015

Contents

Supplemental Table 1 List of ICD-9-CM codes used in the study

ICD-9-CM Diagnosis or Procedure Codes	Description
Coronary artery disease	
410	Acute myocardial infarction
411	Other acute and subacute forms of ischaemic heart disease
412	Old myocardial infarction
413	Angina pectoris
414	Other forms of chronic ischaemic heart disease
Cerebrovascular disease	
430	Subarachnoid haemorrhage
431	Intracerebral haemorrhage
432	Other and unspecified intracranial haemorrhage
433	Occlusion and stenosis of precerebral arteries
434	Occlusion of cerebral arteries
435	Transient cerebral ischemia
436	Acute but ill-defined cerebrovascular disease
437	Other and ill-defined cerebrovascular disease
438	Late effects of cerebrovascular disease
Peripheral artery disease	
440	Atherosclerosis
Percutaneous coronary intervention	
36.01-36.02, 36.05-36.07	Percutaneous transluminal coronary angioplasty
Coronary artery bypass graft	
36.10-36.17, 36.19, 36.2	Coronary artery bypass graft
Other revascularization	
36.03	Open coronary artery angioplasty
36.04	Intracoronary artery thrombolytic infusion
36.09	Removal of coronary artery obstruction
Heart failure	
428	Heart failure
Diabetes	
250	Diabetes mellitus

Hypertension	
401	Essential hypertension
402	Hypertensive heart disease
403	Hypertensive renal disease
404	Hypertensive heart and renal disease
405	Secondary hypertension
Hyperlipidemia	
272	Disorders of lipid metabolism
Obesity	
278.0	Overweight and obesity
278.8	Other hyperalimentation
Renal disease	
581	Nephrotic syndrome
582	Chronic glomerulonephritis
583	Nephritis and nephropathy
585	Chronic kidney disease
586	Renal failure, unspecified
Rheumatoid arthritis	
714	Rheumatoid arthritis
Chronic obstructive pulmonary disease	
492	Emphysema
496	Chronic obstructive pulmonary disease
Liver disease	
570	Acute and subacute necrosis of liver
571	Chronic liver disease and cirrhosis
573	Other disorders of liver

Supplemental Table 2 Number of total statin prescription, statin prescriptions with nondaily frequency, and statin prescriptions according to dose intensity 2004–2015

Year	Total prescriptions	Nondaily frequency	High-intensity	Moderate-intensity	Low-intensity	Missing dose
		Number (%)	Number (%)	Number (%)	Number (%)	No. (%)
2004	44 242	251 (0.57)	980 (2.22)	23 460 (53.03)	13 183 (29.8)	6 619 (14.96)
2005	47 892	315 (0.66)	1 048 (2.19)	25 956 (54.2)	14 402 (30.07)	6 486 (13.54)
2006	53 134	227 (0.43)	909 (1.71)	27 123 (51.05)	17 772 (33.45)	7 330 (13.8)
2007	68 636	322 (0.47)	1 176 (1.71)	31 696 (46.18)	26 398 (38.46)	9 366 (13.65)
2008	86 669	340 (0.39)	1 617 (1.87)	39 795 (45.92)	33 999 (39.23)	11 258 (12.99)
2009	108 810	350 (0.32)	2 255 (2.07)	49 474 (45.47)	42 908 (39.43)	14 173 (13.03)
2010	130 699	553 (0.42)	3 095 (2.37)	60 218 (46.07)	51 022 (39.04)	16 364 (12.52)
2011	155 238	670 (0.43)	4 197 (2.7)	72 199 (46.51)	58 760 (37.85)	20 082 (12.94)
2012	178 285	855 (0.48)	5 129 (2.88)	81 414 (45.67)	68 755 (38.56)	22 987 (12.89)
2013	201 788	890 (0.44)	6 075 (3.01)	92 218 (45.7)	77 831 (38.57)	25 664 (12.72)
2014	215 799	807 (0.37)	7 379 (3.42)	97 280 (45.08)	86 949 (40.29)	24 191 (11.21)
2015	232 138	772 (0.33)	8 670 (3.73)	106 870 (46.04)	97 989 (42.21)	18 609 (8.02)
Total	1 523 330	6 352 (0.42)	42 530 (2.79)	707 703 (46.46)	589 968 (38.73)	183 129 (12.02)

