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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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ABSTRACT

Objectives To determine the associated factors for discontinuation of statin use 1 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 patients with ACS hospitalised in 2007–2010 and discharged with statins from 75 hospitals in China in the Clinical Pathways for Acute Coronary Syndromes in China Study-Phase 2 (CPACS-2), who were followed-up at 6 and 12 months postdischarge.

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

Results Multivariable logistic regression model showed that patients who did not have cholesterol measurement (adjusted OR=1.29; 95% CI: 1.10 to 1.50) and patients with either higher (1.27; 1.13 to 1.43) or lower dose of statin (1.22; 1.07 to 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 to 0.94), patients with medical insurance (0.75; 0.67 to 0.85), history of hypertension (0.83; 0.75 to 0.92), high low-density lipoprotein cholesterol (0.70; 0.57 to 0.87) at the baseline, prior statin use (0.73; 0.63 to 0.84), use of atorvastatin (0.78; 0.70 to 0.88) and those who underwent percutaneous coronary intervention or coronary artery bypass grafting during hospitalisation (0.47; 0.43 to 0.53) were less likely to discontinue statin use. The 1-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.

Trial registration number Australian New Zealand Clinical Trials Registry (ACTRN12609000491268).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ With a large cohort with more than 10 000 patients with acute coronary syndrome (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 low-density lipoprotein cholesterol (LDL-c) level, and two positive associates: non-standard dose use and not having cholesterol measured.

⇒ Data used in the present study were from Clinical Pathways for Acute Coronary Syndromes in China Study-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 overestimation- or underestimation 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 4 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 coronary artery bypass grafting (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.[20] However, to date, few data exist on the factors that influence statin discontinuation in patients with ACS in China.

In this study, we analysed data from the Clinical Pathways for Acute Coronary Syndromes in China Study-Phase 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 analysed the 1-year follow-up data of patients with ACS who were discharged with statin from 75 hospitals across China in the 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-randomised 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 patients with ACS admitted to the participating hospitals and followed-up surviving patients till 1 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 2762 lost to follow-up and therefore these patients were excluded from analysis. The remaining 10 337 patients who were discharged with statin and completed follow-up were included (see figure 1).

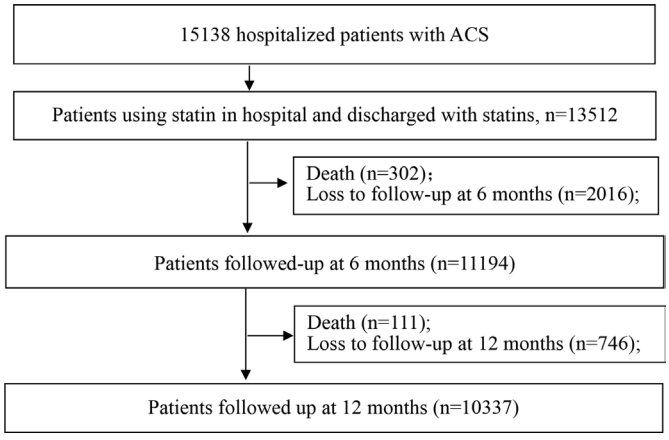

Figure 1 Flow chart of study participants in CPACS-2. ACS, acute coronary syndrome; CPACS, Clinical Pathways for Acute Coronary Syndromes in China Study-2.

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 standardised questionnaire for collecting data on statin use was shown in table S1 in online supplemental file 1.

For our analysis, the dosage of different statins was converted to the equivalent dosage of atorvastatin[25] (online supplemental file 1: table S2).

Patient and public involvement

Patients and the public were not involved in our research design, conduct, reporting or dissemination plans.

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 MACE, in-hospital PCI/CABG, low-density lipoprotein cholesterol (LDL-c) level at enrolment, prior statin use, dose and type of statin at discharge, co-treatments at discharge.

Education level was classified into two categories: lower than high school and high school and above. Prior statin use was defined as any statin use in most days 1 month before the development of ACS.

