Research Article

Baseline LDL-C and Lp(a) Elevations Portend a High Risk of Coronary Revascularization in Patients after Stent Placement

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Background and Aim. Incidence of coronary restenosis after stent placement is high. Our study was going to investigate whether Lp(a) elevation was potential for predicting coronary restenosis and whether the effects of Lp(a) elevation on coronary restenosis were dependent on LDL-C level.

Methods and Results. Totally 832 participants eligible for stent placement were enrolled and followed up for monitoring clinical end points. Baseline characteristics were collected. According to the cut point of Lp(a), participants were divided into low Lp(a) group (Lp(a) < 30 mg/dL) and high Lp(a) group (Lp(a) ≥ 30 mg/dL). Furthermore, based on baseline LDL-C level, participants were divided into LDL-C < 1.8 mmol/L and ≥ 1.8 mmol/L subgroups. Clinical end points including major adverse cardiovascular events (MACE), cardiovascular death, nonfatal myocardial infarction, ischemic stroke, and coronary revascularization (CR) were compared. Patients in high Lp(a) groups more frequently presented with acute coronary syndrome and three vessel stenoses. In subgroup of LDL-C < 1.8 mmol/L, no significant differences of cardiovascular outcomes were found between low and high Lp(a) groups. While in the subgroup of LDL-C ≥ 1.8 mmol/L, incidences of MACE and CR were significantly higher in high Lp(a) group, and odds ratio for CR was 2.05. Conclusion. With baseline LDL-C and Lp(a) elevations, incidence of CR is significantly increased after stent placement.

1. Introduction

Dyslipidemias, especially characterized by high serum level of low density lipoprotein-cholesterol (LDL-C), has been well documented as an important risk factor of atherosclerosis and its manifestation of atherosclerotic cardiovascular diseases (CVD) [1]. In the past decades, accumulating evidence from clinical studies firmly demonstrates that LDL-C decreased by lipid-lowering drug, such as HMG-CoA reductase inhibitor (statins), is crucial for reducing the incidence of coronary heart diseases (CHD), ischemic stroke, and peripheral artery diseases [2–5]. However, some epidemiological studies show that, although target LDL-C level has been achieved by statins therapy, residual cardiovascular risk such as restenosis after stent placement in some population groups is still very high [6–8], suggesting that, besides LDL-C, other risk factors could also play a contributory role in the progression and recurrence of CVD, and identifying those potential risk factors would be useful, helpful, and beneficial for further improving cardiovascular outcome.

Lipoprotein(a) (Lp(a)), composed of an LDL-C enriched core with one molecular of apolipoprotein B-100 (apoB-100) and apolipoprotein(a) (apo(a)) via a disulfide bond, is currently considered a potential important candidate as supported by previous epidemiological, animal, and genetic epidemiological studies [9–12]. In comparison with LDL-C, Lp(a) not only is capable of promoting atherosclerosis, but also has robust effects on enhancing thrombus formation by means of impairing fibrinolysis [13, 14]. Therefore, Lp(a) elevation is believed to be the very likely risk factor accounting for residual cardiovascular risk, especially in patients with target LDL-C level. Nevertheless, findings from previous reported studies and meta-analysis are not consistent [15–19]. For example, some epidemiological studies show that the risk
Lp(a) imposes on cardiovascular system is overlapped with LDL-C [16–18], whereas other studies reveal a quite opposite outcome in which Lp(a) is an independent predictor for cardiovascular risk and traditional risk factor such as LDL-C plays no role in risk estimation for Lp(a) elevation [15, 19]. In retrospect, these discrepancies regarding the predictive value of Lp(a) elevation on cardiovascular outcomes may be partially associated with the level of LDL-C which warrants further investigation.