Supplemental Table 3 Annual estimated statin prescription prevalence rates for the total population and for males and females 2004–2015

Year	Total population[a]			Females			Males		
	Statin user	Population	Prevalence, % (95% CI)	Statin user	Population	Prevalence, % (95% CI)	Statin user	Population	Prevalence, % (95% CI)
2004	9 214	506 700	1.82 (1.78–1.86)	4 023	273 200	1.47 (1.43–1.52)	5 191	233 500	2.22 (2.16–2.28)
2005	10 187	512 700	1.99 (1.95–2.03)	4 413	275 000	1.60 (1.56–1.65)	5 774	237 800	2.43 (2.37–2.49)
2006	11 375	515 700	2.21 (2.17–2.25)	4 923	278 800	1.77 (1.72–1.82)	6 452	237 000	2.72 (2.66–2.79)
2007	13 570	526 200	2.58 (2.54–2.62)	6 061	283 900	2.13 (2.08–2.19)	7 509	242 400	3.10 (3.03–3.17)
2008	16 730	533 300	3.14 (3.09–3.18)	7 638	289 700	2.64 (2.58–2.70)	9 092	243 600	3.73 (3.66–3.81)
2009	20 297	526 000	3.86 (3.81–3.91)	9 380	286 900	3.27 (3.20–3.34)	10 917	239 000	4.57 (4.48–4.65)
2010	24 032	527 600	4.55 (4.50–4.61)	11 177	288 500	3.87 (3.80–3.95)	12 855	239 100	5.38 (5.29–5.47)
2011	28 262	520 000	5.44 (5.37–5.50)	13 169	281 000	4.69 (4.61–4.77)	15 093	239 000	6.32 (6.22–6.41)
2012	32 671	523 300	6.24 (6.18–6.31)	15 339	284 100	5.40 (5.32–5.48)	17 332	239 200	7.25 (7.14–7.35)
2013	37 639	521 300	7.22 (7.15–7.29)	17 627	284 900	6.19 (6.10–6.28)	20 012	236 400	8.47 (8.35–8.58)
2014	41 947	518 000	8.10 (8.02–8.17)	19 650	283 400	6.93 (6.84–7.03)	22 297	234 500	9.51 (9.39–9.63)
2015	44 653	514 700	8.68 (8.60–8.75)	21 006	282 200	7.44 (7.35–7.54)	23 647	232 500	10.17 (10.05–10.29)

[a]Population refers to the population estimates of the hospital catchment area (Central and Western, and Southern Districts). The population estimates for each sex are rounded to the nearest 100 persons and may not sum up exactly to the total population estimate.
Abbreviations: CI, confidence interval.

Supplemental Table 4 Number, proportion, and annual percent change of statin users, grouped according to each statin drug 2004–2015

