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Title

Trend and associated factors of discontinuation to statin use in one year after discharge in patients with acute coronary syndrome in China

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Abstract

Objectives To determine the trend and associated factors of statin discontinuation during the first year after discharge in patients who survived from ACS in China between 2007 and 2010.

Settings 75 hospitals in China.

Participants This study enrolled 10,337 ACS patients from 75 hospitals in China who were hospitalized in 2007-2010 and discharged with statin treatment.

Primary outcome measures The primary outcome was the discontinuation of statin use which was defined as incidence of stopping statin within one year after discharge.

Results: The statin discontinuation rate decreased from 29.5% in 2007-2008 to 17.8% in 2010. Multivariable Logistic regression model showed that the decreasing trend was significant (OR for patients in 2010 versus those in 2007-2008 = 0.60; 95%CI: 0.51-0.70; p<0.001). Patients not having cholesterol measured (OR=1.29, 95%CI: 1.10-1.50) and patients on either high (1.27; 1.13-1.43) or low dose of statin (1.22; 1.07-1.40), compared with those with moderate dose, were more likely to discontinue the use of statin. In addition, patients with clinical pathway intervention (OR=0.83; 95%CI: 0.74-0.94), medical insurance (0.75; 0.67-0.85), history of hypertension (0.83; 0.75-0.92), high LDL-c (0.70; 0.57-0.87), prior statin use (0.73; 0.63-0.84), use of atorvastatin (0.78; 0.70-0.88) and receiving PCI or CABG during hospitalization (0.47; 0.43-0.53) were more unlikely to discontinue statin use.

Conclusion: The trend in discontinuation to statin use in one year after discharge in ACS survivors in China significantly reduced from 2007 to 2010. Implementing clinical pathway, enhancing medical insurance coverage, better attention to cholesterol management, using statin in moderate dosage may help improve the adherence to statin use as secondary preventative measure.

Key words: Acute coronary syndrome, Discontinuation to Statin Use, Trend, Associated Factors

Strengths and limitations of this study

This study investigated the trend and associated factors of statin discontinuation using data from Clinical Pathways for Acute Coronary Syndromes in China Study-2 (CPACS-2), a large well-design clinical trial in 75 hospitals of China.

The long-time span of the CPACS-2 (2007–2010) allowed a thorough examination of the temporal trend of the statin discontinuation.

The large sample size ensures the robustness of the study.

Patients who were lost to follow-up or died might be more likely to discontinue statin and this may lead to underestimation of the rate of discontinuation and attenuated its associations with the related factors.

INTRODUCTION

Statins therapy has been recommended as a core long-term secondary preventive treatment for patients with acute coronary syndrome (ACS) by several guidelines (1-4). Despite to these strong evidences from basic and clinical studies (5-7) and recommendation by the guidelines, about 10%-30% of patients with ACS discontinued their statin treatment usually within four years with highest attrition in the first year (8-10). Moreover, discontinuation to statin therapy increases the risk of major adverse cardiovascular events (MACE) in patients with ACS after discharge (11, 12). To date, few data exist on the magnitude of discontinuation and factors that influence statin persistence up to one year in ACS patients in China.

Many evidences approved that higher doses statin could lower LDL, and reduce risk of subsequent CV events more (13) and was recommended by the guidelines in western countries (3). As a consequence, and because of the additional benefit shown with more intensive statin therapy (13), there has been a trend toward using higher doses of statin. However, higher doses statin increased the risk of adverse events, such as hepatotoxicity(14), which might decrease the adherence to the statin therapy. Thus, it is important to determine an optimal dose which balance the beneficial and adverse effect, and not likely to be discontinued by patients.

In this study, we analyzed data from the Clinical Pathways for Acute Coronary Syndromes in China Study-2 (CPACS-2) to understand the trend from 2007 to 2010 among Chinese patients with ACS in discontinuation to statin use in the first year after discharge and to explore the relationship of statin dose, type, and other factors associated with the discontinuation.

METHODS

Study design

The Clinical Pathways for Acute Coronary Syndromes— Phase 2 (CPACS-2) study design, methodology and main results have been previously reported in detail (15-18). In brief, the CPACS-2 study was an implementation trial with a cluster-randomized design to evaluate the effectiveness of implementing clinical pathways for ACS

management in hospitals in China. The main finding of CPACS-2 has been published previously elsewhere(15). The present study used data from CPACS-2 to assess the relationship of statin dose, type, clinical pathway intervention and other factors with discontinuation to statin after discharged from hospital.

Patients

CPACS-2 recruited ACS patients admitted to 75 hospitals (50 teaching hospitals and 25 non-teaching hospitals) in the cities throughout China from 2007 to 2010 (26). Among 15,138 patients recruited in CPACS-2, a total of 10,337 individuals who received statin in hospital and at discharge and were followed-up till one year after discharge were included in the present study (**see Figure 1**).

Ethical approval

The CPACS-2 study was approved by the ethics committee of Fuwai Hospital and Human Research Ethics Committees of University of Sydney in Australia(number: 09-2007/10276) (15-18). The procedures of the study were in accordance with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants. Confidentiality of subjects were ensured by anonymizing participants' names, initials or hospital numbers.

Data collection

A trained clinical staff (independent to the treating physicians) in each hospital reviewed medical records and administered a structured questionnaire to collect demographic and clinical data of consenting eligible patients, including statin use, history of disease, clinical characteristics, and prior and in-hospital treatments. All surviving patients were followed up at 6 and 12 months after the hospital discharge.

Data on statin use at 6 and 12 months after discharge were collected by the trained medical staff using a standardized questionnaire. The reasons for not taking statin were collected at each interview. For our analysis, the dosage of different statins was converted to the equivalent dosage of atorvastatin (19) (Additional file S1: **Table S1**).

Exposures

Exposures included age, sex, year of enrolment, education, employment, medical insurance, smoking status, subtype of ACS, co-existing cardiovascular diseases or risk, in-hospital major adverse cardiovascular events (MACE), in-hospital PCI/CABG, LDL-c level at the index admission, prior statin use, dose & type of statin at discharge, co-treatments at discharge.

Education level was classified into 2 categories: lower than high school and high school and above. Prior statin use was defined as any statin use in most days one month before the development of ACS.

Clinical pathway intervention

The intervention included three major generic clinical pathways (risk stratification, management of STEMI, and management of non–ST-segment–elevation myocardial infarction/unstable angina pectoris) that were developed in conjunction with the Chinese Society of Cardiology based on the relevant American Heart Association and American College of Cardiology guidelines (1, 2). The first 50 patients in each hospital were recruited for exploring the routine treatments on ACS and were not intervened by clinical pathway. Subsequent patients were under clinical pathway intervention (18).

Main Outcome

The discontinuation to statin use in one year after discharge was the primary outcome, which was defined as not in use of statin at either 6 or 12 months follow ups after discharge.

Statistical methods

SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all analyses. Univariate and multivariable logistic regression models were used to analyze the association of the discontinuation of statin with potential explanatory factors. Our primary analyses included participants who completed both 6 and 12 months follow ups. Since the number of patients in 2007 was small, these patients were grouped into those

recruited in 2008 in our main analyses. Two-sided P value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 10,337 patients (men=70.3%) with ACS (mean age (SD) 63.2±11.6 years) were included in the study. Compared with those excluded, those included were more likely to be younger, employed, had medical insurance, diagnosed as mild subtype of ACS (unstable angina), have had history of dyslipidemia and hypertension, be co-treated by aspirin or β-blocker, but less likely to have history of heart failure and stroke, experience MACE in hospital, be prescribed higher dose of statin at discharge (>=20 mg atorvastatin or equivalence), take atorvastatin, and be co-treated clopidogrel at discharge (all p<0.05) (Table 1).

Trend of discontinuation to statin use from 2007 to 2010

Among our study participants, 25.5% discontinued to statin in one year after discharge. The rate decreased from 29.5% in 2007-2008 to 17.8% in 2010. The multiple logistic regression model confirmed that the deceasing trend in study years was significant after adjustment for co-variables (Table 3).

Factors associated with discontinuation to statin use

In univariate analyses, discontinuation rate was significantly lower in patients who received clinical pathway intervention than those who did not receive, patients with medical insurance than those without, patients with than without history of dyslipidemia, diabetes, and hypertension, prior statin use, higher LDL-c, those who required intervention procedures such as PCI/CABG during hospitalization, those who were given either moderate or high dose than in patients given low dose of statin, in those who were given atorvastatin than those who were given other statins, and lower in patients with than without co-treatments of clopidogrel and β-blocker at discharge. On the other hand, discontinuation rate was significantly higher in women, older patients, patients with lower education level, patients with relatively milder form of ACS subtype (unstable angina), patients whose LDL-c was not measured during

hospitalisation (all p<0.05) (**Table 2**).

Multiple logistic regression models, which included age, sex, and all factors with statistical significance in univariate analyses, found that the trend of discontinuation was significantly decreased over the study duration. In addition, patients with clinical pathway intervention, medical insurance, history of hypertension, LDL-c>=160mg/dl, prior statin use, taking atorvastatin, and receiving PCI or CABG during hospitalization were more unlikely to discontinue statin use, while those on either higher or lower dose of statin (versus moderate dose), and those whose LDL-c was not measured during the hospital admission were more likely to discontinue the use of statin **(Table 3).**

Reason of discontinuation to statin

Among 1063 patients who stopped statin use in one year after discharge, 12.7% were due to intolerance to statin, 38.3% due to expensive cost, 31.4% due to rejection by patients, and 17.6% due to other reasons (**Figure 2**).

DISCUSSION

Using data from a large, prospective cohort of ACS patients in China, we found that (1) the discontinuation of statin use in one year after discharge decreased significantly from 29.5% in 2007-08 to 17.8% in 2010; (2) implementing the clinical pathways for ACS management, enhancing medical insurance coverage, measuring cholesterol, and using statin in moderate dosage should help to reduce the likelihood of the discontinuation to statin use; and (3) nearly a third of patients rejected to continue the use of statin, which indicated that patient education on ACS secondary prevention treatments should be emphasized.

It is interesting that medium dosage of statin (versus low or high dosage) at discharge significantly decreased likelihood of discontinuation, which is independent of other observed predictors of statin discontinuation. Use of high-dose statin in patients with ACS in acute phase was recommended by the guidelines endorsed by the American

Heart Association and American College of Cardiology (AHA/ACC) (3). However, the most recent Chinese guidelines (published in 2016 and 2019) recommend statin therapy in all patients with ACS, but do not provide specific guidance about the intensity of such therapy (20-22). These Chinese guidelines are congruent with observations that Chinese patients, as compared with Caucasian patients, have lower LDL-C levels, and are more likely to experience adverse reactions to statins, especially with high dose statins (23, 24). In consideration of increasing the treatment effects and decrease the risk of adverse effect, medium dose statin or statins in combination with other lipid-regulating drugs (such as ezetimibe, *Yang xin shi* tablet, etc.) might be preferred in Chinese patients (24, 25). Our findings further support this approach as high or low dose statin compared to moderate dose are more likely to be associated with statin discontinuation in Chinese patients with ACS during the first year. For maintenance of statin therapy, guidelines should perhaps consider recommending moderate dose of statin in Chinese patients with ACS.

Atorvastatin use (versus other statins) significantly decreased likelihood of discontinuation, which is independent of other confounders. This finding indicates that Chinese are more likely to adherent to atorvastatin and is helpful to explain the most frequently used statin type transition from simvastatin (60.2% in 2001) to atorvastatin (52.9% in 2011) (26). We do not know why Chinese are better adherent to atorvastatin. We hypothesize that the good adherence to atorvastatin might be due to the better tolerability, and its efficacy and safety. However, two studies with small sample in Chinese showed that no significant differences of MACE and declined renal function between atorvastatin and other statins (27, 28). On the other hand, an large observational study in the United States found 10 or 20 mg of atorvastatin use had lower CV event rates particularly in the first year of use than 20 or 40 mg of simvastatin (29) while another large observational study in the United Kingdom found that the risk of hepatotoxicity (small numbers of events observed) was increased in the first six months of atorvastatin compared to simvastatin treatment (14). These findings suggest that further large-scale studies are needed to explore the differences of efficacy and safety between atorvastatin and other statins using equivalent dosage especially in Chinese patients.

Prior statin usage significantly decreased likelihood of discontinuation in our cohort. Statin use as a primary preventive treatment before ACS among high risk individuals is recommended by several guidelines (4, 19, 22). Our finding indicates that those adherent to primary prevention are likely to adhere to secondary preventive treatment. Logically, prior statin usage indicates that patients have good tolerance to statin, have the ability to pay, pay more attention to their own health, and have more knowledge on the importance of statin in both primary and secondary prevention of ACS, which may help decrease discontinuation of statin after discharge. Moreover, the patients with prior statin were more likely to have higher education level, have history of dyslipidemia (30% versus 11%), diabetes, heart failure, hypertension, and take place MACE in hospital, which were observed to decrease the likelihood of discontinuation to statin in the present study. These results indicate that health education should be promoted among patients who did not use statins before hospital.

We found that not measuring LDL-c during the index admission increased the likelihood of discontinuation and higher LDL-c reduced the likelihood of discontinuation. This finding indicates the cholesterol management is very important for improve adherence to statin therapy. Cholesterol management is recommended by all guidelines on ACS (4, 22). However, in the present study, about 8.8% of patients did not get their LDL-c measured in hospital. Thus, giving attention to the cholesterol measurement during hospital admission with ACS and management may help to further to improve adherence to statin.

As expected, we found that ACS patients who received PCI/CABG treatment during the hospitalization were less likely to discontinue statin use. Similar pattern was also observed in other studies (8, 30). The explanations may include that all major clinical guidelines emphasize the long term use of statin after PCI/CABG for prevention from restenosis (1, 31) and the patients who received PCI/CABG as a major event in life may consider themselves at higher risk and hence more adherent to the physicians' advices (risk marker effect). Probably for the same reason, patients with history of diseases including dyslipidemia, diabetes, and hypertension were more unlikely to discontinue

the statin use. The association remained significant only for hypertension probably due to the co-linearity among these factors. These findings indicate that those patients without PCI/CABG and history of hypertension would potentially benefit from the health education.

We also found that medical insurance significantly decreased the rate of discontinuation after adjusting for potential confounders. This finding is consistent with that in CPACS-1(32). Thus, encouraging patients to take up the medical insurance could increase the capacity of payment and improve the adherence to statin and the outcomes of patients with ACS, resulting decrease in the disease burden.

Our analyses of the reasons for the discontinuation found that the most common reason was the cost of statin therapy, which further confirmed our findings on the association of the discontinuation with lack of medical insurance. As the second common reason, rejection by patients accounted for in nearly a third of our study patients. Although we did not have information on why these patients decided to stop statins, further exploratory analyses revealed that whilst they appeared to have higher capacity for payment (having higher education, more likely to have PCI/CABG in hospital and take clopidogrel at discharge), but would appear to have lower knowledge on statins benefit on secondary prevention (less likely to be intervened by clinical pathway), as compared with those discontinuation due to expense (data not shown). Thus, we hypothesize that rejection to statin might be due to lower level of knowledge of benefit associated with statin use rather than expense. 31.4% of discontinuation were due to rejection by patients, which indicates that it is important to improve knowledge of ACS patients through effective strategies including clinical pathway intervention.

Many strategies have been proposed that attempt to further reduce discontinuation and improve statin therapeutic effectiveness, including patient education on improving ACS and statin literacy, co-payment reduction, and behavior-modification interventions (33-35). In the present study, we confirmed that the clinical pathway intervention can reduce the risk of discontinuation of statin therapy which might be

attributed to the fact that the clinical pathways might have improved the knowledge about the role of statins in management of ACS among physicians and thus leading to a change in their clinical practice. According to the pathways, patients diagnosed as ACS without contraindications would be administered to statins immediately as a long-term medical therapy regardless of LDL-c level. Due to the large evidence-practice gap, we recommend this ACS clinical pathway to be adopted nationally in China and perhaps in other countries with similar circumstances as in China.

It is indeed reassuring and pleasing that discontinuation decreased significantly from 29.5% in 2007-2008 to 17.8% in 2010, given the increasing CVD burden in China. Moreover, the trend of the discontinuation with study year was still significant even after adjustment for the potential confounders. While these results may relate to other confounders which are not controlled for, it is highly plausible that the publication, widespread promulgation, and endorsement of the Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults in 2007-2008 (19, 36-43) might be the one of the factors which likely to have impact on the reduction in discontinuation of statin. This could occur through improving the knowledge level of statin use as secondary prevention of ACS among physicians and among patients who had experienced ACS. Notably, although the withdrawal rate of statins has been greatly reduced, a considerable proportion of patients have stopped taking statins, and the evidence practice gap still exists especially in those without intervention or medical insurance. Thus, more efforts are needed to further improve the adherence to statin.

Limitations

Some limitations are worth highlighting. Firstly, patients who were lost to follow-up or died might be more likely to discontinue statin and this may lead to underestimation of the rate of discontinuation and attenuated its associations with the related factors. Secondly, our study follow-up period was limited to one year, factors that are associated with the longer-term discontinuation should be explored in the future.

Conclusions

In summary, approaches such as implementing clinical guidelines and pathways, encouraging to take up medical insurance, giving attention to cholesterol measurement, and using statin in moderate dosage in Chinese may help to improve the persistence of statin therapy in patients discharged after an acute coronary syndrome in China. Such measures should have major implication to the clinical and public health practices and ultimately will bring about the benefit of patients with reduced CVD burden.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information. Data may be obtained from a third party and are not publicly available.

Supplementary Material

Comparative Dose Efficacy of Statins on lipids (See Table S1 in file S1).

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Statement on previous reports

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Statement of responsibility

The authors had full access to the data and took responsibility for its integrity. All

authors have read and agreed to the written manuscript. Each author believes that the manuscript represents honest work.

Patient and Public Involvement statement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Authors' contributions

GX: concept development, data cleaning analysis, and interpretation, and writing of the manuscript; PKM: critical input in interpretation of results and writing of the manuscript; YS: critical input in interpretation of results and writing of the manuscript; XL: quality control on data collection and review of manuscript; TW: data analysis plan and review of manuscript; RG: review of manuscript and critical input in interpretation of results ; YW: concept development, critical input in interpretation of results, and review and approval of the manuscript.

