Atherosclerosis 233 (2014) 707–712

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

The effect of moderate-dose versus double-dose statins on patients with acute coronary syndrome in China: Results of the CHILLAS trial

Shui-ping Zhao [a,**,1], Bi-lian Yu [a,1], Dao-quan Peng [a,1], Yong Huo [b,*,1]

[a] Department of Cardiology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, PR China
[b] Department of Cardiology, Peking University First Hospital, Beijing, PR China

ARTICLE INFO

Article history:
Received 3 June 2013
Received in revised form
12 December 2013
Accepted 13 December 2013
Available online 8 January 2014

Keywords:
Acute coronary syndrome
LDL cholesterol
Lipid-lowering
Statins

ABSTRACT

Background: Current guidelines recommend intensive low-density lipoprotein (LDL) cholesterol lowering with statins, with a target of 70 mg/dL (1.81 mmol/L) LDL cholesterol for those with a very high risk of coronary artery events. However, there is no multicenter study assessing the effect of intensive lipid-lowering therapy with statins on acute coronary syndrome (ACS) in a Chinese population with low baseline LDL cholesterol levels.

Methods and results: Patients ($n = 1355$) with ACS were treated with a moderate dose of statin (atorvastatin 10 mg/d, or equivalent dose of other statins, $n = 675$) or with an intensive dose of statin (atorvastatin, 20 or 40 mg/d, or equivalent dose of other statins, $n = 680$) for 2 years. The primary end points were cardiac death, non-fatal acute myocardial infarction (MI), revascularization, ischemic stroke and documented unstable angina or severe heart failure requiring emergency hospitalization. Baseline lipid levels were nearly identical in both groups with a mean LDL cholesterol level of 2.7 mmol/L (103 mg/dL). At 3 months, LDL cholesterol levels declined 20.2% in the moderate dose statin group and 26.6% in the intensive statin group, respectively ($P < 0.001$). In a 2-year follow-up, a primary end point event occurred in 20 patients in the moderate dose statin group and in 28 patients in the intensive statin group. There was no significant between-group difference in the primary outcome (hazard ratio, 1.39; 95% confidence interval [CI], 0.78–2.46; $P = 0.245$).

Conclusions: For ACS patients with a relatively low baseline LDL cholesterol level who received optimized current medication and interventional therapy, the incremental LDL cholesterol reduction of 6.4% achieved by double-dose statin did not bring significant clinical effectiveness.

1. Introduction

Within the last few years, several large clinical trials in Western populations have firmly established the clinical benefit of intensive statin therapy in patients with acute coronary syndrome (ACS) [1–3]. Extrapolating from the available data, the 2006 update of the American Heart Association/American College of Cardiology guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease recommended a target LDL cholesterol level of less than 2.59 mmol/L (100 mg/dL) for patients with established coronary heart disease (CHD) or diabetes and intensive LDL-C lowering with statins to less than 1.8 mmol/L (70 mg/dL) as a rational choice for very high-risk patients [4]. The 2011 ESC/EAS Guidelines for the management of dyslipidemias recommended that for patients with very high cardiovascular risk, the treatment target for LDL cholesterol is <1.8 mmol/L (70 mg/dL) or a ≥50% reduction from baseline LDL cholesterol [5]. However, it is not clear whether coronary events can be prevented by intensive cholesterol-lowering therapy in patients who have a lower baseline LDL cholesterol, such as in China.

The China intensive lipid lowering with statins in acute coronary syndrome (CHILLAS) trial was a multicenter study in a Chinese ACS population with relatively low baseline LDL cholesterol levels and used a patient-level analysis to compare the effects and safety of intensive statin therapy with that of moderate dose statin therapy (trial No: NCT00728013).

* Corresponding author. Tel.: +86 10 8357 5262; fax: +86 10 66551383.
** Corresponding author. Tel.: +86 731 85295806; fax: +86 731 85295407.
E-mail addresses: zhaosp@medmail.com.cn (S.-p. Zhao), huoyong@263.net.cn (Y. Huo).
[1] CHILLAS Investigators. See Appendix.

