Prehospital statin use and low-density lipoprotein cholesterol levels at admission in acute coronary syndrome patients with history of myocardial infarction or revascularization: Findings from the Improving Care for Cardiovascular Disease in China (CCC) project

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Background Lowering low-density lipoprotein cholesterol (LDL-C) by statins is a key strategy for secondary prevention of acute coronary syndrome (ACS). However, few studies have examined prehospital statin use and admission LDL-C levels in ACS patients with history of myocardial infarction (MI) or revascularization. This study aimed to assess use of prehospital statins and LDL-C levels at admission in ACS patients with history of MI or revascularization.

Methods Improving Care for Cardiovascular Disease in China project was a nationwide registry, with 192 participating hospitals reporting details of clinical information of ACS patients from November 2014. By May 2018, 80,282 patients with ACS were included. LDL-C levels were obtained from the initial admission lipid testing.

Results Of the 80,282 ACS patients, 6,523 with a history of MI or revascularization were enrolled. Among them, 50.8% were receiving lipid-lowering therapy before hospitalization (statin monotherapy in 98.4%, combination in 1.2%). A total of 30.1% of patients had LDL-C < 70 mg/dL at admission. In patients receiving prehospital statins, 36.1% had LDL-C < 70 mg/dL compared to 24.0% without prehospital statins ($P < .001$). At discharge, 91.8% of patients were treated with statin monotherapy, 90.7% at moderate doses irrespective of prehospital statin use and LDL-C levels at admission.

Conclusions Among ACS patients with history of MI or revascularization, half were not being treated with statin therapy prior to admission, and most had not attained LDL-C < 70 mg/dL despite prehospital statin use. There is an important opportunity to provide intensive statin or combination lipid-lowering therapy to these very high risk patients. (Am Heart J 2019;212:120-8.)

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Coronary heart disease (CHD) is a major cause of death worldwide, including in China. Acute coronary syndrome (ACS) is a serious type of CHD, including ST-segment elevation myocardial infarction (STEMI), non-STEMI, and unstable angina pectoris (UAP). Patients who have had ACS are at very high risk of occurrence of atherosclerotic cardiovascular disease (ASCVD) and at an increased risk of death.[1-3] Lowering low-density lipoprotein cholesterol (LDL-C) with statin therapy is a key strategy to prevent ASCVD events in the secondary prevention of ACS. A meta-analysis revealed that, in patients with CHD, a statin-related 1-mmol/L reduction in LDL-C level is associated with an approximately 20% reduction in the incidence of major vascular events.[4] Consequently, various guidelines strongly recommend management of dyslipidemia and lowering of LDL-C with statins in patients with ACS, irrespective of baseline LDL-C levels.[2,3,5,6] The Chinese guideline for the management of dyslipidemia recommends aiming for LDL-C less than 70 mg/dL (1.8 mmol/L) in patients with ACS.[2]

However, contemporary registries have revealed a wide gap between these clear recommendations and clinical use of statins to lower LDL-C level in patients with ACS in China.[7-10] Yet few studies have reported current statin use and LDL-C levels in ACS patients with history of myocardial infarction (MI) or revascularization even though such information is important in identifying problems and guiding clinical practice. Therefore, this study aimed to assess the performance of lipid-lowering treatment strategies and LDL-C control in hospitalized ACS patients with history of MI or revascularization as a component of a collaborative program of the American Heart Association (AHA) and Chinese Society of Cardiology: Improving Care for Cardiovascular Disease in China (CCC) Project.

Methods

Study design

The CCC-ACS project, a nationwide registry and quality improvement study with an ongoing database focusing on quality of ACS care, was launched in 2014. Details of the design and methodology of the CCC project have been published.[11] Briefly, a standard Web-based data collection platform (Oracle Clinical Remote Data Capture, Oracle) was used. Trained data abstractors in the participating hospitals reported the required data, which they abstracted from the patients' medical records. Medical records about prehospital medication information were self-reported by patients. Eligible patients were consecutively reported to the CCC-ACS database for each month before the middle of the following month. Third-party clinical research associates performed quality audits to ensure that cases were reported consecutively rather than selectively. In addition, about 5% of reported cases were randomly selected, and the provided data were compared with those in the original medical records to ensure accuracy and completeness.