According to the guideline in China,[26] we divided into three 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 ST-segment elevation myocardial infarction 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 1 year after discharge was the primary outcome, which was defined as not in current use of statin at either 6-month or 12-month follow-up. The question 'Is the patient currently taking statins?' was asked to the research physician at the both 6-month 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 V.9.4 (SAS Institute) 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 15138 patients recruited in CPACS-2, 13512 were prescribed statin at discharge. Among them, 413 died and 2762 (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 10337 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 1 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 plot is 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 dyslipidaemia, diabetes and hypertension, prior statin use, higher LDL-c, those who required intervention procedures such as PCI/CABG during hospitalisation, 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 plot is shown in figure 2.

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		
Dyslipidaemia	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
<160 mg/dL	8850	85.6
≥160 mg/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

Continued

Table 1 Continued

Characteristics	n	%
ACEI/ARB	8096	78.3

ACEI, ACE inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; LDL-c, low-density lipoprotein cholesterol ; MACE, major adverse cardiovascular events; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

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 hospitalisation were less likely to discontinue statin, while those on either higher or lower dose of statin (vs 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 dyslipidaemia and diabetes, and co-treatments of clopidogrel and β-blocker at discharge. The Forest plot is shown in figure 3.

DISCUSSION

Using data from a large, prospective cohort of patients with ACS in China, we found that a number of factors were independently associated with the discontinuation of statin use in 1 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, have 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 randomised 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 patients with ACS who received PCI/CABG treatment during the hospitalisation 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 emphasise the long-term use of statin after PCI/CABG for prevention from restenosis.[1 28] In this study, patients who received PCI/CABG had acute myocardial infarction (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 dyslipidaemia, 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 has 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 with 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

Factors	Group	N	Discontinuation 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)
	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)

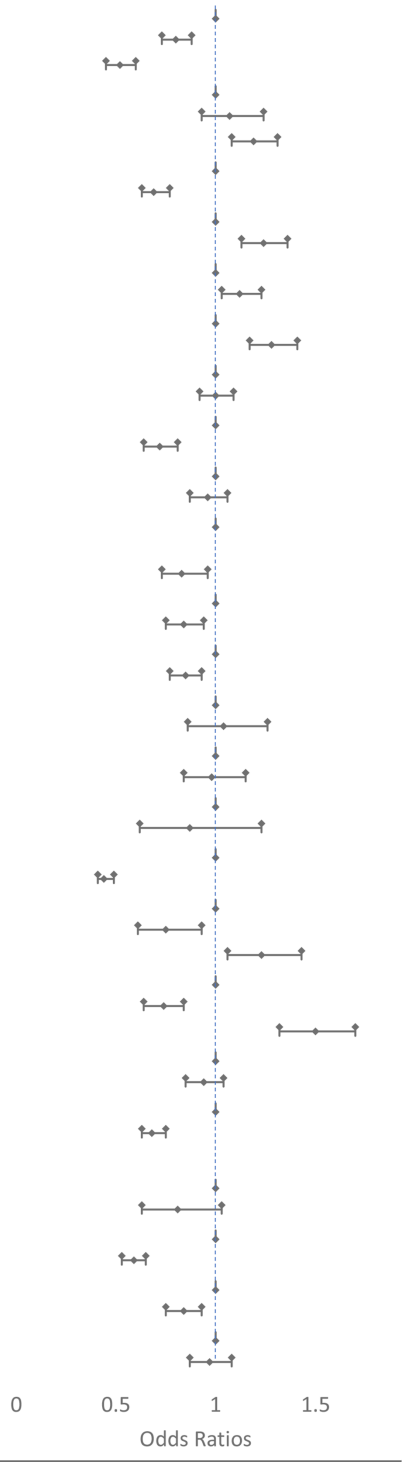

Figure 2 Univariate analysis of factors in association with the discontinuation of statin use in 1 year after discharge with logistic regression models (n=10 337) *Combined 2007 and 2008 due to relatively small sample in 2007. ACEI, ACE inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; LDL-c, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

dose prescription and the early discontinuation in these patients.

