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CLINICAL INVESTIGATIONS

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

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Abstract

Objective: The aim of this study was to investigate statin description on discharge and the benefit on the long-term outcomes in acute coronary syndromes (ACS) patients with very low baseline LDL-cholesterol (LDL-c).

Methods: This is a post-hoc analysis of 3374 ACS patients who were discharged alive and had baseline LDL-c levels below 70 mg/dL (1.8 mmol/L). The propensity score of using statin was estimated with a multivariable Logistic model including patient's demography, social economic status, cardiovascular risk factors, subtype of the diagnosis, and treatments received during hospitalization and current LDL-c level. The risk of major adverse cardiovascular events (MACEs) was compared between patients received and not-received statin with Cox-regression models adjusting for the propensity score plus other factors. A sensitivity analysis was done in propensity score matched patients.

Results: Compared with nonstatin group, the incidence of MACE at 12 months after discharge was lower in the statin group (11.1% vs 5.8%; $P < 0.001$). The propensity score plus other factors-adjusted hazard ratios for MACEs was significant (0.58; 95% CI: 0.39, 0.87). The effect showed a significant dose-response relationship (P for trend = 0.02). The results in analyses with propensity-score matched participants were in consistent with above findings. Analyses on total mortality in 12 months showed similar results.

Conclusions: Among ACS survivors with a very low baseline LDL-c, low to moderate intensity statin therapy was associated significantly with lower risk of MACEs and total mortality at 12 months. The results suggested that ACS survivors should take statin regardless of the baseline of LDL-c.

KEYWORDS

ACS patients, cohort study, major adverse cardiovascular events, statin, very low baseline LDL-c

1 | INTRODUCTION

Acute coronary syndromes (ACS) are the most serious manifestation of ischemic heart diseases, which is the leading cause of death

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worldwide.[1,2] Statins, as LDL-cholesterol (LDL-c) lowering medication have been recommended to reduce the subsequent risk of events and mortality in ACS patients,[2–6] with a suggested target LDL-c level of below 70 mg/dL.[7–9] The most updated American College of Cardiology guidelines further recommended the use of high-intensity statins among all ACS patients, regardless LDL-c level at baseline.[10]

However, the benefits from statin therapy that may be derived for ACS patients with initial LDL-c levels below 70 mg/dL remains controversial.[11–14] Moreover, low to moderate intensity statin therapy is quite common in clinical practice in Asian countries, and whether low-moderate intensity statin therapy is beneficial for ACS patients with very low LDL-c is unclear.[11–14] LDL-c levels are much lower in Chinese compared to western population,[15] with 9.6% of patients with acute myocardial infarction (MI) having LDL-c < 70 mg/dL in one study.[16]

We used data from two large prospective registry-based trials in China to investigate whether statin therapy could be beneficial to previously statin-naïve patients ACS with baseline LDL-c levels below 70 mg/dL. In addition, we explored the extent to which the intensity of statin therapy modified any treatment effect.

2 | METHODS

2.1 | Study population

Clinical Pathways for Acute Coronary Syndromes in China Phase 2 (CPACS-2) and Phase 3 (CAPSC-3) were conducted from 2007 to 2010, and from 2011 to 2014. The designs of these studies have been published elsewhere.[17,18] In brief, these were registry-based cluster-randomized trials to evaluate the effect of quality of care improvement interventions in improving key performance indictors or major cardiovascular events among ACS patients in 75 and 104 Chinese hospitals, respectively. Both studies had similar inclusion and exclusion criteria. Basically, all consecutive patients aged 18 years or older with a final diagnosis of ACS at the time of death or discharge were recruited prospectively in the participating hospitals. Patients were excluded if they were dead on arrival or died within 10 minutes of arriving at hospital. Surviving patients were followed up at 6 months and 12 months after discharge by clinic visit or telephone. Data were collected for each patient using standardized case report forms by trained staff.

In the present study, we included only patients who had baseline LDL-c levels below 70 mg/dL, had not used statins prior to hospitalization, survived for at least 1 week after discharge, and were followed up at least once (at 6 and/or 12 months). There was a total of 3374 patients meeting all these criteria for our analyses (Figure 1).

2.2 | Trial registration

CPACS2 was registered on URL: http://www.anzctr.org.au/default.aspx and unique identifier is ACTRN12609000491268. CPACS3 was registered on www.clinicaltrails.gov, and the registration number is NCT01398228.

2.3 | Ethical considerations

CPACS-2 and -3 studies were conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. The Ethics Committee at Fuwai Hospital and Peking University IRB approved the studies. A written informed consent was acquired from all participants. Patient data in the data management system were protected by password and only available to users designated by the study with appropriate authorization levels. De-identified data were used for data analysis.

2.4 | Clinical characteristics

Data collected during hospitalization included sociodemographic characteristics, medical history, type of ACS diagnosis, and signs of the severity of ACS at admission. The plasma lipid profile including total cholesterol (TC), LDL-c, triglyceride (TG), and high density lipoprotien cholesterol (HDL-c) and assays conducted at local laboratories, were also collected. Estimated glomerular filtration rate (eGRF) was calculated using MDRD equitation.[19] The blood was withdrawn at admission. The prescription of all evidence-based secondary prevention medications at discharge were recorded, including statins, antiplatelet medications, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nitrates, and calcium antagonist.