The CCC project is a collaborative program of AHA and Chinese Society of Cardiology. The AHA was funded by Pfizer for quality improvement initiatives through an independent grant for learning and change. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting of the paper, and its final contents.

Study population

On the basis of principal discharge diagnosis, 80,282 inpatients with STEMI, non-STEMI, or UAP from 150 tertiary hospitals and 42 secondary hospitals were registered, and their data were collected from 1 November 2014 to 31 May 2018. Of these, 6,523 patients with history of MI, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) at least 30 days before the current hospitalization were included in this study (Supplemental Figure A). Approval was granted for this research by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University. Informed consent was not required.

Collection of clinical information

Data collected included relevant patient characteristics, medical history, symptoms on arrival, results of laboratory testing, in-hospital treatment and events, discharge treatment, and counseling. Of note, information about discharge statin dosage was available only for patients enrolled from July 2017 because the report form was amended from July 2017 to include this information.

Definition of variables

ACS patients with history of MI or revascularization were defined as having had prior MI or having undergone PCI or CABG 30 or more days before the current hospitalization. Attainment of the LDL-C target was evaluated according to *2016 Chinese Guideline for the Management of Dyslipidemia in Adults* [2] for the whole population. The 2016 Chinese guideline categorizes patients with ASCVD events as at very high risk and specifies an LDL-C target for them of < 70 mg/dL. Furthermore, we also reported attainment of the LDL-C target in the subgroup of patients with extreme cardiovascular risk according to the 2017 American Association of Clinical Endocrinologists and American College of Endocrinology (AACE) guideline.[5] A new risk category of *extreme risk* was introduced in the updated 2017 AACE guideline. Patients categorized as at extreme risk comprise those with progressive ASCVD after achieving an LDL-C < 70 mg/dL, established clinical cardiovascular disease in patients with the comorbidities of diabetes mellitus (DM), chronic kidney disease 3/4, heterozygous familial hypercholesterolemia comorbidity, or a history of premature ACS (aged < 55 years if male and < 65 years if female). The LDL-C target for such patients is 55 mg/dL in AACE guideline. Patients' cardiovascular risks were stratified on the basis of their in-hospital condition.

In this study, *combination therapy* refers to administration of statins with other lipid-lowering medications. *Hypertension* was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg at admission, having a history of hypertension, or receiving antihypertensive therapy. *DM* was defined as glycated hemoglobin A1c concentration ≥ 6.5% at admission, having a history of DM, receiving glucose-lowering drugs before hospitalization, or diagnosed with DM by the time of discharge.

Statistical analysis

Normally distributed continuous variables are presented as mean ± SD; and non-normally distributed continuous variables, as median with interquartile range. Categorical variables are described as percentages. Statistically significant differences were inferred when the *P* value was < .05. For variables with missing data, we imputed the missing values of baseline characteristics and outcome variables that had a missing rate of less than 10% using the sequential regression multiple imputation method by IVEware software version 0.2 (Survey Research Center, University of Michigan, Ann Arbor, MI). Missing rates of variables and strategies for the management of missing data were presented in Supplemental Table A. Statistical analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC).

Results

Patient characteristics

Of 80,282 patients hospitalized with ACS, 6,523 patients (8.1%) had a history of MI, PCI, or CABG 30 days ago. Of the 6,523 patients, individuals with history of MI, PCI, or CABG accounted for 70.7%, 71.8%, and 4.8%, respectively (Table I). The mean age of the patients was 66.3 ± 11.7 years, and 76.1% were male. Patients with STEMI accounted for 34.7%. The present ACS event occurred within 2 years of the most recent MI or revascularization event in 41.0% of patients. The proportion of patients with prior revascularization was 74.6%, and that of current smoking was 40.8% for men and 6.3% for women. Hypertension and DM were presented in 73.3% and 40.0% of patients, respectively.