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Tables

Table 1. Characteristics of patients with ACS included and excluded in the study

Characteristics	Included (n=10337) n	%	Excluded (n=3175) n	%	P values
Year of enrolment					
2007	383	3.7	177	5.6	0.000
2008	3309	32.0	1025	32.3	
2009	4982	48.2	1385	43.6	
2010	1663	16.1	588	18.5	
Subtype of ACS					
STEMI*	3918	37.9	1501	47.3	0.000
NSTEMI*	1394	13.5	509	16.0	
UA*	5025	48.6	1165	36.7	
Clinical pathway intervention	7908	76.5	2399	75.6	0.275
Sex (Female)	3074	29.7	957	30.1	0.664
Age>=65	4934	47.7	1721	54.2	0.000
Education>=high school	3786	36.6	1123	35.4	0.198
Unemployed	5033	48.7	1747	55.0	0.000
With medical insurance	8678	83.9	2543	80.1	0.000
Current smoker	3192	30.9	1012	31.9	0.290
History of disease					
Dyslipidemia	1359	13.1	356	11.2	0.004
Diabetes	2086	20.2	640	20.2	0.978
Hypertension	7184	69.5	2107	66.4	0.001
Heart Failure	562	5.4	218	6.9	0.003
Stroke	944	9.1	357	11.2	0.000
In-hospital MACE	191	1.8	304	9.6	0.000
In-hospital PCI/CABG	5113	49.5	1559	49.1	0.722
LDL-c level in hospital					
Not measuring	909	8.8	360	11.3	0.000
<70mg/dl	1469	14.2	456	14.4	
70-99mg/dl	3208	31.0	923	29.1	
100-129mg/dl	2880	27.9	845	26.6	
130-159mg/dl	1293	12.5	405	12.8	
>=160mg/dl	578	5.6	186	5.9	
Prior statin use	1467	14.2	434	13.7	0.459
Dose of statin at discharge					
1-9 mg/d	1904	18.4	755	23.8	0.000
10-19 mg/d	3196	30.9	637	20.1	
>=20 mg/d	5237	50.7	1783	56.1	
Type of statin at discharge					
Atorvastatin	5785	56.0	1953	61.5	0.000
Simvastatin	2690	26.0	612	19.3	
Rosuvastatin	502	4.9	71	2.2	
Pravastatin	502	4.9	188	5.9	
Fluvastatin	578	5.6	190	6.0	
Other statin	280	2.7	161	5.1	
Co-treatments at discharge					
Aspirin	10030	97.0	3053	96.2	0.014
Clopidogrel	8404	81.3	2736	86.2	0.000
β-blocker	8155	78.9	2372	74.7	0.000
ACEI/ARB*	8096	78.3	2482	78.2	0.860

* STEMI was ST-segment elevation myocardial infarction; NSTEMI was Non-ST-segment elevation myocardial infarction; UA was unstable angina; ACEI was Angiotensin converting enzyme inhibitor; ARB was Angiotensin Receptor Blocker

Table 2. Univariate analysis of factors in association with the discontinuation to statin use in one year after discharge with Logistic regression models (n=10337)

Factors	Group	N	n	Discontinuation %	OR (95%CI)
Year of enrolment	2007-2008*	3692	1088	29.5	1
	2009	4982	1250	25.1	0.80(0.73-0.88)
	2010	1663	296	17.8	0.52(0.45-0.60)
Subtype of ACS	STEMI	3918	928	23.7	1
	NSTEMI	1394	348	25.0	1.07(0.93-1.24)
	UP	5025	1358	27.0	1.19(1.08-1.31)
Clinical pathway intervention	No	2429	754	31.0	1
	Yes	7908	1880	23.8	0.69(0.63-0.77)
Sex	Male	7263	1761	24.3	1
	Female	3074	873	28.4	1.24(1.13-1.36)
Age group	18-64 years	5403	1320	24.4	1
	≥65 years	4934	1314	26.3	1.12(1.03-1.23)
Education	≥high school	3786	853	22.5	1
	<high school	6551	1781	27.2	1.28(1.17-1.41)
Employment	No	5033	1282	25.5	1
	Yes	5304	1352	25.5	1.00(0.92-1.09)
Medical insurance	No	1659	514	31.0	1
	Yes	8678	2120	24.4	0.72(0.64-0.81)
Current smoker	No	7145	1838	25.7	1
	Yes	3192	796	24.9	0.96(0.87-1.06)
History of disease					
Dyslipidemia	No	8978	2327	25.9	1
	Yes	1359	307	22.6	0.83(0.73-0.96)
Diabetes	No	8251	2155	26.1	1
	Yes	2086	479	23.0	0.84(0.75-0.94)
Hypertension	No	3153	874	27.7	1
	Yes	7184	1760	24.5	0.85(0.77-0.93)
Heart Failure	No	9775	2487	25.4	1
	Yes	562	147	26.2	1.04(0.86-1.26)
Stroke	No	9393	2396	25.5	1
	Yes	944	238	25.2	0.98(0.84-1.15)
In-hospital MACE	No	10146	2590	25.5	1
	Yes	191	44	23.0	0.87(0.62-1.23)
In-hospital PCI/CABG	No	5224	1719	32.9	1
	Yes	5113	915	17.9	0.44(0.41-0.49)
LDL-c level in hospital	Not measuring	909	268	29.5	1.63(1.27-2.09)
	<70mg/dl	1469	362	24.6	1.28(1.01-1.61)
	70-99mg/dl	3208	871	27.2	1.45(1.17-1.80)
	100-129mg/dl	2880	688	23.9	1.22(0.98-1.52)
	130-159mg/dl	1293	327	25.3	1.32(1.04-1.67)
	>=160mg/dl	578	118	20.4	1
Prior statin use	No	8870	2329	26.3	1
	Yes	1467	305	20.8	0.74(0.64-0.84)
Dose of statin at discharge	1-9 mg/d	1904	623	32.7	1.50(1.32-1.70)
	10-19 mg/d	3196	784	24.5	1
	>=20 mg/d	5237	1227	23.4	0.94(0.85-1.04)
Type of statin at discharge	Other statins	4552	1345	29.6	1
	Atorvastatin	5785	1289	22.3	0.68(0.63-0.75)
Co-treatments at discharge					
Aspirin	No	307	91	29.6	1
	Yes	10030	2543	25.4	0.81(0.63-1.03)
Clopidogrel	No	1933	664	34.4	1
	Yes	8404	1970	23.4	0.59(0.53-0.65)
β-blocker	No	2182	615	28.2	1
	Yes	8155	2019	24.8	0.84(0.75-0.93)
ACEI/ARB	No	2241	581	25.9	1
	Yes	8096	2053	25.4	0.97(0.87-1.08)

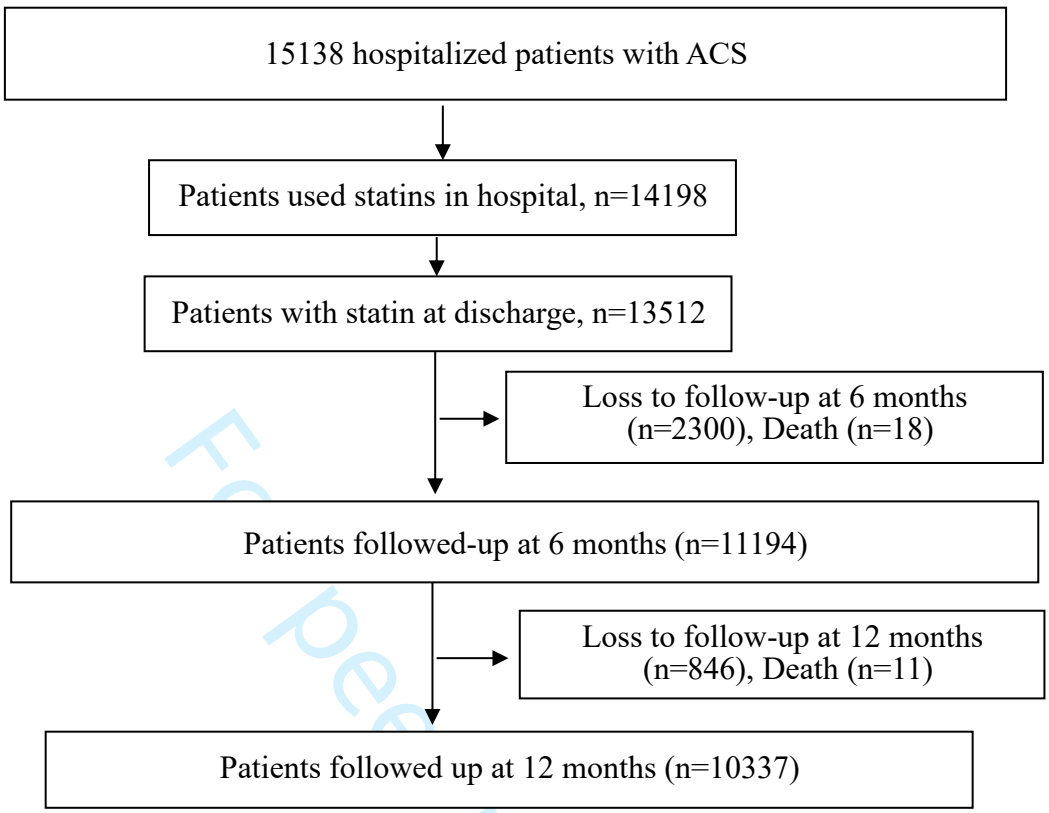
Table 3. Odds Ratios of discontinuation to stain within one year in the Full Final Multivariable Logistic Regression Model in Analyzed patients of CPACS-2 (n=10337)

Factors	OR(95%CI)
Year of enrolment	
2007-2008	1.0
2009	0.91(0.82-1.02)
2010	0.60(0.51-0.70)
Subtype of ACS	
STEMI	1.0
NSTEMI	1.03(0.89-1.20)
UA	1.10(0.99-1.22)
Clinical pathway intervention (Yes/No)	0.83(0.74-0.94)
Sex (Female/Male)	1.09(0.99-1.21)
Age (≥65 years/<65 years)	1.01(0.92-1.12)
Education (<high school/≥high school)	1.05(0.95-1.15)
Medical insurance (Yes/No)	0.75(0.67-0.85)
History of disease	
Dyslipidemia(Yes/No)	0.97(0.84-1.12)
Diabetes(Yes/No)	0.90(0.80-1.01)
Hypertension(Yes/No)	0.83(0.75-0.92)
In-hospital PCI/CABG(Yes/No)	0.47(0.43-0.53)
LDL-c level in hospital	
<160mg/dl	1
>=160mg/dl	0.70(0.57-0.87)
Not measuring	1.29(1.10-1.50)
Prior statin use (Yes/No)	0.73(0.63-0.84)
Statin type at discharge(Atorvastatin/Others)	0.78(0.70-0.88)
Statin dose at discharge	
1-9 mg/d	1.22(1.07-1.40)
10-19 mg/d	1
>=20 mg/d	1.27(1.13-1.43)
Co-treatments at discharge	
Clopidogrel (Yes/No)	0.94(0.83-1.06)
β-blocker (Yes/No)	0.93(0.84-1.04)

Figure legends

Figure 1. Flow chart of study participants in CPACS-2

Figure 2. The reasons of discontinuation to statin use in one year after discharge in CPACS-2 (n=1063)



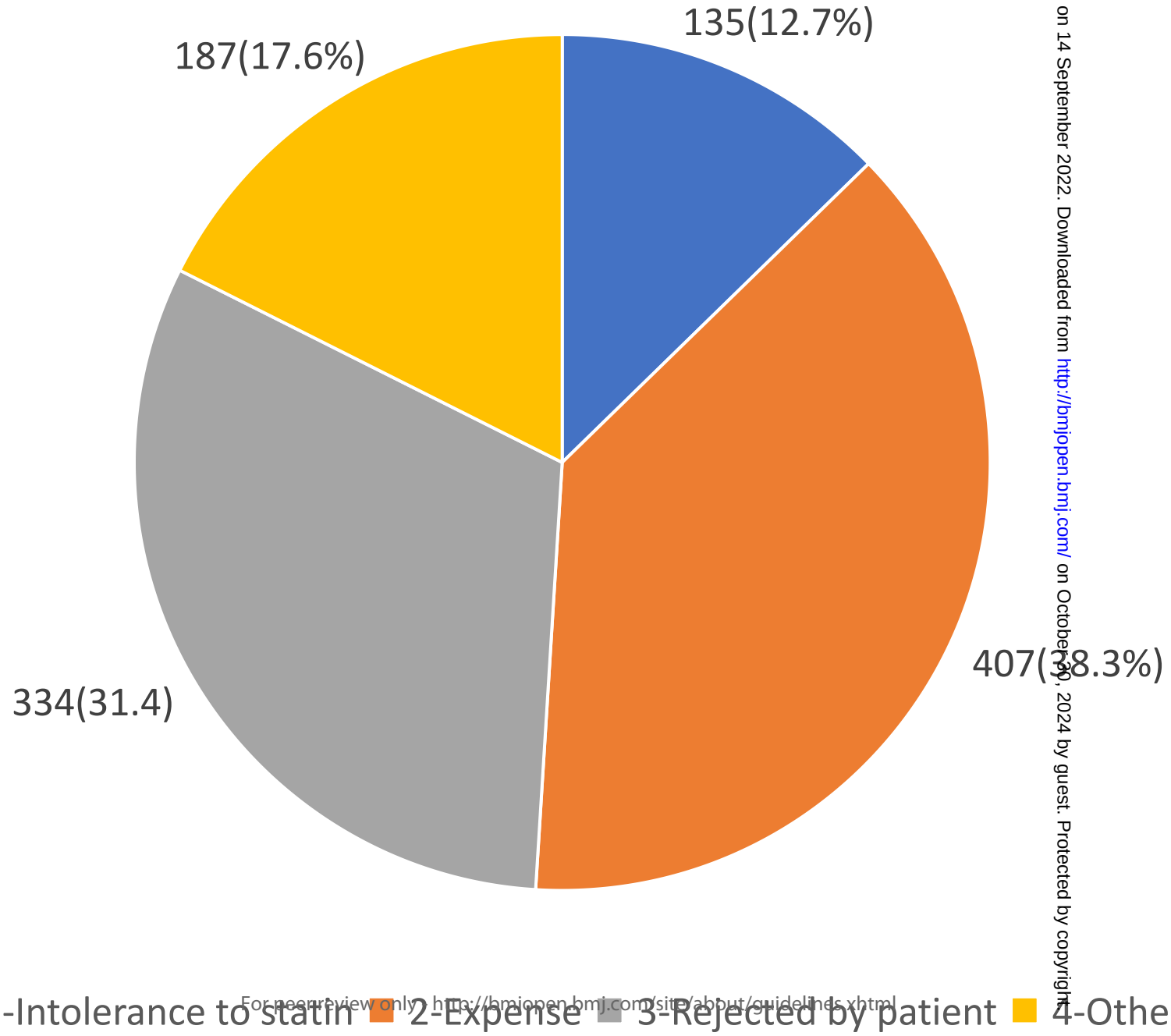


Table S1: Comparative Dose Efficacy of Statins on lipids

Statin(mg)					Change of lipids (%)			
Atorvastatin	**Simvastatin**	**Lovastatin**	**Pravastatin**	**Fluvastatin**	TC	LDL-C	HDL-C	TG
-	10	20	20	40	-22	-27	4~8	-(10~15)
10	20	40	40	80	-27	-34	4~8	-(10~20)
20	40	80			-32	-41	4~8	-(15~25)
40	80				-37	-48	4~8	-(20~30)
80					-42	-55	4~8	-(25~35)

Source: Editor Committee of Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults. Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults in 2007." Chin J Cardiol 35, no. 5 (2007): 390-419.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	√
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	√
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	√
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	√
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	√
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	√
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	√
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	√
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	√
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	√
Recruitment	14a	Dates defining the periods of recruitment and follow-up	√
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	√
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	√
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	√
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	√
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	√
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	√
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	√
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	√
Other information			
Registration	23	Registration number and name of trial registry	√
Protocol	24	Where the full trial protocol can be accessed, if available	√
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	√

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Associated factors of discontinuation to statin use in one year after discharge in patients with acute coronary syndrome in China: a follow up of 10,337 patients from CPACS-2 study

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Title

Associated factors of discontinuation to statin use in one year after discharge in patients with acute coronary syndrome in China: a follow up of 10,337 patients from CPACS-2 study

The type of manuscript: original research

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Abstract

Objectives To determine the associated factors of discontinuation to statin use in one year after discharge in patients who survived from acute coronary syndrome (ACS) in China.

Settings 75 hospitals across China.

Design A cohort follow up study

Participants The study included 10,337 ACS patients hospitalized in 2007-2010 and discharged with statins from 75 hospitals in China in the CPACS-2 study.

Primary outcome measures The primary outcome was the discontinuation of statin use defined as stopping statin use within one year after discharge.

Results: With multivariable logistic regression model, patients not having cholesterol measured (adjusted OR=1.29, 95%CI: 1.10-1.50) and patients with either higher (1.27; 1.13-1.43) or lower dose of statin (1.22; 1.07-1.40), compared with those with standard dose, were more likely to discontinue the use of statin. In addition, patients on the CPACS-2 intervention (adjusted OR=0.83; 95%CI: 0.74-0.94), patients with medical insurance (0.75; 0.67-0.85), history of hypertension (0.83; 0.75-0.92), high LDL-c (0.70; 0.57-0.87) at the baseline, with prior statin use (0.73; 0.63-0.84), and with use of atorvastatin (0.78; 0.70-0.88) and receiving PCI or CABG during hospitalization (0.47; 0.43-0.53) were less likely to discontinue statin use. The one-year statin discontinuation rate decreased from 29.5% in 2007-2008 to 17.8% in 2010 (adjusted OR = 0.60; 95%CI: 0.51 to 0.70).

Conclusion: Implementing clinical pathway, enhancing medical insurance coverage, strengthening health education in both physicians and patients, using statin in standard dosage may help improve the adherence to statin use after discharge in Chinese patients with ACS.

Key words: Acute coronary syndrome, Discontinuation to Statin Use, Trend, Associated Factors

Strengths and limitations of this study

With a large cohort with more than 10000 patients with ACS from 75 hospitals across different areas of China, novel factors associated with the risk of discontinuation of statin use after discharge were identified including two negative associates: clinical pathway intervention and higher baseline LDL-c level, and two positive associates: low dose use and not having cholesterol measured.

Data used in the present study was from CPACS-2, which was a well designed and performed under strict quality control.

There were about 21% study participants lost to follow-up, which might lead to over- or under-estimation of the associations of the discontinuation with associated factors.

INTRODUCTION

Statins therapy has been recommended as a core long-term secondary preventive treatment for patients with acute coronary syndrome (ACS) by several guidelines (1-5). Despite to these strong evidences from basic and clinical studies (6-8) and recommendation by the guidelines, about 10%-30% of patients with ACS discontinued their statin treatment usually within four years with highest attrition in the first year in Sweden, and USA(9-12). Moreover, discontinuation to statin therapy increases the risk of major adverse cardiovascular events (MACE) in patients with ACS after discharge in UK and other countries (13, 14).