0021-9150/$ – see front matter © 2014 Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.atherosclerosis.2013.12.003

2. Methods

2.1. Study overview

CHILLAS, a nationwide, multicenter, prospective, randomized, open-label trial carried out in 20 clinical centers in China, aimed to evaluate the safety and clinical outcomes of ACS patients with intensive lipid lowering therapy. Recruitment and randomization took place from November 2007 to November 2010 and patients were followed up for an average of 2 years. The design and full methodology of CHILLAS were published previously [6]. The study protocol of CHILLAS was approved by the ethics committee at each participating center. All patients gave written informed consent to participate in this study.

2.2. Population

Study participants were 18–80 years of age, hospitalized for acute myocardial infarction (AMI) or unstable angina pectoris, and clinically stable for 24 h. AMI was defined by the presence of symptoms suggestive of ischemia or infarction, with both electrocardiographic evidence and positive cardiac-biomarker evidence of infarction. Unstable angina was defined by the presence of a change from the usual pattern of angina. New ST-wave or T-wave changes in at least two electrocardiographic leads, elevation of cardiac-biomarker levels above the upper limit of normal, but not meeting the criteria for myocardial infarction. An eligible patient with unstable angina required symptoms of ischemia within 24 hours preceding hospitalization. All patients gave written informed consent, and the study was approved by an institutional ethics committee.

Patients were excluded if $\geq$1 of the following conditions were present: hypersensitive to statin, receiving therapy with atorvastatin at a dose greater than 20 mg/d (or equivalent dose of other statins) before enrollment or treatment with other lipid-lowering drugs such as fibric acid derivatives or niacin that could not be discontinued, life expectancy <2 years due to a coexisting condition, in the final stage of chronic congestive heart failure, have obstructive hepatobiliary disease or other serious hepatic or kidney diseases, have an unexplained elevation in creatine kinase (CK) level more than 3 times the upper limit of normal and not related to myocardial infarction, have undergone surgery or serious trauma within the preceding 2 months, or have a baseline level of LDL cholesterol less than 1.29 mmol/L (50 mg/dL).

2.3. Protocol

Starting from 2007, a total of 1355 patients were enrolled in the study. We used electronic medical records in which physical examinations, family medical history, medical history, and laboratory [total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL) cholesterol, LDL cholesterol, apolipoprotein AI, apolipoprotein B, high sensitive C-reactive protein (hs-CRP), liver and renal function measurements, standard 12-lead electrocardiography] and pharmacy data were included. Patients were treated with optimized current medication and interventional therapy for ACS (Table 1), in that angiotensin-converting enzyme inhibitors, β-blockers, aspirin, and clopidogrel were administered to a majority of patients when indicated. All patients received ongoing counseling on therapeutic lifestyle modifications. Patients were not permitted to be treated with any lipid-modifying agent other than the study drug.

Patients were followed up with at 1.5, 3, 12, and 24 months and fasting blood samples for blood lipid were collected at each time point, and hs-CRP levels were also measured. TC and TG were measured by enzymatic, colorimetric methods. HDL cholesterol and LDL cholesterol were measured by homogenous enzymatic colorimetric methods. Liver enzymes and CK were also tested to monitor the side effects of statins. At 6 weeks, if the LDL cholesterol level was greater than 1.81 mmol/L (70 mg/dL), the dose of atorvastatin in the intensive therapy group could be increased to a maximum of 40 mg/d.

Table 1
Baseline characteristics of patients in the intensive and moderate statin groups[a].

Characteristic	Intensive statin therapy ($n=680$)	Moderate statin therapy ($n=675$)
General		
Age	60.8 ± 10.4	60.4 ± 10.6
Gender (male/female)	522/158	520/155
Body mass index (kg/m^2)[b]	24.7 ± 3.0	24.9 ± 3.3
Blood pressure (mmHg)		
Systolic	126.3 ± 16.4	126.5 ± 16.5
Diastolic	75.5 ± 10.4	75.4 ± 9.4
Smoking (%)	342 (51%)	365 (55%)
Drinking alcohol	192 (29%)	189 (29%)
Family history of CAD	30 (4.54%)	29 (4%)
Diabetes (%)	123 (21%)	144 (24%)
Hypertension (%)	369 (61%)	364 (60%)
Cardiovascular status		
Type of ACS (%)		
ST-elevation	278 (40.9%)	273 (40.4%)
Non-ST-elevation	402 (59.1%)	402 (59.6%)
Congestive heart failure (%)	24 (4.0%)	29(4.9%)
Revascularization (%)		
CABG	2 (0.3%)	2 (0.3%)
PTCA	372 (64.2%)	366 (63.6%)