2.5 | Statin dose

For our analysis, the dosage of different statins was converted to the equivalent dosage of atorvastatin according to Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults in 2007[20] (**Table S1, Supporting information**). Then we classified the dosage of statin into: 5, 10, 20 and ≥ 40 mg/d when we analyzed the distribution. In order to increase statistic power, we combined some dose groups and classified into: 5 or 10, and ≥ 20 mg/d when we analyzed the dose-dependent effects.

2.6 | Clinical outcomes

The primary outcome was the first occurrence of major adverse cardiovascular events (MACE) including all-cause death, nonfatal MI, and nonfatal stroke within 12 months of discharge. We also collected events of hospitalization for revascularization during follow-up. The definitions of nonfatal MI and nonfatal stroke have been described before.[17] Nonfatal MI included recurrent MI for the patients hospitalized for MI, which defined by dynamic changes of myocardial injury biomarkers. The potential cardiovascular endpoint events were reviewed and adjudicated by an independent cardiovascular endpoint adjudication committee, which was masked to treatment allocation in CPACS-3 study.

2.7 | Statistical analyses

For descriptive purpose, means or medians were calculated to present continuous variables depending on sample distribution and were compared by *t*-tests or appropriate nonparametric tests between statin prescribed and not prescribed groups. Categorical

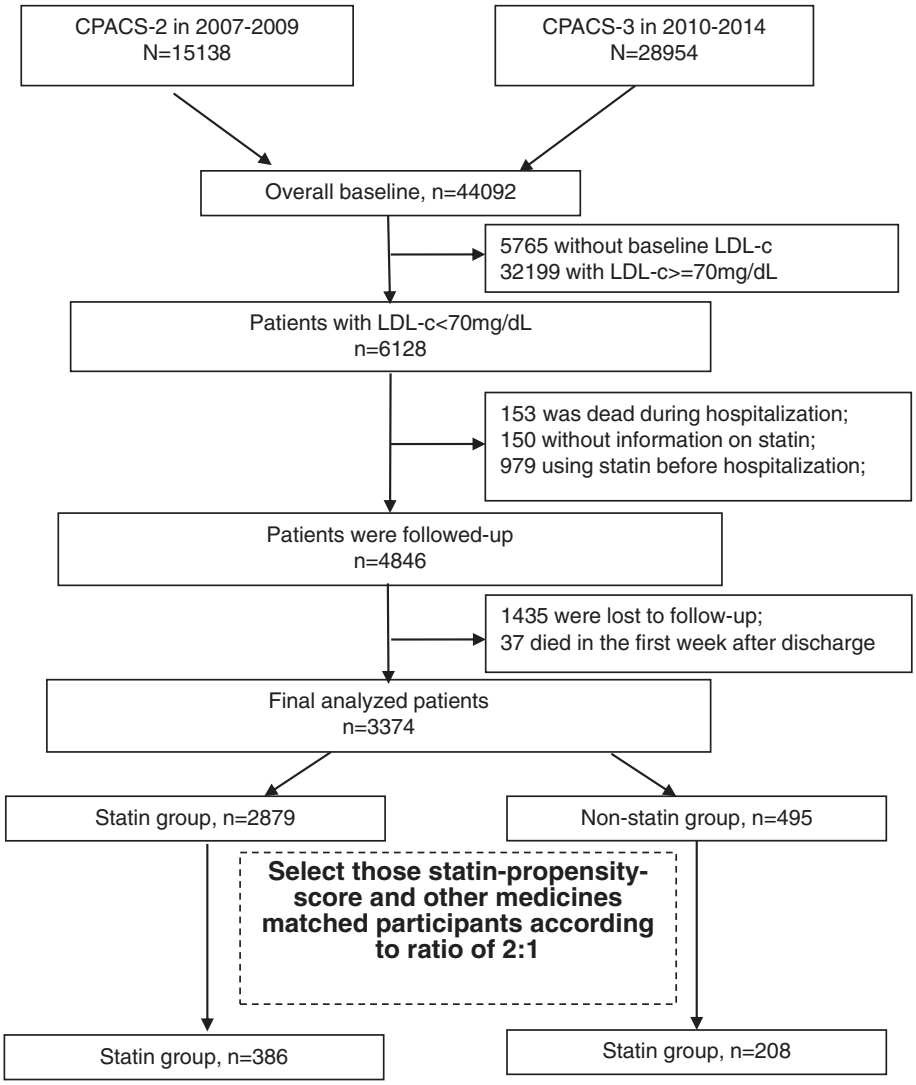

FIGURE 1 Flow chart of study participants

variables were presented as numbers or percentages and differences between groups were tested by Pearson χ^2 analysis. Cox proportional hazards regression were fitted to calculate hazard ratios (HR) and corresponding 95% confidence intervals (CI) of MACEs in 12 months after discharge, in unadjusted model, propensity score of statin prescription-adjusted model and multivariable models that accounted for other treatments during hospitalization (such as cardiorespiratory resuscitation, thrombolysis and PCI/CABG, aspirin, clopidogrel, beta-blocker, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, nitrate esters, and calcium antagonist) as well as the other medical treatments prescribed at discharge (aspirin, clopidogrel, beta-blocker, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, nitrate esters, and calcium antagonist), in addition to the propensity score.

