The Impact of Changes in Population LDL-C Levels on LDL-C Control in Patients After PCI in China: A Retrospective Cohort Study

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Research

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Abstract

BACKGROUND: Mortality from coronary artery disease continues to rise, and secondary prevention and treatment are particularly important.

OBJECTIVE: The objective of this study is to evaluate low-density lipoprotein cholesterol (LDL-C) levels in patients after percutaneous coronary intervention (PCI), to describe how treatment outcomes for individual patients changed over time and to examine the potential impact of lipid control rates through population LDL-C levels changes.

METHODS: This retrospective study was conducted in patients who underwent PCI between July 2017 and June 2019. The main results included LDL-C levels after PCI. To assess the outcome of prevention, three separate measures of LDL-C were considered: baseline, first follow-up, and final follow-up, and LDL-C control rates were analyzed according to different guidelines. We examine the impact of 0.1 mmol/l decreases or increases in population LDL-C levels on LDL-C control.

RESULTS: Data were analyzed for 423 patients (mean age, 62 ± 10 years), and the baseline LDL-C level was 3.11 ± 0.99 mmol/l. 51.5% of the patients achieved the Chinese Lipids Guidelines treatment goal, 22% and 11.6% of the patients achieved the 2016 ESC Lipids Guidelines and 2019 ESC Lipids Guidelines treatment goal at the final follow-up period respectively. LDL-C levels fluctuated during the follow-up period, and the long-term maintenance results could not be guaranteed after PCI. Population LDL-C levels changes in lifestyle could have a very large impact on LDL-C control in China.

CONCLUSION: LDL-C control with statins is not ideal in patients after PCI, which is far from the requirements of the latest guidelines. Although clinicians understand the lipid-lowering effect of statins, they should not give up active lifestyle changes, and should strengthen the comprehensive management of blood lipid control.

Background

Systematic analysis of the Global Burden of Disease Study in 2017 showed that cardiovascular disease remained the leading cause of death worldwide, with 8.9 million deaths from ischemic cardiomyopathy, a 22.3% increase over 2007.[1] China is the world's most populous country, with 290 million people suffering from cardiovascular disease and 5 million patients with coronary artery disease (CAD). Mortality from CAD continues to rise, with cardiovascular reports in 2018 showing 113.46 per 100,000 urban residents and 118.74 per 100,000 rural residents.[2] Over the past 30 years, the levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in adults have decreased significantly in the United States[3], and cholesterol control has contributed the most to the reduction of cardiovascular mortality by 24%.[4] Studies in China have shown that the 77% increase in mortality from CAD is attributed to elevated cholesterol.[5] There was a high correlation between LDL-C level and cardiovascular events and mortality. For every 1 mmol/l decrease in LDL-C level, the risk of cardiovascular events was reduced by 20%.[6]
The European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) Lipids Guidelines (hereinafter referred to as 2016 ESC Lipids Guidelines) were published in August 2016, recommending LDL-C <1.8 mmol/l or a 50% reduction from baseline of 1.8-3.5 mmol/l in patients with very high Cardiovascular risk.[7] In August 2019, ESC/EAS re-updated lipid management (hereinafter referred to as 2019 ESC Lipids Guidelines) with a higher requirement: an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/l are recommended.[8] However, despite sufficient evidence, in practice, lipid control in patients remains difficult and often inadequate.[9, 10] Previous studies on lipid-lowering drugs for the control of blood lipids in patients with coronary heart disease have been numerous. Lifestyle changes, such as dietary reduction of cholesterol and saturated fatty acids intake, increased dietary fiber and phytosterol intake, physical activity and weight loss have a positive impact on TC and LDL-C reduction.(Table 1) However, there are insufficient studies on the effect of lifestyle intervention on lipid control in patients with CAD. Therefore, this study decided to analyze the lipids control rates in patients after percutaneous coronary intervention (PCI), to describe how treatment outcomes for individual patients changed over time and to investigate the potential impact of LDL-C control rates through population LDL-C levels changes.

**Methods**

1 **Data**

This retrospective analysis of PCI patients was conducted through the database of coronary intervention treatment in the Second Affiliated Hospital of Nanchang University and the previous inpatient and outpatient records. Information on age, gender, smoking history, comorbidities (hypertension and diabetes), treatment and lipid levels, and other laboratory values were collected from the medical records.

