High-Sensitivity C-Reactive Protein Combined with Low-Density Lipoprotein Cholesterol as the Targets of Statin Therapy in Patients with Acute Coronary Syndrome

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Summary

To investigate the combination of high-sensitivity C-reactive protein (hs-CRP) and Low-density lipoprotein (LDL)-C as the targets for statin treatment in patients with acute coronary syndrome (ACS). This single-center, prospective, randomized study was performed in 400 patients treated with atorvastatin 40 mg/day for 1 month and then with atorvastatin 20 mg/day as maintenance. The patients were randomized to the LDL group (LDL-C target of < 2.07 mmol/L according to the Chinese dyslipidemia guidelines) and to the LDL-CRP group (LDL-C target of < 2.07 mmol/L and hs-CRP target of < 3 mg/L). The patients were followed up for major adverse cardiac events (MACE) at 6, 12, and 18 months. The two groups had similar baseline characteristics and 391 patients completed the follow-up. No differences were found in LDL-C between the two groups, but a difference was found in hs-CRP at 12 and 18 months. There was a significant difference in revascularization (8.7% versus 3.6%, \(P = 0.04\)) and MACE (16.8% versus 9.7%; \(P = 0.04\)) between the LDL and LDL-CRP groups at 18 months. Compared to LDL-C as the single target, targeting both LDL-C and hs-CRP by statin therapy in patients with ACS could further reduce the incidence of MACE and the residual cardiovascular risk.

Key words: Major adverse cardiac events, Inflammation, Cardiovascular risk

Atherosclerosis is an aggressive inflammatory process.\(^1,2\) It leads to the narrowing of coronary arteries, which is often asymptomatic early in the course of the disease, but progresses with plaque thickening or plaque rupture, ultimately leading to angina and/or myocardial infarction.\(^3,4\) The consequences of atherosclerosis represent the most important cause of death in the United States, where the prevalence of atherosclerosis is approximately 6.2% in people > 20 years of age.\(^5\) Low-density lipoprotein (LDL) particles modified by oxidative stress associated with the inflammation observed in atherosclerosis accumulate in the arterial wall, leading to plaque formation and progression.\(^6\) Controlling LDL-cholesterol (LDL-C) levels is the main strategy in patients in primary and secondary cardiovascular prevention.\(^7,8\)

Statins are HMG-CoA reductase inhibitors known to increase the expression of the LDL receptor, leading to a decrease in the plasma LDL-C levels.\(^9,10\) But beyond their lipid-lowering effects, statins have a number of pleiotropic effects attributed to anti-inflammatory activity, enhanced endothelial function, inhibition of platelet activation, and inhibition of oxidative stress that are independent from their lipid-lowering effect.\(^9,10\)

LDL-C is the target of statin therapy in various available guidelines.\(^5,6,12,13\) Reaching a target LDL-C level of < 2.07 mmol/L will lead to a greatly decreased risk of major adverse cardiovascular events (MACE), but there is still a residual cardiovascular risk from inflammation that is overlooked by these guidelines.\(^14,15\)

Therefore, the present study investigated targeting both high-sensitivity C-reactive protein (hs-CRP) and LDL-C levels in patients with acute coronary syndrome (ACS) treated with statin. The results of the present study could help optimizing statin therapy and prevent the occurrence of MACE.

Methods

Study design and setting: This was a prospective, single-center, double-blind, randomized clinical trial that was performed between July 2013 and June 2015 at the cardiology department of the Shanghai Pudong New District
Zhoupu Hospital. All eligible patients received atorvastatin treatment. They were randomized at a 1:1 ratio to hs-CRP combined with LDL-C or to LDL-C alone as the clinical endpoint of atorvastatin management after percutaneous coronary intervention (PCI).

The study protocol was approved by the ethics committee of the Shanghai Pudong New District Zhoupu Hospital (#20130017). Written informed consent was obtained from each patient.