We used multivariable logistic regression to fit the model of the propensity score of prescribing statin at discharge with variables that are often considered by cardiologists at the time of prescribing statins to the patients with ACS, including the level of hospital that the patient admitted and the patient's demography (sex and age), social economic status (education and profession), presence of cardiovascular risk factors (dyslipidemia, smoking, diabetes, and history of myocardial infarction, angina, or stroke), subtype of the diagnosis (STEMI, NSTEMI, or UA), and revascularization treatments the patient received during hospitalization (thrombolysis and PCI/CABG) as well as the patient's current LDL-c level.

In order to explore the dose-response effect of statins on outcomes, all above Cox models were re-constructed for the subgroup analyses of patient groups by different dosages of statin as compared with the nonstatin group.

Subgroup analyses were also performed with the Cox models in populations defined by age (< or ≥ 65 years), sex, type of ACS, presence of hypertension or, diabetes at baseline, smoking level, hospital type, baseline LDL-c level, eGFR, and coronary revascularization during hospital admission.

To ensure the completeness of adjustment for possible confounders, we repeated out main analyses only among those propensity score plus other medicines matched participants (ratio of statin to nonstatin users = 2:1, including 386 statin users, and 208 nonstatin users) (Figure 1).

All *P* values were two sided, and values <0.05 were considered statistically significant. All analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, North Carolina).

3 | RESULTS

3.1 | Baseline characteristics

The baseline characteristics of the study population are presented in Table 1. The proportion of patients diagnosed as STEMI, NSTEMI, and UA was 34.53%, 13.16%, and 52.31%. The statin prescription rate was 85% (2879/3374) in the study patients with LDL-c < 70 mg/dL measured at admission. At baseline, the mean LDL-c was 55.61 mg/dL in statin group and 54.77 mg/dL in nonstatin group. Those prescribed statins at hospital discharge were more likely to be men, smokers, have a higher educational level and to have been treated at tertiary level hospitals. They were more likely to have been diagnosed with STEMI and received percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The level of LDL-c, triglycerides, non-HDL-c, and eGFR were all greater at baseline in the statin group. At discharge, more patients in statin group were prescribed other cardioprotective drugs, compared to those who were not discharged with a statin.

3.2 | Statins prescription at discharge and dosing

The predominant dose used was the dose of 20 mg/d atorvastatin or equivalent. Less than 3% of the patients were given a dose of ≥40 mg/d atorvastatin or equivalent. Patients in tertiary hospitals were more likely to be prescribed a higher dose than their counterparts in level 2 hospitals.

3.3 | Prescription of statin at discharge and MACEs in 12 months of follow-up

At 12 months after discharge, the risk of MACEs was significantly lower in the statin group than in nonstatin group. Both all-cause mortality and cardiac death were also significantly lower in statin group (Table 2). The propensity score adjusted plus other factors-adjusted hazard ratios for MACEs was still significant (0.58; 95%CI: 0.39, 0.87) (Table 2).

Compared with nonstatin group, the propensity-score-plus-other-factors-adjusted hazard ratio for MACEs was 0.61 (95%CI, 0.40-0.94) for those using 5 to 10 mg/d atorvastatin equivalent dose and 0.53 (0.34-0.83) for those using ≥ 20 mg atorvastatin equivalent dose. The *P* value for trend was statistically significant ($P = 0.02$) (Figure 2). A similar trend was observed for total death ($P < 0.001$).

3.4 | Subgroup analysis

All associations were consistent in subgroups defined according to baseline characteristics including the subtypes of ACS (Figure 3).

3.5 | Baseline and MACEs in propensity-score matched participants

Among these propensity-score matched participants, all of baseline characteristics were not significantly different between statin and nonstatin group (Table 1). The risk of MACEs was also significantly lower in the statin group than in nonstatin group after adjusted by other risk factors (0.44, 95%CI, 0.22-0.89). The results were very similar to our main analyses regarding to total death and cardiac death (Table 2, Figure 2 and Figure S1).

4 | DISCUSSION

In this large registry-based Chinese ACS cohort with LDL-c < 70 mg/dL (1.8 mmol/L) (mean 55 mg/dL [1.5 mmol/L]) at baseline, low-to-moderate intensity statin therapy was significantly associated with lower risk of MACEs and all-cause mortality at 12 months following discharge. This finding supports the current guidelines recommending statin therapy for all ACS patients regardless of baseline LDL-c level. In addition, our finding indicates that ACS patients with very low LDL-c level could benefit from statins with a dose as low as 5 to 10 mg/d atorvastatin equivalent, but the trend analysis clearly indicates that a higher dose would reduce the risk of MACE further.

