




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

Gaoqiang Xie <sup>1,2</sup>, Phyo Kyaw Myint <sup>3,4</sup>, Yihong Sun <sup>5</sup>, Xian Li,<sup>6</sup> Tao Wu,<sup>6</sup> Run-lin Gao,<sup>7</sup> Yangfeng Wu<sup>1,6,8</sup>

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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 used 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

Statin therapy has been recommended as a core long-term secondary preventive treatment for patients with acute coronary syndrome (ACS) by several guidelines.<sup>1–5</sup> Despite strong evidence from basic and clinical studies<sup>6–8</sup> 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.<sup>9–12</sup> 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.<sup>13 14</sup>

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



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For numbered affiliations see end of article.

### Correspondence to

Dr Yangfeng Wu;  
wuyf@bjmu.edu.cn

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.<sup>9 15–19</sup> A big European survey showed that statin therapy was discontinued in 11.6% of patients with coronary heart disease.<sup>20</sup> 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.

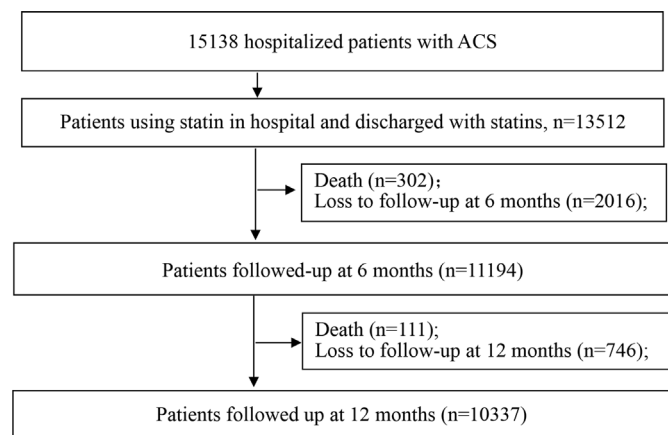
## METHODS

### 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.<sup>21–24</sup> 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.<sup>21</sup>

### 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<sup>25</sup> (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,<sup>26</sup> 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.<sup>1 2</sup> For more details, please refer to the previous publications.<sup>21 24</sup>

#### 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 15 138 patients recruited in CPACS-2, 13 512 were prescribed statin at discharge. Among them, 413 died and 2762 (21% of those who survived) were lost to follow-up. Finally, 10 337 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 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 decreasing 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  $\beta$ -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=10 337)

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 $\geq$ 65	4934	47.7
Education $\geq$ 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
$\geq$ 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
$\geq$ 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
$\beta$ -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  $\beta$ -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.