Atorvastatin use (vs 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

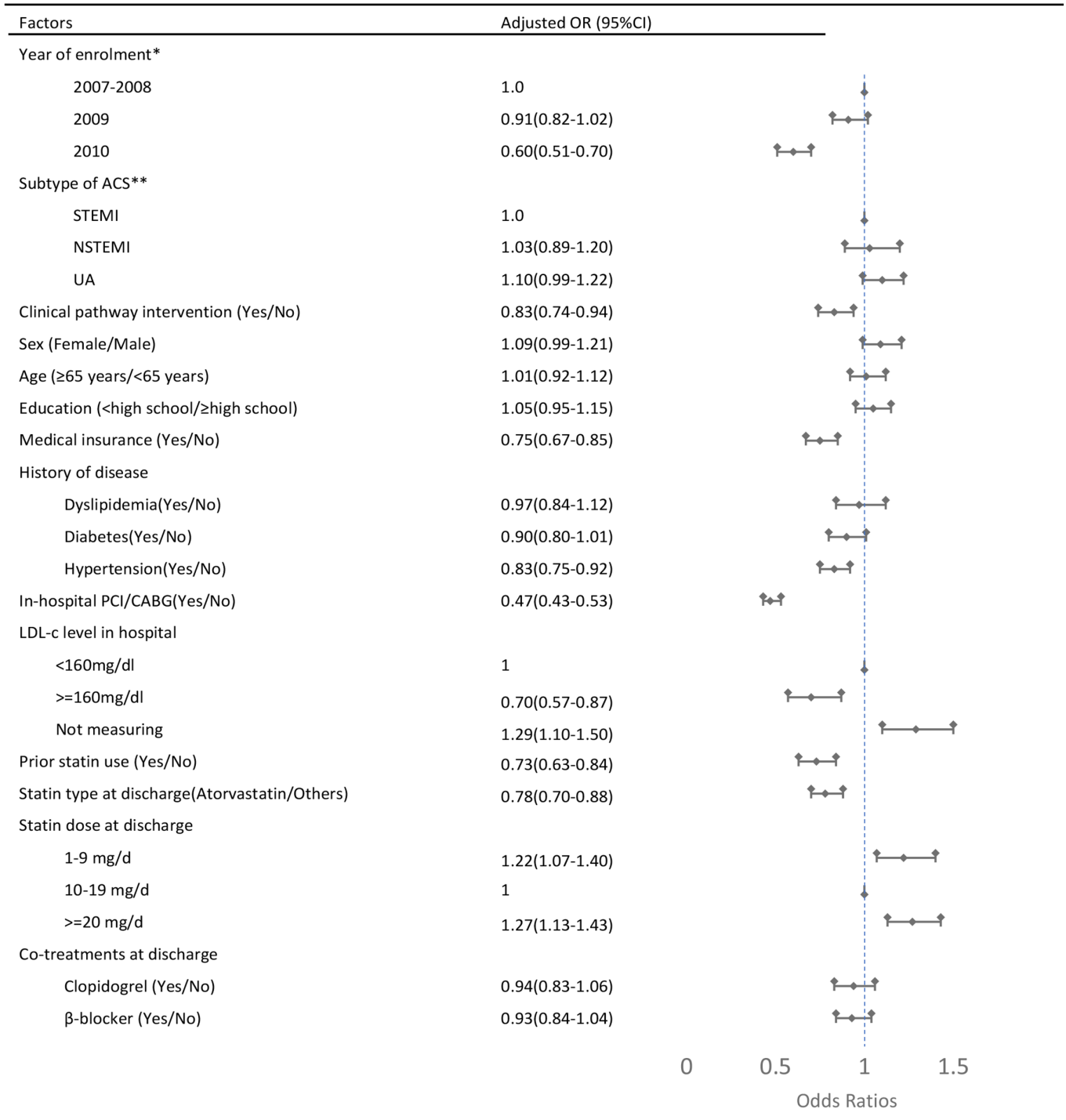

Figure 3 ORs of discontinuation of stain within 1 year in the full final multivariable logistic regression model in analysed patients of CPACS-2 (n=10 337). *p for trend <0.001; **p for trend=0.232. ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; LDL-c, low-density lipoprotein cholesterol; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