Previous studies have shown that ACS patients with very low LDL-c are common in Asian countries.[17] In our study, about 16% had LDL-c less than 70 mg/dL. Thus, how to treat this group of patients with statins bears clinical importance in Asian populations. A study in 1054 Korean AMI patients with baseline LDL-c level below 70 mg/dL similarly showed that stain prescription at discharge was associated with a lower risk of cardiac death (HR: 0.47; 95% CI: 0.23 to 0.93) and coronary revascularization at 1 year.[15]

Data from randomized clinical trials relating to use of statin therapy among individuals with very low initial LDC-c levels are generally lacking. The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) study[11] suggested that more intensive LDL-c cholesterol lowering with atorvastatin 80 mg compared with pravastatin 40 mg was not beneficial among those patients in the lowest quartile of baseline LDL-c (≤92 mg/dL). However, the size of this subgroup was small, limiting the ability to draw reliable conclusions.

In the pivotal trials comparing statins with placebo for secondary prevention, HPS study showed no significant differences in reduction of the risk of major vascular events among the subgroups of baseline LDL-c but cut off for the lowest group was <116 mg/dL, far above 70 mg/dL.[21] The CTT meta-analysis of data from 170 000 participants showed the RR of about 25% per 34 mmol/L further reduction in LDL-c is independent on the baseline LDL-c, but the proportions of the patients with LDL-c less than 70 mmol/L were very small in that study.[22] In contrast, CARE study showed significant interaction between baseline level of LDL-c and the level of risk reduction where the lower the value of baseline LDL-c the smaller the reduction in risk.[23] Nevertheless, the patients with lower level of LDL-c in CARE study were very few too. The evidences from clinical trials comparing stain and placebo among individuals with very low initial LDL-c levels were also lacking. It is still unclear which dosage should be used in these ACS patients with extremely low initial LDL-c levels. The significant dose-response trend observed in our study indicates that more vs less intensive statin therapy may result in even greater benefits among such individuals.

In our study, the estimated mean LDL-c level is much lower than the target endorsed by several guidelines.[9,10,20] In the IMPROVE-IT

TABLE 1 Baseline characteristics

Variables	Analyzed participants			Propensity-score matched participants		
	Statin group (*n* = 2879)	Nonstatin group (*n* = 495)	*P* value	Statin group (*n* = 386)	Nonstatin group (*n* = 208)	*P* value
Propensity score of statin	0.86 (0.06)	0.82 (0.06)	<0.001	0.85 (0.06)	0.85 (0.06)	0.524
Male, *n* (%)	2123 (73.74)	313 (63.23)	<0.001	255 (66.06)	140 (67.31)	0.759
Age, years, mean (STD)	63.95 (11.51)	64.35 (12.36)	0.427	64.21 (11.64)	65.67 (12.16)	0.138
High school or higher education, *n* (%)	657 (22.82)	82 (16.57)	0.002	81 (20.98)	43 (20.67)	0.929
Tertiary hospital, *n* (%)	802 (27.86)	61 (12.32)	<0.001	82 (21.24)	47 (22.60)	0.703
Medical insurance, *n* (%)	2219 (77.08)	365 (73.74)	0.105	303 (78.50)	161 (77.40)	0.758
Smoking, *n* (%)	888 (30.84)	115 (23.23)	0.001	88 (22.80)	50 (24.04)	0.733
Type of ACS, *n* (%)			0.002			
STEMI	1027 (35.67)	138 (27.88)		109 (28.24)	50 (24.04)	0.519
NSTEMI	378 (13.13)	66 (13.33)		47 (12.18)	25 (12.02)	
Unstable angina	1474 (51.20)	291 (58.79)		230 (59.59)	133 (63.94)	
History of disease, *n* (%)						
Dyslipidemia	139 (4.83)	19 (3.84)	0.336	18 (4.66)	12 (5.77)	0.557
Hypertension	1466 (50.92)	262 (52.93)	0.409	212 (54.92)	116 (55.77)	0.843
Diabetes mellitus	461 (16.01)	80 (16.16)	0.933	66 (17.10)	30 (14.42)	0.398
MI	259 (9.00)	47 (9.49)	0.721	34 (8.81)	22 (10.58)	0.482
Angina	779 (27.06)	143 (28.89)	0.398	117 (30.31)	75 (36.06)	0.153
Heart failure	100 (3.47)	26 (5.25)	0.054	21 (5.44)	16 (7.69)	0.279
Stroke	235 (8.16)	44 (8.89)	0.588	30 (7.77)	20 (9.62)	0.440
Family history of premature CHD, *n* (%)	74 (2.57)	8 (1.62)	0.203	17 (4.40)	5 (2.40)	0.218
Disease severity at presentation, *n* (%)						
SBP < 90 mmHg	65 (2.28)	9 (1.82)	0.526	6 (1.56)	3 (1.44)	0.912
Killip class ≥ III	208 (7.22)	40 (8.08)	0.500	31 (8.03)	16 (7.69)	0.884
Heart rate ≥ 100	299 (10.39)	70 (14.14)	0.024	52 (13.47)	29 (13.94)	0.577
Continuous ECG monitoring	1971 (68.46)	292 (58.99)	<0.001	225 (58.29)	122 (58.65)	0.932
Symptom to admission time (h)	102 (226)	107 (227)	0.401	132.01 (256.71)	125.91 (247.82)	0.782
Total cholesterol, mg/dL	132.10 (34.69)	129.26 (36.31)	0.008	132.55 (43.08)	132.54 (37.67)	0.741
LDL-c, mg/dL	55.61 (12.09)	54.77 (11.31)	0.012	54.86 (11.93)	55.02 (11.02)	0.733
HDL-c, mg/dL	44.03 (17.56)	43.19 (15.31)	0.671	43.79 (16.47)	43.73 (15.88)	0.773
Triglycerides, mg/dL	149.89 (150.92)	135.09 (125.35)	0.004	156.50 (158.70)	150.75 (143.95)	0.428
Non-HDL-c, mg/dL	88.02 (33.85)	86.37 (33.92)	0.035	88.74 (43.07)	89.30 (37.14)	0.577
eGFR, mL/min/1.73 m^2	105.48 (33.67)	101.38 (37.41)	0.008	103.90 (33.86)	99.40 (35.58)	0.101
PCI/ CABG, *n* (%)	631 (21.92)	40 (8.08)	<0.001	68 (17.62)	36 (17.31)	0.925
Thrombolysis	315 (10.94)	34 (6.87)	0.006	24 (6.22)	13 (6.25)	0.988
Medications at discharge, *n* (%)						
Aspirin	2771 (96.25)	252 (50.91)	<0.001	370 (95.85)	194 (93.27)	0.170
Clopidogrel	2215 (76.94)	132 (26.67)	<0.001	212 (54.92)	107 (51.44)	0.417
Beta-blocker	2046 (71.07)	172 (34.75)	<0.001	250 (64.77)	130 (62.50)	0.583
Nitrates	1993 (69.23)	191 (38.59)	<0.001	255 (66.06)	137 (65.87)	0.961
Calcium antagonist	602 (20.91)	80 (16.16)	0.015	97 (25.13)	54 (25.96)	0.824