Lipid-lowering therapy before hospitalization

Of the 6,523 patients, 2,951 (50.8%) were receiving lipid-lowering therapy before hospitalization (Figure 1), this comprising monotherapy with statins in 98.4% of them and combination therapy in 1.2%. It was found that the longer the interval between the previous event and the present event was, the lower the rate of prehospital statin use (<0.5 year vs 0.5-2 years vs ≥2 years, 64.9% vs 55.9% vs 44.3%, respectively; $P < .001$). Prehospital statin use over calendar years from the previous event to the present event was shown in Supplemental Figure B.

Table I. Characteristics at admission of ACS patients with history of MI or revascularization

	% (n) or mean ± SD (N = 6523)
Age, y (mean ± SD)	66.3 ± 11.7
Men (%)	76.1 (4961)
Last events of MI or revascularization	
MI	70.7 (4614)
PCI	71.8 (4681)
CABG	4.8 (310)
Status of medical insurance	
High reimbursement	46.7 (3043)
Median reimbursement	35.7 (2326)
Low reimbursement	17.7 (1154)
Type of ACS	
STEMI	34.7 (2264)
NSTEMI	34.5 (2253)
UAP	30.8 (2006)
Time from the last event, y	
<0.5	16.8 (1097)
0.5-2	24.2 (1577)
≥2	59.0 (3849)
Comorbidity	
Hypertension	73.3 (4780)
Diabetes	40.0 (2606)
Smoking	32.5 (2122)
Prior dyslipidemia	18.5 (1206)
Prior heart failure	9.6 (628)
Prior stroke	13.8 (901)
Prior renal failure	4.6 (298)
Family history of CHD	4.6 (303)
Prior revascularization	74.6 (4867)
Prehospital statins	50.6 (3301)

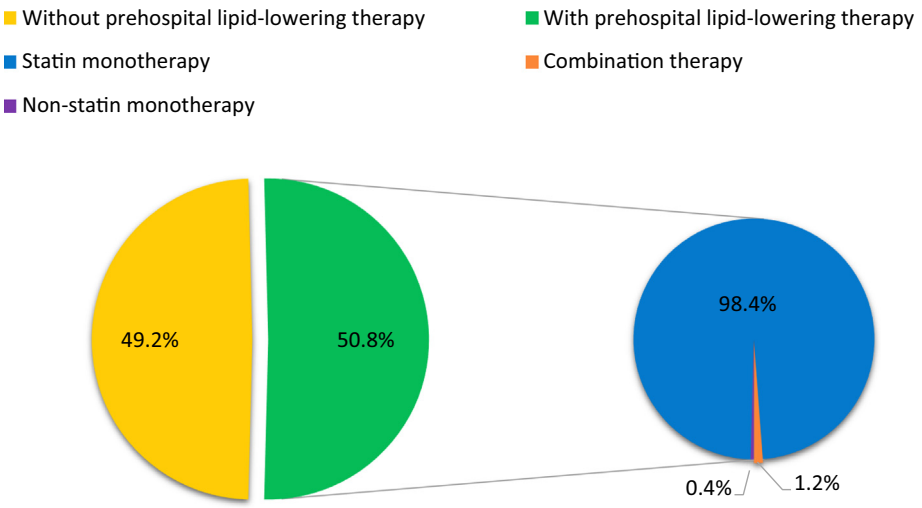
ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CHD, coronary heart disease; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UAP, unstable angina pectoris.

There were no significant differences in prehospital statin use between age groups. Both male and female non-smoking patients had a higher rate of prehospital statin use than smoking patients (men: 52.6% vs 45.0%, $P < .001$; women: 55.0% vs 42.4%, $P = .015$). Patients with medical insurance of high reimbursement had a higher rate of prehospital statin use than those with median or low reimbursement (53.7% vs 48.4% vs 47.1%; $P < .001$). Patients who had undergone prior revascularization had a higher rate of prehospital statin use than those who had not (54.4% vs 39.5%; $P < .001$) (Table II).