most frequently used statin type.[34] We do not know why Chinese are better adherent to atorvastatin. We hypothesise 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 USA found that 10 mg or 20 mg of atorvastatin use had lower cardiovascular (CV) event rates particularly in the first year of use than 20 mg or 40 mg of simvastatin[37] while another large observational study in the UK found that the risk of hepatotoxicity (small numbers of events observed) was increased in the first 6 months of atorvastatin compared with 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 dyslipidaemia (30% vs 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 behaviour-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 hospitalisation, no prior use of statin and so on 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 cardiovascular disease (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%–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. First, 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 and so on) which might have led to overestimation or underestimation of the associations with the related factors (table S3 in online supplemental file 1). Second, our study follow-up period was limited to 1 year; factors that are associated with the longer-term discontinuation should be explored in the future. Third, 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 (eg, 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 ACS 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.

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REFERENCES

1 Anderson JL, Adams CD, Antman EM, *et al*. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American heart association Task force on practice guidelines (writing Committee to revise the 2002 guidelines for the management of patients with unstable Angina/Non-ST-Elevation myocardial infarction) developed in collaboration with the American College of emergency physicians, the Society for cardiovascular angiography and interventions, and the Society of thoracic surgeons endorsed by the American association of cardiovascular and pulmonary rehabilitation and the Society for academic emergency medicine. *J Am Coll Cardiol* 2007;50:e1–157.
2 Antman EM, Hand M, Armstrong PW, *et al*. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American heart association Task force on practice guidelines: developed in collaboration with the Canadian cardiovascular Society endorsed by the American Academy of family physicians: 2007 writing group to review new evidence and update the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction, writing on behalf of the 2004 writing Committee. *Circulation* 2008;117:296–329.
3 Stone NJ, Robinson JG, Lichtenstein AH, *et al*. ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American heart association Task force on practice guidelines. *J Am Coll Cardiol* 2013;2014:2889–934.
4 Grundy SM, Stone NJ, Bailey AL, *et al*. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American heart association Task force on clinical practice guidelines. *Circulation* 2019;139:e1082–143.
5 Catapano AL, Graham I, De Backer G. ESC/EAS Guidelines for the Management of Dyslipidaemias.. In: *Revista espanola de cardiologia (English).* , 2016: 70(2), 115.
6 Li S-D, Zhang S-Y, Peng B. Statins as candidate therapeutic agents for coronavirus disease 2019 (COVID-19). *Chin Med J* 2020;134:407–9.
7 Sun Y, Xie G, Patel A, *et al*. Prescription of statins at discharge and 1-year risk of major clinical outcomes among acute coronary syndromes patients with extremely low LDL-cholesterol in clinical pathways for acute coronary syndromes studies. *Clin Cardiol* 2018;41:1192–200.
8 Xie G, Sun Y, Myint PK, *et al*. Six-Month adherence to statin use and subsequent risk of major adverse cardiovascular events (mace) in patients discharged with acute coronary syndromes. *Lipids Health Dis* 2017;16:155.
9 Daniel H, Christian W, Robin H, *et al*. Statin treatment after acute coronary syndrome: adherence and reasons for non-adherence in a randomized controlled intervention trial. *Sci Rep* 2019;9:12079.
10 Eagle KA, Kline-Rogers E, Goodman SG, *et al*. Adherence to evidence-based therapies after discharge for acute coronary syndromes: an ongoing prospective, observational study. *Am J Med* 2004;117:73–81.
11 Boklage SH, Malangone-Monaco E, Lopez-Gonzalez L, *et al*. Statin utilization patterns and outcomes for patients with acute coronary syndrome during and following inpatient admissions. *Cardiovasc Drugs Ther* 2018;32:273–80.
12 Vonbank A, Drexel H, Agewall S, *et al*. Reasons for disparity in statin adherence rates between clinical trials and real-world observations: a review. *Eur Heart J Cardiovasc Pharmacother* 2018;4:230–6.
13 Turner RM, Yin P, Hanson A, *et al*. Investigating the prevalence, predictors, and prognosis of suboptimal statin use early after a non-ST elevation acute coronary syndrome. *J Clin Lipidol* 2017;11:204–14.
14 De Vera MA, Bhole V, Burns LC, *et al*. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. *Br J Clin Pharmacol* 2014;78:684–98.
15 Faulkner MA, Wadibia EC, Lucas BD, *et al*. Impact of pharmacy counseling on compliance and effectiveness of combination lipid-lowering therapy in patients undergoing coronary artery revascularization: a randomized, controlled trial. *Pharmacotherapy* 2000;20:410–6.
16 Khanderia U, Townsend KA, Eagle K, *et al*. Statin initiation following coronary artery bypass grafting: outcome of a hospital discharge protocol. *Chest* 2005;127:455–63.
17 O'Brien EC, McCoy LA, Thomas L, *et al*. Patient adherence to generic versus brand statin therapy after acute myocardial infarction: insights from the can rapid stratification of unstable angina patients suppress adverse outcomes with early implementation of

