**Low baseline LDL-cholesterol is associated with decreased all-cause mortality in Chinese patients with first coronary revascularization: A single-center Cohort Study**

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###### Abstract

**Objectives:** We aimed to examine the relationship between baseline LDL-C and clinical outcomes in CAD patients.

**Background:** The role of baseline LDL-C on the clinic outcome in CAD patients undergoing first coronary revascularization remains controversial.

**Methods and results:** This retrospective cohort study included 2056 patients undergoing first coronary revascularization in 2014-2016. All participants were classiﬁed into two groups based on baseline LDL-C = 2.6mmol/L (100 mg/dl), and were followed for at least 9 months. Outcomes of interest included major adverse cardiovascular events (MACE), all-cause death, recurrent nonfatal myocardial infarction (MI), unexpected coronary revascularization or any nonfatal stroke. All-cause death occurred in 8 patients (0.7%) in low-LDL-C group and 12 patients (2.4%) in high-LDL-C group. The risk of all-cause death was significantly lower in low-LDL-C group (adjusted HR 4.030, 95% CI 1.088 to 14.934, P = 0.037). However, there were no signiﬁcant differences for the risk of MACE or other secondary end points such as unexpected revascularization, any nonfatal stroke between the two groups.

**Conclusion:** lower baseline LDL-C levels are associated with lower risk of all-cause death in CAD patients undergoing first coronary revascularization. The "cholesterol paradox" was not detected in the present study, higher baseline LDL-C levels has no protective effect in Chinese CAD patients.

**Keywords**

secondary prevention, Baseline low-density lipoprotein cholesterol, statin-naïve

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###### 1 | INTRODUCTION

Coronary artery disease (CAD) is a major cause of death and disability in developed countries. Although CAD mortality rates have declined over the past four decades, it remains responsible for about one-third or more of all deaths in individuals over age 35 (1-3). Percutaneous coronary intervention (PCI) is commonly performed to relieve ischemic symptoms in CAD, and low-density lipoprotein cholesterol (LDL-C) plays a key role in the pathogenesis and perpetuation of atherosclerotic cardiovascular disease (CVD) (4-10).

In patients with high-risk factors, such as acute coronary syndrome (ACS), coronary artery disease, carotid or peripheral vascular disease, or secondary prevention, LDL-C < 70 mg/dl (1.8 mmol/L) is recommended(11,12). Mendelian randomization analysis has shown that a lifelong very low LDL-C is associated with a much lower risk of CVD(9). In some trials(13-17), the lower is better with regard to LDL-C level and there is no threshold below which there is no incremental benefit. Furthermore, large-scale lipid-lowering trials have suggested that statins can reduce recurrent ischemic coronary events in patients with hypercholesterolemia as well as in those with a normal cholesterol level(18-20). However, even with optimally lowering lipid treatment, many patients still experience one or more adverse event. In a meta-analysis of nearly 29,000 patients with CVD in 14 randomized trials comparing statin with no statin, 21.2% statin treated patients experienced a major cardiovascular event during five-year follow-up(21), suggesting that, besides LDL-C treatment goal, other risk factors, such as older age, increased body-mass index, male gender, hypertension, diabetes, baseline apolipoprotein B, blood urea nitrogen could also play a contributory role in the progression (22).

Recent reports suggested that higher baseline LDL-C levels are associated with favorable clinical outcomes after PCI in patients with AMI (the cholesterol paradox) (23). In the PROVE IT-TIMI 22 trial, the protection against death or major cardiovascular events appeared to be greater among patients with a baseline LDL-C ≥ 125 mg/dl, with a 34% reduction in the HR, as compared with a 7% reduction among patients with a baseline LDL-C < 125 mg/dl (P for interaction = 0.02)(24). Meanwhile, another study had shown that elevated baseline levels of LDL-C was significant predictors of death from cardiovascular disease(6). Therefore, the effect of baseline LDL-C on the clinical outcome after coronary revascularization remains controversial.

This study sought to examine the relationship between baseline LDL-C and clinical outcomes in patients undergoing first coronary revascularization.