LDL-C levels at admission

The mean LDL-C level of the whole study population was 92.0 ± 36.7 mg/dL. The distribution of admission LDL-C levels is shown in Figure 2, *A*. The distribution of LDL-C levels categorized from < 55 mg/dL to ≥ 160 mg/dL is displayed in Supplemental Table B. The LDL-C target (< 70 mg/dL) was achieved in 30.1% of the study population. In patients with LDL-C ≥ 70 mg/dL, the median distance from the target was 31.3 mg/dL (interquartile range [IQR] 15.1-53.7 mg/dL) (Supplemental Figure C), and the maximum distance was 469.8 mg/dL. In

Figure 1



Lipid-lowering therapy before hospitalization in ACS patients with history of MI or revascularization.

about 3.9% of patients, the distance from the target was ≥ 100 mg/dL.

Patients who had been receiving prehospital statins had a significantly lower mean LDL-C than those who had not (86.4 vs 97.8 mg/dL; $P < .001$) and a higher rate of attaining the LDL-C goal (36.1% vs 24.0%; $P < .001$) (Figure 2, *B*). Patients who had been receiving combination therapy of statins and an additional lipid-lowering medicine before hospitalization had a significantly higher rate of attaining the LDL-C goal than those with monotherapy of statins (51.3% vs 35.9%; $P < .05$). Attainment of the LDL-C target by various subgroups analyzed in overall patients and in patients with and without prehospital statin therapy is shown in Supplemental Table C.

In the whole study population, 75.3% of patients (n = 4,913) were identified by cardiovascular risk stratification at admission as at extreme risk, and 40.0% of them (n = 1,964) were classified according to the definition of having progressive ASCVD after achieving an LDL-C < 70 mg/dL. The mean LDL-C level of extreme-risk patients was 87.5 ± 38.0 mg/dL, and their LDL-C target (< 55 mg/dL) was achieved in 18.2% of them. The median distance from the target (< 55 mg/dL) was 35.1 mg/dL (IQR 14.2-61.0 mg/dL) (Supplemental Figure C).

Statin prescription at discharge

Most (91.8%) of the ACS patients with history of MI or revascularization without contraindications to statins and alive at discharge (n = 6,372) were prescribed statin monotherapy at discharge; only 2.8% of them received an additional lipid-lowering medicine. Additionally, combination therapy was prescribed for 2.9% of the patients at extreme risk, without contraindications to statins and alive at discharge (n = 4794) (Figure 3, *A*). In particular, evaluation of prescription of lipid-lowering therapy at discharge in 4 subgroups of patients divided according to their prehospital statin use and achievement of their LDL-C targets at admission (Figure 3, *B*) showed that patients who had been taking prehospital statins but had not attained LDL-C goal were prescribed combination therapy slightly more frequently than patients in the other groups. However, the numbers receiving combination therapy were still far from ideal (2.2% of patients who had been taking prehospital statin and had attained LDL-C goal; 3.2% of patients who had been taking prehospital statins but had not attained LDL-C goal; 1.6% of patients who had not been taking prehospital statins but had attained LDL-C goal; and 3.1% of patients who had not been taking prehospital statins and had not attained LDL-C goal).

Detailed information about statin dosage prescribed at discharge was available for 1,368 patients. Prescription of lipid-lowering therapy at discharge differed moderately from that prescribed overall, 92.6% of these patients being prescribed statin monotherapy and 3.2% combination therapy. Of the patients who were prescribed statin monotherapy at discharge (n = 1,267), 90.7% were prescribed moderate doses and 8.6% high doses (Supplemental Figure D). Of the patients who were at extreme risk and prescribed statin monotherapy at discharge (n = 954), 91.6% were prescribed moderate doses and 8.1% high doses (Supplemental Figure D). Evaluation of statin dosage in 4 subgroups of patients divided according to their prehospital statin use and LDL-C achievement at admission showed that high-dose statins were more often prescribed for patients who had not attained their LDL-C goal, but this percentage was not very high (3.8% of patients who had been taking prehospital statins and had attained LDL-C goal; 10.0% of patients who had been taking prehospital statins