2 **Patient population**

The study excluded out of the line of lipid-lowering therapy in patients with recent 3 months, because this part of patients is difficult to get information between baseline lipid, we were retrospectively analyzed in July 2017 to June 2019 in the second affiliated hospital of nanchang university of cardiology PCI postoperative follow-up of at least one clinic or hospital records lipid parallel detection of 1016 cases of patients, lack of follow-up records of 231 patients for the first time, the lack of the final follow-up records of 190 patients, also ruled out part of the patients who were not in the specified during follow-up, 172 patients. A total of 423 eligible patients were eventually included.

3 **Study design**

The status of LDL-C and lipid-lowering therapy was recorded at three independent measurement points defined based on LDL-C measurement: 1) baseline, 2) first follow-up, and 3) final follow-up. The baseline level was defined as the LDL-C recorded by PCI during hospitalization or the latest results before PCI (but no more than 1 month). The first follow-up level was defined as the results of the first LDL-C test after PCI. The test must be conducted at least 1 month and no later than 3 months after PCI. The final follow-
up level was defined as the latest LDL-C test results recorded during the follow-up period of 12 months. The test must be carried out 6 months after PCI. Patients may have had more LDL-C tests, but only these three were considered. Because this study is a retrospective analysis, informed consent of patients is abstained. However, during and after the study, data confidentiality was maintained and patient privacy was protected.

3 Outcome measures

LDL-C level of patients after PCI was analyzed in three different guidelines: 2016 ESC Lipids Guidelines (LDL-C <1.8mmol/l or a reduction in LDL-C level at least 50% if the baseline is between 1.8-3.5mmol/l)[7], 2019 ESC Lipids Guidelines (an LDL-C reduction of ≥50% from baseline and LDL-C <1.4 mmol/L)[8], and Chinese Lipids Guidelines (LDL-C < 1.8 mmol/l or a reduction in LDL-C level at least 50%).[11]

The aim of the study was analyze lipids control rates in patients after PCI under different guidelines, to describe how treatment outcomes for individual patients changed over time. LDL-C levels decreased or increased by 0.1-0.5 mmol/l at two follow-up visits after PCI, and then the impact of LDL-C changes levels on LDL-C control rate was analyzed.

4 Statistical Analysis

All the data were recorded in Excel 2003 spreadsheet and analyzed by SPSS13.0 software. Continuous variables were analyzed by using standard descriptive statistics. Data are presented as mean (SD), for normally distributed data, or median ± interquartile range, for nonnormally distributed data. Categorical variables are presented by using number and percentage. Difference in percentage of patients attaining target outcome were compared by using $\chi^2$ tests; absolute or percentage change was tested by using t tests or nonparametric tests.

Results

Of the 423 patients included, the majority were elderly (62 ± 10 years), 333 (78.8%) were male, 105 were former or current smokers, and the complications were also very common, with a prevalence of hypertension of 57.0% and diabetes mellitus of 29.1%. According to the diagnosis, there were 162 (38.3%) ST-Elevation Myocardial Infarction (STEMI), 41 (9.7%) non-ST-elevation myocardial infarction (NSTEMI) and 220 (52.0%) Unstable angina (UA). Among them, 290 (69%) patients used atorvastatin, 133 (31%) patients used rosuvastatin. (Table 2)

All of our patients did not receive lipid-lowering therapy within 1 month before PCI, and the baseline LDL level was 3.11 ± 0.99 mmol/l. Nearly half (49%) of the patients had LDL-C levels above 3.0 mmol/l, and only a few (3%) had LDL-C levels less than 1.8 mmol/l, Which increased to 50% at the first follow-up and slightly decreased to 48% at the final follow-up. Overall, the distribution of LDL-C levels remained relatively stable during the two follow-up periods, with 40% of patients experiencing classification
changes during the two follow-up periods and 26% fluctuating between <1.8 mmol/l and ≥ 1.8 mmol/l. (Figure 1)