[a] Plus–minus values are means ± SD. Except for the use of insulin and diuretic agent, differences between the groups were not significant. CABG: coronary artery bypass grafting, PTCA: percutaneous transluminal coronary angioplasty, DES: drug-eluting stent, ACE: angiotensin-converting enzyme, LDL: low-density lipoprotein, and HDL: high density lipoprotein.
[b] The body mass index is the weight in kilograms divided by the square of the height in meters.

2.4. Randomization and masking

Patients fulfilling the eligibility criteria with LDL cholesterol <3.6 mmol/L (140 mg/dL) were randomly assigned (1:1) to receive moderate fixed-dose of statin (atorvastatin, 10 mg/d, or equivalent dose of other statins) or intensive statin therapy (atorvastatin, 20–40 mg/d, or equivalent dose of other statins). For this study, an atorvastatin dose of 10 mg was considered therapeutically equivalent to a simvastatin dose of 20 mg, pravastatin dose of 40 mg, and rosuvastatin dose of 5 mg. Allocation was balanced by each center. Participants, care providers, and investigators were unblended to group assignment.

2.5. Outcome measures

Cardiac death, non-fatal AMI, revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) at least 30 days after randomization, documented unstable angina or severe heart failure requiring emergency rehospitalization, and ischemic stroke were counted as primary end points. All clinical events were adjudicated by a monitoring committee consisting of 6 cardiologists, who were blinded to treatment assignment to minimize any bias.

2.6. Statistics

The initial sample size requirement was 1600 patients, based on the assumption of 20% occurrence of a primary end point event in

Table 2
Medication use of the patients in the intensive and moderate statin groups.

	Intensive statin therapy ($n = 680$)	Moderate statin therapy ($n = 675$)
Aspirin (%)	501 (73.7%)	497 (73.6%)
Clopidogrel (%)	478 (70.3%)	490 (72.6%)
Beta-blocker (%)	379 (55.7%)	395 (58.5%)
Nitrate (%)	170 (25.0%)	173 (25.6%)
Calcium-channel blocker (%)	158 (23.2%)	155 (23.0%)
ACE inhibitor or ARB (%)	372 (54.7%)	397 (58.8%)
Diuretic agent (%)	33 (4.85%)	23 (3.41%)
Insulin (%)	23 (3.38%)	42 (6.22%)
Oral hypoglycemic agent (%)	79 (11.6%)	80 (11.9%)

the moderate statin-treated group and 14% occurrence in the intensive statin-treated group. All data analyses were performed using SAS9.2 statistical software. Continuous variable values data that were normally distributed were reported as mean ± standard, non-normally distributed data were expressed as median, interquartile range, and categorical data were reported as percentages. In the assessment of baseline characteristics, the Wilcoxon rank-sum test and *t* test were used to analyze the differences in continuous variables for non-normally and normally distributed values, respectively, in analysis of differences in categorical variables. The Fisher's exact test was used when the expected frequency was <5, otherwise the chi-square test was applied. A Cox proportional hazards model including clinically important variables (treatment, age, gender, smoking, drinking, hypertension, obesity, diabetes, and baseline LDL cholesterol level) was used for the analysis of associations between the intensity of statin therapy and occurrence of clinical end points. All statistical tests were two-tailed and a value of $P < 0.05$ was considered to be statistically significant.

2.7. Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had final responsibility for the decision to submit for publication.

3. Results

3.1. Patients

Between November 2007 and November 2010, 1355 patients were enrolled; 675 patients were randomly assigned to receive moderate dose statin therapy and 680 patients were to receive intensive statin therapy. Demographic and clinical characteristics of the patients assigned to the 2 treatment groups were similar at baseline (Table 1). The great majority of patients (98.1%) were statin-naïve. Similar medications were administered to patients in the moderate or intensive statin groups (Table 2). Aspirin, clopidogrel, and β-blockers were administered to a majority of patients. Overall, 63.9% of patients underwent coronary revascularization. PCI drug-eluting stent implantations were reported in 93.1% of patients.