A series of study in European or American showed that sex, intervention (nurse-led annual follow-up and medical titration by telephone, weekly pharmacist-led telephone contact for 12 weeks, a physician education protocol to implement statin in all patients admitted for CABG), generic versus branded drugs, insurance and prescription cost assistance were the main factors influencing the adherence to statin therapy among patients discharged with ACS(9, 15-19). However, to date, few data exist on the factors that influence statin persistence use in ACS patients in China.

In this study, we analyzed data from the Clinical Pathways for Acute Coronary Syndromes in China Study-2 (CPACS-2) to understand the trend from 2007 to 2010 among Chinese patients with ACS in discontinuation to statin use in the first year after discharge and to explore the factors that drove the trend and/or were associated with the discontinuation.

METHODS

Study design

The present study analyzed the one-year follow up data of patients with ACS who were discharged with statin from 75 hospitals across China in the Clinical Pathways for Acute Coronary Syndromes— Phase 2 (CPACS-2) study. The design, methodology and main results of CPACS-2 study have been previously reported in detail (20-23). In brief, the CPACS-2 study was an implementation trial with a cluster-randomized design to evaluate the effectiveness of implementing clinical pathways for ACS management in

75 hospitals in China from 2007 to 2010 (20).

Patients

CPACS-2 recruited consecutive ACS patients admitted to the participating hospitals and followed up the survived patients till one year after discharge. Among all 15,138 patients recruited in CPACS-2, these 1626 patients discharged without statins, 413 patients died during the follow up and 2,762 lost to follow up were excluded from analyses dataset. The remaining 10,337 patients who were discharge with statin and have complete follow up data were included in the present study for analysis (**see Figure 1**).

Ethical approval

The CPACS-2 study was approved by the ethics committee of Fuwai Hospital and Human Research Ethics Committees of University of Sydney in Australia (number: 09-2007/10276) (20-23). Informed consent was obtained from all participants. Confidentiality of subjects were ensured by anonymizing participants' names, initials or hospital numbers.

Data collection

A trained clinical staff (independent to the treating physicians) in each hospital reviewed medical records and administered a structured questionnaire to collect demographic and clinical data including statin use, history of disease, clinical characteristics, and prior and in-hospital treatments. All surviving patients were followed up at 6 and 12 months after the hospital discharge through interviews by either telephone calls (88%) or face-to-face clinic visit (12%). The standardized questionnaire for collecting data on statin followed up was shown in Table S1 in additional file S1.

For our analysis, the dosage of different statins was converted to the equivalent dosage of atorvastatin (24) (Additional file S1: **Table S2** (24)).

Data analyses

Exposures included for analysis

Exposures included the CPACS-2 intervention, year of enrolment, age, sex, education, employment, medical insurance, smoking status, subtype of ACS, co-existing cardiovascular diseases or risk, in-hospital major adverse cardiovascular events (MACE), in-hospital PCI/CABG, LDL-c level at enrolment, prior statin use, dose & type of statin at discharge, co-treatments at discharge.

Education level was classified into 2 categories: lower than high school and high school and above. Prior statin use was defined as any statin use in most days one month before the development of ACS.

According to the guideline in China(25), we divided into 3 groups: lower (<10 mg atorvastatin or equivalence) (18.4%), standard dose(10-19 mg atorvastatin) (30.9%), and high dose of statin (>=20 mg atorvastatin or equivalence) (50.7%) .

The CPACS-2 intervention included three major generic clinical pathways (risk stratification, management of STEMI, and management of non–ST-segment–elevation myocardial infarction/unstable angina pectoris) that were developed in conjunction with the Chinese Society of Cardiology based on the relevant American Heart Association and American College of Cardiology guidelines (1, 2). For more details please refer to the previous publications(20, 23).

Main outcome for analysis

The discontinuation to statin use in one year after discharge was the primary outcome, which was defined as not in current use of statin at the timepoints of either 6 or 12 months follow ups after discharge.

Statistical methods

SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all analyses. Univariate and multivariable logistic regression models were used to analyze the association of the discontinuation of statin with potential explanatory factors. Our primary analyses included only participants who completed both 6 and 12 months follow ups. Since the

number of patients in 2007 was small, these patients were grouped into those recruited in 2008 in our main analyses. Two-sided P value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Among all 15,138 patients recruited in CPACS-2, 13512 were prescribed to use statin at discharge. Among them, 433 died and 2742 (21% of survived) were lost to follow up. Finally, 10337 with complete data on statin therapy and related factors were analyzed (**Figure 1**). The baseline characteristics were shown in Table 1. Briefly, a total of 10,337 patients (men=70.3%) with ACS (mean age (SD) 63.2±11.6 years) were included in the study for analysis. Among them, 383 (3.7%), 3309(32.0%), 4982 (48.2%), and 1663 (16.1%) were enrolled in each year from 2007 to 2010 respectively. 7908 (76.5%) patients were enrolled after the hospitals had implemented the clinical pathway intervention (Table 1).

Trend of discontinuation to statin use from 2007 to 2010

Among our study participants, 25.5% (n=2634) discontinued to statin in one year after discharge. The rate decreased from 29.5% in 2007-2008 to 17.8% in 2010 (Table 2). The multiple logistic regression model confirmed that the deceasing trend in study years was significant after adjustment for co-variables including the CPACS-2 intervention (Table 3).

Factors associated with discontinuation to statin use

In univariate analyses, discontinuation rate was significantly lower in patients who received CPACS-2 intervention than those who did not receive, patients with medical insurance than those without, patients with than without history of dyslipidemia, diabetes, and hypertension, prior statin use, higher LDL-c, those who required intervention procedures such as PCI/CABG during hospitalization, those who were given either standard or high dose than in patients given low dose of statin, in those who were given atorvastatin than those who were given other statins, and lower in patients with than without co-treatments of clopidogrel and β-blocker at discharge.

On the other hand, discontinuation rate was significantly higher in women, older patients, patients with lower education level, patients with relatively milder form of ACS subtype (unstable angina), patients whose LDL-c was not measured during hospitalisation (all p<0.05) (**Table 2**).

Multiple logistic regression models confirmed that the trend of discontinuation with year of enrollment was significant and the patients with CPACS-2 intervention were less likely to discontinue use of statins. In addition, patients with medical insurance, history of hypertension, higher LDL-c level, prior statin use, taking atorvastatin, and receiving PCI or CABG during hospitalization were less likely to discontinue statin use, while those on either higher or lower dose of statin (versus standard dose), and those whose LDL-c was not measured during the hospital admission were more likely to discontinue the use of statin **(Table 3).** Other associated factors that were significant in univariate analysis became no longer significant, these including age, sex, history of dyslipidemia and diabetes, and co-treatments of clopidogrel and β-blocker at discharge.

DISCUSSION

Using data from a large, prospective cohort of ACS patients in China, we found that a number of factors were independently associated with the discontinuation of statin use in one year after discharge. Our findings bear important clinical significances, demonstrating that the discontinuation of statin use has multiple causes and the solutions should also be multiple.

First, our findings demonstrated that the implementing the CPACS-2 intervention was associated with a lower risk of the discontinuation of statin use, which was independent to the time trend and other covariates. It indicates that the clinical pathways for ACS management, although implemented within hospital, has effect in reducing the discontinuation of statin use after discharge. This finding is newly reported but expected. Our previous study on the basis of the CPACS-2 randomized comparison data showed that the intervention had significantly increased the use of

evidence-based secondary prevention medications at discharge(20, 21). We recommend this ACS clinical pathway to be adopted nationally in China and perhaps in other countries with similar circumstances as in China.

Second, like findings from other studies on medication adherence (26), we found that patients with medical insurance coverage were associated with a lower likelihood to discontinue the use of statin after discharge, indicating that enhancing the coverage of medical insurance should help to reduce the number of patients to discontinue the use of statin. In China, medical insurance has not yet covered all population and certainly not for all services. Therefore, having medical insurance may play an important factor which was associated with the adherence to statin use in our study.

Third, as expected, we found that ACS patients who received PCI/CABG treatment during the hospitalization were less likely to discontinue statin use. Similar pattern was also observed in other studies (9, 27). The explanations may include that all major clinical guidelines emphasize the long-term use of statin after PCI/CABG for prevention from restenosis (1, 28). In addition, the patients who received PCI/CABG are mainly suffering from AMI that is more severe than UP. Thus, patients with PCI/CABG may be encouraged by both doctors and themselves to be more adherent to the physicians' advices (risk marker effect). Probably for the same reason, patients with higher LDL-c level ($\geqslant$ 160 mg/dL), history of dyslipidemia, diabetes, and hypertension were less likely to discontinue the statin use. The association remained significant only for higher LDL-c and hypertension probably due to the co-linearity among these factors.

Fourth, it is interesting that both low and high dosages, compared with standard dosage, of statin at discharge were more likely to discontinue, which is independent of other observed predictors of statin discontinuation. Use of high-dose statin are more likely to experience adverse reactions to statins (29, 30). Thus, side effects, such as muscle complaints due to myopathy(31), and rhabdomyolysis (32, 33), might decrease the adherence to the statin therapy. The drivers of discontinuation for people taking a low dose may be differ from those for people taking a high dose. First, patients receiving a low dose might had a less severe disease or fewer lipid-associated

risk factors that could easily returned to normal in a relatively shorter period after discharge and thus perceived lower risk of subsequent events. Second, the low dose use of statin in Chinese patients might be a reflection that a higher risk of adverse effects of statin among Asians compared to Western populations. Studies found that the incidence of adverse reactions in Chinese patients was significantly higher than that in European patients (29). The increase rate of consecutive alanine transaminase (> 3 times the upper limit of normal value) is 10 times higher than that of European patients when moderate dose of statin was used (29). However, whether Chinese patients should be given a lower dose of statin remains controversial and requires more strong and solid evidences. Third, in Chinese culture many people believe chemical drugs have side effects so that they would stop using medications as soon as they think the disease has gone and their health is recovered. All these factors alone or in combination could lead to the low dose prescription and the early discontinuation in these patients.

Atorvastatin use (versus other statins) significantly decreased likelihood of discontinuation, which is independent of other confounders. This finding indicates that Chinese are more likely to adherent to atorvastatin and is helpful to explain the most frequently used statin type transition from simvastatin (60.2% in 2001) to atorvastatin (52.9% in 2011) (34). We do not know why Chinese are better adherent to atorvastatin. We hypothesize that the good adherence to atorvastatin might be due to the better tolerability, and its efficacy and safety. However, two studies with small sample in Chinese showed that no significant differences of MACE and declined renal function between atorvastatin and other statins (35, 36). On the other hand, a large observational study in the United States found 10 or 20 mg of atorvastatin use had lower CV event rates particularly in the first year of use than 20 or 40 mg of simvastatin (37) while another large observational study in the United Kingdom found that the risk of hepatotoxicity (small numbers of events observed) was increased in the first six months of atorvastatin compared to simvastatin treatment (38). It might also a reflection of the strong marketing activities that led to a better confidence in the brand among both doctors and patients, but we have no evidence to support this hypothesis. These findings suggest that further large-scale studies are needed to explore the

differences of efficacy and safety between atorvastatin and other statins using equivalent dosage especially in Chinese patients.

Prior statin usage significantly decreased likelihood of discontinuation in our cohort. This finding was consistent with two previous studies(39, 40). Logically, prior statin usage indicates that patients have good tolerance to statin, have the ability to pay, pay more attention to their own health, and have more knowledge on the importance of statin in both primary and secondary prevention of ACS, which may help decrease discontinuation of statin after discharge. Moreover, the patients with prior statin were more likely to have higher education level, have history of dyslipidemia (30% versus 11%), diabetes, heart failure, hypertension, and take place MACE in hospital, which were observed to decrease the likelihood of discontinuation to statin in the present study.

Fifth, we found that not measuring LDL-c during the index admission increased the likelihood of discontinuation and higher LDL-c reduced the likelihood of discontinuation. This finding indicates the cholesterol management is very important for improve adherence to statin therapy. Cholesterol management is recommended by all guidelines on ACS (4, 41). However, in the present study, about 8.8% of patients did not get their LDL-c measured in hospital. Thus, giving attention to the cholesterol measurement during hospital admission with ACS and management may help to further to improve adherence to statin.

Many strategies have been proposed that attempt to further reduce discontinuation and improve statin therapeutic effectiveness, including patient education on improving ACS and statin literacy, co-payment reduction, and behavior-modification interventions (42-44). In the present study, we confirmed that the clinical pathway intervention can reduce the risk of discontinuation of statin therapy. We also confirmed that enhancing health insurance would reduce the risk of discontinuation of statin use. Besides, we found that some important patient characteristics such as low dose of statin use, not having lipids measured during hospitalization, prior not use of statin, etc. were common in Chinese patients but associated with an additional and

independent higher risk of discontinuation of statin use. It indicates that the education on knowledge of statin and cardiovascular secondary prevention should be further strengthen in both physicians and patients in China. Our results also suggest that high quality studies that could generate data for appropriate dose of statin in Chinese patients would help to reduce the statin discontinuation. It is indeed reassuring and pleasing that discontinuation decreased significantly from 29.5% in 2007-2008 to 17.8% in 2010, given the increasing CVD burden in China. The clinical pathway intervention could partly explain the decreasing discontinuation proportions over time. However, the trend of the discontinuation with study year was still significant even after adjustment for the intervention and other potential confounders. While these results may relate to other confounders which are not controlled for, it is highly plausible that the publication, widespread promulgation, and endorsement of the first Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults in 2007-2008 (25, 45-52) might be the most important influential factor that were likely to have impact on the reduction in discontinuation of statin. This could occur through improving the knowledge level of statin use as secondary prevention of ACS among physicians and among patients who had experienced ACS. Notably, although the withdrawal rate of statins has been greatly reduced, a considerable proportion of patients have stopped taking statins, and the evidence practice gap still exists especially in those without intervention or medical insurance. In one more recent publication in China, the 1-year discontinuation to statin therapy was still about 19.3% to 23.8% in real-world patients (53). Thus, our findings are still valuable for improving the statin adherence in China currently, and more efforts are needed to further improve the adherence to statin.

Limitations

Some limitations are worth highlighting. Firstly, patients who were lost to follow-up were significantly different in some characteristics (years of enrolment, subtypes of ACS, ages, occupations, medical insurance, baseline LDL-c, comorbidities, in-hospital MACE, in-hospital PCI/CABG, doses and types of statin, co-treatments of other medications, etc.) might lead to over- or under-estimation of the associations with the related factors (Table S3 in file S1). Secondly, our study follow-up period was limited to one year, factors that are associated with the longer-term discontinuation should

be explored in the future. Thirdly, the data about statin use were prospectively collected through interviews. The possible reporting bias made by the patients should therefore be small and if any, this misclassification would have underestimated the association. Thus, for the associations with statistical significance the true associations should be even stronger than what we observed.

Conclusions

In summary, approaches such as implementing clinical guidelines and pathways, enhancing medical insurance coverage, strengthening health education in physicians and patients, and using statin in standard dosage in Chinese may help to improve the persistence of statin therapy in patients discharged after an acute coronary syndrome in China. Such measures should have major implication to the clinical and public health practices and ultimately will bring about the benefit of patients with reduced CVD burden.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Supplementary Material

Standardized questionnaire for collecting data on statin followed up (See Table S1 in file S1).

Comparative Dose Efficacy of Statins on lipids (See Table S2 in file S1).

Comparison of characteristics of patients with ACS between those followed-up and those lost to follow-up (See Table S3 in file S1).

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Statement on previous reports

We confirm that the contents of this manuscript have not been copyrighted or published previously, and that the manuscript is not under consideration for publication elsewhere, in whole or in part in any language, including publicly accessible web sites or e-print servers.

Trial Registration identifier in ANZCTR (Australian New Zealand Clinical Trials Registry): ACTRN12609000491268, http://www.anzctr.org.au/default.aspx .

Conflict of Interest Disclosures:

No disclosures were reported.

Statement of responsibility

The authors had full access to the data and took responsibility for its integrity. All authors have read and agreed to the written manuscript. Each author believes that the manuscript represents honest work.

Patient and Public Involvement statement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Authors' contributions

GX: concept development, data cleaning analysis, and interpretation, and writing of the manuscript; PKM: critical input in interpretation of results and writing of the manuscript; YS: critical input in interpretation of results and writing of the manuscript; XL: quality control on data collection and review of manuscript; TW: data analysis plan and review of manuscript; RG: review of manuscript and critical input in interpretation of results ; YW: concept development, critical input in interpretation of results, and review and approval of the manuscript.