the American College of Cardiology/American heart association guidelines registry. *Am Heart J* 2015;170:55–61.
18 Choudhry NK, Avorn J, Glynn RJ, *et al*. Full coverage for preventive medications after myocardial infarction. *N Engl J Med* 2011;365:2088–97.
19 Mathews R, Wang TY, Honeycutt E, *et al*. Persistence with secondary prevention medications after acute myocardial infarction: insights from the TRANSLATE-ACS study. *Am Heart J* 2015;170:62–9.
20 Reiner Ž, De Backer G, Fras Z, *et al*. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries--Findings from the EUROASPIRE IV survey. *Atherosclerosis* 2016;246:243–50.
21 Du X, Gao R, Turnbull F, *et al*. Hospital quality improvement initiative for patients with acute coronary syndromes in China: a cluster randomized, controlled trial. *Circ Cardiovasc Qual Outcomes* 2014;7:217–26.
22 Du X, Patel A, Li X, *et al*. Treatment and outcomes of acute coronary syndromes in women: an analysis of a multicenter quality improvement Chinese study. *Int J Cardiol* 2017;241:19–24.
23 Li M, Huang Y, Du X, *et al*. Impact of Prior Use of Four Preventive Medications on Outcomes in Patients Hospitalized for Acute Coronary Syndrome--Results from CPACS-2 Study. *PLoS One* 2016;11:e0163068.
24 Rong Y, Turnbull F, Patel A, *et al*. Clinical pathways for acute coronary syndromes in China: protocol for a hospital quality improvement initiative. *Crit Pathw Cardiol* 2010;9:134–9.
25 Jones P, Kafonek S, Laurora I, *et al*. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the curves study). *Am J Cardiol* 1998;81:582–7.
26 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* 2007;35:390–419.
27 Bi Y, Gao R, Patel A, *et al*. Evidence-Based medication use among Chinese patients with acute coronary syndromes at the time of hospital discharge and 1 year after hospitalization: results from the clinical pathways for acute coronary syndromes in China (cPACs) study. *Am Heart J* 2009;157:509–16.
28 Chinese Medical Association Cardiovascular Branch,. Editorial Committee of Chinese Journal of cardiology. guidelines for percutaneous coronary intervention. *Chin J Cardiol* 2002;30:707–18.
29 HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J* 2013;34:1279–91.
30 Meng P-N, Yin D-L, Lu W-Q, *et al*. Intensive statin versus low-dose statin + ezetimibe treatment for fibrous cap thickness of coronary vulnerable plaques. *Chin Med J* 2020;133:2415–21.
31 Šimić I, Reiner Željko. Adverse effects of statins - myths and reality. *Curr Pharm Des* 2015;21:1220–6.
32 Armitage J. The safety of statins in clinical practice. *Lancet* 2007;370:1781–90.
33 Brahmachari B, Chatterjee S. Myopathy induced by statin-ezetimibe combination: evaluation of potential risk factors. *Indian J Pharmacol* 2015;47:563–4.
34 Zhang L, Li J, Li X, *et al*. National assessment of statin therapy in patients hospitalized with acute myocardial infarction: insight from China PEACE-Retrospective AMI study, 2001, 2006, 2011. *PLoS One* 2016;11:e0150806.
35 He W, Cao M, Li Z. Effects of different doses of atorvastatin, rosuvastatin, and simvastatin on elderly patients with ST-elevation acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI). *Drug Dev Res* 2020;81:551–6.
36 Ma H, Liu Y, Xie H, *et al*. The renoprotective effects of simvastatin and atorvastatin in patients with acute coronary syndrome undergoing percutaneous coronary intervention: an observational study. *Medicine* 2017;96:e7351.