3.2. Serum lipid levels and hs-CRP levels

At the time of randomization, serum lipid levels were nearly identical in both groups with a mean LDL cholesterol level of 2.7 mmol/L (103 mg/dL), mean TG level of 1.8 mmol/L (160 mg/dL), and mean HDL cholesterol level of 1.08 mmol/L (41 mg/dL) (Table 3).

Atorvastatin (79.9%) was the most frequently prescribed statin followed by simvastatin (16.5%), rosuvastatin (1.9%), pravastatin (1.1%) and fluvastatin (0.60%). At 3 months, the intensive statin therapy group's LDL cholesterol lowered by 26.6% and maintained a mean level of 1.99 mmol/L (78 mg/dL) throughout the follow-up; whereas, the moderate dose statin group's LDL cholesterol lowered by 20.2% and maintained a mean level of 2.1 mmol/L (81 mg/dL). Therefore, the LDL cholesterol level was 6.4% lower in the intensive group than in the moderate group ($P < 0.001$). There were no differences in the changes in HDL cholesterol and TG levels in these two groups (Fig. 1).

The hs-CRP levels were not significantly different in the 2 groups at baseline (8.0 ± 16.3 mg/L in the intensive vs. 8.7 ± 18.8 mg/L in the moderate group, $P > 0.05$) or after 3 months of therapy (3.1 ± 6.4 mg/L in the intensive vs. 2.9 ± 6.6 mg/L in the moderate group, $P > 0.05$); however, after 3 months of therapy, hs-CRP levels decreased significantly in both groups compared to baseline (both $P < 0.001$).

3.3. End point events

During the 2-year study period, a primary end point event occurred in 20 patients (3.9%) in the moderate dose statin therapy group and in 28 patients (5.5%) in the intensive statin therapy group. There was no significant between-group difference in the primary outcome (hazard ratio, 1.39; 95% confidence interval [CI], 0.78–2.46; $P = 0.261$) (Fig. 2). In the patients who presented with elevated LDL cholesterol levels (>2.7 mmol/L), the primary end point occurred in 3.8% of patients allocated to moderate statin group, compared with 6.6% in the intensive statin group ($P = 0.215$); there was also no significant difference in patients with LDL cholesterol ≤2.7 mmol/L ($P = 0.487$).

3.4. Safety

Elevated serum aminotransferase levels [>3 times upper limit of normal (ULN)] were found in 13 patients in the intensive statin therapy and 10 patients in the moderate statin therapy group. Two patients had elevated serum CK (>5 times ULN) in the intensive statin group and 1 patient in the moderate dose statin group, with no significant difference between the groups. There was no documented case of rhabdomyolysis. Two patients in the moderate dose therapy group were hospitalized with a diagnosis of cerebral hemorrhage.

Table 3
Blood lipids at baseline and 3 months after treatment.

	Intensive statin therapy			Moderate statin therapy		
	Baseline	At 3 months	*P* value	Baseline	At 3 months	*P* value
TC (mmol/L)	4.61 ± 1.48	3.95 ± 2.68	<0.001	4.73 ± 2.62	4.14 ± 3.80	<0.001
TG (mmol/L)	1.82 ± 1.19	1.50 ± 0.84	<0.001	1.78 ± 1.14	1.55 ± 0.78	<0.001
LDL-C (mmol/L)	2.72 ± 0.83	1.99 ± 0.74	<0.001	2.71 ± 0.91	2.17 ± 0.75	<0.001
HDL-C (mmol/L)	1.09 ± 0.32	1.23 ± 0.58	<0.001	1.07 ± 0.32	1.21 ± 0.41	<0.001