During the two follow-up periods, 16.5% and 18.4% of the patients had LDL-C level below 1.4 mmol/l, respectively; 18.9% and 23.6% of the patients had a reduction of LDL-C level by more than 50%; 52.2% and 51.5% patients had LDL-C level below 1.8 mmol/l or a reduction of more than 50% from baseline, respectively; 8.0% and 11.6% of the patients had LDL-C level below 1.4 mmol/l and a reduction of more than 50% from baseline, respectively. (Table 3) When using the Chinese Lipids Guideline treatment goal, the population LDL-C levels were reduced by 0.1 mmol/l, and the LDL-C control rate increased from 52.2%, 51.5% to 58.6%, 62.4% during the two follow-up periods; the population LDL-C levels decreased by 0.5 mmol/l, increased to 82.7% at the first follow-up, and increased to 82.3% at the final follow-up. When more stringent 2019 ESC Lipids Guidelines treatment goal were adopted, the rate of LDL-C control increased from 8.0%, 11.6% to 17.3%, 18.0% during the two follow-up periods, and the rate of compliance nearly doubled. The same changes were found when assessed in accordance with the 2016 ESC Lipids Guidelines treatment goal. Increasing the LDL-C levels by 0.1 mmol/l had the opposite effect. According to different guidelines, the control rate of LDL-C decreased from 52.2%, 19.1%, 8.0% to 42.8%, 15.1%, 3.8% in the first follow-up and from 51.5%, 22.0%, 11.6% to 44.9%, 16.5%, 8.0% in the final follow-up. When the LDL-C levels of the population rises by 0.5 mmol/l, few people can meet the requirements of the guidelines using the more stringent 2016 ESC Lipids Guidelines and 2019 ESC Lipids Guidelines treatment goal. Only a few patients met the requirements of the Chinese Lipids Guidelines treatment goal, about 12.5% and 15.6%. (Table 4)

**Discussion**

This study used LDL-C level as an indicator to evaluate the effect of secondary prevention of coronary heart disease in China and analyzed the temporal trend of LDL-C levels. The subjects included in this study did not take lipid-lowering drugs within 1 month before PCI, which has not been analyzed in previous studies. Another study in China did not report the use of lipid-lowering drugs, and their LDL-C level baseline levels were 2.93 ±0.94 mmol/l.[12] In Leskel's study, Fifty-eight percent of patients had previously used lipid-lowering drugs, and their LDL-C levels of baseline were 2.77 mmol/l.[10] Their LDL-C levels of baseline were higher than our study (3.11 ±0.99 mmol/l). At the final follow-up, 51.5% of our patients reached the LDL-C target level, compared with only 31% in other studies at the same LDL-C target level (LDL-C < 1.8 mmol/l or a reduction in LDL-C level at least 50%).[10] A study in China reported a higher rate of LDL-C control, with 56.3% of patients reaching the target level at 1-month follow-up after PCI, but the LDL-C target level was LDL-C level <1.8 mmol/l or a reduction of LDL-C level at least 50% or LDL-C level >30% if baseline LDL-C level <1.8 mmol/l.[9] Our explanation is that this study did not report previous use of lipid-lowering drugs, and its defined LDL-C target level was somewhat different from our study, as well as the short follow-up period, so it showed a higher achievement rate than ours.

In previous studies, the temporal trend of LDL-C levels was analyzed, and the distribution of LDL-C levels remained relatively stable during the two follow-up periods[10], as did our results. 50% of patients
experienced a change in classification during both follow-ups, and 26% fluctuated between <1.8 and ≥1.8, so it is not sufficient to look only at the population mean when assessing the quality of treatment because individuals switch LDL-C levels.

Although the vast majority of patients after PCI were prescribed statins after discharge, from the current study, a large proportion of patients did not reach the LDL-C target level. The latest 2019 ESC Guidelines has proposed stricter LDL-C targets level, based on a 20% reduction in cardiovascular risk for each 1 mmol/l reduction.[6] The greater the absolute LDL-C reduction, the greater the cardiovascular risk reduction.[13, 14] There was no increase in adverse events when LDL-C levels reached very low levels (e.g. LDL-C decreased to <0.5 mmol/L).[15] But LDL-C control rate in our study is very low, only 8%, according to the 2019 ESC Lipids Guidelines. This suggests that statins alone may not be sufficient to achieve LDL-C targets level and requires combination therapy, such as the addition of ezetimibe or Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors (PCSK9i). At present, many studies have reported that ezetimibe or PCSK9i significantly reduce LDL-C level, combined lipid-lowering therapy can better control LDL-C level.[15, 16] So the 2019 ESC Lipids Guidelines raise the recommended level of ezetimibe and PCSK9i. But some surveys of the economic burden have found that any further lipid reduction could impose a huge economic burden on cardiovascular-related management.[17]