###### 2 | METHODS

###### 2.1 | Data source and study population

It is a retrospective, single-center, observational cohort study to assess the relationship between baseline LDL-C and long-term outcome in CAD patients after first coronary revascularization. The data was collected from cardiac catheterization laboratories of Sir Run Run Shaw Hospital (zhejiang, China). The process of the present study was shown in Figure 1. The inclusion criteria are: The patients underwent first coronary revascularization. The exclusion criteria are: (ⅰ) history of PCI; (ⅱ) receiving long-term lipid-lowering therapy before PCI (>8 weeks lipid-lowering therapy); (ⅲ) absent of baseline LDL-C; (ⅳ) creatinine clearance of less than 30 ml/min.

Between January 2014 and August 2016, 6004 patients underwent first coronary revascularization, and 2056 patients were enrolled in the study.

All the patients were treated with statin with or without ezetimibe, fibrates during administration or upon discharge. The baseline LDL-C was measured at administration or before PCI. All participants were classiﬁed into two groups based on LDL-C = 2.6mmol/L (100 mg/dl); The target LDL-C level is less than 1.8 mmol/L (70 mg/dl)(11,12). Patients had follow-up visits at 1, 6, 9, and 12 months, and every 6 months thereafter. All patients were followed-up in an outpatient clinic or by a telephone interview. Blood samples were obtained at admission, at 1, 6, 9, and 12 months, and every 6 months thereafter for those attending clinic visits.

**2.2 | Endpoints**

The primary end point was major adverse cardiac events (MACE), deﬁned as a composite of all-cause death, recurrent nonfatal myocardial infarction (MI), unexpected coronary revascularization (occurring at least 30 days after PCI) or any nonfatal stroke during follow-up, assessed from the time of randomization until the first occurrence of one of the events.

The secondary end points were a composite of cardiac death, MI, or unexpected revascularization; a composite of cardiac death, or MI; a composite of any nonfatal stroke; and individual components of MACE, including all-cause death, MI, ischemic stroke, hemorrhagic stroke and revascularization.

AMI was deﬁned as elevation of cardiac biomarkers (troponin T, troponin I, or creatine kinase-MB) and speciﬁc changes on the electrocardiogram or symptoms according to the third universal MI definition(25). All-cause death was deﬁned as death due to any cause. Revascularization was deﬁned as repeat PCI or coronary artery bypass graft surgery after the index procedure.

Medications were prescribed during hospitalization and discharge. Coronary artery angiography and PCI were performed by standard methods, and decision for detailed treatment was left to the physician's discretion.

**2.3 | Statistical analysis**

All data were analyzed by using SPSS version 22.0 (SPSS Institute Inc. Cary, North Carolina). We used students-*t* test or Mann-Whitney U tests for continuous variables and chi-square tests for categorical variable. Survival curves were estimated by the Kaplan-Meier method and compared with the log-rank test. Multivariate analysis(26,27) was performed to reduce potential bias. Propensity score-matching analysis(27) was also performed as a sensitivity analysis. All tests were 2-tailed and *p* < 0.05 represents signiﬁcant.

To evaluate the independent effect of baseline LDL-C level on clinical outcomes, multivariable-adjusted Cox proportional hazard model analysis was estimated and the covariates were significant on univariate analysis or clinically relevant. Covariates included in model were age, gender, hypertension, current smoker, ACS, eGFR, left anterior descending, left circumﬂex, right coronary artery, stent length, primary PCI, coronary calcification, clopidogrel, warfarin, statin, fibrates, ezetimibe and LDL-C level during follow-up.

Propensity scores were estimated by logistic-regression analysis that included covariates such as age, gender, hypertension, ACS, eGFR, left circumﬂex (culprit vessel), primary PCI, ezetimibe, beta-blocker, triglyceride, and HDL-C. A 1:1 matching was done with the greedy algorithm and we used the nearest neighbor method in patients with an individual propensity score. In matched population, we also used multivariable-adjusted Cox proportional hazard model analysis, covariates included in model were triglyceride, ACS, multivessel coronary disease, left anterior descending, right coronary artery, stent length, statin, fibrates, ezetimibe and LDL-C level during follow-up.