Table II. Prehospital statin use in subgroups of patients

	Prehospital statin use % (n/N)
Total	50.6 (3301/6523)
Age group, y	
<45	45.1 (107/237)
45-59	51.4 (826/1607)
60-74	50.7 (1465/2892)
≥75	50.5 (903/1787)
Sex	
Men	49.5 (2454/4961)
Women	54.2 (847/1562)
Prior MI	
Yes	48.1 (2219/4614)
No	56.7 (1082/1909)
Prior revascularization	
Yes	54.4 (2647/4867)
No	39.5 (654/1656)
Status of medical insurance	
High reimbursement	53.7 (1633/3043)
Middle reimbursement	48.4 (1125/2326)
Low reimbursement	47.1 (543/1154)
Time from the last event, y	
<0.5	64.9 (712/1097)
0.5-2	55.9 (882/1577)
≥2	44.3 (1707/3849)
Smoking	
Yes	44.9 (952/2122)
No	53.4 (2349/4401)
Diabetes	
Yes	53.2 (1387/2606)
No	48.9 (1914/3917)
Prior dyslipidemia	
Yes	72.0 (868/1206)
No	45.8 (2433/5317)
Prior heart failure	
Yes	61.5 (386/628)
No	49.4 (2915/5895)

MI, myocardial infarction.

but had not attained LDL-C goal; 2.7% of patients who had not been taking prehospital statins but had attained LDL-C goal; and 12.0% of patients who had not been taking prehospital statins and had not attained LDL-C goal).