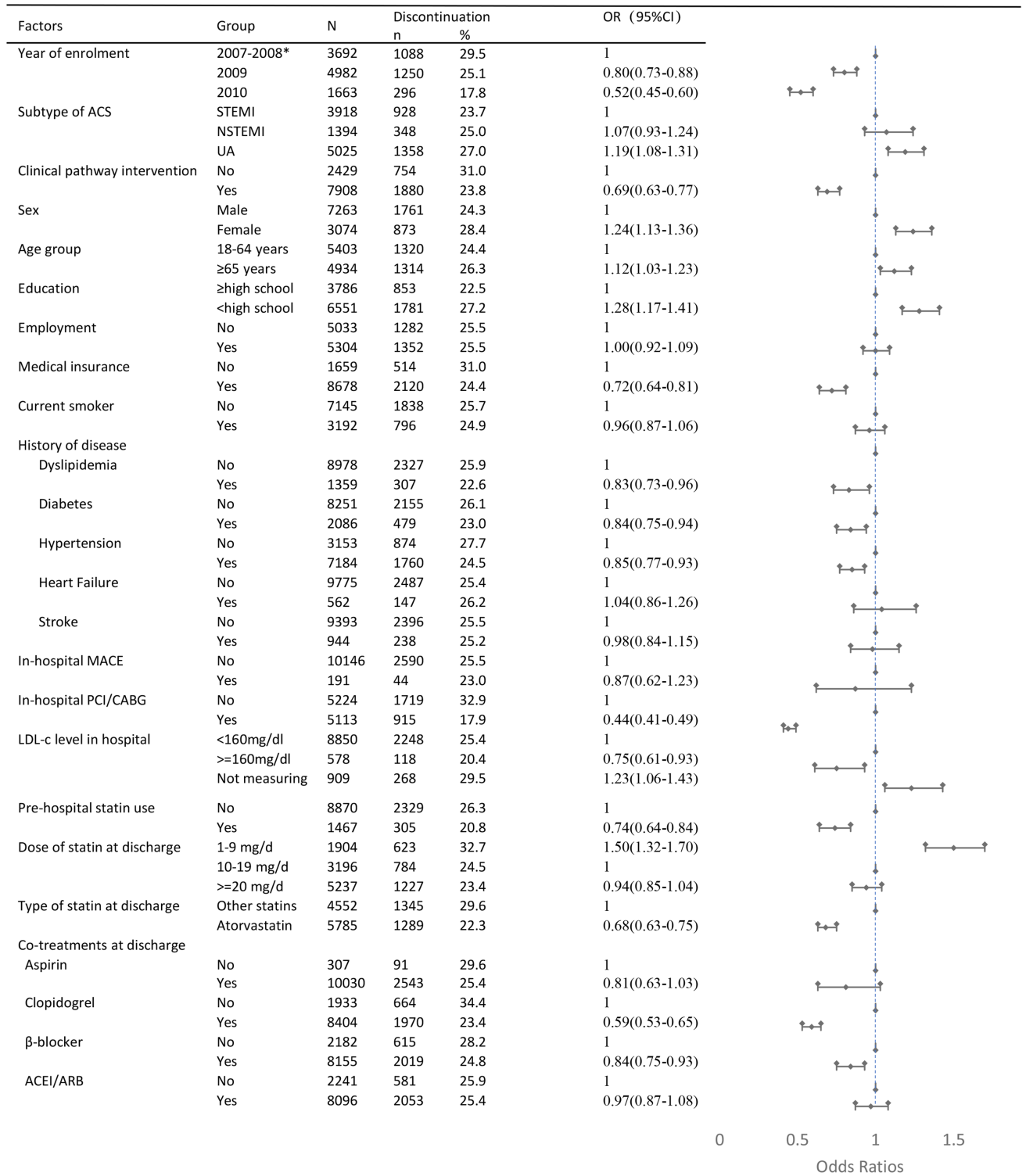
First, our findings demonstrated that the implementing of CPACS-2 intervention was associated with a higher adherence of statin use, which was independent of the time trend and other covariates. It indicates that the clinical pathways for ACS management, although implemented within hospital, have effect 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.<sup>21 22</sup> 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,<sup>27</sup> 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.<sup>9 20</sup> The explanations may include that all major clinical guidelines emphasise the long-term use of statin after PCI/CABG for prevention from restenosis.<sup>1 28</sup> 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 ( $\geq 160$  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.<sup>29 30</sup> Thus, side effects, such as muscle complaints due to myopathy,<sup>31</sup> and rhabdomyolysis,<sup>32 33</sup> 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.<sup>29</sup> 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.<sup>29</sup> 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