###### 3 | RESULTS

**3.1 | Baseline demographics and angiographic findings**

As shown in Figure 1, finally, totaling 2056 patients undergoing PCI during 2014-2016 were included, 261 patients were lost to follow up, 1795 were analysis, 1202 patients in low-LDL-C group (LDL-C < 100 mg/dl) and 593 in high-LDL-C group (LDL-C ≥ 100 mg/dl). The median follow-up was 20.2 months (range from 9-39.6 months).

Baseline clinical characteristics and angiographic ﬁndings were shown in Table 1, Table 2, Table 3 and Table 4. The mean age of the patients was 64.9 ± 10.6 years, 72.4% were men and 22.3% had diabetes mellitus. Overall, patients in high-LDL-C group had relatively higher risk factors. Compared with the low-LDL-C group, the high-LDL-C group had a higher prevalence of previous ACS, left circumﬂex culprit vessel, but had a lower prevalence of elderly, hypertension, chronic kidney disease, primary PCI. Ezetimibe were more frequently used in high-LDL-C group.

After 1:1 propensity-score matching, 886 patients were matched (Table 1). In the propensity-matched population, there were no significant differences in baseline characteristics between the two groups except for triglyceride.

**3.2 | LDL-C data**

At admission, the median LDL-C level were 1.85 mmol/L and 3.15 mmol/l in each group (p < 0.001, Table 5). Among patients who had blood samples obtained at a median of 20.2 months follow up, the median LDL-C level was 1.46 mmol/l in low-LDL-C group, and 1.89 mmol/l in high-LDL-C group (p < 0.001, Table 5). During the follow-up, the reduction of LDL-C level was 0.39 mmol/l (21.1%) in low-LDL-C group and 1.26 mmol/l (40.0 %) in high-LDL-C group. In the overall population, 66.8% achieved the target LDL-C level, 75.9% in low-LDL-C group and 46.5% in high-LDL-C group. After 1:1 propensity-score matching, 73.8% patients in low-LDL-C and 49.5% in high-LDL-C group achieved the target LDL-C level. To account for patients in the two groups who did not have blood samples obtained, LDL-C levels were imputed with the use of the LDL-C levels measured at randomization.

**3.3 | Clinical outcome**

Clinical outcomes in the overall population

The clinical outcomes were shown in Table 6. During follow-up, MACE occurred in 202 patients (11.3%), whereas 20 patients (1.1%) had all-cause death, 11 patients (0.6%) had cardiac death, 2 patients (0.1%) had MI, 171 patients (9.5%) had revascularization, 13 patients (2.2%) had ischemic stroke and 2 patients had hemorrhagic stroke. Figure 2, Figure 4 and Table 5 demonstrate the cumulative incidence of clinical outcomes in the two groups.

Kaplan–Meier event rates for the risk of all-cause death was significantly lower in low-LDL-C group than in high-LDL-C group (adjusted hazard ratio [HR] 4.030, 95% confidence interval [CI] 1.088 to 14.934; P = 0.037, Table 6, Figure 2, Figure 4). However, there were no signiﬁcant differences in the rates of MACE or other secondary end points between the two groups (Table 6, Figure 2, Figure 4).

Clinical outcomes in propensity matched population

After adjustment for potential confounders, including triglyceride, ACS, multivessel coronary disease, left anterior descending, right coronary artery, stent length, statin, fibrates, ezetimibe and LDL-C during follow-up in propensity matched population, low-LDL-C group had a trend of decreased all-cause death risk (adjusted HR: 6.887, 95%CI 0.748 to 63.371, p = 0.088, Table 6, Figure 3, Figure 4). However, there were no signiﬁcant differences in the risk of MACE or other secondary end points between the two groups.

###### 4 | DISCUSSION

The present study demonstrated that lower baseline LDL-C was associated with a lower risk of all-cause death among statin-naïve patients undergoing first coronary revascularization. However, no significant differences in the rate of MACE and other secondary end points, such as unexpected revascularization, any nonfatal stroke was observed.