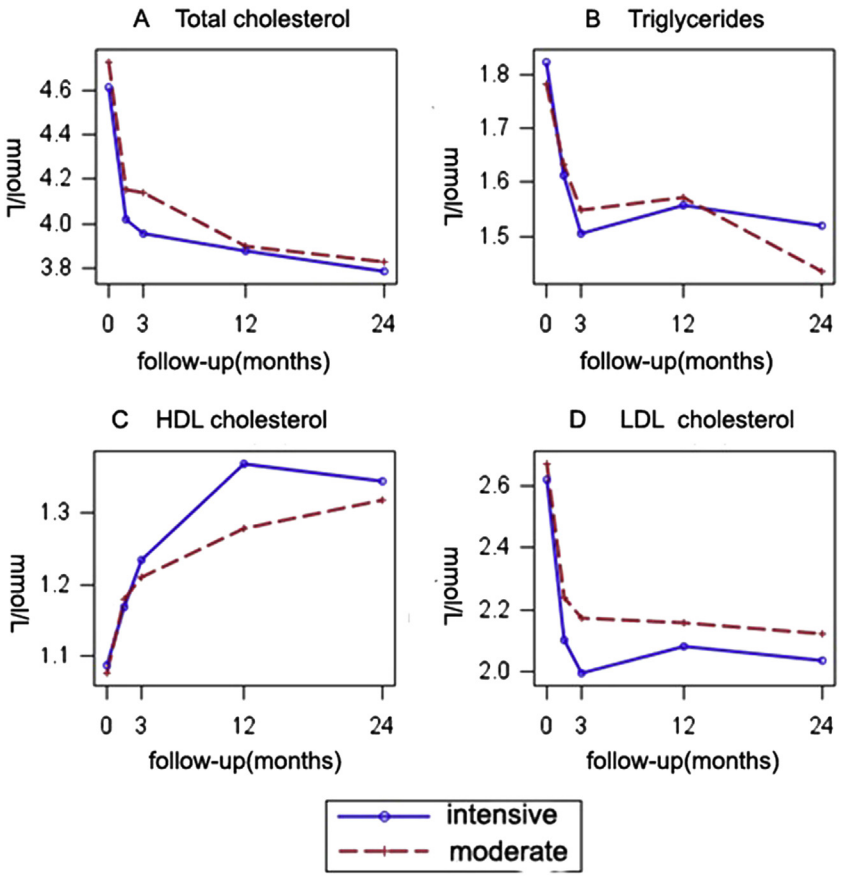

Fig. 1. Serum lipid levels in intensive versus moderate statin groups. Values are means (95% confidence interval).

4. Discussion

Intensive statin therapy is associated with important benefits for patients with established ACS. There is widespread interest in whether intensive-dose statin still yields clinical benefits in patients with low LDL cholesterol levels at baseline. The results of this trial showed that ACS patients in a Chinese population had relatively low baseline LDL cholesterol concentrations. Although doubling the dose of statins resulted in an additional 6.4% incremental reduction in LDL cholesterol, it did not provide more benefit in reduction of primary end points, including cardiac death, non-fatal acute MI, revascularization with either PCI or CABG, ischemic stroke and documented unstable angina or severe heart failure requiring emergency hospitalization, as compared with moderate dose statin therapy. The findings in our trial were unexpected and might be best interpreted in the context of the patients' relatively low LDL cholesterol level and low cardiovascular event rates.

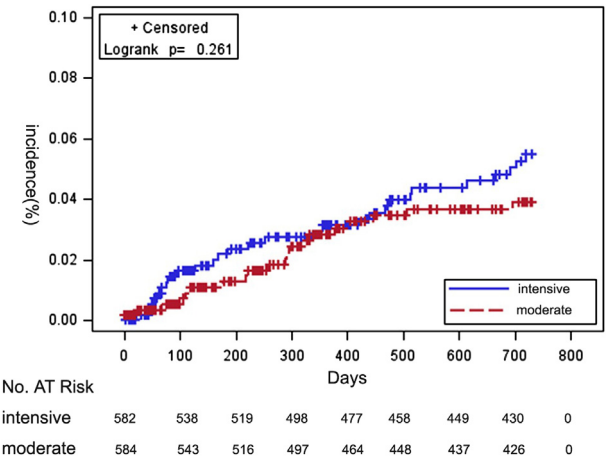

Fig. 2. Kaplan–Meier estimates of the incidence of primary events in the intensive and moderate statin groups.