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Tables

Table 1. Characteristics of patients with ACS in these patients followed-up (n=10337)

Characteristics	n	%
Year of enrolment		
2007	383	3.7
2008	3309	32.0
2009	4982	48.2
2010	1663	16.1
Subtype of ACS		
STEMI*	3918	37.9
NSTEMI*	1394	13.5
UA*	5025	48.6
Clinical pathway intervention	7908	76.5
Sex (Female)	3074	29.7
Age>=65	4934	47.7
Education>=high school	3786	36.6
Unemployed	5033	48.7
With medical insurance	8678	83.9
Current smoker	3192	30.9
History of disease		
Dyslipidemia	1359	13.1
Diabetes	2086	20.2
Hypertension	7184	69.5
Heart Failure	562	5.4
Stroke	944	9.1
In-hospital MACE	191	1.8
In-hospital PCI/CABG	5113	49.5
LDL-c level in hospital		
Not measuring	909	8.8
<160mg/dl	8850	85.6
>=160mg/dl	578	5.6
Prior statin use	1467	14.2
Dose of statin at discharge		
1-9 mg/d	1904	18.4
10-19 mg/d	3196	30.9
>=20 mg/d	5237	50.7
Type of statin at discharge		
Atorvastatin	5785	56.0
Simvastatin	2690	26.0
Rosuvastatin	502	4.9
Pravastatin	502	4.9
Fluvastatin	578	5.6
Other statin	280	2.7
Co-treatments at discharge		
Aspirin	10030	97.0
Clopidogrel	8404	81.3
β-blocker	8155	78.9
ACEI/ARB*	8096	78.3

* STEMI was ST-segment elevation myocardial infarction; NSTEMI was Non-ST-segment elevation myocardial infarction; UA was unstable angina; ACEI was Angiotensin converting enzyme inhibitor; ARB was Angiotensin Receptor Blocker

Table 2. Univariate analysis of factors in association with the discontinuation to statin use in one year after discharge with Logistic regression models (n=10337)

Factors	Group	N	Discontinuation		OR (95%CI)
			n	%	
Year of enrolment	2007-2008*	3692	1088	29.5	1
	2009	4982	1250	25.1	0.80(0.73-0.88)
	2010	1663	296	17.8	0.52(0.45-0.60)
Subtype of ACS	STEMI	3918	928	23.7	1
	NSTEMI	1394	348	25.0	1.07(0.93-1.24)
	UA	5025	1358	27.0	1.19(1.08-1.31)
Clinical pathway intervention	No	2429	754	31.0	1
	Yes	7908	1880	23.8	0.69(0.63-0.77)
Sex	Male	7263	1761	24.3	1
	Female	3074	873	28.4	1.24(1.13-1.36)
Age group	18-64 years	5403	1320	24.4	1
	≥65 years	4934	1314	26.3	1.12(1.03-1.23)
Education	≥high school	3786	853	22.5	1
	<high school	6551	1781	27.2	1.28(1.17-1.41)
Employment	No	5033	1282	25.5	1
	Yes	5304	1352	25.5	1.00(0.92-1.09)
Medical insurance	No	1659	514	31.0	1
	Yes	8678	2120	24.4	0.72(0.64-0.81)
Current smoker	No	7145	1838	25.7	1
	Yes	3192	796	24.9	0.96(0.87-1.06)
History of disease					
Dyslipidemia	No	8978	2327	25.9	1
	Yes	1359	307	22.6	0.83(0.73-0.96)
Diabetes	No	8251	2155	26.1	1
	Yes	2086	479	23.0	0.84(0.75-0.94)
Hypertension	No	3153	874	27.7	1
	Yes	7184	1760	24.5	0.85(0.77-0.93)
Heart Failure	No	9775	2487	25.4	1
	Yes	562	147	26.2	1.04(0.86-1.26)
Stroke	No	9393	2396	25.5	1
	Yes	944	238	25.2	0.98(0.84-1.15)
In-hospital MACE	No	10146	2590	25.5	1
	Yes	191	44	23.0	0.87(0.62-1.23)
In-hospital PCI/CABG	No	5224	1719	32.9	1
	Yes	5113	915	17.9	0.44(0.41-0.49)
LDL-c level in hospital	<160mg/dl	8850	2248	25.4	1
	>=160mg/dl	578	118	20.4	0.75(0.61-0.93)
	Not measuring	909	268	29.5	1.23(1.06-1.43)
Pre-hospital statin use	No	8870	2329	26.3	1
	Yes	1467	305	20.8	0.74(0.64-0.84)
Dose of statin at discharge	1-9 mg/d	1904	623	32.7	1.50(1.32-1.70)
	10-19 mg/d	3196	784	24.5	1
	>=20 mg/d	5237	1227	23.4	0.94(0.85-1.04)
Type of statin at discharge	Other statins	4552	1345	29.6	1
	Atorvastatin	5785	1289	22.3	0.68(0.63-0.75)
Co-treatments at discharge					
Aspirin	No	307	91	29.6	1
	Yes	10030	2543	25.4	0.81(0.63-1.03)
Clopidogrel	No	1933	664	34.4	1
	Yes	8404	1970	23.4	0.59(0.53-0.65)
β-blocker	No	2182	615	28.2	1
	Yes	8155	2019	24.8	0.84(0.75-0.93)
ACEI/ARB	No	2241	581	25.9	1
	Yes	8096	2053	25.4	0.97(0.87-1.08)

*Combined 2007 and 2008 due to relative small sample in 2007.

Table 3. Odds Ratios of discontinuation to stain within one year in the full final multivariable Logistic regression model in analyzed patients of CPACS-2 (n=10337)

Factors	Adjusted OR (95%CI)
Year of enrolment*	
2007-2008	1.0
2009	0.91(0.82-1.02)
2010	0.60(0.51-0.70)
Subtype of ACS**	
STEMI	1.0
NSTEMI	1.03(0.89-1.20)
UA	1.10(0.99-1.22)
Clinical pathway intervention (Yes/No)	0.83(0.74-0.94)
Sex (Female/Male)	1.09(0.99-1.21)
Age (≥65 years/<65 years)	1.01(0.92-1.12)
Education (<high school/≥high school)	1.05(0.95-1.15)
Medical insurance (Yes/No)	0.75(0.67-0.85)
History of disease	
Dyslipidemia(Yes/No)	0.97(0.84-1.12)
Diabetes(Yes/No)	0.90(0.80-1.01)
Hypertension(Yes/No)	0.83(0.75-0.92)
In-hospital PCI/CABG(Yes/No)	0.47(0.43-0.53)
LDL-c level in hospital	
<160mg/dl	1
>=160mg/dl	0.70(0.57-0.87)
Not measuring	1.29(1.10-1.50)
Prior statin use (Yes/No)	0.73(0.63-0.84)
Statin type at discharge(Atorvastatin/Others)	0.78(0.70-0.88)
Statin dose at discharge	
1-9 mg/d	1.22(1.07-1.40)
10-19 mg/d	1
>=20 mg/d	1.27(1.13-1.43)
Co-treatments at discharge	
Clopidogrel (Yes/No)	0.94(0.83-1.06)
β-blocker (Yes/No)	0.93(0.84-1.04)

* p for trend<0.001

**p for trend=0.232;

Figure legends

Figure 1. Flow chart of study participants in CPACS-2

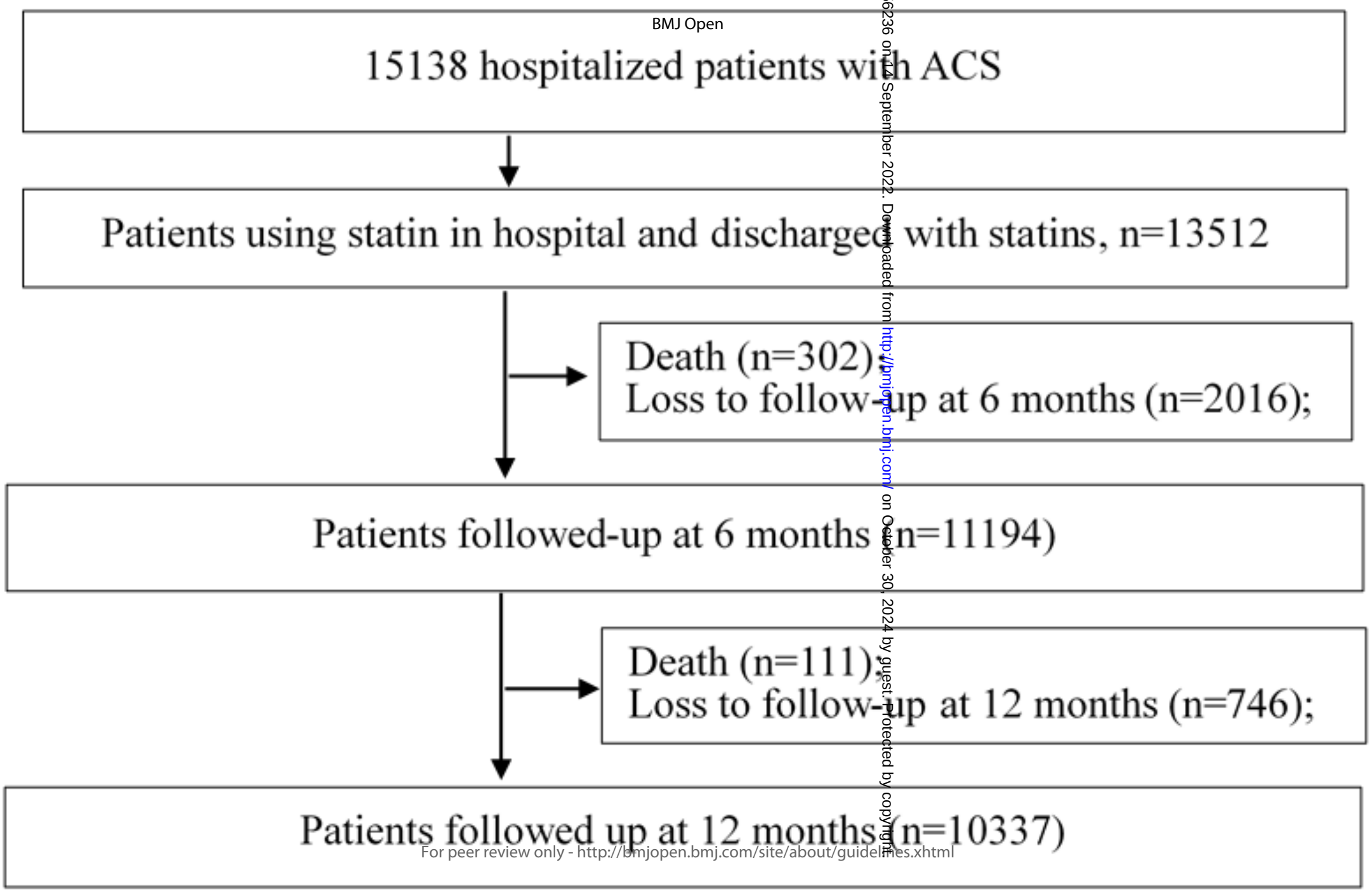

Table S1. Standardized questionnaire for collecting data on statin followed up

SECTION 3: CURRENT MEDCIATIONS (if patient alive)	
3.25	Statin ☐ Yes If yes, trade name is:_____ Dose _____mg/day ☐ No *If no, reason is: (select one)* ☐ Not prescribed ☐ Patient refused Reason is: (select one) ☐ Cost ☐ Other ☐ Intolerance ☐ Unknown ☐ Other(*specify)*_____

Table S2: Dosage of different type of statins with equivalent efficacy on lipid measures

Equivalent dosages of statins (mg)					**Efficacy in mean reduction of lipid measures (%)**			
Atorva-statin	**Simva-statin**	**Lova-statin**	**Prava-statin**	**Fluva-statin**	TC	LDL-C	HDL-C	TG
-	10	20	20	40	-22	-27	4~8	-(10~15)
10	20	40	40	80	-27	-34	4~8	-(10~20)
20	40	80			-32	-41	4~8	-(15~25)
40	80				-37	-48	4~8	-(20~30)
80					-42	-55	4~8	-(25~35)

Source: P Jones 1, S Kafonek, I Laurora, D Hunninghake. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study) .Am J Cardiol, 1998 Mar 1;81(5):582-7. doi: 10.1016/s0002-9149(97)00965-x. (Reference No. 24 in the main text).

Table S3. Comparison of characteristics of patients with ACS between those followed-up and those lost to follow-up

	Followed-up (n=10337)		Lost to follow-up (n=2742)		
Characteristics	n	%	n	%	P values
Year of enrolment					
2007	383	3.7	161	5.9	<0.001
2008	3309	32.0	874	31.9	
2009	4982	48.2	1170	42.7	
2010	1663	16.1	537	19.6	
Subtype of ACS					
STEMI*	3918	37.9	1284	46.8	<0.001
NSTEMI*	1394	13.5	409	14.9	
UA*	5025	48.6	1049	38.3	
Clinical pathway intervention	7908	76.5	2077	75.8	0.409
Sex (Female)	3074	29.7	791	28.9	0.364
Age>=65	4934	47.7	1381	50.4	0.014
Education>=high school	3786	36.6	1028	37.5	0.404
Unemployed	5033	48.7	1494	54.5	<0.001
With medical insurance	8678	83.9	2172	79.2	<0.001
Current smoker	3192	30.9	906	33.0	0.030
History of disease					
Dyslipidemia	1359	13.1	315	11.5	0.021
Diabetes	2086	20.2	529	19.3	0.302
Hypertension	7184	69.5	1798	65.6	<0.001
Heart Failure	562	5.4	160	5.8	0.417
Stroke	944	9.1	278	10.1	0.107
In-hospital MACE	191	1.8	283	10.3	<0.001
In-hospital PCI/CABG	5113	49.5	1471	53.7	<0.001
LDL-c level in hospital					
Not measuring	909	8.8	299	10.9	0.003
<160mg/dl	8850	85.6	2287	83.4	
>=160mg/dl	578	5.6	156	5.7	
Prior statin use	1467	14.2	381	13.9	0.692
Dose of statin at discharge					
1-9 mg/d	1904	18.4	672	24.5	<0.001
10-19 mg/d	3196	30.9	500	18.2	
>=20 mg/d	5237	50.7	1570	57.3	
Type of statin at discharge					
Atorvastatin	5785	56.0	1712	62.4	<0.001
Simvastatin	2690	26.0	509	18.6	
Rosuvastatin	502	4.9	40	1.5	
Pravastatin	502	4.9	163	5.9	

Fluvastatin	578	5.6	166	6.1	
Other statin	280	2.7	152	5.5	
Co-treatments at discharge					
Aspirin	10030	97.0	2645	96.5	0.127
Clopidogrel	8404	81.3	2416	88.1	<0.001
β-blocker	8155	78.9	2076	75.7	<0.001
ACEI/ARB*	8096	78.3	2161	78.8	0.579

* STEMI was ST-segment elevation myocardial infarction; NSTEMI was Non-ST-segment elevation myocardial infarction; UA was unstable angina; ACEI was Angiotensin converting enzyme inhibitor; ARB was Angiotensin Receptor Blocker

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a)Title and Line 6 of page 3; (b)Line 7-25 of page 3.	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1. Line 7-8 of page 3. 1.2. Line 7-8 of page 3. 1.3. Not applicable.
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	The first and second paragraph of the introduction section.		
Objectives	3	State specific objectives, including any prespecified hypotheses	The third paragraph of the introduction section.		
Methods					
Study Design	4	Present key elements of study design early in the paper	The first line of the study design section.		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	The first paragraph of the methods section.		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	(a) The second paragraph of the methods section. (b) Not applicable.	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1. The second paragraph of the methods section. 6.2. Not applicable. 6.3. Not applicable.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	The data analyses of the methods section.	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	The data analyses of the methods section.
Data sources/ measurement	8	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	Page 6-7 in the methods section.		

Bias	9	Describe any efforts to address potential sources of bias	To control information bias in the first paragraph of data collection section.		
Study size	10	Explain how the study size was arrived at	The first paragraph of design section.		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	The data analyses of the methods section.		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Statistical methods in page 8.		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	The first paragraph of study design.

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	The second sentence of patient section in page 6.
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	The first paragraph of page 7.
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	a & b. First paragraph of results section in page 8. c. Figure 1.	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	13.1. First paragraph of results section in page 8 and Figure 1.
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	The first paragraph of the result section.		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time	The second paragraph of the result section.		

		Case-control study - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2 & 3.		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Figure 2.		
Discussion					
Key results	18	Summarise key results with reference to study objectives	First paragraph of the discussion section.		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	The last paragraph of the discussion section in page 14.	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	The last paragraph of the discussion section .

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Paragraph 2-10 of the discussion section.		
Generalisability	21	Discuss the generalisability (external validity) of the study results	The first paragraph of page 14.		
Other Information					
Funding	22	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	Source(s) of support of page 15.		
Accessibility of protocol, raw data, and programming code		The first paragraph of the design section in page 5.		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	The first paragraph of the design section in page 5.

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Associated factors of discontinuation to statin use in one year after discharge in patients with acute coronary syndrome in China

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Title

Associated factors of discontinuation to statin use in one year after discharge in patients with acute coronary syndrome in China

The type of manuscript: original research

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Abstract

Objectives To determine the associated factors of discontinuation to statin use in one year after discharge in patients who survived from acute coronary syndrome (ACS) in China.

Settings 75 hospitals across China.

Design A cohort follow up study

Participants The study included 10,337 ACS patients hospitalized in 2007-2010 and discharged with statins from 75 hospitals in China in the CPACS-2 study, who were followed- up at 6- and 12- months post-discharge.

Primary outcome measures The primary outcome was the discontinuation of statin use defined as not in current use of statin at either 6 or 12 months follow up.

Results: Multivariable logistic regression model showed, patients who did not have cholesterol measurement (adjusted OR=1.29, 95%CI: 1.10-1.50) and patients with either higher (1.27; 1.13-1.43) or lower dose of statin (1.22; 1.07-1.40), compared with those with standard dose, were more likely to discontinue the use of statin. In addition, patients on the CPACS-2 intervention pathway (adjusted OR=0.83; 95%CI: 0.74-0.94), patients with medical insurance (0.75; 0.67-0.85), history of hypertension (0.83; 0.75-0.92), high LDL-c (0.70; 0.57-0.87) at the baseline, prior statin use (0.73; 0.63-0.84), use of atorvastatin (0.78; 0.70-0.88) and those who underwent PCI or CABG during hospitalization (0.47; 0.43-0.53) were less likely to discontinue statin use. The one-year statin discontinuation rate decreased from 29.5% in 2007-2008 to 17.8% in 2010 (adjusted OR = 0.60; 95%CI: 0.51 to 0.70).

Conclusion: Implementing clinical pathway, enhancing medical insurance coverage, strengthening health education in both physicians and patients, using statin at standard dosage may help improve the adherence to statin use after discharge in Chinese patients with ACS.

Key words: Acute coronary syndrome, Discontinuation to Statin Use, Trend, Associated Factors

Strengths and limitations of this study

With a large cohort with more than 10,000 patients with ACS from 75 hospitals across different areas of China, novel factors associated with the risk of discontinuation of statin use after discharge were identified including two negative associates: clinical pathway intervention and higher baseline LDL-c level, and two positive associates: non-standard dose use and not having cholesterol measured.

Data used in the present study was from CPACS-2, which was a well-designed and conducted under strict quality control.

There were about 21% study participants lost to follow-up, which might have led to over- or under-estimation of the associations of the discontinuation of statin after ACS.

INTRODUCTION

Statins therapy has been recommended as a core long-term secondary preventive treatment for patients with acute coronary syndrome (ACS) by several guidelines (1-5). Despite strong evidence from basic and clinical studies (6-8) and recommendation by the guidelines, about 10%-30% of patients with ACS discontinued their statin treatment usually within four years with highest attrition in the first year in western countries (9-12). It has been shown that discontinuation of statin therapy increases the risk of major adverse cardiovascular events (MACE) in patients with ACS after discharge in several countries including UK (13, 14).

Several studies in Europe and America showed that sex, intervention (nurse-led annual follow-up and medical titration by telephone, weekly pharmacist-led telephone contact for 12 weeks, a physician education protocol to implement statin in all patients admitted for CABG), generic versus branded drugs, insurance and prescription cost assistance were the main factors influencing the adherence to statin therapy among patients discharged with ACS (9, 15-19). A big European survey showed that statin therapy was discontinued in 11.6% of patients with coronary heart disease (CHD)(20). However, to date, few data exist on the factors that influence statin discontinuation in ACS patients in China.

In this study, we analyzed data from the Clinical Pathways for Acute Coronary Syndromes in China Study-2 (CPACS-2) to understand the trend from 2007 to 2010 among Chinese patients with ACS in discontinuation of statin use in the first year after discharge and to explore the factors that drove the trend and factors that were associated with discontinuation.