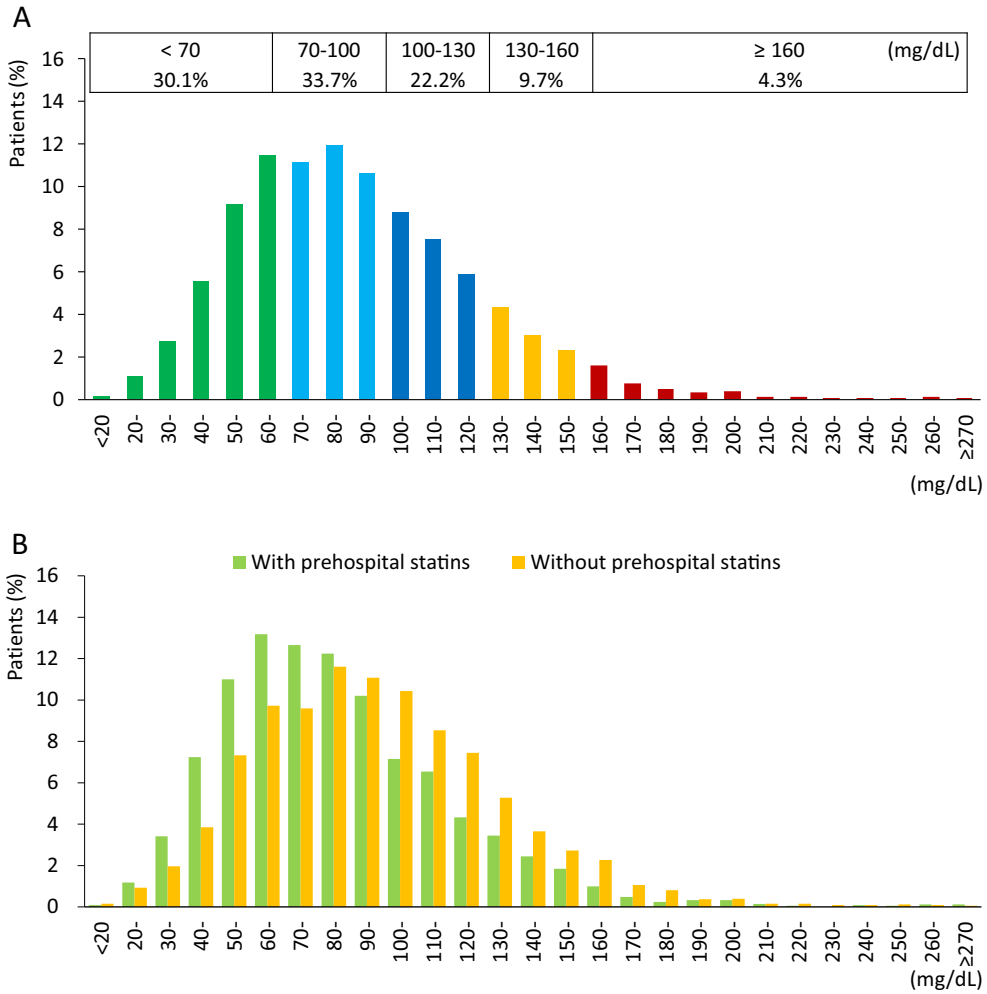
Discussion

In this study, we evaluated statin use and LDL-C control in ACS patients with history of MI or revascularization in China, the study population comprising a nationally representative sample of patients from 192 hospitals. This is the first study focused on the ACS patients with history of MI or revascularization to assess the management of elevated LDL-C in the secondary prevention of ACS in China. There were 3 main findings. First, only half of ACS patients with history of MI or revascularization had been receiving statin therapy before this hospitalization. Second, LDL-C was not well controlled in ACS patients with history of MI or revascularization, even among those who had received prehospital statins. Third, few of the patients who had been taking prehospital statins but had not attained LDL-C goal were prescribed additional lipid-lowering agents at discharge as the Chinese guideline recommends.

In this study, half the ACS patients with history of MI or revascularization were on prehospital lipid-lowering therapy. This unsatisfactory rate of utilization of lipid-modifying medication for secondary prevention of ACS is consistent with that found in previous studies.[7-9,12] The Prospective Urban and Rural Epidemiological study[8] reported that only 2% of CHD patients in China received statins. This extremely low rate may be attributable to community patients having poorer concept about medicine use than inpatients and outpatients. Additionally, those data were collected about 10 years before our study. The Clinical Pathways for Acute Coronary Syndromes in China study[7] showed that although 92.0% of inpatients with ACS were prescribed statins at discharge, statin use declined to 74.8% at 12 months and 66.1% at 24 months after discharge. The continuing decline in use of statin over time following discharge from hospital is consistent with our finding that the longer the interval between the previous event and the present event, the lower was the rate of prehospital statin use. The reason for the unsatisfactory adherence to statins is multifactor.[12] Our study found that nonsmoking patients had higher rate of prehospital statin use than smoking patients, which could be explained by that the healthier lifestyle was, the better medication compliance. In addition, reimbursement status may also impact on the adherence to treatment. This study found that patients with medical insurance of high reimbursement had a better adherence to statins than those with median/low reimbursement. Therefore, expanding insurance coverage and reducing out-of-pocket payments might be useful to increase treatment adherence in the future. Given all those, a coordinated effort among patients, physicians, and the health policy makers is necessary to improve utilization and adherence to treatment.

It has been shown that, in patients with CHD, reduction of LDL-C level by 1 mmol/L by taking statins reduces the incidence of major vascular events by approximately 20%.[4] However, in our study, only 3 in 10 of patients had achieved the LDL-C target of 70 mg/dL at admission as recommended by the Chinese guideline, even among those receiving prehospital statins. A nationally representative survey of 163,641 Chinese adults found that 93.2% of individuals at very high risk of cardiovascular disease do not achieve the LDL-C target.[13] There are 2 possible explanations for the unexpected rate of attaining the LDL-C goal. The first is the unsatisfactory prehospital statin use in these patients, as previously mentioned. The second is that few patients receive combination therapy after a previous acute CHD event. The Dyslipidemia International Study of China study showed that only 39.7% of patients who were on statin therapy and at very high risk attained the LDL-C goal of < 80 mg/dL suggested by the 2007 Chinese