The United States reported cost-effectiveness of PCSK9i added to statin therapy: an increase of $141699 per Quality-adjusted life-years.[18] At a 60% reduction in the price of PCSK9i in the United States, the cost-effective was $56655 to $7667 per quality-adjusted life-year for very high-risk patients with atherosclerotic cardiovascular disease, meeting acceptable cost-effectiveness threshold criteria.[19] In countries with low per capita gross domestic product, a 97% reduction would be considered cost-effective.[20] The results of some studies are cost-effective when ezetimibe is added to ongoing statin therapy and the costs and benefits of maintaining current doses of statin therapy[21]. However, in a 5-10 year follow-up model, ezetimibe combined with statin therapy is not a cost-effective alternative, but when the follow-up period is extended to a lifetime, combination therapy becomes a cost-effective treatment.[22] In a Chinese study, LDL-C<1.8 mmol/l was 26.2% and 28.2% in patients using high-intensity and moderate-intensity statins, respectively.[23] Another study showed that 63.8% of acute coronary syndrome patients had LDL-C level greater than 1.80 mmol/L, and 71.5% received high-intensity statin therapy.[24] LDL-C control with high-intensity statins is not ideal, which requires more price reductions for ezetimibe and PCSK9i to benefit patients.

Pharmacological lipid control is one aspect of treatment, and lifestyle interventions are also important. To our knowledge, ours is the only study to report the impact of population lipid changes on major lipid indicators. Both increases and decreases in population lipid can occur with population changes in the major determinants of lipid (eg, diet, physical activity, weight loss). Randomized controlled trials have confirmed that lifestyle changes significantly affect LDL-C level.(Table 1) An Australian study urged lifestyle changes by sending health education-related text messages, leading to lower LDL-C levels in patients with CAD.[25] Although lifestyle interventions have less impact on lipids than statins, we found a significant improvement in LDL-C control rates. Clinicians may rely excessively on lipid-lowering drugs
(i.e., statins) to control blood lipids. We believe that positive lifestyle changes, such as dietary reduction of cholesterol, saturated fatty acids intake, increased dietary fiber and phytosterol intake, physical activity, weight loss, etc., should not be abandoned.

**Limitation**

There are only four limitations of this study. First, a large number of patients were lost to follow-up, which may produce some potential bias. Second, this study is a retrospective study, so we do not know the compliance of patients with lipid-lowering treatment. However, the follow-up data show that most patients achieved lipid reduction in both follow-up visits. Third, we cannot get more detailed basic information about patients, including BMI, blood pressure level, dietary habits, etc. Fourth, this is a single-center study in which all participants were from a tertiary hospital in central China, so we may not be able to generalize the results to other populations. Further multicenter, prospective cohort studies are needed to investigate the impact of population lipid changes on lipid control rates. In this study, as a secondary prevention study of coronary heart disease, a large number of studies often focus on the magnitude of benefit, few people focus on the basis of benefit, often small changes can get a great benefit.

**Conclusion**

LDL-C control with statins is not ideal in patients after PCI, which is far from the requirements of the latest guidelines. Although clinicians understand the lipid-lowering effect of statins, they should not give up active lifestyle changes, and should strengthen the comprehensive management of blood lipid control.

**Abbreviations**

LDL-C: Low-density lipoprotein cholesterol; PCI: Percutaneous coronary intervention; CAD: Coronary artery disease; TC: Total cholesterol; ESC/EAS: European Society of Cardiology and European Atherosclerosis Society; STEMI: ST-Elevation Myocardial Infarction; NSTEMI: non-ST-elevation myocardial infarction; UA: Unstable angina; 2016 China: 2016 Chinese Lipids Guidelines treatment goal (LDL-C < 1.8 mmol/l or a reduction in LDL-C level at least 50%); 2016 ESC: 2016 ESC Lipids Guidelines treatment goal (LDL-C < 1.8 mmol/l or a reduction in LDL-C level at least 50% if the baseline is between 1.8-3.5 mmol/l); 2019 ESC: 2019 ESC Lipids Guidelines treatment goal (an LDL-C reduction of ≥ 50% from baseline and LDL-C < 1.4 mmol/L); PCSK9i: Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors;

**Declarations**

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Not applicable.

**Authors’ contributions**
The study was designed by Yanqing Wu and Jinsong Xu; Huan Liu and Zhipeng Zhou analyzed, interpreted the data and responsible for drafting the manuscript. The manuscript was reviewed by Yanqing Wu and Jinsong Xu. All authors have read and approved the final manuscript for publication.

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Availability of data and materials

All data generated and analyzed in this study are included in this published article. The datasets are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University (2020-047). Because of the retrospective nature of this study, informed consent was waived.

Consent for publication

All authors provide consent for publication of this paper.

Competing interests

All authors of this paper have no competing interests to disclose.