METHODS

Study design

The present study analyzed the one-year follow up data of patients with ACS who were discharged with statin from 75 hospitals across China in the Clinical Pathways for Acute Coronary Syndromes— Phase 2 (CPACS-2) study. The design, methodology and main results of CPACS-2 study have been previously reported in detail (21-24). In brief, the

CPACS-2 study was an implementation trial with a cluster-randomized design to evaluate the effectiveness of implementing clinical pathways for ACS management in 75 hospitals in China from 2007 to 2010 (21).

Patients

CPACS-2 recruited consecutive ACS patients admitted to the participating hospitals and followed up surviving patients till one year after discharge. Of 15,138 patients recruited in CPACS-2, 1626 patients were discharged without statins, 413 patients died during the follow up and 2,762 lost to follow up and therefore these patients were excluded from analysis. The remaining 10,337 patients who were discharge with statin and completed follow up were included (**see Figure 1**).

Ethical approval

The CPACS-2 study was approved by the ethics committee of Fuwai Hospital and Human Research Ethics Committees of University of Sydney in Australia (number: 09-2007/10276) (21-24). Informed consent was obtained from all participants. Confidentiality of subjects were ensured by anonymizing participants' names, initials or hospital numbers.

Data collection

A trained clinical staff (independent to the treating physicians) in each hospital reviewed medical records and administered a structured questionnaire and collected demographic and clinical data including statin use, history of disease, clinical characteristics, and prior and in-hospital treatments. Data on statin use at 6 and 12 months after the hospital discharge were collected through interviews by either telephone calls (88%) or face-to-face clinic visit (12%). The standardized questionnaire for collecting data on statin use was shown in Table S1 in additional file S1.

For our analysis, the dosage of different statins was converted to the equivalent dosage of atorvastatin (25) (Additional file S1: **Table S2** (25)).

Data analyses

Exposures included for analysis

Exposures included the CPACS-2 intervention, year of enrolment, age, sex, education, employment, medical insurance, smoking status, subtype of ACS, co-existing cardiovascular diseases or risk, in-hospital major adverse cardiovascular events (MACE), in-hospital PCI/CABG, LDL-c level at enrolment, prior statin use, dose & type of statin at discharge, co-treatments at discharge.

Education level was classified into 2 categories: lower than high school and high school and above. Prior statin use was defined as any statin use in most days one month before the development of ACS.

According to the guideline in China(26), we divided into 3 groups of statin dose: lower (<10 mg atorvastatin or equivalent) (18.4%), standard dose (10-19 mg atorvastatin) (30.9%), and high dose of statin (>=20 mg atorvastatin or equivalent) (50.7%).

The CPACS-2 intervention included three major generic clinical pathways (risk stratification, management of STEMI, and management of non–ST-segment–elevation myocardial infarction/unstable angina pectoris) that were developed in conjunction with the Chinese Society of Cardiology based on the relevant American Heart Association and American College of Cardiology guidelines (1, 2). For more details, please refer to the previous publications (21, 24).

Main outcome for analysis

The discontinuation to statin use in one year after discharge was the primary outcome, which was defined as not in current use of statin at either 6 or 12 months follow up.

Statistical methods

SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all analyses. Univariate and multivariable logistic regression models were used to analyse the association of the discontinuation of statin with potential explanatory factors. Our primary analyses included only participants who completed both 6 and 12 months follow ups. Since the number of patients in 2007 was small, these patients were grouped into those

recruited in 2008 in our main analyses. Two-sided P value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Among all 15,138 patients recruited in CPACS-2, 13512 were prescribed statin at discharge. Among them, 433 died and 2742 (21% of those who survived) were lost to follow up. Finally, 10337 patients with complete data on statin therapy and related factors were analysed (**Figure 1**). The baseline characteristics are shown in Table 1. Briefly, a total of 10,337 patients (men=70.3%) with ACS (mean age (SD) 63.2±11.6 years) were included. Of them, 383 (3.7%), 3309(32.0%), 4982 (48.2%), and 1663 (16.1%) were enrolled in each year from 2007 to 2010 respectively. A total of 7908 (76.5%) patients were enrolled after the hospitals had implemented the clinical pathway intervention (Table 1).

Trend of discontinuation to statin use from 2007 to 2010

Among our study participants, 25.5% (n=2634) discontinued statin in one year after discharge. The discontinuation rate decreased from 29.5% in 2007-2008 to 17.8% in 2010 (Table 2). The multiple logistic regression model confirmed that the deceasing trend in study years was significant after adjustment for co-variables including the CPACS-2 intervention (Table 3).

Factors associated with discontinuation to statin use

In univariate analyses, discontinuation rate was significantly lower in patients who received CPACS-2 intervention than those who did not receive the pathway, patients with medical insurance than those without, patients with history of dyslipidemia, diabetes, and hypertension, prior statin use, higher LDL-c, those who required intervention procedures such as PCI/CABG during hospitalization, those who were given either standard or high dose than in patients given low dose of statin, in those who were given atorvastatin than those who were given other statins, and lower in patients with than without co-treatments of clopidogrel and β-blocker at discharge. On the other hand, discontinuation rate was significantly higher in women, older

patients, patients with lower education level, patients with relatively milder form of ACS subtype (unstable angina), patients whose LDL-c was not measured during hospitalisation (all p<0.05) (**Table 2**).

Multiple logistic regression models confirmed that the trend of discontinuation with year of enrollment was significant and the patients with CPACS-2 intervention were less likely to discontinue use of statins. In addition, patients with medical insurance, history of hypertension, higher LDL-c level, prior statin use, taking atorvastatin, and those who underwent PCI or CABG during hospitalization were less likely to discontinue statin, while those on either higher or lower dose of statin (versus standard dose), and those whose LDL-c was not measured during the hospital admission were more likely to discontinue the use of statin **(Table 3).** Other associated factors that were significant in univariate analysis became no longer significant in multivariable model; these include age, sex, history of dyslipidemia and diabetes, and co-treatments of clopidogrel and β-blocker at discharge.

DISCUSSION

Using data from a large, prospective cohort of ACS patients in China, we found that a number of factors were independently associated with the discontinuation of statin use in one year after discharge. Our findings bear important clinical significance, demonstrating that the discontinuation of statin use has multiple causes and thus multiple approaches are required to address this important issue.

First, our findings demonstrated that the implementing of CPACS-2 intervention was associated with a higher adherence of statin use, which was independent of the time trend and other covariates. It indicates that the clinical pathways for ACS management, although implemented within hospital, has effect in reducing the discontinuation of statin use after discharge. This finding is newly reported but expected. Our previous study on the basis of the CPACS-2 randomized comparison data showed that the intervention had significantly increased the use of evidence-based secondary prevention medications at discharge (21, 22). We recommend this ACS clinical

pathway to be adopted nationally in China and perhaps in other countries with similar circumstances as in China.

Second, similar to the findings from other studies on medication adherence (27), we found that patients who had medical insurance were significantly more likely to continue the use of statin after discharge, indicating that improving medical insurance coverage in the population should help to reduce the number of patients who discontinue the use of statin. In China, medical insurance has not yet covered for the whole population and certainly not for all services. Therefore, having medical insurance might have been an important factor and hence it was associated with the adherence to statin use in our study.

Third, as expected, we found that ACS patients who received PCI/CABG treatment during the hospitalization were more likely to continue statin use. Similar pattern was also observed in other studies (9, 20). The explanations may include that all major clinical guidelines emphasize the long-term use of statin after PCI/CABG for prevention from restenosis (1, 28). In this study, patients who received PCI/CABG had AMI that is more severe than unstable angina pectoris. Thus, patients with PCI/CABG might have been encouraged by both doctors and thus they were more likely to adhere to the physicians' advices (risk marker effect). Probably for the same reason, patients with higher LDL-c level (⩾160 mg/dL), history of dyslipidemia, diabetes, and hypertension were less likely to discontinue the use of statin. The association remained significant only for higher LDL-c and hypertension in multivariable analysis probably due to the co-linearity among these factors.

Fourth, it is interesting that both low and high dosages, compared with standard dosage, of statin at discharge were more likely to discontinue, which is independent of other observed predictors of statin discontinuation. Use of high-dose statin have been shown to be associated with adverse reactions (29, 30). Thus, side effects, such as muscle complaints due to myopathy (31), and rhabdomyolysis (32, 33), might have decreased the adherence to the statin therapy in our study. However, the drivers for discontinuation in people taking a low dose might have been different from those who

were taking a high dose. First, patients who were prescribed a low dose might have had a less severe disease or fewer lipid-associated risk factors that could easily returned to normal in a relatively shorter period after discharge and thus perceived lower risk of subsequent events. Second, the low dose use of statin in Chinese patients might be a reflection that a higher risk of adverse effects of statin among Asians compared to Western populations. Studies found that the incidence of adverse reactions in Chinese patients was significantly higher than that in European patients (29). The increase rate of consecutive alanine transaminase (> 3 times the upper limit of normal value) is 10 times higher than that of European patients when moderate dose of statin was used (29). However, whether Chinese patients should be given a lower dose of statin remains controversial and requires further robust evidence. Third, in Chinese culture many people believe chemical drugs have side effects so that they would stop using medications as soon as they think the disease has gone and their health is improved. All these factors alone or in combination could lead to the association between low dose prescription and the early discontinuation in these patients.

Atorvastatin use (versus other statins) was significantly associated with a higher likelihood of continuation, which is independent of other confounders. This finding indicates that Chinese are more likely to adherent to atorvastatin and is helpful to explain transition from simvastatin (60.2% in 2001) to atorvastatin (52.9% in 2011) as the most frequently used statin type (34). We do not know why Chinese are better adherent to atorvastatin. We hypothesize that the good adherence to atorvastatin might be due to the better tolerability, and its efficacy and safety. However, two studies with relatively small sample sizes in Chinese showed that no significant differences of MACE and declined renal function between atorvastatin and other statins (35, 36). On the other hand, a large observational study in the United States found 10 or 20 mg of atorvastatin use had lower CV event rates particularly in the first year of use than 20 or 40 mg of simvastatin (37) while another large observational study in the United Kingdom found that the risk of hepatotoxicity (small numbers of events observed) was increased in the first six months of atorvastatin compared to simvastatin treatment (38). It might also be a reflection of the strong marketing

activities that led to a better confidence in the brand among both doctors and patients, but we have no evidence to support this hypothesis and also it is beyond the scope of the current report. These findings suggest that further large-scale studies are needed to explore the differences of efficacy and safety between atorvastatin and other statins using equivalent dosage especially in Chinese patients.

Prior statin usage was significantly associated with a higher likelihood of continuation in our cohort. This finding was consistent with two previous studies(39, 40). Logically, prior statin usage indicates that the patient has good tolerance to statin, has the ability to pay, gives more attention to their own health, and has more knowledge on the importance of statin in both primary and secondary prevention of ACS, which may help decrease discontinuation of statin after discharge. Moreover, patients who used prior statin were more likely to have attained higher education level, had history of dyslipidemia (30% versus 11%), diabetes, heart failure, hypertension, and experienced MACE in hospital, which were observed to decrease the likelihood of discontinuation to statin in the present study.

Fifth, we found that not measuring LDL-c during the index admission increased the likelihood of discontinuation and higher LDL-c reduced the likelihood of discontinuation. This finding indicates that the cholesterol management is very important to improve adherence of statin. Cholesterol management is recommended by all guidelines on ACS (4, 41). However, in the present study, about 8.8% of patients did not get their LDL-c measured in hospital. Thus, giving attention to the cholesterol measurement during hospital admission with ACS and management may help to further improve adherence to statin.

Many strategies have been proposed that attempt to further reduce discontinuation and improve statin therapeutic effectiveness, including improving patient education on ACS and statin literacy, co-payment reduction, and behavior-modification interventions (42-44). In the present study, we confirmed that the clinical pathway intervention can reduce the risk of discontinuation of statin therapy. We also confirmed that enhancing health insurance would reduce the risk of discontinuation

of statin use. In addition, we found that some important patient characteristics such as low dose statin use, not having lipids measured during hospitalization, no prior use of statin, etc. were common in Chinese patients and these factors were associated with an additional and independent higher risk of discontinuation of statin use. It indicates that the education on knowledge of statin and cardiovascular secondary prevention should be further strengthened in both physicians and patients in China. Our results also suggest that high quality studies that could generate data for appropriate dose of statin in Chinese patients would help to reduce the statin discontinuation. It is indeed reassuring and pleasing that discontinuation of statins decreased significantly from 29.5% in 2007-2008 to 17.8% in 2010, given the increasing CVD burden in China. The clinical pathway intervention could partly explain the decreasing trends in discontinuation over time. However, the trend of the discontinuation with study year was still significant even after adjustment for the intervention and other potential confounders. While these results may relate to other confounders which were not controlled for, it is highly plausible that the publication, widespread promulgation, and endorsement of the first Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults in 2007-2008 (26, 45-52) might be the most important influential factor that was likely to have impact on the reduction in discontinuation of statin. This could occur through improving the knowledge level of statin use as secondary prevention of ACS among physicians and among patients who experienced ACS. Notably, although the withdrawal rate of statins has been greatly reduced, a considerable proportion of patients have stopped taking statins, and the evidence practice gap still exists especially in those without intervention or medical insurance. In one more recent publication in China, the 1-year discontinuation to statin therapy was still about 19.3% to 23.8% in real-world patients (53). Thus, our findings are still valuable for improving the statin adherence in China currently, and more efforts are needed to further improve the adherence to statin.

Limitations

Some limitations are worth highlighting. Firstly, patients who were lost to follow-up were significantly different in some characteristics (years of enrolment, subtypes of ACS, age, occupation, medical insurance, baseline LDL-c, comorbidities, in-hospital

MACE, in-hospital PCI/CABG, dose and type of statin, co-treatments of other medications, etc.) which might have led to over- or under-estimation of the associations with the related factors (Table S3 in file S1). Secondly, our study follow-up period was limited to one year; factors that are associated with the longer-term discontinuation should be explored in the future. Thirdly, the possible reporting bias might occur when patients reported their statin use to the medical staff - telling what they thought the interviewers would want to hear. This could potentially lead to mis-classification, it would have underestimated the associations of the discontinuation of statin use with its associated factors. Thus, any observed significant associations are likely to be stronger.

Conclusions

In summary, approaches such as implementing clinical guidelines and pathways, enhancing medical insurance coverage, strengthening health education in physicians and patients, and using statin in standard dosage in Chinese may help to improve the persistence of statin therapy in patients discharged after an acute coronary syndrome in China. Such measures should have major implication to the clinical and public health practices and ultimately will bring about the benefit of patients with reduced CVD burden.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Supplementary Material

Standardized questionnaire for collecting data on statin followed up (See Table S1 in file S1).

Comparative Dose Efficacy of Statins on lipids (See Table S2 in file S1).

Comparison of characteristics of patients with ACS between those followed-up and those lost to follow-up (See Table S3 in file S1).

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Statement on previous reports

We confirm that the contents of this manuscript have not been copyrighted or published previously, and that the manuscript is not under consideration for publication elsewhere, in whole or in part in any language, including publicly accessible web sites or e-print servers.

Trial Registration identifier in ANZCTR (Australian New Zealand Clinical Trials Registry): ACTRN12609000491268, http://www.anzctr.org.au/default.aspx .

Conflict of Interest Disclosures:

No disclosures were reported.

Statement of responsibility

The authors had full access to the data and took responsibility for its integrity. All authors have read and agreed to the written manuscript. Each author believes that the manuscript represents honest work.

Patient and Public Involvement statement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Authors' contributions

GX: concept development, data cleaning analysis, and interpretation, and writing of the manuscript; PKM: critical input in interpretation of results and writing of the manuscript; YS: critical input in interpretation of results and writing of the manuscript; XL: quality control on data collection and review of manuscript; TW: data analysis plan and review of manuscript; RG: review of manuscript and critical input in interpretation of results ; YW: concept development, critical input in interpretation of results, and review and approval of the manuscript.

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Tables

Table 1. Characteristics of patients with ACS in these patients followed-up (n=10337)

Characteristics	n	%
Year of enrolment		
2007	383	3.7
2008	3309	32.0
2009	4982	48.2
2010	1663	16.1
Subtype of ACS		
STEMI*	3918	37.9
NSTEMI*	1394	13.5
UA*	5025	48.6
Clinical pathway intervention	7908	76.5
Sex (Female)	3074	29.7
Age>=65	4934	47.7
Education>=high school	3786	36.6
Unemployed	5033	48.7
With medical insurance	8678	83.9
Current smoker	3192	30.9
History of disease		
Dyslipidemia	1359	13.1
Diabetes	2086	20.2
Hypertension	7184	69.5
Heart Failure	562	5.4
Stroke	944	9.1
In-hospital MACE	191	1.8
In-hospital PCI/CABG	5113	49.5
LDL-c level in hospital		
Not measuring	909	8.8
<160mg/dl	8850	85.6
>=160mg/dl	578	5.6
Prior statin use	1467	14.2
Dose of statin at discharge		
1-9 mg/d	1904	18.4
10-19 mg/d	3196	30.9
>=20 mg/d	5237	50.7
Type of statin at discharge		
Atorvastatin	5785	56.0
Simvastatin	2690	26.0
Rosuvastatin	502	4.9
Pravastatin	502	4.9
Fluvastatin	578	5.6
Other statin	280	2.7
Co-treatments at discharge		
Aspirin	10030	97.0
Clopidogrel	8404	81.3
β-blocker	8155	78.9
ACEI/ARB*	8096	78.3

* STEMI was ST-segment elevation myocardial infarction; NSTEMI was Non-ST-segment elevation myocardial infarction; UA was unstable angina; ACEI was Angiotensin converting enzyme inhibitor; ARB was Angiotensin Receptor Blocker