Figure 2

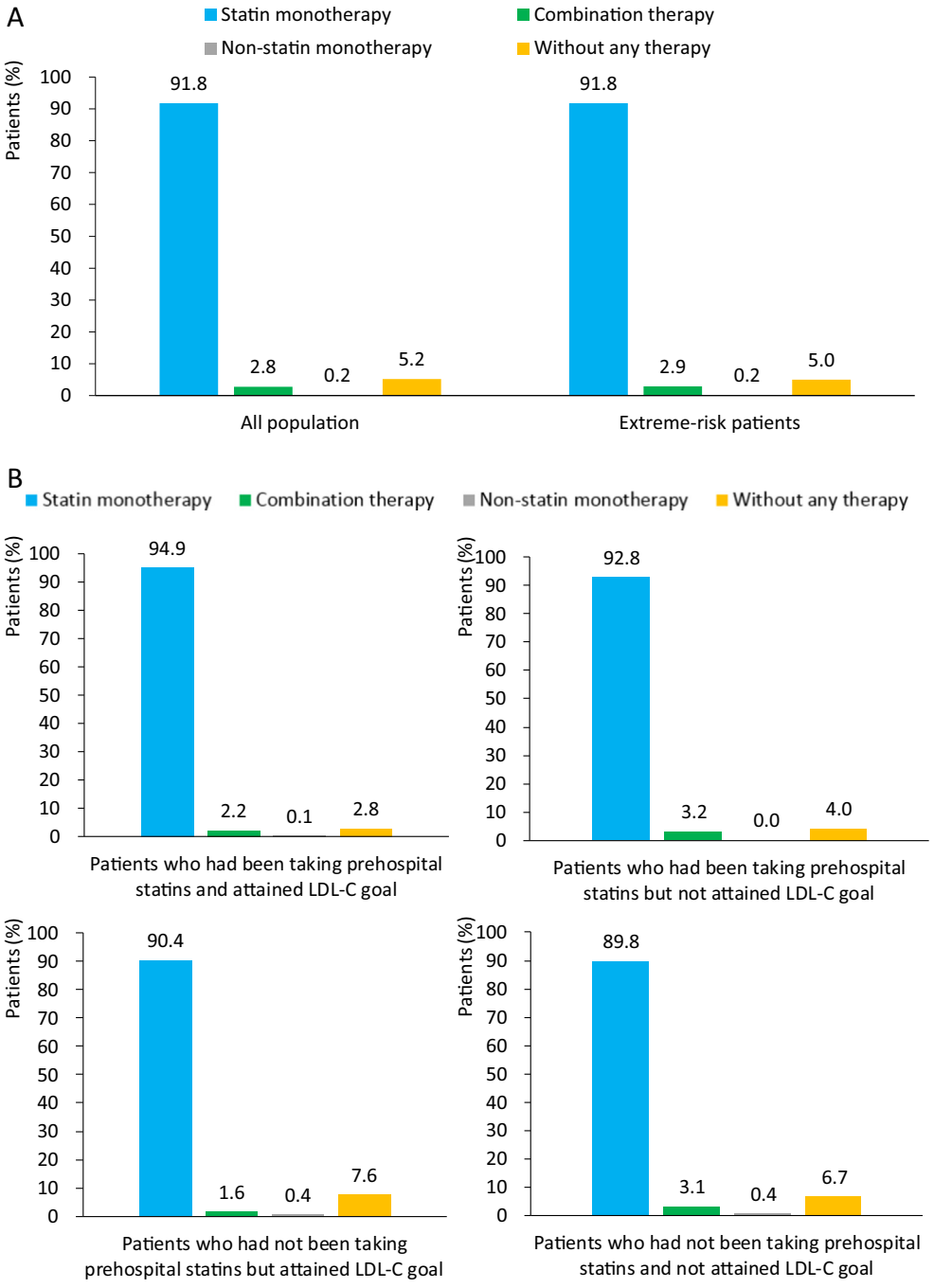


A, Distribution of admission LDL-C levels in ACS patients with history of MI or revascularization. **B**, Distribution of admission LDL-C levels in ACS patients with history of MI or revascularization according to prehospital statin use.

guideline and only 2.0% of these patients were receiving combination therapy.[14]

Underutilization of combination therapy in patients with CHD who have not achieved their LDL-C target indicates that there is a gap between clinical practice and guideline recommendations. During the study period, most of the nonstatin lipid-lowering medications were available in China, such as ezetimibe, probucol, bile acid sequestrants, fibrates, and some traditional Chinese medicines like Xuezhikang. Inhibition of proprotein convertase subtilisin-kexin type 9 (PCSK9) was approved in August 2018 in China. Hence, the accessibility of the drugs is not the main reason for underutilization of combination therapy. However, the cost of the drug, especially of ezetimibe, may be a barrier to prescribe combination treatment because ezetimibe was just covered by insurance system from 2017 in China. Another explanation could be that health care providers lack awareness of prescribing combination therapy as guideline recommended. The 2016 Chinese guideline for the management of dyslipidemia in adults[2] suggests combining an additional lipid-modifying agent with moderate-dose statins in patients taking statins but not attaining their LDL-C goal. However, our results showed that very few patients who were receiving prehospital statins but had not attained their LDL-C goal were prescribed combination therapy at discharge. This indicates that the quality of care from the health care providers' aspect regarding lipid management in secondary prevention of ACS needs to be improved. There is considerable room for improvement in LDL-C control in Chinese patients with ACS by prescription of additional