Year	Total statin users	Atorvastatin		Fluvastatin		Lovastatin		Pravastatin		Rosuvastatin		Simvastatin	
		Number (% change)	Proportion	Number (% change)	Proportion	Number (% change)	Proportion	Number (% change)	Proportion	Number (% change)	Proportion	Number (% change)	Proportion
2004	9 214	4 765 (--)	51.7%	426 (--)	4.6%	1 (--)	0.01%	239 (--)	2.59%	89 (--)	1.0%	4 089 (--)	44.4%
2005	10 187	5 303 (11.3)	52.1%	506 (18.8)	5.0%	4 (300.0)	0.04%	184 (-23.0)	1.81%	466 (423.6)	4.6%	4 473 (9.4)	43.9%
2006	11 375	5 102 (-3.8)	44.9%	406 (-19.8)	3.6%	8 (100.0)	0.07%	67 (-63.6)	0.59%	989 (112.2)	8.7%	6 521 (45.8)	57.3%
2007	13 570	4 086 (-19.9)	30.1%	156 (-61.6)	1.1%	6 (-25.0)	0.04%	24 (-64.2)	0.18%	1 015 (2.6)	7.5%	9 071 (39.1)	66.8%
2008	16 730	4 315 (5.6)	25.8%	115 (-26.3)	0.7%	8 (33.3)	0.05%	20 (-16.7)	0.12%	1 236 (21.8)	7.4%	11 728 (29.3)	70.1%
2009	20 297	4 447 (3.1)	21.9%	85 (-26.1)	0.4%	11 (37.5)	0.05%	19 (-5.0)	0.09%	1 622 (31.2)	8.0%	14 902 (27.1)	73.4%
2010	24 032	4 579 (3.0)	19.1%	75 (-11.8)	0.3%	11 (0.0)	0.05%	19 (0.0)	0.08%	2 145 (32.2)	8.9%	18 372 (23.3)	76.4%
2011	28 262	4 723 (3.1)	16.7%	74 (-1.3)	0.3%	11 (0.0)	0.04%	10 (-47.4)	0.04%	2 727 (27.1)	9.6%	21 973 (19.6)	77.7%
2012	32 671	5 268 (11.5)	16.1%	77 (4.1)	0.2%	12 (9.1)	0.04%	9 (-10.0)	0.03%	3 184 (16.8)	9.7%	25 378 (15.5)	77.7%
2013	37 639	6 080 (15.4)	16.2%	67 (-13.0)	0.2%	13 (8.3)	0.03%	8 (-11.1)	0.02%	3 866 (21.4)	10.3%	29 093 (14.6)	77.3%
2014	41 947	6 568 (8.0)	15.7%	58 (-13.4)	0.1%	7 (-46.2)	0.02%	9 (12.5)	0.02%	4 314 (11.6)	10.3%	32 419 (11.4)	77.3%
2015	44 653	7 512 (14.4)	16.8%	52 (-10.3)	0.1%	5 (-28.6)	0.01%	8 (-11.1)	0.02%	4 581 (6.2)	10.3%	34 055 (5.0)	76.3%

Proportions may not add up to 100% because of switching between statins within each year.

Supplemental Table 5 Annual estimated statin prescription initiation rates of new statin users for the total population, and for males and females 2004–2015

Year	Total population[a]			Females			Males		
	Statin user	Population	Initiation rate, % (95% CI)	Statin user	Population	Initiation rate, % (95% CI)	Statin user	Population	Initiation rate, % (95% CI)
2004	2 235	506 700	0.44 (0.42–0.46)	1 041	273 200	0.38 (0.36–0.40)	1 194	233 500	0.51 (0.48–0.54)
2005	2 203	512 700	0.43 (0.41–0.45)	990	275 000	0.36 (0.34–0.38)	1 213	237 800	0.51 (0.48–0.54)
2006	2 744	515 700	0.53 (0.51–0.55)	1 354	278 800	0.49 (0.46–0.51)	1 390	237 000	0.59 (0.56–0.62)
2007	3 048	526 200	0.58 (0.56–0.60)	1 554	283 900	0.55 (0.52–0.58)	1 494	242 400	0.62 (0.59–0.65)
2008	3 850	533 300	0.72 (0.70–0.75)	1 891	289 700	0.65 (0.62–0.68)	1 959	243 600	0.80 (0.77–0.84)
2009	4 509	526 000	0.86 (0.83–0.88)	2 187	286 900	0.76 (0.73–0.79)	2 322	239 000	0.97 (0.93–1.01)
2010	4 817	527 600	0.91 (0.89–0.94)	2 275	288 500	0.79 (0.76–0.82)	2 542	239 100	1.06 (1.02–1.11)
2011	5 512	520 000	1.06 (1.03–1.09)	2 611	281 000	0.93 (0.89–0.97)	2 901	239 000	1.21 (1.17–1.26)
2012	5 700	523 300	1.09 (1.06–1.12)	2 737	284 100	0.96 (0.93–1.00)	2 963	239 200	1.24 (1.20–1.28)
2013	6 417	521 300	1.23 (1.20–1.26)	2 961	284 900	1.04 (1.00–1.08)	3 456	236 400	1.46 (1.41–1.51)
2014	5 944	518 000	1.15 (1.12–1.18)	2 716	283 400	0.96 (0.92–0.99)	3 228	234 500	1.38 (1.33–1.42)
2015	4 631	514 700	0.90 (0.87–0.93)	2 285	282 200	0.81 (0.78–0.84)	2 346	232 500	1.01 (0.97–1.05)