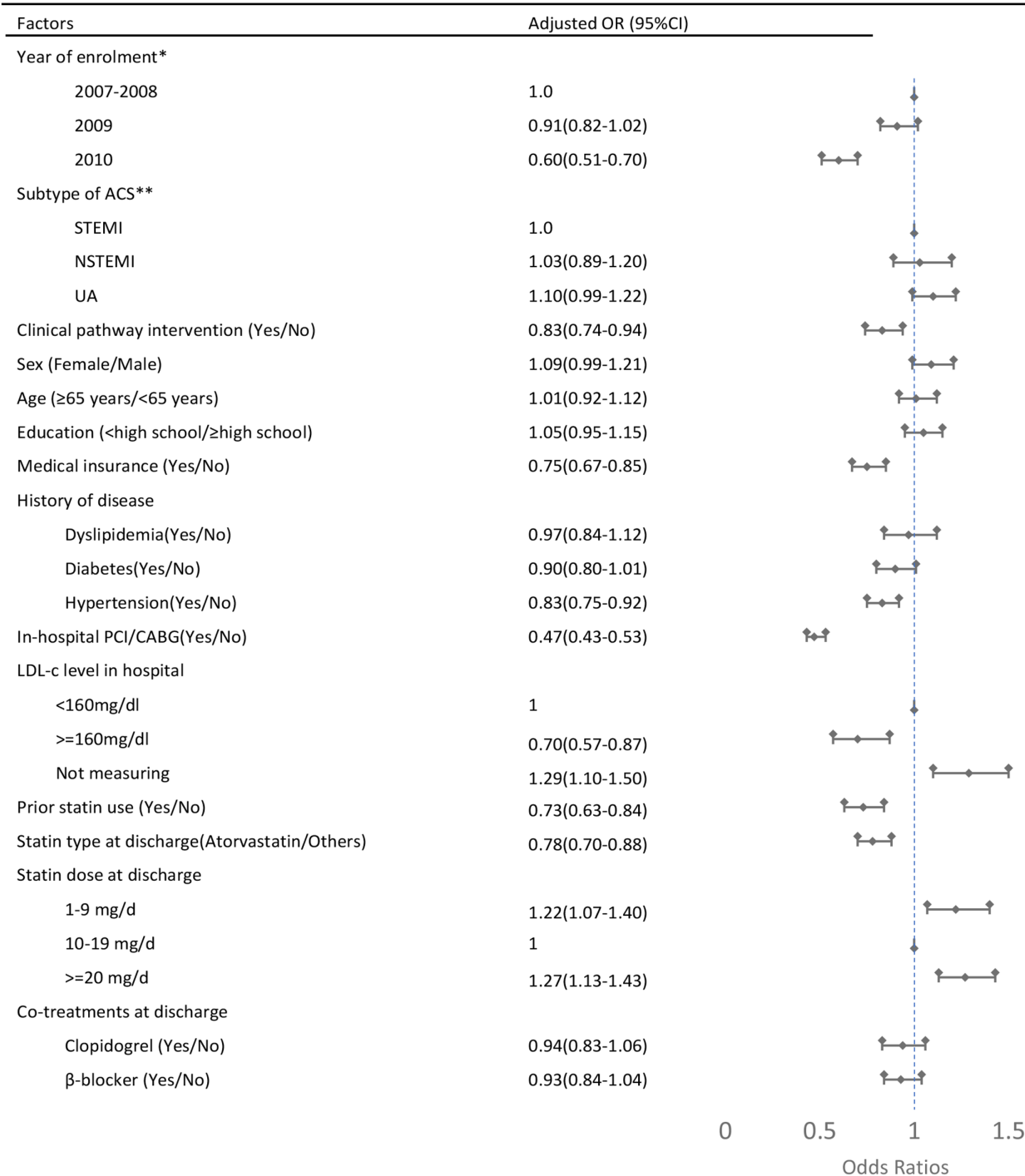


**Figure 2** Univariate analysis of factors in association with the discontinuation of statin use in 1 year after discharge with logistic regression models (n=10337) \*Combined 2007 and 2008 due to relatively small sample in 2007. ACEI, ACE inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor 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 adhere 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=10337). \*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.<sup>34</sup> 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.<sup>35 36</sup> 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<sup>37</sup> 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.<sup>38</sup> 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.<sup>39 40</sup> 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.<sup>4 41</sup> 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.<sup>42–44</sup> 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<sup>26 45–52</sup> 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.<sup>53</sup> 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.

#### Author affiliations

<sup>1</sup>Peking University Clinical Research Institute, Peking University First Hospital, Beijing, China

<sup>2</sup>Key Laboratory of Molecular Cardiovascular Sciences, Ministry of Education, Beijing, China

<sup>3</sup>Aberdeen Cardiovascular & Diabetes Centre, University of Aberdeen, Aberdeen, UK

<sup>4</sup>Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK

<sup>5</sup>Heart Center, China-Japan Friendship Hospital, Beijing, China

<sup>6</sup>The George Institute for Global Health, Peking University Health Science Center, Beijing, China

<sup>7</sup>Department of Cardiology, Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital, Xicheng District, Beijing, China

<sup>8</sup>Department of Epidemiology and Biostatistics, Peking University School of Public Health, Beijing, China

**Contributors** GX contributed to concept development, data cleaning analysis, and interpretation, and writing of the manuscript. PKM contributed to critical input in interpretation of results and writing of the manuscript. YS contributed to critical input in interpretation of results and writing of the manuscript. XL contributed to quality control on data collection and review of manuscript. TW contributed to data analysis plan and review of manuscript. RG contributed to review of manuscript and critical input in interpretation of results. YW contributed to concept development, critical input in interpretation of results, and review and approval of the manuscript. GX and YW are responsible for the overall content as the guarantor.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants. 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). Participants gave informed consent to participate in the study before taking part. Confidentiality of subjects were ensured by anonymizing participants' names, initials or hospital numbers.

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

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#### ORCID iDs

Gaoqiang Xie <http://orcid.org/0000-0002-4123-3535>

Phyo Kyaw Myint <http://orcid.org/0000-0003-3852-6158>

Yihong Sun <http://orcid.org/0000-0001-7812-9793>

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