Abbreviations: ACS, acute coronary syndrome; CHD, coronary heart disease; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HDL-c, high density lipoprotein-cholesterol; HF, heart failure; LDL-c, low density lipoprotein-cholesterol; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.

trial, the addition of ezetimibe to background moderate intensity statin (simvastatin 40 mg) reduced cardiovascular events by 6.4% over an average of 6 years in patients post ACS, with consistent benefit even among patients in the lowest quartile of baseline LDL-c (<64 mg/dL).[24] The emerging of PCSK9 inhibitors provide an opportunity to reduce the LDL-c to extremely low level.[25] In the FORURIER study, evolocumab treatment significantly reduced the risk of the primary end point by 15% and the benefit were consistent regardless of whether the baseline LDL-c was <70 or > 70 mg/dL. Our data, therefore support the concept of the lower the LDL-c, the better the CV outcomes.[26]

We did not find any significant heterogeneity in the associations in relation to any other patient subgroup. In particular, the associations did not differ between patients with lower (<58 mg/dL) and

TABLE 2 MACEs at 6 and 12 months according to statin prescription at discharge

Participants	Outcome variables	Statin group (n = 2879)	Nonstatin group (n = 495)	P value	Unadjusted HR (95%CI)	Propensity-score-adjusted HR[a]	Propensity score plus others adjusted HR[b]
All	MACEs	168 (5.84)	55 (11.11)	<0.001	0.51 (0.38,0.7)	0.56 (0.41,0.77)	0.58 (0.39,0.87)
	Total death	125 (4.34)	47 (9.49)	<0.001	0.45 (0.32,0.62)	0.53 (0.37,0.74)	0.49 (0.31,0.75)
	Cardiac death	55 (1.91)	17 (3.43)	0.030	0.57 (0.32,0.99)	0.63 (0.36,1.12)	0.55 (0.26,1.15)
	Nonfatal MI/stroke	43 (1.49)	8 (1.62)	0.836	0.9 (0.42,1.91)	0.84 (0.4,1.8)	1.2 (0.38,3.76)

Propensity-score matched participants		Statin group (n = 386)	Nonstatin group (n = 208)	P value	Unadjusted HR (95%CI)	Age and sex-adjusted HR[a]	Multi-adjusted HR[b]
	MACEs	19 (4.92)	26 (12.50)	0.001	0.4 (0.22,0.73)	0.44 (0.24,0.8)	0.44 (0.22,0.89)
	Total death	17 (4.40)	22 (10.58)	0.004	0.42 (0.22,0.79)	0.48 (0.25,0.9)	0.53 (0.25,1.13)
	Cardiac death	3 (0.78)	7 (3.37)	0.019	0.24 (0.06,0.91)	0.26 (0.07,1.02)	0.03 (0,2.25)
	Nonfatal MI/stroke	2 (0.52)	4 (1.92)	0.1024	0.28 (0.05-1.51)	0.28 (0.05-1.50)	—

Abbreviations: HR, hazard ratios; MACEs, major adverse cardiovascular events; MI, myocardial infarction. &Ratio of nonstatin (n = 208) vs statin (n = 386) was 1:2, difference of propensity score < 0.01 (range: 0-1).