**Patients:** Patients with ACS were selected using one of the two following criteria: 1) unstable angina, defined as the new onset or worse angina over the previous month at the time of presentation coinciding with appropriate objective evidence of myocardial ischemia on electrocardiography (ECG) or myocardial perfusion imaging, and at least one de novo lesion with >50% stenosis was detected by coronary angiography (CAG); or 2) acute myocardial infarction, defined as chest pain lasting > 30 minutes and levels of troponin-T and creatine kinase muscle B increased to three times the upper limit of normal with or without ST-segment elevation on ECG, and plaque rupture and thrombosis confirmed by CAG. The exclusion criteria were: 1) previous myocardial infarction; 2) previous revascularization; 3) history of recent infection; 4) inflammatory conditions (such as arthritis or lupus) or taking immunosuppressant agents; 5) hepatic dysfunction or renal dysfunction; or 6) concurrent severe illness with expected survival of < 5 years.

In this study, 400 eligible patients were randomized 1:1 to the LDL group (n = 200) or the LDL-CRP group (n = 200) using an interactive voice-response system.

**Revascularization:** All patients received 300 mg of aspirin and 450 mg of clopidogrel before surgery. PCI was only performed for lesions with ≥70% stenosis. All eligible patients were treated with rapamycin-eluting stents and stent implantation required the whole lesion coverage. Surgical success criteria included residual stenosis of ≤30%, forward flow TIMI III grade, and no acute complications.

**Statin treatment:** Patients undergoing PCI were treated with atorvastatin 40 mg/day for one month, and then with atorvastatin 20 mg/day until reaching the clinical endpoint of atorvastatin management. The patients in the LDL group were managed using LDL-C < 2.07 mmol/L as the clinical endpoint of atorvastatin management. The patients in the LDL-CRP group were managed using LDL-C < 2.07 mmol/L and hs-CRP < 3 mg/L as the clinical endpoints of atorvastatin management. For patients in either study group who had not reached the clinical endpoint, the atorvastatin dose was increased to 40 mg for 4-6 weeks. For patients who had reached the target level, a daily dose of 10 mg atorvastatin was given for long-term maintenance and blood lipid control was recommended based on improved lifestyle.

**Follow-up:** The patients were followed up at the 6th, 12th, and 18th months after PCI. The clinical characteristics were collected, including the levels of LDL-C and hs-CRP and the occurrence of MACE.

**Outcomes:** The primary outcome was the rate of MACE during the 18-month follow-up, which included cardiovascular death, angiographically confirmed nonfatal myocardial infarction from plaque rupture and thrombosis, and symptom-driven revascularization by either coronary angioplasty or bypass surgery. The secondary outcomes included hospitalization for unstable angina, secondary hepatic dysfunction (defined as alanine aminotransferase levels > 2 times the upper limit of the normal range), and cumulative 18-month survival. In case of secondary hepatic dysfunction, the patient was withdrawn from the study and the drug was changed; the patient was also excluded from the analyses.

**Laboratory Studies:** Routine biochemistry and blood levels were measured using standard hospital methods before and after PCI, at baseline, and at each follow-up visit.

**Statistical analysis:** Continuous data were expressed as mean ± standard deviation and analyzed with two-tailed unpaired Student’s t-test for normally distributed variables and by the Mann-Whitney U test for variables with skewed distribution. Categorical data were expressed as frequency and percentage and analyzed using the chi-squared test. Kaplan-Meier curves were used to assess MACE-free survival. Differences between the curves were tested with a log-rank statistic. Statistical analysis was performed using SPSS 17.0 software (IBM, Armonk, NY, USA). Two-sided P-values < 0.05 were considered statistically significant.

**Results**

**Baseline characteristics of the patients:** Figure 1 presents the study flowchart; 391 eligible patients with ASC were included in this study: 196 patients in the LDL group and 195 patients in the LDL-CRP group. There were no significant differences in age, sex, and other characteristics at baseline between the two groups (Table I).

**Comparison of the incidence of MACE between the LDL and LDL-CRP groups at the 18-month follow-up:** The occurrence of MACE at 18 months was significantly lower in the LDL-CRP group compared to the LDL group (9.7% versus 16.8%, P = 0.039) (Table II). The occurrence of revascularization (TVR) was significantly lower in the LDL-CRP group than in the LDL group at 18 months after PCI (3.6% versus 8.7%, P = 0.036). No significant difference was observed in the occurrence of MACE at 6 and 12 months between the two groups.

**Comparison of the cumulative MACE-free survival and cumulative hazard rate of MACE at the 18-month follow-up:** Cumulative MACE-free survival and cumulative hazard in the two groups was analyzed using a Kaplan-Meier curve (Figures 2, 3). The cumulative survival in the LDL-CRP group was significantly higher than in the LDL group (P = 0.035). The cumulative hazard of MACE in the LDL group was significantly higher (P = 0.035).