Figure 3



A, Prescribed lipid-lowering therapy at discharge for all eligible population (n = 6,372) and patients at extreme risk (n = 4,794). **B**, Prescribed lipid-lowering therapy at discharge for eligible patients who had been taking prehospital statins and had attained LDL-C goal (n = 1,168), patients who had been taking prehospital statins but had not attained LDL-C goal (n = 2,069), patients who had not been taking prehospital statins but had attained LDL-C goal (n = 748), and patients who had not been taking prehospital statins and had not attained LDL-C goal (n = 2,387).

lipid-modified agents. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial study showed that ezetimibe added to statin therapy after ACS can further reduce LDL-C levels by 24% and reduce the incidence of ASCVD events.[15] PCSK9 inhibitor has also been shown to benefit patients with ASCVD by lowering LDL-C levels.[16] As PCSK9 inhibitor becomes covered by insurance system in the future and with the improvement of physicians' awareness of combination therapy as guideline recommended, lipid management in secondary prevention of ACS would be better in China.

The Chinese guideline for the management of dyslipidemia recommends moderate-dose statins for patients with ASCVD. In contrast, the American College of Cardiology/AHA[6] and European Society of Cardiology guidelines[3] recommend high-dose statins as the first-line treatment. The reason for recommendation of moderate-dose statins in Chinese guideline was that there was a lack of clear evidence regarding optimal statin dosages in Asian individuals. However, a recently published study[17] has shown that high-dose (4 mg/d) compared with low-dose (1 mg/d) pitavastatin therapy significantly reduced cardiovascular events in Japanese patients with stable coronary artery disease. Further studies are needed to test the efficacy and safety of high-dose statins in Asians individuals.

Furthermore, although high LDL-C is a major risk factor for ACS, patients may present with ACS despite LDL-C at goal. In this study, about 30% of ACS patients with history of MI or revascularization achieved LDL-C target. Attention should be paid to the control of other cardiovascular risk factors while LDL-C is at low levels.

This study had some limitations. The first was that the study population, selected on the criteria of having recurrent acute CHD event, cannot represent all patients with previous coronary event in the secondary prevention of CHD. However, our findings regarding lipid-lowering therapy and LDL-C control in ACS inpatients with history of MI or revascularization do to some degree reflect the management of LDL-C lowering in secondary prevention of CHD. The second was that the LDL-C levels we assessed were obtained at admission. A prior study has shown that LDL-C levels decrease after ACS events; however, this decline is not clinically meaningful.[18] In addition, this decline could have resulted in an overestimation of target achievement, that is, secondary prevention by LDL-C control may be even worse than we have demonstrated.

Conclusions

Prehospital statin use was inadequate in ACS patients with history of MI or revascularization. Most of them did not attain LDL-C goal whether they used statin before hospitalization or not. Although most patients were discharged on statin therapy, this was mostly of moderate intensity, and there remains an important opportunity to provide intensive statin or combination lipid-lowering therapy to these very high risk patients.

Declaration of interest

Dr Fonarow reports consulting for Amgen, Bayer, Janssen, and Novartis and serving on the American Heart Association's Quality Oversight Committee.

The other authors have no conflicts of interest to declare.

Authors' contributions

Prof. D. Z. has full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Y. X. analyzed the data and drafted the manuscript. Y. H., S. C. S., J. G., C. M., G. C. F., K. A. T., and D. Z. conceived the study idea. J. L., Y. H., J. L., Y. H., L. M., N.Y., and M. Z. made substantial contributions to the development of the study protocol. All authors contributed to critical revisions of the paper, and the final manuscript was read and approved by all authors.

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Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.02.019.

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