[a] The propensity score was estimated using a logistic regression model including sex, age, education, profession, hospital level, dyslipidemia, smoking, history of myocardial infarction, stroke, diabetes, ACS type, thrombolysis, and PCI/CABG during hospitalization.

[b] Adjusted for sex, age, education, profession, hospital level, years of in-hospital, symptom to admission time, dyslipidemia, smoking, history of myocardial infarction, stroke, diabetes, ACS type, thrombolysis and PCI/CABG during hospitalization, LDL-c, high heart rate (≥ 100 times/min), Continuous ECG monitoring, treatments during hospitalization (such as cardiorespiratory resuscitation, thrombolysis and PCI/CABG, aspirin, clopidogrel, beta-blocker, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, nitrate esters, and calcium antagonist) as well as the other medical treatments prescribed at discharge (aspirin, clopidogrel, beta-blocker, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, nitrate esters, and calcium antagonist).

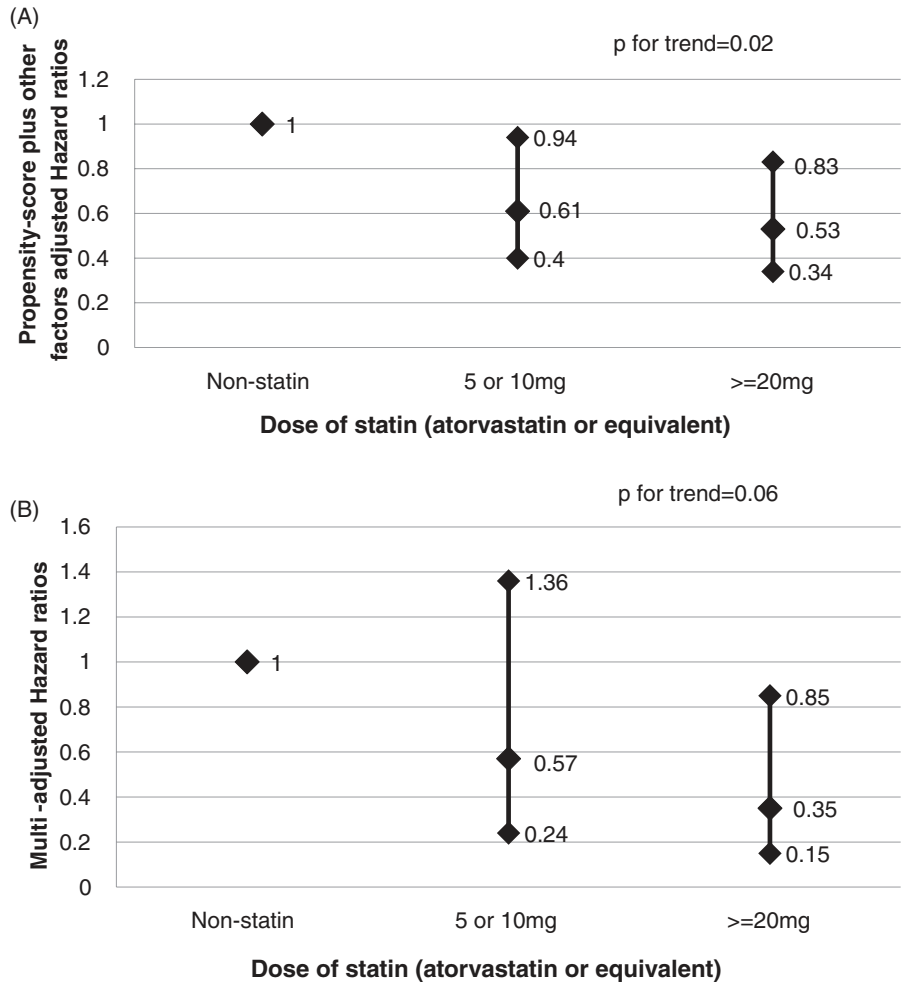

FIGURE 2 Hazard ratios of the major adverse cardiovascular events (MACEs) in 12 months after discharge by dosage of statin at discharge in full-adjusted cox model for all analyzed population (section a) (495 nonstatin group vs and 2879 statin group) and propensity-score-plus-other-medicines matched population (section B) (208 nonstatin group vs and 386 matched statin group)