[a] Population refers to the population estimates of the hospital catchment area (Central and Western, and Southern Districts). The population estimates for each sex are rounded to the nearest 100 persons and may not sum up exactly to the total population estimate.
Abbreviations: CI, confidence interval.

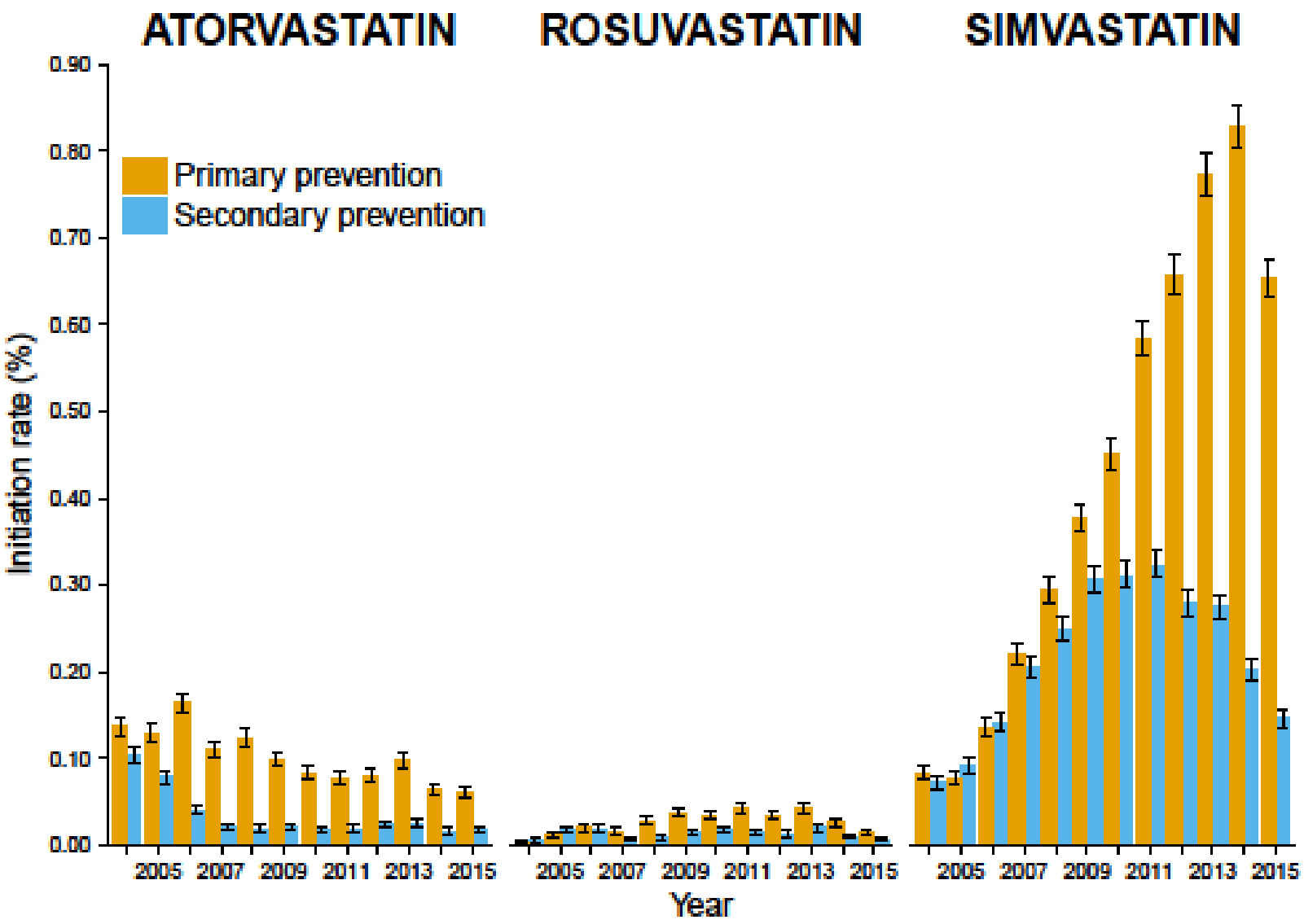
Supplemental Table 6 Number of new statin users, their proportion of statin users, and the number of new patients grouped by their initial statin drug 2004–2015