In this study, the mean baseline LDL cholesterol level of the patients enrolled was 2.7 mmol/L (105 mg/dL). This level is lower than the mean baseline LDL cholesterol level in the 3 previous Western trials with statins therapy in patients with ACS (3.1–3.6 mmol/L, 120–140 mg/dL) [1–3]. To date, controversy remains regarding the influence of pretreatment LDL cholesterol levels on the clinical benefit of lipid-lowering therapy. Previous studies in patients with acute and chronic coronary disease have evaluated the role of baseline LDL cholesterol on the benefit of statin treatment. Although the Scandinavian Simvastatin Survival Study (4S study) [7] and Heart Protection Study (HPS) [8] found a similar benefit of simvastatin over placebo irrespective of baseline LDL cholesterol, the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) [9] and Cholesterol And Recurrent Events (CARE) [10] trials showed a threshold of LDL cholesterol for the benefit of statin therapy with pravastatin (40 mg). Besides these placebo-controlled studies that randomized patients with chronic coronary disease, two trials performed in patients with ACS showed the lipid-lowering benefit of statins may be limited by baseline LDL cholesterol values. The subgroup analysis of Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In

Myocardial Infarction 22 (PROVE IT–TIMI 22) study showed that the benefit of intensive therapy progressively declined as baseline LDL cholesterol decreased. Patients with LDL cholesterol ≤2.38 mmol/L (92 mg/dL) experienced similar rates of primary and secondary end points in the pravastatin (40 mg) and atorvastatin (80 mg) groups [11]. Another study performed in Korea revealed that the beneficial effects of statin therapy in AMI seem to vanish when LDL cholesterol is below 2.72 mmol/L (105 mg/dL) [12], which is consistent with the pretreatment concentration in our study. Furthermore, the beneficial changes of cholesterol lowering on regression of coronary atherosclerosis demonstrated by angiography are also directly related to the pretreatment level of LDL cholesterol, with little benefit occurring in patients with low LDL cholesterol levels [13]. Together, these results suggest that the reduction in the rate of coronary events with statins is influenced by the pretreatment level of LDL cholesterol and the benefit of statin therapy could decline or even vanish when LDL cholesterol is below a certain level.

In the present trial, low frequencies of the primary end points cardiac event rate (3.6%) was observed in Chinese patients with ACS, which was similar to another large trial of CHD in Chinese [14]. Furthermore, it has been reported that although cardiovascular diseases have rapidly increased recently, CHD mortality remains low in China. For example, CHD mortality (85.5/105 person-years) was only one-third of stroke mortality (276.9/105 person-years) in the Chinese population [15,16]. These findings are contrary to the high rate of major adverse cardiac events in patients with ACS in Western countries. In a cohort of 1321 consecutive ACS patients, a major adverse clinical event occurred in 331 patients (one-year probability 0.25) for 12 months [17]. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study of 3086 patients with ACS, a primary end point event occurred in 228 patients (14.8%) in the atorvastatin group and 269 patients (17.4%) in the placebo group within a 16-week follow-up [1]. The reasons underlying this gap are likely multifactorial. A low serum total cholesterol level related to a low habitual dietary intake of fat and cholesterol was considered the main underlying reason for the low atherosclerotic cardiovascular mortality in China [18]. The low rate of primary end points in our study may also be partly related to the inclusion criteria, which defined that the patients could be enrolled after being clinically stable for 24 h, because factors that are unlikely to be affected by cholesterol lowering, such as left ventricular dysfunction, ventricular arrhythmias, and mechanical complications, represent the major determinants of short-term outcome. Thus, major adverse cardiac events that occurred during hospitalization were not counted as primary end points in the trial. Furthermore, it is noted that the majority of patients with ACS in the trial received optimized current medication and interventional therapy, which has been widely demonstrated to be effective for the secondary prevention of cardiac events in patients with ACS. With improved uptake of guideline-recommended medical and intervention therapies, the rate of cardiovascular events in patients with ACS can be substantially reduced [19].