Nowadays, percutaneous coronary intervention (PCI) is the preferred choice for revascularization worldwide. However, it is noted that a large number of patients after stent placement, in spite of achieving recommended LDL-C level with statins therapy, have target vessel restenoses which require revascularization. Therefore, preventing and reducing the incidence of coronary restenosis after stent placement is of paramount importance. Notably, the pathophysiological process of coronary artery restenosis is featured by smooth muscle cells’ overproliferation, endothelial dysfunction, and fibrin accumulation, and with respect to Lp(a) unique features as to proatherosclerosis and prothrombosis, we speculated that Lp(a) elevation might be the potential factor responsible for increased incidence of cardiovascular events, particularly for coronary artery restenosis in patients after stent placement. Furthermore, whether the effects of Lp(a) elevation on cardiovascular events’ recurrence after stent placement are dependent on LDL-C level or not would also be investigated.

2. Method

2.1. Study Population and Protocol. Our current study has been registered in the Chinese Clinical Trial Registry (Registration number: ChiCTR-OCH-1100198). Written informed consent was obtained and the ethics committee of the Guangdong General Hospital approved present study. All participants were enrolled from Guangdong General Hospital.

After coronary artery angiography, participants eligible for coronary artery stent placement were enrolled. Demographic and clinical characteristics of all participants were collected at the initial clinical contact (see Table 1), and all participants were followed up after stent placement via outpatient visit or telephone call for monitoring event occurrence for totally 1 year. Accordingly [1], patient with poststent placement is recommended to achieve target LDL-C level of less than 1.8 mmol/L; therefore, we used 1.8 mmol/L of LDL-C as cut-off point to categorize all patients into two subgroups.

2.2. Laboratory Measurement. Blood samples were drawn by venipuncture in the morning when participants were fasting for at least 8 hours for the variables measurement. Of note, plasma level of Lp(a) was measured with sandwich enzyme-linked immune-sorbert assays (ELISA kit, Yaji Biosystems, Shanghai, China). All the procedures were performed in accordance with the manual instructions and were evaluated by SYNCHRON LX20 UniCel DxC800 analyzer (Beckman Coulter Inc., USA). Accordingly [9], plasma level of Lp(a) lower than 30 mg/dL is considered within the normal range and equal or higher than 30 mg/dL is recognized as abnormal.

2.3. Clinical End Points Definition and Assessment. In our current study, clinical end points after stent placement were defined as cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, and coronary revascularization. Assessment of the incidence of clinical end points after stent placement was performed during followup by means of outpatient visit and/or telephone call after discharge.

2.4. Statistical Analysis. Continuous data was presented as mean ± SD or median (interquartile range) appropriately and compared by Student’s t-test when data was normally distributed, otherwise compared by the Wilcoxon rank-sum test. Categorical data was presented as percentage and compared by χ2 test. Statistical analyses were performed by using SPSS software version 16.0 (SPSS, Inc., Chicago, Illinois). A value of P < 0.05 was considered significant.

3. Results

3.1. Baseline Characteristics of Low and High Lp(a) Groups. As shown in Table 1, the percentages of patients presented with acute coronary syndrome and three vessel stenoses were significantly higher in high Lp(a) group than those in low Lp(a) groups, indicating that patients with Lp(a) elevation were more prone to have more critical coronary artery stenoses. And the percentage of left main coronary artery lesion in high Lp(a) group was higher than that in the low Lp(a) group though without insignificant difference (14.3% versus 11.8%, P = 0.321). Other baseline characteristics between these two groups were comparable. All participants enrolled in our study were well followed up and were strictly adhering to recommended medications such as dual antiplatelet and statins therapies.

3.2. Cardiovascular Outcomes Comparison in the Subgroup of LDL-C Lower Than 1.8 mmol/L after Stent Placement. Selecting LDL-C level of 1.8 mmol/L as the cut-off point, 823 participants were divided into two groups. In the subgroup of LDL-C level lower than 1.8 mmol/L, there were 287 patients with Lp(a) level lower than 30 mg/dL, while another 92 were with Lp(a) level higher than 30 mg/dL. As shown in Table 2, no significant differences of MACE were found between low and high Lp(a) groups (16.3% versus 18.5%, P = 0.755). And each individual end point between these two groups was also comparable. Notably, among each individual outcome, the incidence of coronary revascularization was higher than the others in both groups.