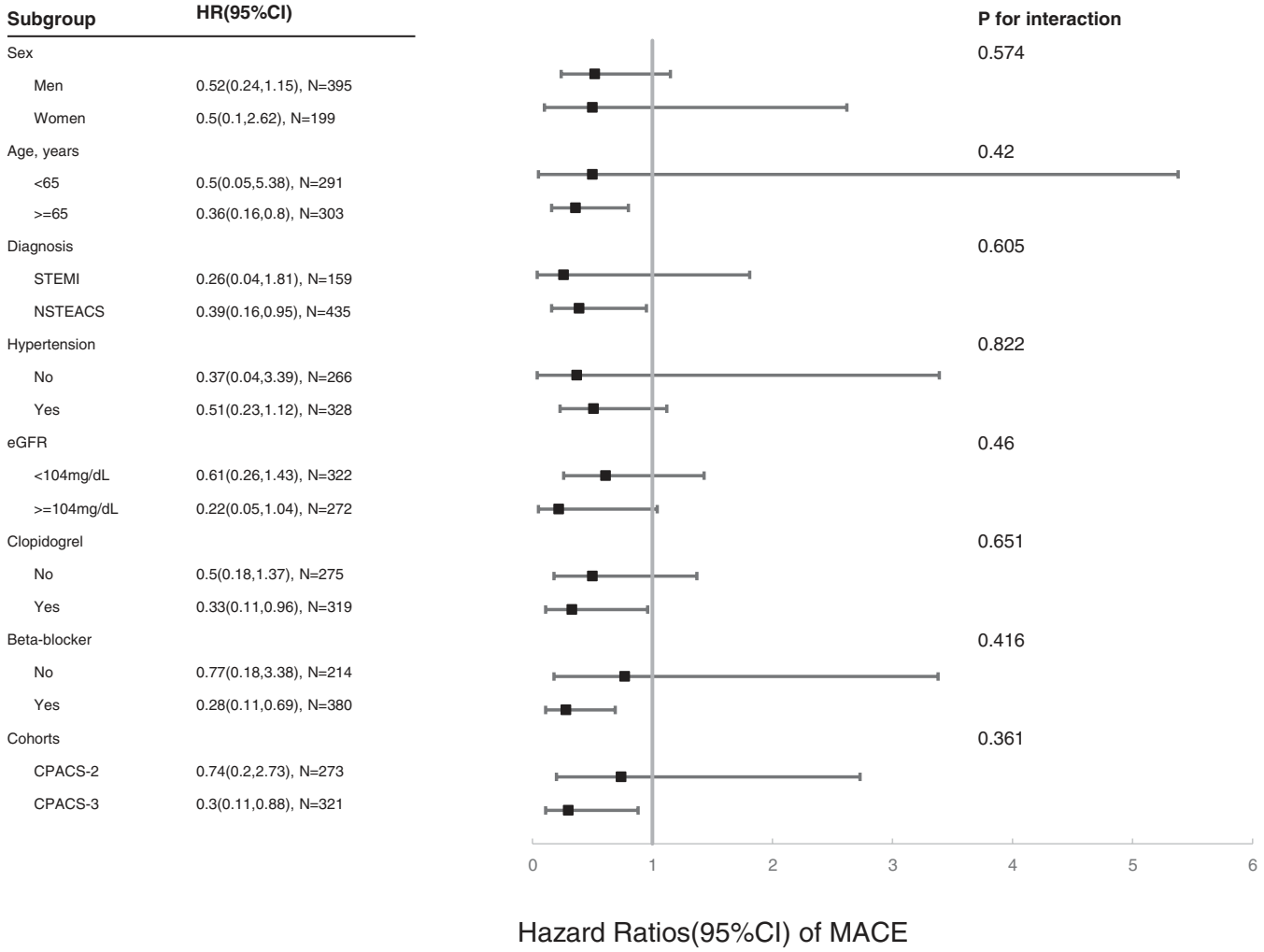

FIGURE 3 Hazard ratios of major adverse cardiovascular events (MACEs) in full-adjusted cox model between statin group (n = 2879) and nonstatin group (n = 495) in subgroups by baseline characteristics

higher serum levels of LDL-c (58-69 mg/dL), suggesting that the threshold of LDL-c level for prescription of statins among ACS patients may not exist or be very low.

4.1 | Strengths and limitations

Our study bears the strengths of large sample size, a prospective cohort, well-designed original studies with high quality assurance, and accounting for propensity score for statin prescription possible. Furthermore, the results were similar after we adjusted confounding factors, especially the cardioprotective medication at discharge. Several limitations also should be noted. First and foremost, these are observational analyses and residual confounding bias is highly likely, and any real effect of statin therapy is likely to be less than the magnitude of the associations observed in this study would suggest. In addition, we used statin prescription information instead of actual use and we did not account for changes in statin use or other time-varying confounders, such as side effects of statin may also impact the adherence of statins. A previous study showed that nonadherence rate was about 17.6% in 1 year.[27] And we did not collect the compliance of statin treatment. Further, as an observational cohort study we could not eliminate entirely the confounding bias that could be introduced by unknown or unmeasured factors, although we have adjusted the propensity score of statin prescription and other known factors such as age, gender, subtypes of ACS, co-medications, etc. Compared with analyzed participants, those lost to follow-up were more likely to be women, have lower education, be treated in lower hospital, have medicare, but less likely to smoke, have higher LDL-c level, hypertension, diabetes, have history of angina, and thus had low risk of MACEs and less use statin, aspirin, clopidogrel, beta-blocker, nitrate esters, and calcium antagonist (**Table S2**). Because interaction analyses showed that all above factors did not modify the association of statin and MACEs. Thus, excluding those lost to follow-up may not introduce significant bias on our results. We did not collect the time of LDL-c measured, as cholesterol level in the acute phase of ACS maybe lower than stable patients. In this study, compared with 96.6% in patients with STEMI and 96.3% in patients with NSTEMI, the rate of measurement of myocardial injury biomarkers (CK-MB or troponin) was only 85.8% in patients with UA. The low percentage of high sensitivity troponin test may explain the higher frequency of UA in this study. We did not collect data on LDL-c after discharge and thus cannot assess the changes of LDL-c between statin group and nonstatin group. This prevent us from inferencing the effect of statin use from