LDL-C plays a key role in the pathogenesis and perpetuation of atherosclerotic CVD (4-10), and is a predictor of increased morbidity and mortality (19,28) for CAD. In several trials(13-17), the lower LDL-C results in the better outcome, and there is no threshold below which there is no incremental benefit. The benefit seen in these trials could be due to a greater degree of LDL-C lowering, to pleiotropic effects of a higher statin dose, or both. However, there is still controversial about whether baseline LDL-C will predict the clinical outcome for CAD patients. In our study, it is consistent with those previous reports (6,29), that is, elevated baseline LDL-C was associated with an increased risk of MACE. Nonetheless, recent trials also reported that, low LDL-C level at admission was associated with increased mortality in patients with acute coronary syndromes (23,30,31). Rauchhaus et al(32)demonstrated that higher cholesterol levels were associated with better survival in patients with chronic heart failure. The phenomenon is deﬁned as “cholesterol paradox”, and its mechanism remains unclear. However, the paradox describe above was not detected in the present study. It might be caused by a number of different factors. For example, the patients enrolled in those trials(23,30,31) were with acute coronary syndromes, which may lead to abnormal lipid metabolism, leading to lower preoperative LDL-C(33) and poor prognosis. The patients enrolled in Rauchhaus et al’s(32) study were with chronic heart failure, in which lower LDL-C may reflect reduced food intake and reduced intestinal absorption due to bowel edema and may possibly be a result of increased metabolic stress(34).

It is well known that Japanese healthy patients showed longer occlusion time compared with UK Westerners (545 vs 364 sec, P<0.0001), which may mean the lower level of thrombogenicity in East Asians vs Westerners (the Japanese paradox)(35). The recent analysis of the NCDR (National Cardiovascular Data Registry CathPCI Registry) database (n=423,965 Americans) also supported the favorable clinical outcomes in Asians(36). The mechanisms of this Japanese paradox are not clear. However, recent studies have demonstrated that the differences in genetic polymorphisms between the races may be a piece of underlying mechanism(37). For example, factor V Leiden (G1691A) and prothrombin G20210A gene mutations are more common in Caucasians compared with Asians. Similarly, in our study, Cox regression analysis revealed that higher baseline LDL-C levels had no protective effect in CAD patients undergoing first coronary revascularization. Hence, it might be caused by a number of different factors. For example, the previous study(23) showed that in patients with AMI, clinical outcomes decreased as LDL-C increased, except for patients with LDL-C levels ≥160 mg/dl. patients with lower LDL-C levels were older and had more co-morbidities and unfavorable hemodynamic status. However, in the present study, patients with baseline LDL-C ≥ 160 mg/dl were also included in the analysis. patients with lower LDL-C levels were likely to be older and had more co-morbidities (hypertension, chronic kidney disease), but had a lower prevalence of previous ACS, left circumﬂex. In the present study, patients in high-LDL-C group had a lower median LDL-C level (1.46 mmol/l vs. 1.89 mmol/l), while the lower is the better with regard to LDL-C levels(13-17), it could be hypothesized that a greater reduction in risk of higher baseline LDL-C level might be counterbalanced by an increase in a higher median LDL-C level during the follow-up.

###### 5 | LIMITATIONS

This study had several limitations. First, it was a retrospective study with selection bias. To overcome the limitation, Cox multivariate analysis and propensity-matching analysis with adjustment for potential confounders were performed, but unmeasured potential confounders could not be adjusted. Second, as the included patients were statin naïve, our founding could not be generalized to patients with long-term statin treatment before PCI. Third, cardiac death, any nonfatal strokes and ischemic stroke were low probability events, thus we failed to find the effect of baseline LDL-C on them. Fourth, the target LDL-C level (< 1.8 mmol/l) may not be rigorous enough, in facts, a lower target LDL-C levels was recommended for individuals at extreme risk (< 1.4 mmol/l) (11). Finally, the present study had not assessed the effect of the variability of LDL-C levels on clinical outcome during the follow up.

###### 6 | CONCLUSION

Lower baseline LDL-C levels are associated with lower risk of all-cause death in CAD patients undergoing first coronary revascularization. The "cholesterol paradox" was not detected in the present study, higher baseline LDL-C levels has no protective effect in Chinese CAD patients. Further large population studies are required to directly assess the relationship between baseline LDL-C levels and the occurrence of cardiovascular events.

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H.C. and M.W. contributed to the concept and design of the study. Y.L. was responsible for data acquisition. All authors were involved in the evaluation and interpretation of the results and the reviewing and approval of the manuscript.

**CONFLICT OF INTEREST**

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