Figure legends

Figure 1. Flow chart of study participants in CPACS-2

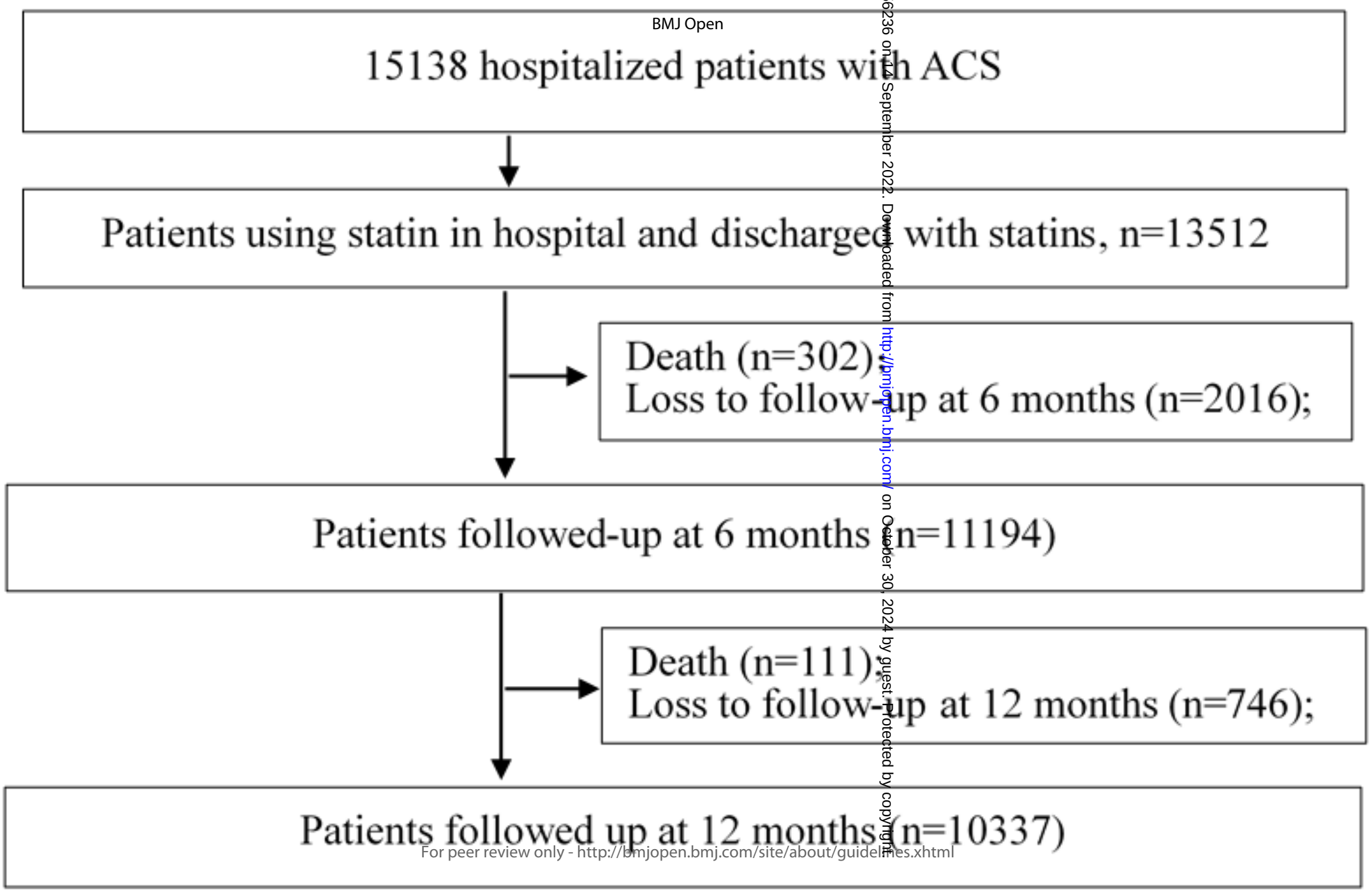
Figure 2. Univariate analysis of factors in association with the discontinuation to statin use in one year after discharge with Logistic regression models (n=10337)

*Combined 2007 and 2008 due to relatively small sample in 2007.

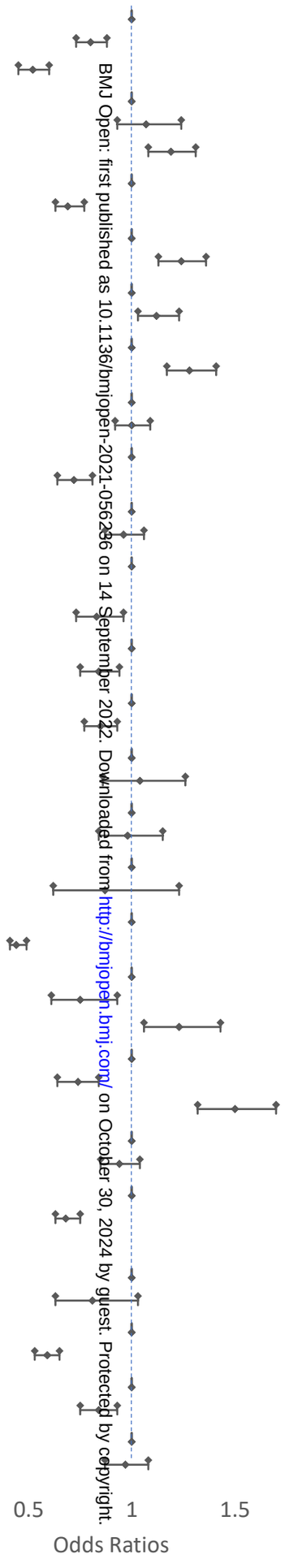
Figure 3. Odds Ratios of discontinuation to stain within one year in the full final multivariable Logistic regression model in analyzed patients of CPACS-2 (n=10337)

* p for trend<0.001

**p for trend=0.232;



Factors	Group	N	Discontinuation n	%	OR (95%CI)
Year of enrolment	2007-2008*	3692	1088	29.5	1
	2009	4982	1250	25.1	0.80(0.73-0.88)
	2010	1663	296	17.8	0.52(0.45-0.60)
Subtype of ACS	STEMI	3918	928	23.7	1
	NSTEMI	1394	348	25.0	1.07(0.93-1.24)
	UA	5025	1358	27.0	1.19(1.08-1.31)
Clinical pathway intervention	No	2429	754	31.0	1
	Yes	7908	1880	23.8	0.69(0.63-0.77)
Sex	Male	7263	1761	24.3	1
	Female	3074	873	28.4	1.24(1.13-1.36)
Age group	18-64 years	5403	1320	24.4	1
	≥65 years	4934	1314	26.3	1.12(1.03-1.23)
Education	≥high school	3786	853	22.5	1
	<high school	6551	1781	27.2	1.28(1.17-1.41)
Employment	No	5033	1282	25.5	1
	Yes	5304	1352	25.5	1.00(0.92-1.09)
Medical insurance	No	1659	514	31.0	1
	Yes	8678	2120	24.4	0.72(0.64-0.81)
Current smoker	No	7145	1838	25.7	1
	Yes	3192	796	24.9	0.96(0.87-1.06)
History of disease					
Dyslipidemia	No	8978	2327	25.9	1
	Yes	1359	307	22.6	0.83(0.73-0.96)
Diabetes	No	8251	2155	26.1	1
	Yes	2086	479	23.0	0.84(0.75-0.94)
Hypertension	No	3153	874	27.7	1
	Yes	7184	1760	24.5	0.85(0.77-0.93)
Heart Failure	No	9775	2487	25.4	1
	Yes	562	147	26.2	1.04(0.86-1.26)
Stroke	No	9393	2396	25.5	1
	Yes	944	238	25.2	0.98(0.84-1.15)
In-hospital MACE	No	10146	2590	25.5	1
	Yes	191	44	23.0	0.87(0.62-1.23)
In-hospital PCI/CABG	No	5224	1719	32.9	1
	Yes	5113	915	17.9	0.44(0.41-0.49)
LDL-c level in hospital	<160mg/dl	8850	2248	25.4	1
	>=160mg/dl	578	118	20.4	0.75(0.61-0.93)
	Not measuring	909	268	29.5	1.23(1.06-1.43)
Pre-hospital statin use	No	8870	2329	26.3	1
	Yes	1467	305	20.8	0.74(0.64-0.84)
Dose of statin at discharge	1-9 mg/d	1904	623	32.7	1.50(1.32-1.70)
	10-19 mg/d	3196	784	24.5	1
	>=20 mg/d	5237	1227	23.4	0.94(0.85-1.04)
Type of statin at discharge	Other statins	4552	1345	29.6	1
	Atorvastatin	5785	1289	22.3	0.68(0.63-0.75)
Co-treatments at discharge					
Aspirin	No	307	91	29.6	1
	Yes	10030	2543	25.4	0.81(0.63-1.03)
Clopidogrel	No	1933	664	34.4	1
	Yes	8404	1970	23.4	0.59(0.53-0.65)
β-blocker	No	2182	615	28.2	1
	Yes	8155	2019	24.8	0.84(0.75-0.93)
ACEI/ARB	No	2241	581	25.9	1
	Yes	8096	2053	25.4	0.97(0.87-1.08)



Factors	Adjusted OR (95%CI)
Year of enrolment*	
2007-2008	1.0
2009	0.91(0.82-1.02)
2010	0.60(0.51-0.70)
Subtype of ACS**	
STEMI	1.0
NSTEMI	1.03(0.89-1.20)
UA	1.10(0.99-1.22)
Clinical pathway intervention (Yes/No)	0.83(0.74-0.94)
Sex (Female/Male)	1.09(0.99-1.21)
Age (≥65 years/<65 years)	1.01(0.92-1.12)
Education (<high school/≥high school)	1.05(0.95-1.15)
Medical insurance (Yes/No)	0.75(0.67-0.85)
History of disease	
Dyslipidemia(Yes/No)	0.97(0.84-1.12)
Diabetes(Yes/No)	0.90(0.80-1.01)
Hypertension(Yes/No)	0.83(0.75-0.92)
In-hospital PCI/CABG(Yes/No)	0.47(0.43-0.53)
LDL-c level in hospital	
<160mg/dl	1
>=160mg/dl	0.70(0.57-0.87)
Not measuring	1.29(1.10-1.50)
Prior statin use (Yes/No)	0.73(0.63-0.84)
Statin type at discharge(Atorvastatin/Others)	0.78(0.70-0.88)
Statin dose at discharge	
1-9 mg/d	1.22(1.07-1.40)
10-19 mg/d	1
>=20 mg/d	1.27(1.13-1.43)
Co-treatments at discharge	
Clopidogrel (Yes/No)	0.94(0.83-1.06)
β-blocker (Yes/No)	0.93(0.84-1.04)

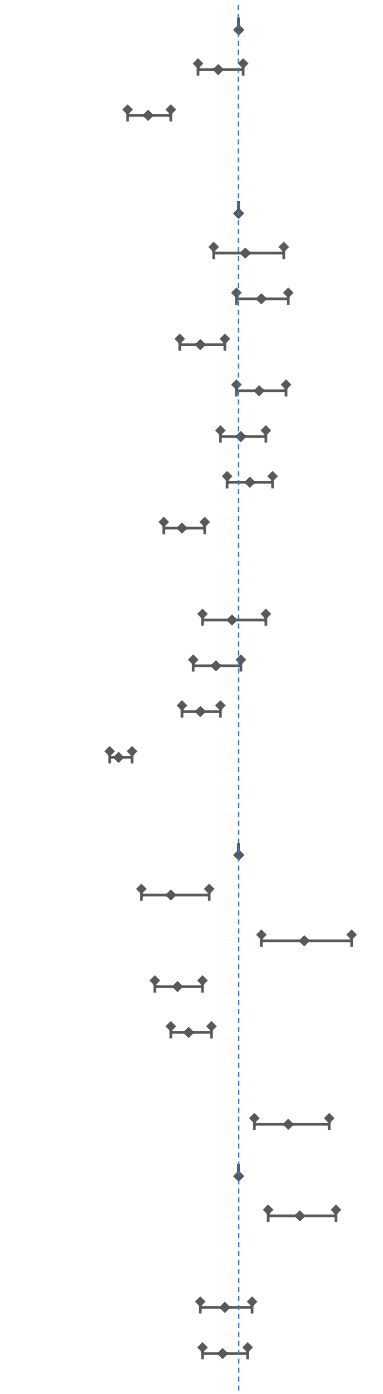


Table S1. Standardized questionnaire for collecting data on statin followed up

SECTION 3: CURRENT MEDCIATIONS (if patient alive)	
3.25	Statin ☐ Yes If yes, trade name is:_____ Dose _____mg/day ☐ No *If no, reason is: (select one)* ☐ Not prescribed ☐ Patient refused Reason is: (select one) ☐ Cost ☐ Other ☐ Intolerance ☐ Unknown ☐ Other(*specify)*_____

Table S2: Dosage of different type of statins with equivalent efficacy on lipid measures

Equivalent dosages of statins (mg)					**Efficacy in mean reduction of lipid measures (%)**			
Atorva-statin	**Simva-statin**	**Lova-statin**	**Prava-statin**	**Fluva-statin**	TC	LDL-C	HDL-C	TG
-	10	20	20	40	-22	-27	4~8	-(10~15)
10	20	40	40	80	-27	-34	4~8	-(10~20)
20	40	80			-32	-41	4~8	-(15~25)
40	80				-37	-48	4~8	-(20~30)
80					-42	-55	4~8	-(25~35)

Source: P Jones 1, S Kafonek, I Laurora, D Hunninghake. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study) .Am J Cardiol, 1998 Mar 1;81(5):582-7. doi: 10.1016/s0002-9149(97)00965-x. (Reference No. 24 in the main text).

Table S3. Comparison of characteristics of patients with ACS between those followed-up and those lost to follow-up

	Followed-up (n=10337)		Lost to follow-up (n=2742)		
Characteristics	n	%	n	%	P values
Year of enrolment					
2007	383	3.7	161	5.9	<0.001
2008	3309	32.0	874	31.9	
2009	4982	48.2	1170	42.7	
2010	1663	16.1	537	19.6	
Subtype of ACS					
STEMI*	3918	37.9	1284	46.8	<0.001
NSTEMI*	1394	13.5	409	14.9	
UA*	5025	48.6	1049	38.3	
Clinical pathway intervention	7908	76.5	2077	75.8	0.409
Sex (Female)	3074	29.7	791	28.9	0.364
Age>=65	4934	47.7	1381	50.4	0.014
Education>=high school	3786	36.6	1028	37.5	0.404
Unemployed	5033	48.7	1494	54.5	<0.001
With medical insurance	8678	83.9	2172	79.2	<0.001
Current smoker	3192	30.9	906	33.0	0.030
History of disease					
Dyslipidemia	1359	13.1	315	11.5	0.021
Diabetes	2086	20.2	529	19.3	0.302
Hypertension	7184	69.5	1798	65.6	<0.001
Heart Failure	562	5.4	160	5.8	0.417
Stroke	944	9.1	278	10.1	0.107
In-hospital MACE	191	1.8	283	10.3	<0.001
In-hospital PCI/CABG	5113	49.5	1471	53.7	<0.001
LDL-c level in hospital					
Not measuring	909	8.8	299	10.9	0.003
<160mg/dl	8850	85.6	2287	83.4	
>=160mg/dl	578	5.6	156	5.7	
Prior statin use	1467	14.2	381	13.9	0.692
Dose of statin at discharge					
1-9 mg/d	1904	18.4	672	24.5	<0.001
10-19 mg/d	3196	30.9	500	18.2	
>=20 mg/d	5237	50.7	1570	57.3	
Type of statin at discharge					
Atorvastatin	5785	56.0	1712	62.4	<0.001
Simvastatin	2690	26.0	509	18.6	
Rosuvastatin	502	4.9	40	1.5	
Pravastatin	502	4.9	163	5.9	

Fluvastatin	578	5.6	166	6.1	
Other statin	280	2.7	152	5.5	
Co-treatments at discharge					
Aspirin	10030	97.0	2645	96.5	0.127
Clopidogrel	8404	81.3	2416	88.1	<0.001
β-blocker	8155	78.9	2076	75.7	<0.001
ACEI/ARB*	8096	78.3	2161	78.8	0.579

* STEMI was ST-segment elevation myocardial infarction; NSTEMI was Non-ST-segment elevation myocardial infarction; UA was unstable angina; ACEI was Angiotensin converting enzyme inhibitor; ARB was Angiotensin Receptor Blocker

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a)Title and Line 6 of page 3; (b)Line 7-25 of page 3.	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1. Line 7-9 of page 3. 1.2. Line 7-9 of page 3. 1.3. Not applicable.
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	The first and second paragraph of the introduction section.		
Objectives	3	State specific objectives, including any prespecified hypotheses	The third paragraph of the introduction section.		
Methods					
Study Design	4	Present key elements of study design early in the paper	The first line of the study design section.		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	The first paragraph of the methods section.		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	(a) The second paragraph of the methods section. (b) Not applicable.	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1. The second paragraph of the methods section. 6.2. Not applicable. 6.3. Not applicable.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	The data analyses of the methods section.	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	The data analyses of the methods section.
Data sources/ measurement	8	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	Page 6-7 in the methods section.		

Bias	9	Describe any efforts to address potential sources of bias	To control information bias in the first paragraph of data collection section.		
Study size	10	Explain how the study size was arrived at	The first paragraph of design section.		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	The data analyses of the methods section.		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Statistical methods in page 8.		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	The first paragraph of study design.

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	The second sentence of patient section in page 6.
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	The first paragraph of page 7.
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	a & b. First paragraph of results section in page 8. c. Figure 1.	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	13.1. First paragraph of results section in page 8 and Figure 1.
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	The first paragraph of the result section.		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time	The second paragraph of the result section.		

		Case-control study - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Figure 2 & 3.		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	None.		
Discussion					
Key results	18	Summarise key results with reference to study objectives	First paragraph of the discussion section.		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	The last paragraph of the discussion section in page 13.	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	The last paragraph of the discussion section .

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Paragraph 2-10 of the discussion section.		
Generalisability	21	Discuss the generalisability (external validity) of the study results	The first paragraph of page 14.		
Other Information					
Funding	22	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	Source(s) of support of page 15.		
Accessibility of protocol, raw data, and programming code		The first paragraph of the design section in page 5.		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	The first paragraph of the design section in page 5.

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Associated factors for discontinuation of statin use one year after discharge in patients with acute coronary syndrome in China

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Title

Associated factors for discontinuation of statin use one year after discharge in patients with acute coronary syndrome in China

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Abstract

Objectives To determine the associated factors for discontinuation of statin use one year after discharge in patients who survived from acute coronary syndrome (ACS) in China.

Settings 75 hospitals across China.

Design A cohort follow up study

Participants The study included 10,337 ACS patients hospitalized in 2007-2010 and discharged with statins from 75 hospitals in China in the CPACS-2 study, who were followed- up at 6- and 12- months post-discharge.

Primary outcome measures The primary outcome was the discontinuation of statin use defined as not in current use of statin at either 6 or 12 month follow up.

Results: Multivariable logistic regression model showed, patients who did not have cholesterol measurement (adjusted OR=1.29, 95%CI: 1.10-1.50) and patients with either higher (1.27; 1.13-1.43) or lower dose of statin (1.22; 1.07-1.40), compared with those with standard dose, were more likely to discontinue the use of statin. In addition, patients on the CPACS-2 intervention pathway (adjusted OR=0.83; 95%CI: 0.74-0.94), patients with medical insurance (0.75; 0.67-0.85), history of hypertension (0.83; 0.75-0.92), high LDL-c (0.70; 0.57-0.87) at the baseline, prior statin use (0.73; 0.63-0.84), use of atorvastatin (0.78; 0.70-0.88) and those who underwent PCI or CABG during hospitalization (0.47; 0.43-0.53) were less likely to discontinue statin use. The one-year statin discontinuation rate decreased from 29.5% in 2007-2008 to 17.8% in 2010 (adjusted OR = 0.60; 95%CI: 0.51 to 0.70).