3.3. Cardiovascular Outcomes Comparison in the Subgroup of LDL-C Equal or Higher Than 1.8 mmol/L after Stent Placement. Another 383 patients with LDL-C level equal or higher than 1.8 mmol/L were divided into two groups according to the cut-off point of Lp(a). As shown in Table 2, there was significant difference of incident MACE after stent placement between high and low Lp(a) groups (26.1% versus 16.6%,
Table 1: Comparison of baseline characteristics of low-Lp(a) and high-Lp(a) groups.

| Variables       | Low-Lp(a) (n = 552) | High-Lp(a) (n = 280) | P value |
|-----------------|---------------------|----------------------|---------|
| Age (years)     | 62.2 ± 10.3         | 62.3 ± 11.1          | 0.107   |
| Male (%)        | 83.9                | 87.5                 | 0.181   |
| Smoking (%)     | 48.6                | 43.2                 | 0.162   |
| SBP (mmHg)      | 130.4 ± 20.5        | 126.3 ± 17.8         | 0.089   |
| DBP (mmHg)      | 75.8 ± 11.3         | 74.5 ± 10.0          | 0.192   |
| HTN (%)         | 56.9                | 51.1                 | 0.122   |
| GLU (mmol/L)    | 5.84 ± 1.67         | 5.80 ± 1.82          | 0.920   |
| GHBA1C (%)      | 6.31 ± 1.02         | 6.31 ± 1.17          | 0.968   |
| DM (%)          | 24.6                | 20.0                 | 0.140   |
| CHOL (mmol/L)   | 4.05 ± 1.13         | 4.31 ± 1.19          | 0.406   |
| LDL-C (mmol/L)  | 2.33 ± 0.88         | 2.64 ± 0.89          | 0.184   |
| HDL-C (mmol/L)  | 1.04 ± 0.31         | 1.04 ± 0.30          | 0.500   |
| Log TG (mmol/L) | 0.16 ± 0.25         | 0.11 ± 0.20          | 0.001   |
| APOA (mmol/L)   | 1.01 ± 0.23         | 0.97 ± 0.24          | 0.465   |
| APOB (mmol/L)   | 0.67 ± 0.17         | 0.75 ± 0.18          | 0.364   |
| CREA (umol/L)   | 97.3 ± 31.9         | 96.2 ± 34.4          | 0.984   |
| Uric acid (umol/L) | 366.1 ± 154.8      | 380.0 ± 101.6        | 0.893   |
| LVEF (%)        | 60.65 ± 10.45       | 59.58 ± 10.77        | 0.534   |
| ACS (%)         | 67.0                | 78.2                 | 0.001   |
| LM (%)          | 11.8                | 14.3                 | 0.321   |
| Trivessel (%)   | 35.5                | 48.2                 | 0.001   |
| Previous PCI (%)| 2.5                 | 4.3                  | 0.205   |
| Previous CAGB (%)| 1.4                 | 1.1                  | 0.759   |
| Previous stroke (%) | 4.5             | 4.3                  | 1.000   |
| Aspirin (%)     | 100                 | 100                  |        |
| Clopidogrel (%) | 100                 | 100                  |        |
| Statins (%)     | 100                 | 100                  |        |

HTN: hypertension, GLU: glucose (fasting), HA1C: glycated hemoglobin, DM: diabetes mellitus, CHOL: total cholesterol, TG: triglyceride, CREA: creatinine, LVEF: left ventricular ejection fraction, ACS: acute coronary syndrome, LM: left main.