furthering lowering LDL-c or other mechanisms. Lastly, we could not assess the protection effect of high-intensity statin due to its very low frequency of prescription (only 2.3%).

5 | CONCLUSIONS

In conclusion, based on a large real-world cohort of hospitalized Chinese ACS survivors with very low baseline LDL-c, our study demonstrated that prescription of low to moderate intensity of statin therapy was significantly associated with lower risk of MACEs and total death in 12 months after discharge. Randomized trials are required to confirm the extent to which ACS patients with very low LDL-c levels benefit from moderate or high-intensity statin therapy.

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Conflict of interest

The authors declare no potential conflict of interests.

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REFERENCES

1. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;385:117-171.
2. Hulten E, Jackson JL, Douglas K, George S, Villines TC. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2006;166:1814-1821.
3. Larsen AI, Tomey MI, Mehran R, et al. Comparison of outcomes in patients with ST-segment elevation myocardial infarction discharged on versus not on statin therapy (from the harmonizing outcomes with revascularization and stents in acute myocardial infarction trial). *Am J Cardiol*. 2014;113:1273-1279.
4. Lenderink T, Boersma E, Gitt AK, et al. Patients using statin treatment within 24 h after admission for ST-elevation acute coronary syndromes had lower mortality than non-users: a report from the first euro heart survey on acute coronary syndromes. *Eur Heart J*. 2006;27:1799-1804.
5. O'Brien EC, Wu J, Schulte PJ, et al. Statin use, intensity, and 3-year clinical outcomes among older patients with coronary artery disease. *Am Heart J*. 2016;173:27-34.
6. Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA*. 2005;294:2437-2445.
7. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227-239.
8. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. *J Clin Lipidol*. 2014;8:473-488.
9. Perk J, De Backer G, Gohlke H, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The fifth joint task force of the European Society of Cardiology and Other Societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*. 2012;33:1635-1701.
10. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 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*. 2014;63:2889-2934.
11. Giraldez RR, Giugliano RP, Mohanavelu S, et al. Baseline low-density lipoprotein cholesterol is an important predictor of the benefit of intensive lipid-lowering therapy: a PROVE IT-TIMI 22 (pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22) analysis. *J Am Coll Cardiol*. 2008;52:914-920.
12. Lee KH, Jeong MH, Kim HM, et al. Benefit of early statin therapy in patients with acute myocardial infarction who have extremely low low-density lipoprotein cholesterol. *J Am Coll Cardiol*. 2011;58:1664-1671.
13. Leeper NJ, Ardehali R, deGoma EM, Heidenreich PA. Statin use in patients with extremely low low-density lipoprotein levels is associated with improved survival. *Circulation*. 2007;116:613-618.
14. Afilalo J, Majdan AA, Eisenberg MJ. Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials. *Heart*. 2007;93:914-921.
15. Yang W, Xiao J, Yang Z, et al. Serum lipids and lipoproteins in Chinese men and women. *Circulation*. 2012;125:2212-2221.
16. 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.
17. Li S, Wu Y, Du X, et al. Rational and design of a stepped-wedge cluster randomized trial evaluating quality improvement initiative for reducing cardiovascular events among patients with acute coronary syndromes in resource-constrained hospitals in China. *Am Heart J*. 2015;169:349-355.
18. Rong Y, Turnbull F, Patel A, Du X, Wu Y, Gao R. Clinical pathways for acute coronary syndromes in China: protocol for a hospital quality improvement initiative. *Crit Pathw Cardiol*. 2010;9:134-139.
19. Kong X, Ma Y, Chen J, et al. Evaluation of the chronic kidney disease epidemiology collaboration equation for estimating glomerular filtration rate in the Chinese population. *Nephrol, Dialysis, Transplant*. 2013;28:641-651.
20. Joint Committee for Developing Chinese guidelines on Prevention and Treatment of Dyslipidemia in Adults. Chinese guidelines on prevention and treatment of dyslipidemia in adults. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2007;35:390-419.
21. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360, 7:22.
22. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670-1681.
23. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and recurrent events trial investigators. *N Engl J Med*. 1996;335:1001-1009.
24. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387-2397.
25. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713-1722.

26. Giugliano RP, Pedersen TR, Park JG, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet*. 2017;390:1962-1971.

27. Xie G, Zaman MJ, Myint PK, Liang L, Zhao L, Wu Y. Factors associated with compliance to lipid-lowering treatment in China. *Eur J Prev Cardiol*. 2013;20:229-237.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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