Year	New users (% of statin users)	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
		Number (%)	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)
2004	2 235 (24.3)	1 219 (54.54)	160 (7.16)	0 (0.00)	27 (1.21)	41 (1.83)	788 (35.26)
2005	2 203 (21.6)	1 068 (48.48)	115 (5.22)	4 (0.18)	15 (0.68)	145 (6.58)	856 (38.86)
2006	2 744 (24.1)	1 056 (38.48)	46 (1.68)	3 (0.11)	8 (0.29)	202 (7.36)	1 429 (52.08)
2007	3 048 (22.5)	687 (22.54)	7 (0.23)	2 (0.07)	4 (0.13)	116 (3.81)	2 232 (73.23)
2008	3 850 (23.0)	759 (19.71)	2 (0.05)	2 (0.05)	3 (0.08)	191 (4.96)	2 893 (75.14)
2009	4 509 (22.2)	633 (14.04)	8 (0.18)	3 (0.07)	2 (0.04)	276 (6.12)	3 587 (79.55)
2010	4 817 (20.0)	525 (10.90)	1 (0.02)	4 (0.08)	3 (0.06)	273 (5.67)	4 011 (83.27)
2011	5 512 (19.5)	496 (9.00)	2 (0.04)	3 (0.05)	3 (0.05)	294 (5.33)	4 714 (85.52)
2012	5 700 (17.4)	549 (9.63)	3 (0.05)	4 (0.07)	2 (0.04)	246 (4.32)	4 896 (85.89)
2013	6 417 (17.0)	638 (9.94)	1 (0.02)	4 (0.06)	0 (0.00)	317 (4.94)	5 457 (85.04)
2014	5 944 (14.2)	416 (7.00)	1 (0.02)	0 (0.00)	1 (0.02)	186 (3.13)	5 340 (89.84)
2015	4 631 (10.4)	403 (8.70)	2 (0.04)	1 (0.02)	1 (0.02)	109 (2.35)	4 115 (88.86)

Supplemental Table 7 Total number of statin prescriptions, and number and annual percent change of statin containing combination product prescriptions

Year	Total statin prescriptions	Number of combination product[a] prescriptions (% change)
2004	44 242	0 (--)
2005	47 892	13 (--)
2006	53 134	102 (684.6)
2007	68 636	57 (-44.1)
2008	86 669	62 (8.8)
2009	108 810	72 (16.1)
2010	130 699	83 (15.3)
2011	155 238	101 (21.7)
2012	178 285	101 (0.0)
2013	201 788	96 (-5.0)
2014	215 799	96 (0.0)
2015	232 138	110 (14.6)

[a]During the study period, two combination products containing a statin were available in Hong Kong: Vytorin (simvastatin and ezetimibe; Merck Sharp & Dohme Ltd) and Caduet (atorvastatin and amlodipine; Pfizer Inc).



Supplemental Figure 1 The estimated initiation rates for new statin users, stratified by cardiovascular prevention status, for the three most prescribed statin drugs—atorvastatin, rosuvastatin, and simvastatin—from 2004 to 2015. Solid error bars represent the upper and lower bounds of the 95% confidence intervals.