The results of the CHILLAS study could be considered representative of what can be achieved by lipid-lowering treatment, over and above other strategies currently employed in the modern, comprehensive treatment of patients with a history of ACS and low baseline cholesterol levels. In such a population, moderate doses of statins is capable of lowering LDL cholesterol to a mean level of 2.0 mmol/L (80 mg/dL), which is the optimal target recommended by Chinese guidelines for the management of dyslipidemias [20]; whereas, a double dose or more statin does not afford further clinical benefit. These findings are supported by a previously published Japan-ACS trial in which atorvastatin (10 mg or equivalent dose of other statins) decreased LDL cholesterol to less than 90 mg/dL [21]. A possible reason for the greater effect of moderate statin doses could be the difference in statin pharmacokinetics in Asian and Western populations [22]. Each doubling of the statin dose only produces an incremental LDL cholesterol reduction of approximately 5–6% of the baseline LDL cholesterol value, while the side effects of statins are dose-related: side effects occur more frequently and severely with stronger doses of statins [23,24]. Taking all these factors into account, although our findings cannot be considered definitive and require confirmation, the observations suggest that further upward dose titration of statins does not bring additional benefit in a Chinese ACS population with a low cardiac event rate and low baseline LDL cholesterol level. Taking pharmacoeconomics into account, it is reasonable to prescribe moderate doses of statins (those used in current clinical practice) in a Chinese population.

Notably, statins have been reported to improve outcomes in patients with ACS by lipid-independent, so-called pleiotropic effects, particularly by modulation of inflammation [25]. It has been shown that although the hs-CRP levels decreased significantly in both groups after 3 months of therapy, there were no significant differences in the 2 groups. The decrease of hs-CRP seems largely due to the resolution of acute inflammation in 3 months rather than stains treatment. Hence, it is likely that the anti-inflammatory effects of statin did not play a vital role in the reducing of cardiac events.

However, there are several limitations in our trial. First, the sample size was determined on the basis of a 20% event rate and an expected 30% reduction of primary end points in the intensive statin group compared with the moderate dose statin group. Therefore, the sample size is not adequate. Although the great majority of patients were prescribed atorvastatin, the type of statins employed varied due to non-free drug supply and cost constraints. Furthermore, the dose of statins used in the intensive treatment group (20 or 40 mg/d atorvastatin), which was comparable with the usual clinical prescribing practice in China, differs from the higher dose of atorvastatin (80 mg/d) employed in Western populations. Some available evidence suggests that the benefits of statin treatment come from the reduction of LDL cholesterol. In this trial, the incremental LDL cholesterol reduction of 6.4% achieved by intensive statin treatment may not be adequate to bring a further risk reduction. Thus, further trials with higher doses of statin could provide more information. Other limitations include the short follow-up time and bias due to the open-label design.

In conclusion, in the present study, we show that an incremental LDL cholesterol reduction of 6.4% achieved by double-dose statin cannot bring significant clinical effectiveness in ACS patients with relatively low baseline LDL cholesterol levels. Further head-to-head studies with larger sample sizes are needed to confirm this result.

Conflict of interest

No conflict of interest was declared.

Acknowledgments

This study is sponsored by “The 11th Five-Year Plan” of PR China.

Appendix

The investigators are as follows: Shuiping Zhao, Daoquan Peng, Department of Cardiology, the Second Xiangya Hospital, Central South University; Weiyi Fang, Yinjia Xu, Department of Cardiology, Shanghai Chest Hospital; Yuegai Lu, Yang Xia, Department of Cardiology, Chinese PLA General Hospital; Wei Gao, Jie Niu,