**Comparison of hospitalization for unstable angina and serum levels of LDL-C and hs-CRP between the LDL and LDL-CRP groups at the 18-month follow-up:** No significant difference in re-hospitalization for angina pectoris was found between the two groups (Table III). The serum levels of LDL-C were not significantly different between the LDL and LDL-CRP groups at 6, 12, and 18 months (all P > 0.05). On the other hand, significant dif-
ferences were found in the hs-CRP levels between the LDL and LDL-CRP groups at 12 (5.96 ± 3.51 versus 3.85 ± 2.23 mg/L, \( P = 0.033 \)) and 18 months (4.68 ± 2.81 versus 2.05 ± 1.21 mg/L, \( P = 0.018 \)).

**Discussion**

LDL-C is the target of statin therapy in various available guidelines, but the residual risk from inflammation is overlooked. Therefore, this study investigated the combination of hs-CRP and LDL-C as the targets for statin treatment in patients with ACS. The results showed that compared to LDL-C as the single target, targeting both LDL-C and hs-CRP with statin therapy in patients with ACS could further reduce the incidence of MACE and the residual cardiovascular risk.

Inflammation plays an important role in coronary heart disease. The anti-inflammatory and anti-oxidative effects of statins can improve the endothelial function and stabilize plaques, which are independent of the lipid-lowering effect of statins.9-11,18-20) CRP, especially hs-CRP, is closely related to cardiovascular diseases and could effectively reflect the inflammation status of patients with atherosclerosis.11,22) There are many studies that have demonstrated that CRP is significantly associated with cardiovascular risk and that it could be used as an independent predictive factor of cardiovascular diseases.23-25) Primary preventive studies have demonstrated that after adjustment for several risk factors, including age, blood pressure, diabetes, and obesity, hs-CRP could better predict the cardiovascular risk in women than using LDL-C alone.26) Cushman, et al.27) performed a study in 3,971 subjects of > 65 years of age and found that high hs-CRP levels were positively correlated with a 10-year cardiovascular disease risk; for women at high risk, the value of hs-CRP for risk prediction seems to be greater than that of other previously confirmed risk factors.27)

The JUPITER trial published in 2008 was performed in 17,802 apparently healthy subjects with hs-CRP > 2 mg/L and LDL-C < 130 mg/dL, and demonstrated that statin treatment could reduce the risk of MACE by 44% and all-cause mortality by 20%.28) In several secondary preventive studies such as the PROVE IT-TIMI22 trial, the findings demonstrated that the incidence of MACE was the lowest for patients who had achieved therapeutic targets (LDL-C < 70 mg/dL and hs-CRP < 1 mg/L), and that statin treatment could also benefit the patients with LDL-C < 70 mg/dL and hs-CRP > 2 mg/L or the ones with LDL-C > 70 mg/dL and hs-CRP < 2 mg/L.29) Another secondary preventive study, the Aggrastat-to-Zocor trial, demonstrated that patients who had achieved the
therapeutic targets for LDL-C and hs-CRP could benefit the most from the treatment.\(^{30}\) Similarly, the REVERSAL trial demonstrated that reducing CRP and LDL-C at the same time could help reduce the size of atherosclerotic plaques.\(^{31}\) In the present study, among patients with ACS, significant differences were found in the rates of TVR and MACE at 18 months between the LDL and LDL-CRP groups, with the results in favor of the patients who had achieved both LDL-C and hs-CRP targets. The cumulative MACE rate was significantly lower in the LDL-CRP group than in the LDL group, which is consistent with the PROVE IT-TIMI 22 and Aggrastat-to-Zocor trials. These findings suggest that inflammation plays a critical role in the development of atherosclerosis.

Dibra, et al. showed that for patients with increased CRP levels after PCI, the rates of disability and restenosis were also increased,\(^{32}\) which was confirmed by our findings. In the present study, patients in the LDL group had higher hs-CRP after PCI, which may be associated with higher levels of chemokines and inflammatory mediators. These changes then, in turn, induce intimal hyperplasia and cause restenosis, thereby increasing the TVR rate.