Conclusion: Implementing clinical pathway, enhancing medical insurance coverage, strengthening health education in both physicians and patients, using statin at standard dosage may help improve the adherence to statin use after discharge in Chinese patients with ACS.

Key words: Acute coronary syndrome, Discontinuation to Statin Use, Trend, Associated Factors

Strengths and limitations of this study

With a large cohort with more than 10,000 patients with ACS from 75 hospitals across different areas of China, novel factors associated with the risk of discontinuation of statin use after discharge were identified including two negative associates: clinical pathway intervention and higher baseline LDL-c level, and two positive associates: non-standard dose use and not having cholesterol measured.

Data used in the present study was from CPACS-2, which was a well-designed and conducted under strict quality control.

There were about 21% study participants lost to follow-up, which might have led to over- or under-estimation of the associations of the discontinuation of statin after ACS.

INTRODUCTION

Statins therapy has been recommended as a core long-term secondary preventive treatment for patients with acute coronary syndrome (ACS) by several guidelines (1-5). Despite strong evidence from basic and clinical studies (6-8) and recommendation by the guidelines, about 10%-30% of patients with ACS discontinued their statin treatment usually within four years with highest attrition in the first year in western countries (9-12). It has been shown that discontinuation of statin therapy increases the risk of major adverse cardiovascular events (MACE) in patients with ACS after discharge in several countries including UK (13, 14).

Several studies in Europe and America showed that sex, intervention (nurse-led annual follow-up and medical titration by telephone, weekly pharmacist-led telephone contact for 12 weeks, a physician education protocol to implement statin in all patients admitted for CABG), generic versus branded drugs, insurance and prescription cost assistance were the main factors influencing the adherence to statin therapy among patients discharged with ACS (9, 15-19). A big European survey showed that statin therapy was discontinued in 11.6% of patients with coronary heart disease (CHD)(20). However, to date, few data exist on the factors that influence statin discontinuation in ACS patients in China.

In this study, we analyzed data from the Clinical Pathways for Acute Coronary Syndromes in China Study-2 (CPACS-2) to understand the trend from 2007 to 2010 among Chinese patients with ACS in discontinuation of statin use in the first year after discharge and to explore the factors that drove the trend and factors that were associated with discontinuation.

METHODS

Study design

The present study analyzed the one-year follow up data of patients with ACS who were discharged with statin from 75 hospitals across China in the Clinical Pathways for Acute Coronary Syndromes— Phase 2 (CPACS-2) study. The design, methodology and main results of CPACS-2 study have been previously reported in detail (21-24). In brief, the

CPACS-2 study was an implementation trial with a cluster-randomized design to evaluate the effectiveness of implementing clinical pathways for ACS management in 75 hospitals in China from 2007 to 2010 (21).

Patients

CPACS-2 recruited consecutive ACS patients admitted to the participating hospitals and followed up surviving patients till one year after discharge. Of 15,138 patients recruited in CPACS-2, 1626 patients were discharged without statins, 413 patients died during the follow up and 2,762 lost to follow up and therefore these patients were excluded from analysis. The remaining 10,337 patients who were discharge with statin and completed follow up were included (**see Figure 1**).

Ethical approval

The CPACS-2 study was approved by the ethics committee of Fuwai Hospital and Human Research Ethics Committees of University of Sydney in Australia (number: 09-2007/10276) (21-24). Informed consent was obtained from all participants. Confidentiality of subjects were ensured by anonymizing participants' names, initials or hospital numbers.

Data collection

A trained clinical staff (independent to the treating physicians) in each hospital reviewed medical records and administered a structured questionnaire and collected demographic and clinical data including statin use, history of disease, clinical characteristics, and prior and in-hospital treatments. Data on statin use at 6 and 12 months after the hospital discharge were collected through interviews by either telephone calls (88%) or face-to-face clinic visit (12%). The standardized questionnaire for collecting data on statin use was shown in Table S1 in additional file S1.

For our analysis, the dosage of different statins was converted to the equivalent dosage of atorvastatin (25) (Additional file S1: **Table S2** (25)).

Data analyses

Exposures included for analysis

Exposures included the CPACS-2 intervention, year of enrolment, age, sex, education, employment, medical insurance, smoking status, subtype of ACS, co-existing cardiovascular diseases or risk, in-hospital major adverse cardiovascular events (MACE), in-hospital PCI/CABG, LDL-c level at enrolment, prior statin use, dose & type of statin at discharge, co-treatments at discharge.

Education level was classified into 2 categories: lower than high school and high school and above. Prior statin use was defined as any statin use in most days one month before the development of ACS.

According to the guideline in China(26), we divided into 3 groups of statin dose: lower (<10 mg atorvastatin or equivalent) (18.4%), standard dose (10-19 mg atorvastatin) (30.9%), and high dose of statin (>=20 mg atorvastatin or equivalent) (50.7%).

The CPACS-2 intervention included three major generic clinical pathways (risk stratification, management of STEMI, and management of non–ST-segment–elevation myocardial infarction/unstable angina pectoris) that were developed in conjunction with the Chinese Society of Cardiology based on the relevant American Heart Association and American College of Cardiology guidelines (1, 2). For more details, please refer to the previous publications (21, 24).

Main outcome for analysis

The discontinuation of statin use one year after discharge was the primary outcome, which was defined as not in current use of statin at either 6 or 12 month follow up. The question ”Is the patient currently taking statins?” was asked to the research physician at the both 6- and 12-month follow-ups. “Yes” response to the question was defined as the current use. We do not have more data to define the discontinuation more specifically.

Statistical methods

SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all analyses. Univariate

and multivariable logistic regression models were used to analyse the association of the discontinuation of statin with potential explanatory factors. Our primary analyses included only participants who completed both 6 and 12 months follow ups. Since the number of patients in 2007 was small, these patients were grouped into those recruited in 2008 in our main analyses. Two-sided P value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Among all 15,138 patients recruited in CPACS-2, 13512 were prescribed statin at discharge. Among them, 433 died and 2742 (21% of those who survived) were lost to follow up. Finally, 10337 patients with complete data on statin therapy and related factors were analysed (**Figure 1**). The baseline characteristics are shown in Table 1. Briefly, a total of 10,337 patients (men=70.3%) with ACS (mean age (SD) 63.2±11.6 years) were included. Of them, 383 (3.7%), 3309(32.0%), 4982 (48.2%), and 1663 (16.1%) were enrolled in each year from 2007 to 2010 respectively. A total of 7908 (76.5%) patients were enrolled after the hospitals had implemented the clinical pathway intervention (Table 1).

Trend of discontinuation to statin use from 2007 to 2010

Among our study participants, 25.5% (n=2634) discontinued statin in one year after discharge. The discontinuation rate decreased from 29.5% in 2007-2008 to 17.8% in 2010 (Figure 2). The multiple logistic regression model confirmed that the deceasing trend in study years was significant after adjustment for co-variables including the CPACS-2 intervention. The forest plots are shown in Figure 3.

Factors associated with discontinuation to statin use

In univariate analyses, discontinuation rate was significantly lower in patients who received CPACS-2 intervention than those who did not receive the pathway, patients with medical insurance than those without, patients with history of dyslipidemia, diabetes, and hypertension, prior statin use, higher LDL-c, those who required intervention procedures such as PCI/CABG during hospitalization, those who were

given either standard or high dose than in patients given low dose of statin, in those who were given atorvastatin than those who were given other statins, and lower in patients with than without co-treatments of clopidogrel and β-blocker at discharge. On the other hand, discontinuation rate was significantly higher in women, older patients, patients with lower education level, patients with relatively milder form of ACS subtype (unstable angina), patients whose LDL-c was not measured during hospitalisation (all $p<0.05$). The forest plots are shown in Figure 2.

Multiple logistic regression models confirmed that the trend of discontinuation with year of enrollment was significant and the patients with CPACS-2 intervention were less likely to discontinue use of statins. In addition, patients with medical insurance, history of hypertension, higher LDL-c level, prior statin use, taking atorvastatin, and those who underwent PCI or CABG during hospitalization were less likely to discontinue statin, while those on either higher or lower dose of statin (versus standard dose), and those whose LDL-c was not measured during the hospital admission were more likely to discontinue the use of statin **(Figure 3).** Other associated factors that were significant in univariate analysis became no longer significant in multivariable model; these include age, sex, history of dyslipidemia and diabetes, and co-treatments of clopidogrel and β-blocker at discharge. The forest plots are shown in Figure 3.

DISCUSSION

Using data from a large, prospective cohort of ACS patients in China, we found that a number of factors were independently associated with the discontinuation of statin use in one year after discharge. Our findings bear important clinical significance, demonstrating that the discontinuation of statin use has multiple causes and thus multiple approaches are required to address this important issue.

First, our findings demonstrated that the implementing of CPACS-2 intervention was associated with a higher adherence of statin use, which was independent of the time trend and other covariates. It indicates that the clinical pathways for ACS management,

although implemented within hospital, has effect in reducing the discontinuation of statin use after discharge. This finding is newly reported but expected. Our previous study on the basis of the CPACS-2 randomized comparison data showed that the intervention had significantly increased the use of evidence-based secondary prevention medications at discharge (21, 22). We recommend this ACS clinical pathway to be adopted nationally in China and perhaps in other countries with similar circumstances as in China.

Second, similar to the findings from other studies on medication adherence (27), we found that patients who had medical insurance were significantly more likely to continue the use of statin after discharge, indicating that improving medical insurance coverage in the population should help to reduce the number of patients who discontinue the use of statin. In China, medical insurance has not yet covered for the whole population and certainly not for all services. Therefore, having medical insurance might have been an important factor and hence it was associated with the adherence to statin use in our study.

Third, as expected, we found that ACS patients who received PCI/CABG treatment during the hospitalization were more likely to continue statin use. Similar pattern was also observed in other studies (9, 20). The explanations may include that all major clinical guidelines emphasize the long-term use of statin after PCI/CABG for prevention from restenosis (1, 28). In this study, patients who received PCI/CABG had AMI that is more severe than unstable angina pectoris. Thus, patients with PCI/CABG might have been encouraged by both doctors and thus they were more likely to adhere to the physicians' advices (risk marker effect). Probably for the same reason, patients with higher LDL-c level ($\geqslant$160 mg/dL), history of dyslipidemia, diabetes, and hypertension were less likely to discontinue the use of statin. The association remained significant only for higher LDL-c and hypertension in multivariable analysis probably due to the co-linearity among these factors.

Fourth, it is interesting that both low and high dosages, compared with standard dosage, of statin at discharge were more likely to discontinue, which is independent

of other observed predictors of statin discontinuation. Use of high-dose statin have been shown to be associated with adverse reactions (29, 30). Thus, side effects, such as muscle complaints due to myopathy (31), and rhabdomyolysis (32, 33), might have decreased the adherence to the statin therapy in our study. However, the drivers for discontinuation in people taking a low dose might have been different from those who were taking a high dose. First, patients who were prescribed a low dose might have had a less severe disease or fewer lipid-associated risk factors that could easily returned to normal in a relatively shorter period after discharge and thus perceived lower risk of subsequent events. Second, the low dose use of statin in Chinese patients might be a reflection that a higher risk of adverse effects of statin among Asians compared to Western populations. Studies found that the incidence of adverse reactions in Chinese patients was significantly higher than that in European patients (29). The increase rate of consecutive alanine transaminase (> 3 times the upper limit of normal value) is 10 times higher than that of European patients when moderate dose of statin was used (29). However, whether Chinese patients should be given a lower dose of statin remains controversial and requires further robust evidence. Third, in Chinese culture many people believe chemical drugs have side effects so that they would stop using medications as soon as they think the disease has gone and their health is improved. All these factors alone or in combination could lead to the association between low dose prescription and the early discontinuation in these patients.

Atorvastatin use (versus other statins) was significantly associated with a higher likelihood of continuation, which is independent of other confounders. This finding indicates that Chinese are more likely to adherent to atorvastatin and is helpful to explain transition from simvastatin (60.2% in 2001) to atorvastatin (52.9% in 2011) as the most frequently used statin type (34). We do not know why Chinese are better adherent to atorvastatin. We hypothesize that the good adherence to atorvastatin might be due to the better tolerability, and its efficacy and safety. However, two studies with relatively small sample sizes in Chinese showed that no significant differences of MACE and declined renal function between atorvastatin and other statins (35, 36). On the other hand, a large observational study in the United States

found 10 or 20 mg of atorvastatin use had lower CV event rates particularly in the first year of use than 20 or 40 mg of simvastatin (37) while another large observational study in the United Kingdom found that the risk of hepatotoxicity (small numbers of events observed) was increased in the first six months of atorvastatin compared to simvastatin treatment (38). It might also be a reflection of the strong marketing activities that led to a better confidence in the brand among both doctors and patients, but we have no evidence to support this hypothesis and also it is beyond the scope of the current report. These findings suggest that further large-scale studies are needed to explore the differences of efficacy and safety between atorvastatin and other statins using equivalent dosage especially in Chinese patients.

Prior statin usage was significantly associated with a higher likelihood of continuation in our cohort. This finding was consistent with two previous studies(39, 40). Logically, prior statin usage indicates that the patient has good tolerance to statin, has the ability to pay, gives more attention to their own health, and has more knowledge on the importance of statin in both primary and secondary prevention of ACS, which may help decrease discontinuation of statin after discharge. Moreover, patients who used prior statin were more likely to have attained higher education level, had history of dyslipidemia (30% versus 11%), diabetes, heart failure, hypertension, and experienced MACE in hospital, which were observed to decrease the likelihood of discontinuation of statin in the present study.

Fifth, we found that not measuring LDL-c during the index admission increased the likelihood of discontinuation and higher LDL-c reduced the likelihood of discontinuation. This finding indicates that the cholesterol management is very important to improve adherence of statin. Cholesterol management is recommended by all guidelines on ACS (4, 41). However, in the present study, about 8.8% of patients did not get their LDL-c measured in hospital. Thus, giving attention to the cholesterol measurement during hospital admission with ACS and management may help to further improve adherence to statin.

Many strategies have been proposed that attempt to further reduce discontinuation

and improve statin therapeutic effectiveness, including improving patient education on ACS and statin literacy, co-payment reduction, and behavior-modification interventions (42-44). In the present study, we confirmed that the clinical pathway intervention can reduce the risk of discontinuation of statin therapy. We also confirmed that enhancing health insurance would reduce the risk of discontinuation of statin use. In addition, we found that some important patient characteristics such as low dose statin use, not having lipids measured during hospitalization, no prior use of statin, etc. were common in Chinese patients and these factors were associated with an additional and independent higher risk of discontinuation of statin use. It indicates that the education on knowledge of statin and cardiovascular secondary prevention should be further strengthened in both physicians and patients in China. Our results also suggest that high quality studies that could generate data for appropriate dose of statin in Chinese patients would help to reduce the statin discontinuation. It is indeed reassuring and pleasing that discontinuation of statins decreased significantly from 29.5% in 2007-2008 to 17.8% in 2010, given the increasing CVD burden in China. The clinical pathway intervention could partly explain the decreasing trends in discontinuation over time. However, the trend of the discontinuation with study year was still significant even after adjustment for the intervention and other potential confounders. While these results may relate to other confounders which were not controlled for, it is highly plausible that the publication, widespread promulgation, and endorsement of the first Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults in 2007-2008 (26, 45-52) might be the most important influential factor that was likely to have impact on the reduction in discontinuation of statin. This could occur through improving the knowledge level of statin use as secondary prevention of ACS among physicians and among patients who experienced ACS. Notably, although the withdrawal rate of statins has been greatly reduced, a considerable proportion of patients have stopped taking statins, and the evidence practice gap still exists especially in those without intervention or medical insurance. In one more recent publication in China, the 1-year discontinuation of statin therapy was still about 19.3% to 23.8% in real-world patients (53). Thus, our findings are still valuable for improving the statin adherence in China currently, and more efforts are needed to further improve the adherence to statin.

Limitations

Some limitations are worth highlighting. Firstly, patients who were lost to follow-up were significantly different in some characteristics (years of enrolment, subtypes of ACS, age, occupation, medical insurance, baseline LDL-c, comorbidities, in-hospital MACE, in-hospital PCI/CABG, dose and type of statin, co-treatments of other medications, etc.) which might have led to over- or under-estimation of the associations with the related factors (Table S3 in file S1). Secondly, our study follow-up period was limited to one year; factors that are associated with the longer-term discontinuation should be explored in the future. Thirdly, the possible reporting bias might occur when patients reported their statin use to the medical staff - telling what they thought the interviewers would want to hear. If misclassification of statin exposure status was differential (e.g. different in one group vs another), this could result in underestimation or overestimation of an association of interest, depending on which group was more likely to have misreported their exposure status.

Conclusions

In summary, approaches such as implementing clinical guidelines and pathways, enhancing medical insurance coverage, strengthening health education in physicians and patients, and using statin in standard dosage in Chinese may help to improve the persistence of statin therapy in patients discharged after an acute coronary syndrome in China. Such measures should have major implication to the clinical and public health practices and ultimately will bring about the benefit of patients with reduced CVD burden.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Supplementary Material

Standardized questionnaire for collecting data on statin followed up (See Table S1 in file S1).

Comparative Dose Efficacy of Statins on lipids (See Table S2 in file S1).

Comparison of characteristics of patients with ACS between those followed-up and those lost to follow-up (See Table S3 in file S1).

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Statement on previous reports

We confirm that the contents of this manuscript have not been copyrighted or published previously, and that the manuscript is not under consideration for publication elsewhere, in whole or in part in any language, including publicly accessible web sites or e-print servers.

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Conflict of Interest Disclosures:

No disclosures were reported.

Statement of responsibility

The authors had full access to the data and took responsibility for its integrity. All authors have read and agreed to the written manuscript. Each author believes that the manuscript represents honest work.

Patient and Public Involvement statement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Authors' contributions

GX: concept development, data cleaning analysis, and interpretation, and writing of the manuscript; PKM: critical input in interpretation of results and writing of the manuscript; YS: critical input in interpretation of results and writing of the manuscript; XL: quality control on data collection and review of manuscript; TW: data analysis plan and review of manuscript; RG: review of manuscript and critical input in interpretation of results ; YW: concept development, critical input in interpretation of results, and review and approval of the manuscript.