Department of Cardiology, Peking University Third Hospital; Guoxiang He, Tao Jing, Department of Cardiology, Southwest Hospital, Third Military Medical University; Yuqing Hong, Zhongjiang Zhou, Department of Cardiology, Nanfang Hospital, Southern Medical University; Qi Hua, Lilan Yang, Cardiovascular Department, Xuan Wu Hospital, Capital Medical University; Weiming Wang, Qi Li, Department of Cardiology, People's Hospital, Peking University; Yawei Xu, Xuejing Yu, Department of Cardiology, Tongji University; Tianlun Yang, Guolong Yu, Department of Cardiology, Xiangya Hospital, Central South University; Xinchun Yang, Department of Cardiology, Beijing Chao-yang Hospital, Capital Medical University; Yuejin Yang, Haiyan Xu, Department of Cardiology, Fu Wai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College; Qiutang Zeng, Songnan Li, Department of Cardiology, Wuhan Union Hospital, Huazhong University of Science and technology; Shuyang Zhang, Ran tian, Department of Cardiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences; Yongquan Wu, Bing Sun, Department of Cardiology, Tongji Hospital, Tongji University; Guoxian Qi, Lidong Zhu, Department of Cardiology, the First Affiliated Hospital, China Medical University; Xiaomei Guo, Wei Zhou, Department of Cardiology, Tongji Hospital, Huazhong University of Science and technology; Jiyan Chen, Department of Cardiology, Guangdong Cardiovascular Institution; Zhimin Du, Weiyi Mai, Department of Cardiology, the First Affiliated Hospital, Sun Yat-Sen University; Weimin Li, Wei Han, Department of Cardiology, the First Clinical College, Harbin Medical University.

References

[1] Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA 2001;285:1711–8.
[2] Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–504.
[3] Ray KK, Cannon CP, McCabe CH, et al. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2005;46:1405–10.
[4] Smith Jr SC, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006;113:2363–72.
[5] European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011;32:1769–818.
[6] Zhao SP, Peng DQ, Yu BL, et al. Rationale and design of China intensive lipid lowering with statins in acute coronary syndrome: the CHILLAS study. Am Heart J 2009;158:509–512.e1. http://dx.doi.org/10.1016/j.ahj.2009.07.030.
[7] Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study (4S). Lancet 1995;345:1274–5.
[8] MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebocontrolled trial. Lancet 2002;360:7–22.
[9] Pfeffer MA, Sacks FM, Moyé LA, et al. Influence of baseline lipids on effectiveness of pravastatin in the CARE trial. Cholesterol and recurrent events. J Am Coll Cardiol 1999;33:125–30.
[10] Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med 1998;339:1349–57.
[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;52:914–20.
[12] Lee JH, Park SH, Yang DH, et al. Threshold level of low-density lipoprotein cholesterol for the short-term benefit of statin therapy in the acute phase of myocardial infarction. Clin Cardiol 2012;35:211–8.
[13] Sacks FM, Pasternak RC, Gibson CM, et al. Effect on coronary atherosclerosis of decrease in plasma cholesterol concentrations in normocholesterolaemic patients. Harvard Atherosclerosis Reversibility Project (HARP) Group. Lancet 1994;344:1182–6.
[14] Lu Z, Kou W, Du B, et al. Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. Am J Cardiol 2008;101:1689–93.
[15] He J, Gu D, Wu X, et al. Major causes of death among men and women in China. N Engl J Med 2005;353:1124–34.
[16] Yang W, Xiao J, Yang Z, et al. Serum lipids and lipoproteins in Chinese men and women. Circulation 2012;125:2212–21.
[17] Colivicchi F, Tubaro M, Santini M. Clinical implications of switching from intensive to moderate statin therapy after acute coronary syndromes. Int J Cardiol 2011;152:56–60.
[18] Aliprandi-Costa B, Ranasinghe I, Chow V, et al. Management and outcomes of patients with acute coronary syndromes in Australia and New Zealand, 2000–2007. Med J Aust 2011;195:116–21.
[19] Tao SC, Huang ZD, Wu XG, et al. CHD and its risk factors in the People's Republic of China. Int J Epidemiol 1989;18:S159–63.
[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] Miyauchi K, Kimura T, Morimoto T, et al. Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome (JAPAN-ACS): rationale and design. Circ J 2006;70:1624–8.
[22] Lee E, Ryan S, Birmingham B, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther 2005;78:330–41.
[23] LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425–35.
[24] Alsheikh-Ali AA, Maddukuri PV, Han H, et al. Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer: insights from large randomized statin trials. J Am Coll Cardiol 2007;50:409–18.
[25] Ray KK, Cannon CP. The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes. J Am Coll Cardiol 2005;4:1425–33.