The 18-month follow-up revealed that the revascularization rate in the LDL-CRP group was significantly lower than that in the LDL group. In addition, the occurrence of cardiac death and nonfatal myocardial infarction and the re-hospitalization rate were lower in the LDL-CRP group than in the LDL group, but there was no significant difference between the two groups, which could have been influenced by the small sample size and the short follow-up time in the present study. The anti-inflammation effects allow statins to improve the vascular endothelial function, increase the stability of atherosclerotic plaques, reduce the risk of developing thrombus, and finally decrease the incidence of cardiac death and nonfatal myocardial infarction.\(^{4,15}\) Therefore, in addition to the lower revascularization rate, the decreased incidence of MACE in the LDL-CRP group could also be partially caused by cardiac death and nonfatal myocardial infarction. However, further studies are needed to further validate these findings.

### Table I. Characteristics of Patients

|                        | LDL group \((n = 196)\) | LDL-CRP group \((n = 195)\) | \(P\) |
|------------------------|-------------------------|-----------------------------|------|
| Men, \(n(\%)\)         | 147 (75)                | 134 (69.2)                  | 0.06 |
| Age (years)            | 68.6 ± 16.6             | 70.1 ± 17.5                 | 0.22 |
| Current smoking, \(n(\%)\) | 115 (58.7%)            | 93 (47.7%)                  | 0.34 |
| Diabetes, \(n(\%)\)    | 55 (28.1%)              | 50 (25.6%)                  | 0.41 |
| Hypertension, \(n(\%)\) | 119 (60.7%)             | 128 (65.6%)                 | 0.29 |
| Family history of CHD, \(n(\%)\) | 28 (14.3%)            | 36 (18.5%)                  | 0.56 |
| Acute myocardial infarction, \(n(\%)\) | 78 (39.8%)            | 83 (42.6%)                  | 0.07 |
| Alanine aminotransferase (U/L) | 31.6 ± 6.2            | 24.3 ± 7.5                  | 0.13 |
| No. of diseased vessels | 2.06 ± 0.89             | 1.96 ± 0.85                 | 0.33 |
| No. of stents per patient | 2.10 ± 1.11            | 1.90 ± 0.89                 | 0.31 |
| Dose of atorvastatin (mg) | 14.73 ± 8.91           | 23.69 ± 10.55               | 0.04 |
| LDL-C (mmol/L)         | 2.67 ± 0.78             | 2.71 ± 0.82                 | 0.27 |
| hs-CRP (mg/L)          | 20.15 ± 9.65            | 19.88 ± 9.12                | 0.18 |

LDL indicates low-density lipoprotein; CRP, C-reactive protein; CHD, coronary heart disease; and hs-CRP, high-sensitivity C-reactive protein.

### Table II. Comparison of Occurrence of MACE between Two Groups during the 18-Month Follow-Up

|                        | LDL group \((n = 196)\) | LDL-CRP group \((n = 195)\) | \(P\) |
|------------------------|-------------------------|-----------------------------|------|
| MACE, \(n(\%)\)       | 9 (5.1%)                | 20 (10.2%)                  | 0.06 |
| Cardiac death, \(n(\%)\) | 3 (1.5%)               | 6 (3.1%)                    | 0.10 |
| Nonfatal myocardial infarction, \(n(\%)\) | 1 (0.5%)               | 4 (2.0%)                    | 0.05 |
| Revascularization, \(n(\%)\) | 5 (2.6%)              | 10 (5.1%)                   | 0.01 |
| Hospitalization for unstable angina, \(n(\%)\) | 4 (2.0%)               | 8 (4.1%)                    | 0.00 |
| Secondary hepatic dysfunction, \(n(\%)\) | 2                      | 1                           | 0    |

\(^*P < 0.05\) versus LDL-C group at 18 months. LDL indicates low-density lipoprotein; CRP, C-reactive protein; and MACE, major adverse cardiac events.

### Conclusion

Compared to LDL-C as the single target, targeting both LDL-C and hs-CRP with statin therapy in patients with ACS could further reduce the incidence of MACE and the residual cardiovascular risk.

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Figure 2. Kaplan-Meier analysis of survival over the 18-month follow-up. Log-rank $P = 0.035$. Time is given in months. Cum indicates cumulative.

Figure 3. Kaplan-Meier analysis of major adverse cardiac events hazard over the 18-month follow-up. Log-rank $P = 0.035$. Time is given in months. Cum indicates cumulative.
Conflicts of interest: All authors declare that they have no competing interests.

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