37 Willke RJ, Zhou S, Vogel RA. Differences in cardiovascular event rates between atorvastatin and simvastatin among new users: managed-care experience. *Curr Med Res Opin* 2008;24:2873–82.
38 Clarke AT, Johnson PCD, Hall GC, *et al*. High dose atorvastatin associated with increased risk of significant hepatotoxicity in comparison to simvastatin in UK GPRD cohort. *PLoS One* 2016;11:e0151587.
39 Ofori-Asenso R, Jakhu A, Curtis AJ, *et al*. A systematic review and meta-analysis of the factors associated with nonadherence and discontinuation of statins among people aged ≥65 years. *J Gerontol A Biol Sci Med Sci* 2018;73:798–805.
40 Lemstra M, Blackburn D, Crawley A, *et al*. Proportion and risk indicators of nonadherence to statin therapy: a meta-analysis. *Can J Cardiol* 2012;28:574–80.
41 Cooperative Committee of Chinese guidelines on prevention and treatment of dyslipidemia in adults. Chinese guidelines on prevention and treatment of dyslipidemia in adults (revised version in 2016). *Chinese Circulation Journal* 2016;31:937–53.
42 Phan K, Gomez Y-H, Elbaz L, *et al*. Statin treatment non-adherence and discontinuation: clinical implications and potential solutions. *Curr Pharm Des* 2014;20:6314–24.
43 Peterson ED, Roe MT, Mulgund J, *et al*. Association between hospital process performance and outcomes among patients with acute coronary syndromes. *JAMA* 2006;295:1912–20.
44 Huffman MD, Mohanan PP, Devarajan R, *et al*. Effect of a quality improvement intervention on clinical outcomes in patients in India with acute myocardial infarction: the ACS Quik randomized clinical trial. *JAMA* 2018;319:567–78.
45 Shuiping Z. Key points and interpretation of guidelines for prevention and treatment of dyslipidemia in Chinese adults. *Practical Journal of Clinical Medicine* 2008;5:3–6.
46 Xu H, Xu Z, Lu Z. Summary and interpretation of guidelines for prevention and treatment of dyslipidemia in Chinese adults (2007). *Chinese Journal of Geriatric Heart Brain and Vessel Diseases* 2008;10:238–40.
47 Ye P, Sun X. Standardized lipid-lowering therapy based on comprehensive evaluation. *Chinese Journal of Arteriosclerosis* 2008;16:253–5.
48 Li X. Interpretation of 2007 guidelines for prevention and treatment of adult dyslipidemia in China. *Medicine and philosophy* 2008;29:22–6.
49 Xie J. Interpretation of the main points of prevention and treatment guidelines for dyslipidemia in Chinese adults in 2007. *The First Annual Meeting of the Second Geriatric Professional Committee of Zhejiang Association of Integrated Traditional Chinese and Western Medicine* 2007.
50 Zhao S. Editor interpretation of guidelines for prevention and treatment of dyslipidemia in Chinese adults. *The 7th Southern Great Wall Cardiology Conference and Xiaoxiang Cardiovascular Intervention Forum*, 2008.
51 Xu J. Understanding and Interpretation of "Guidelines for Prevention and Treatment of Adult Dyslipidemia in China". *The First National Forum of Young and Middle-aged Physicians of Cardiovascular Diseases with Integrated Traditional Chinese and Western Medicine*, 2008.
52 Xu H. Brief introduction and analysis of Chinese adult dyslipidemia prevention and treatment guidelines (2007). *The 11th National Conference on Clinical Pharmacology*, 2008.
53 Wang X, Li Y, Li J, *et al*. [Medication compliance for secondary prevention and long-term outcome among patients with acute coronary syndrome after percutaneous coronary intervention in different regions]. *Zhonghua Xin Xue Guan Bing Za Zhi* 2021;49:143–9.

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