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Tables

Table 1 Approximate changes in LDL-C with some lifestyle change
Table 2 Demographic and baseline characteristics

| Characteristics       | Value |
|-----------------------|-------|
| male                  | 333   |
| age                   | 62±10 |
| Hypertension          | 241   |
| Diabetes mellitus     | 123   |
| Smoking               | 105   |
| STEMI                 | 162   |
| NSTEMI                | 41    |
| UA                    | 220   |
| Atorvastatin          | 292   |
| Rosuvastatin          | 131   |

STEMI: ST-Elevation Myocardial Infarction, NSTEMI: non-ST-elevation myocardial infarction, UA: Unstable angina

Table 3 Patient segmentation based on the ability to achieve treatment target during follow-up
| Segment                          | First follow-up | Final follow-up |
|---------------------------------|-----------------|-----------------|
| decrease 25-50%                 | 232 (54.8%)     | 223 (52.7%)     |
| decrease ≥ 50%                  | 80 (18.9%)      | 100 (23.6%)     |
| <1.40 mmol/l                    | 70 (16.5%)      | 78 (18.4%)      |
| <1.80 mmol/l                    | 209 (49.4%)     | 203 (48.0%)     |
| <1.40 mmol/l or decrease ≥ 50%  | 116 (27.4%)     | 127 (30.0%)     |
| <1.40 mmol/l and decrease ≥ 50% | 34 (8.0%)       | 49 (11.6%)      |
| <1.80 mmol/l or decrease ≥ 50%  | 221 (52.2%)     | 218 (51.5%)     |
| <1.80 mmol/l and decrease ≥ 50% | 68 (16.1%)      | 83 (19.6%)      |

Table 4  The impact of increases and decreases in population LDL-C levels (at intervals of 0.1 mmol/l) on LDL-C control rate according three different guidelines
| change  | 2016China | 2016ESC | 2019ESC | 2016China | 2016ESC | 2019ESC |
|---------|-----------|---------|---------|-----------|---------|---------|
| -0.5    | 350*      | 252*    | 195*    | 348*      | 261*    | 206*    |
|         | 82.7%     | 59.6%   | 46.1%   | 82.3%     | 61.7%   | 48.7%   |
| -0.4    | 325*      | 228*    | 171*    | 333*      | 233*    | 173*    |
|         | 76.8%     | 53.9%   | 40.4%   | 78.7%     | 55.1%   | 40.9%   |
| -0.3    | 308*      | 194*    | 127*    | 313*      | 193*    | 138*    |
|         | 72.8%     | 45.9%   | 30.0%   | 74.0%     | 45.6%   | 32.6%   |
| -0.2    | 288*      | 150*    | 98*     | 287*      | 155*    | 100*    |
|         | 68.1%     | 35.5%   | 23.2%   | 67.8%     | 36.6%   | 23.6%   |
| -0.1    | 248*      | 119*    | 73*     | 264*      | 123*    | 76*     |
|         | 58.6%     | 28.1%   | 17.3%   | 62.4%     | 29.1%   | 18.0%   |
| 0       | 221/423   | 81/423  | 34/423  | 218/423   | 93/423  | 49/423  |
|         | 52.2%     | 19.1%   | 8.0%    | 51.5%     | 22.0%   | 11.6%   |
| +0.1    | 181*      | 64      | 16      | 190*      | 70*     | 34      |
|         | 42.8%     | 15.1%   | 3.8%    | 44.9%     | 16.5%   | 8.0%    |
| +0.2    | 151*      | 45*     | 11*     | 149*      | 50*     | 21*     |
|         | 35.7%     | 10.6%   | 2.6%    | 35.2%     | 11.8%   | 5.0%    |
| +0.3    | 117*      | 27*     | 4*      | 117*      | 37*     | 9*      |
|         | 27.7%     | 6.4%    | 0.9%    | 27.7%     | 8.7%    | 2.1%    |
| +0.4    | 87*       | 17*     | 2*      | 89*       | 27*     | 6*      |
|         | 20.6%     | 4.0%    | 0.5%    | 21.0%     | 6.4%    | 1.4%    |
| +0.5    | 53*       | 13*     | 1*      | 66*       | 17*     | 4*      |
|         | 12.5%     | 3.1%    | 0.2%    | 15.6%     | 4.0%    | 0.9%    |

2016China: 2016 Chinese Lipids Guidelines treatment goal; 2016ESC: 2016 ESC Lipids Guidelines treatment goal; 2019ESC: 2019 ESC Lipids Guidelines treatment goal.

* p<0.05, compare with the change 0.
Figure 1

The distribution of LDL-C levels remained relatively stable during the two follow-up periods, with 40% of patients experiencing classification changes during the two follow-up periods and 26% fluctuating between <1.8 mmol/l and ≥ 1.8 mmol/l. (Figure 1)
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