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Tables

Table 1. Characteristics of patients with ACS in these patients followed-up (n=10337)

Characteristics	n	%
Year of enrolment		
2007	383	3.7
2008	3309	32.0
2009	4982	48.2
2010	1663	16.1
Subtype of ACS		
STEMI*	3918	37.9
NSTEMI*	1394	13.5
UA*	5025	48.6
Clinical pathway intervention	7908	76.5
Sex (Female)	3074	29.7
Age>=65	4934	47.7
Education>=high school	3786	36.6
Unemployed	5033	48.7
With medical insurance	8678	83.9
Current smoker	3192	30.9
History of disease		
Dyslipidemia	1359	13.1
Diabetes	2086	20.2
Hypertension	7184	69.5
Heart Failure	562	5.4
Stroke	944	9.1
In-hospital MACE	191	1.8
In-hospital PCI/CABG	5113	49.5
LDL-c level in hospital		
Not measuring	909	8.8
<160mg/dl	8850	85.6
>=160mg/dl	578	5.6
Prior statin use	1467	14.2
Dose of statin at discharge		
1-9 mg/d	1904	18.4
10-19 mg/d	3196	30.9
>=20 mg/d	5237	50.7
Type of statin at discharge		
Atorvastatin	5785	56.0
Simvastatin	2690	26.0
Rosuvastatin	502	4.9
Pravastatin	502	4.9
Fluvastatin	578	5.6
Other statin	280	2.7
Co-treatments at discharge		
Aspirin	10030	97.0
Clopidogrel	8404	81.3
β-blocker	8155	78.9
ACEI/ARB*	8096	78.3

* STEMI was ST-segment elevation myocardial infarction; NSTEMI was Non-ST-segment elevation myocardial infarction; UA was unstable angina; ACEI was Angiotensin converting enzyme inhibitor; ARB was Angiotensin Receptor Blocker

Figure legends

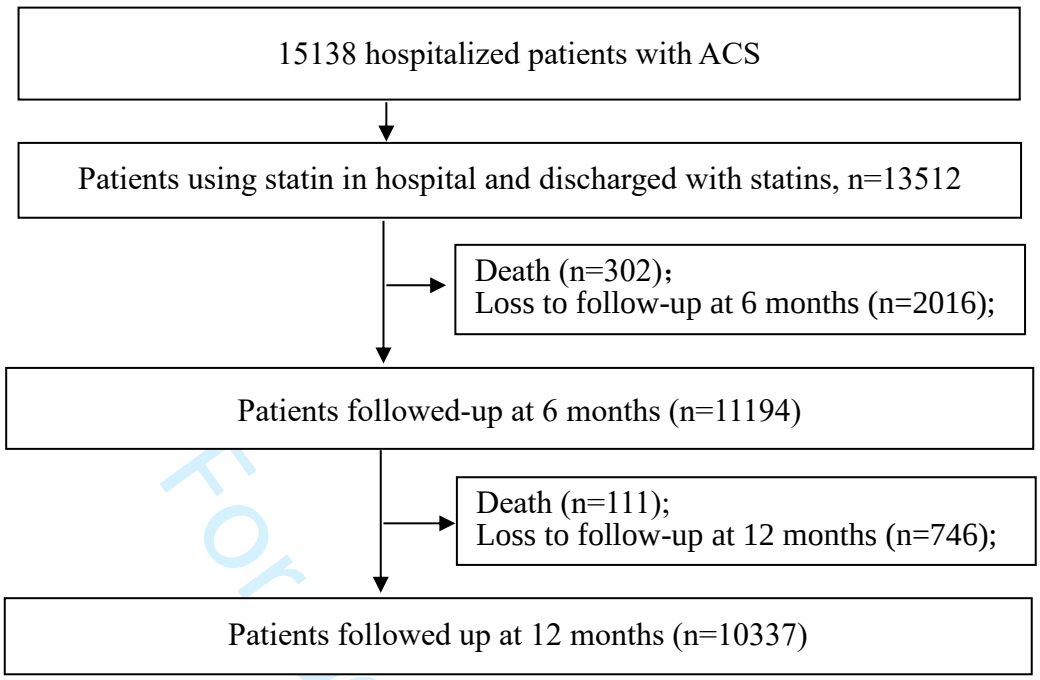
Figure 1. Flow chart of study participants in CPACS-2

Figure 2. Univariate analysis of factors in association with the discontinuation of statin use in one year after discharge with Logistic regression models (n=10337)

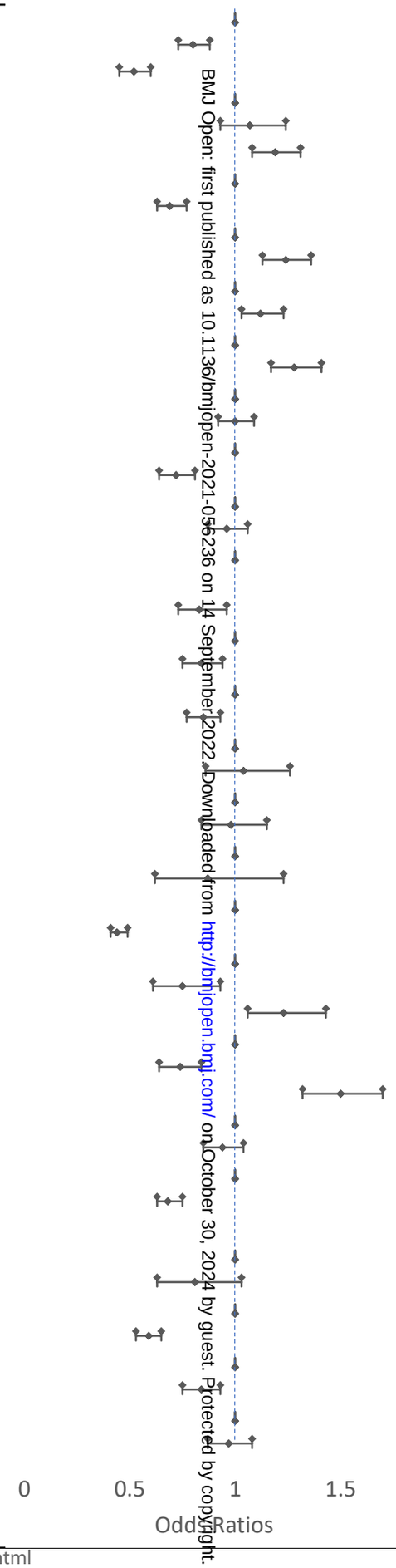
*Combined 2007 and 2008 due to relatively small sample in 2007.

Figure 3. Odds Ratios of discontinuation of stain within one year in the full final multivariable Logistic regression model in analyzed patients of CPACS-2 (n=10337)

* p for trend<0.001; **p for trend=0.232.



Factors	Group	N	Discontinuation n	%	OR（95%CI）
Year of enrolment	2007-2008*	3692	1088	29.5	1
	2009	4982	1250	25.1	0.80(0.73-0.88)
	2010	1663	296	17.8	0.52(0.45-0.60)
Subtype of ACS	STEMI	3918	928	23.7	1
	NSTEMI	1394	348	25.0	1.07(0.93-1.24)
	UA	5025	1358	27.0	1.19(1.08-1.31)
Clinical pathway intervention	No	2429	754	31.0	1
	Yes	7908	1880	23.8	0.69(0.63-0.77)
Sex	Male	7263	1761	24.3	1
	Female	3074	873	28.4	1.24(1.13-1.36)
Age group	18-64 years	5403	1320	24.4	1
	≥65 years	4934	1314	26.3	1.12(1.03-1.23)
Education	≥high school	3786	853	22.5	1
	<high school	6551	1781	27.2	1.28(1.17-1.41)
Employment	No	5033	1282	25.5	1
	Yes	5304	1352	25.5	1.00(0.92-1.09)
Medical insurance	No	1659	514	31.0	1
	Yes	8678	2120	24.4	0.72(0.64-0.81)
Current smoker	No	7145	1838	25.7	1
	Yes	3192	796	24.9	0.96(0.87-1.06)
History of disease					
Dyslipidemia	No	8978	2327	25.9	1
	Yes	1359	307	22.6	0.83(0.73-0.96)
Diabetes	No	8251	2155	26.1	1
	Yes	2086	479	23.0	0.84(0.75-0.94)
Hypertension	No	3153	874	27.7	1
	Yes	7184	1760	24.5	0.85(0.77-0.93)
Heart Failure	No	9775	2487	25.4	1
	Yes	562	147	26.2	1.04(0.86-1.26)
Stroke	No	9393	2396	25.5	1
	Yes	944	238	25.2	0.98(0.84-1.15)
In-hospital MACE	No	10146	2590	25.5	1
	Yes	191	44	23.0	0.87(0.62-1.23)
In-hospital PCI/CABG	No	5224	1719	32.9	1
	Yes	5113	915	17.9	0.44(0.41-0.49)
LDL-c level in hospital	<160mg/dl	8850	2248	25.4	1
	>=160mg/dl	578	118	20.4	0.75(0.61-0.93)
	Not measuring	909	268	29.5	1.23(1.06-1.43)
Pre-hospital statin use	No	8870	2329	26.3	1
	Yes	1467	305	20.8	0.74(0.64-0.84)
Dose of statin at discharge	1-9 mg/d	1904	623	32.7	1.50(1.32-1.70)
	10-19 mg/d	3196	784	24.5	1
	>=20 mg/d	5237	1227	23.4	0.94(0.85-1.04)
Type of statin at discharge	Other statins	4552	1345	29.6	1
	Atorvastatin	5785	1289	22.3	0.68(0.63-0.75)
Co-treatments at discharge					
Aspirin	No	307	91	29.6	1
	Yes	10030	2543	25.4	0.81(0.63-1.03)
Clopidogrel	No	1933	664	34.4	1
	Yes	8404	1970	23.4	0.59(0.53-0.65)
β-blocker	No	2182	615	28.2	1
	Yes	8155	2019	24.8	0.84(0.75-0.93)
ACEI/ARB	No	2241	581	25.9	1
	Yes	8096	2053	25.4	0.97(0.87-1.08)



Factors	Adjusted OR (95%CI)
Year of enrolment*	
2007-2008	1.0
2009	0.91(0.82-1.02)
2010	0.60(0.51-0.70)
Subtype of ACS**	
STEMI	1.0
NSTEMI	1.03(0.89-1.20)
UA	1.10(0.99-1.22)
Clinical pathway intervention (Yes/No)	0.83(0.74-0.94)
Sex (Female/Male)	1.09(0.99-1.21)
Age (≥65 years/<65 years)	1.01(0.92-1.12)
Education (<high school/≥high school)	1.05(0.95-1.15)
Medical insurance (Yes/No)	0.75(0.67-0.85)
History of disease	
Dyslipidemia(Yes/No)	0.97(0.84-1.12)
Diabetes(Yes/No)	0.90(0.80-1.01)
Hypertension(Yes/No)	0.83(0.75-0.92)
In-hospital PCI/CABG(Yes/No)	0.47(0.43-0.53)
LDL-c level in hospital	
<160mg/dl	1
>=160mg/dl	0.70(0.57-0.87)
Not measuring	1.29(1.10-1.50)
Prior statin use (Yes/No)	0.73(0.63-0.84)
Statin type at discharge(Atorvastatin/Others)	0.78(0.70-0.88)
Statin dose at discharge	
1-9 mg/d	1.22(1.07-1.40)
10-19 mg/d	1
>=20 mg/d	1.27(1.13-1.43)
Co-treatments at discharge	
Clopidogrel (Yes/No)	0.94(0.83-1.06)
β-blocker (Yes/No)	0.93(0.84-1.04)

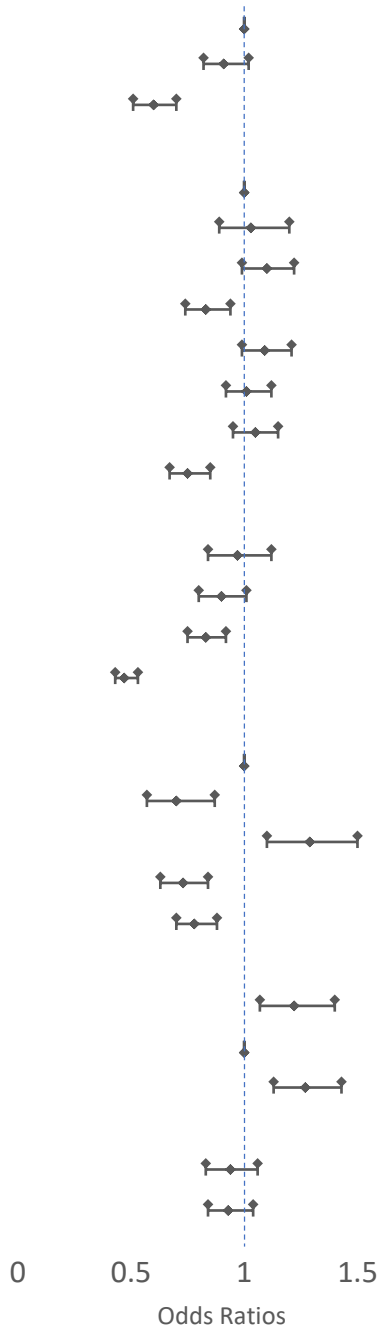


Table S1. Standardized questionnaire for collecting data on statin followed up

SECTION 3: CURRENT MEDCIATIONS (if patient alive)	
3.25	Statin ☐ Yes If yes, trade name is:_____ Dose _____mg/day ☐ No *If no, reason is: (select one)* ☐ Not prescribed ☐ Patient refused Reason is: (select one) ☐ Cost ☐ Other ☐ Intolerance ☐ Unknown ☐ Other(*specify)*_____

Table S2: Dosage of different type of statins with equivalent efficacy on lipid measures

Equivalent dosages of statins (mg)					**Efficacy in mean reduction of lipid measures (%)**			
Atorva-statin	**Simva-statin**	**Lova-statin**	**Prava-statin**	**Fluva-statin**	TC	LDL-C	HDL-C	TG
-	10	20	20	40	-22	-27	4~8	-(10~15)
10	20	40	40	80	-27	-34	4~8	-(10~20)
20	40	80			-32	-41	4~8	-(15~25)
40	80				-37	-48	4~8	-(20~30)
80					-42	-55	4~8	-(25~35)

Source: P Jones 1, S Kafonek, I Laurora, D Hunninghake. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study) .Am J Cardiol, 1998 Mar 1;81(5):582-7. doi: 10.1016/s0002-9149(97)00965-x. (Reference No. 24 in the main text).

Table S3. Comparison of characteristics of patients with ACS between those followed-up and those lost to follow-up

	Followed-up (n=10337)		Lost to follow-up (n=2742)		
Characteristics	n	%	n	%	P values
Year of enrolment					
2007	383	3.7	161	5.9	<0.001
2008	3309	32.0	874	31.9	
2009	4982	48.2	1170	42.7	
2010	1663	16.1	537	19.6	
Subtype of ACS					
STEMI*	3918	37.9	1284	46.8	<0.001
NSTEMI*	1394	13.5	409	14.9	
UA*	5025	48.6	1049	38.3	
Clinical pathway intervention	7908	76.5	2077	75.8	0.409
Sex (Female)	3074	29.7	791	28.9	0.364
Age>=65	4934	47.7	1381	50.4	0.014
Education>=high school	3786	36.6	1028	37.5	0.404
Unemployed	5033	48.7	1494	54.5	<0.001
With medical insurance	8678	83.9	2172	79.2	<0.001
Current smoker	3192	30.9	906	33.0	0.030
History of disease					
Dyslipidemia	1359	13.1	315	11.5	0.021
Diabetes	2086	20.2	529	19.3	0.302
Hypertension	7184	69.5	1798	65.6	<0.001
Heart Failure	562	5.4	160	5.8	0.417
Stroke	944	9.1	278	10.1	0.107
In-hospital MACE	191	1.8	283	10.3	<0.001
In-hospital PCI/CABG	5113	49.5	1471	53.7	<0.001
LDL-c level in hospital					
Not measuring	909	8.8	299	10.9	0.003
<160mg/dl	8850	85.6	2287	83.4	
>=160mg/dl	578	5.6	156	5.7	
Prior statin use	1467	14.2	381	13.9	0.692
Dose of statin at discharge					
1-9 mg/d	1904	18.4	672	24.5	<0.001
10-19 mg/d	3196	30.9	500	18.2	
>=20 mg/d	5237	50.7	1570	57.3	
Type of statin at discharge					
Atorvastatin	5785	56.0	1712	62.4	<0.001
Simvastatin	2690	26.0	509	18.6	
Rosuvastatin	502	4.9	40	1.5	
Pravastatin	502	4.9	163	5.9	

Fluvastatin	578	5.6	166	6.1	
Other statin	280	2.7	152	5.5	
Co-treatments at discharge					
Aspirin	10030	97.0	2645	96.5	0.127
Clopidogrel	8404	81.3	2416	88.1	<0.001
β-blocker	8155	78.9	2076	75.7	<0.001
ACEI/ARB*	8096	78.3	2161	78.8	0.579

* STEMI was ST-segment elevation myocardial infarction; NSTEMI was Non-ST-segment elevation myocardial infarction; UA was unstable angina; ACEI was Angiotensin converting enzyme inhibitor; ARB was Angiotensin Receptor Blocker

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a)Title and Line 6 of page 3; (b)Line 7-25 of page 3.	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1. Line 7-9 of page 3. 1.2. Line 7-9 of page 3. 1.3. Not applicable.
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	The first and second paragraph of the introduction section.		
Objectives	3	State specific objectives, including any prespecified hypotheses	The third paragraph of the introduction section.		
Methods					
Study Design	4	Present key elements of study design early in the paper	The first line of the study design section.		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	The first paragraph of the methods section.		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	(a) The second paragraph of the methods section. (b) Not applicable.	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1. The second paragraph of the methods section. 6.2. Not applicable. 6.3. Not applicable.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	The data analyses of the methods section.	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	The data analyses of the methods section.
Data sources/ measurement	8	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	Page 6-7 in the methods section.		

Bias	9	Describe any efforts to address potential sources of bias	To control information bias in the first paragraph of data collection section.		
Study size	10	Explain how the study size was arrived at	The first paragraph of design section.		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	The data analyses of the methods section.		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Statistical methods in page 8.		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	The first paragraph of study design.

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	The second sentence of patient section in page 6.
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	The first paragraph of page 7.
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	a & b. First paragraph of results section in page 8. c. Figure 1.	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	13.1. First paragraph of results section in page 8 and Figure 1.
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	The first paragraph of the result section.		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time	The second paragraph of the result section.		

		Case-control study - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Figure 2 & 3.		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	None.		
Discussion					
Key results	18	Summarise key results with reference to study objectives	First paragraph of the discussion section.		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	The last paragraph of the discussion section in page 13.	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	The last paragraph of the discussion section .

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Paragraph 2-10 of the discussion section.		
Generalisability	21	Discuss the generalisability (external validity) of the study results	The first paragraph of page 14.		
Other Information					
Funding	22	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	Source(s) of support of page 15.		
Accessibility of protocol, raw data, and programming code		The first paragraph of the design section in page 5.		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	The first paragraph of the design section in page 5.

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.