Table 2: Cardiovascular outcomes comparison in the different LDL-C subgroup after stent placement.

| Variables       | Low-Lp(a) (n = 287) | High-Lp(a) (n = 92) | P value |
|-----------------|---------------------|---------------------|---------|
| LDL-C < 1.8 subgroup (n = 379) |                     |                     |         |
| MACE (%)        | 53 (18.5)           | 15 (16.3)           | 0.755   |
| Death (%)       | 6 (2.1)             | 2 (2.2)             | 0.617   |
| MI (%)          | 4 (1.4)             | 2 (2.2)             | 0.449   |
| Stroke (%)      | 5 (1.7)             | 3 (3.3)             | 0.302   |
| CR (%)          | 38 (13.2)           | 8 (8.7)             | 0.164   |
| LDL-C > 1.8 subgroup (n = 453) |                     |                     |         |
| MACE (%)        | 44 (16.6)           | 49 (26.1)           | 0.018   |
| Death (%)       | 15 (5.7)            | 10 (5.3)            | 0.525   |
| MI (%)          | 6 (2.3)             | 5 (2.7)             | 0.509   |
| Stroke (%)      | 3 (1.1)             | 5 (2.7)             | 0.196   |
| CR (%)          | 20 (7.5)            | 29 (15.4)           | 0.006   |

MACE: major adverse cardiovascular event, MI: myocardial infarction (nonfatal), CR: coronary revascularization.
that significant residual cardiovascular risks still remain in patient despite with aggressive LDL-C reduction, and LDL-C alone is inadequate to fully evaluate and predict the residual cardiovascular risk. In lieu of evidence from epidemiological studies \[20–22\], Lp(a) elevation has been recognized as a potential candidate at least partially responsible for high residual cardiovascular risk in patient achieving target LDL-C level. However, interaction between Lp(a) and LDL-C on cardiovascular outcome has been observed and whether the effects of Lp(a) elevation on cardiovascular outcome are independent of or dependent on LDL-C is still unclear.

Our current study showed that the predictive value of Lp(a) elevation for MACE, exclusively for coronary revascularization, in CHD patients with stent placement is predominantly dependent on baseline level of LDL-C. In the subgroup of baseline LDL-C level ≥ 1.8 mmol/L, the incidence of revascularization for patients in high Lp(a) group was significantly increased and the odds ratio was 2.05 when compared to low level group (15.4% versus 7.5%, \(P = 0.006\)), whereas there was no significant difference of other individual outcome (see Table 2). Furthermore, in the subgroup of LDL-C < 1.8 mmol/L, all cardiovascular outcomes between low and high Lp(a) groups were insignificantly different (see Table 2). The unique features of Lp(a) may be partially responsible for these findings. Accordingly, the key component of Lp(a) in terms of LDL-C enriched core abounds with oxidized phospholipid (OxPL) which is a potent proinflammatory and prooxidative compound that can significantly enhance the proatherosclerotic potential of Lp(a) \[23\], while in patients with extreme low level of LDL-C (less than 1.8 mmol/L accordingly), the risk of Lp(a) elevation on cardiovascular system is diminished or even disappeared, and the underlying mechanisms are not fully understood yet. To our best knowledge, there may be two aspects attributed. In the first place, it was reported that Lp(a) degradation is partially mediated by LDL-C receptor, although the role by this pathway is not fully conclusive yet \[24\]. Therefore, higher LDL-C level may compete for LDL-C receptor which in turn reduces Lp(a) catabolism and amplifies Lp(a) biological effects, and this may be one of the underlying mechanisms attributed to the synergistic effects of both LDL-C and Lp(a) elevations, while in very low LDL-C level (<1.8 mmol/L), this synergistic effect between LDL-C and Lp(a) may be waned and unappreciated as indicated by our current study and previous studies \[18, 21\]. Secondly, it has been identified that, in the normolipidemic individuals, Lp(a) is capable of removing oxidized phospholipids (such as oxLDL-C) from circulation system via its ability to biding these proinflammatory and prothrombosis materials \[23\]. Therefore, with the higher level of LDL-C, increased Lp(a) level has higher risk of cardiovascular events than that with lower Lp(a) level, while in the lower level of LDL-C, presumed lower oxLDL-C level, Lp(a) elevation may be beneficial both for oxLDL-C clearance and cardiovascular outcomes, as supported by our current study that, in the subgroup of LDL-C lower than 1.8 mmol/L, the incidence of MACE was slightly lower in high Lp(a) group than that in low Lp(a) group (16.3% versus 18.5%, \(P = 0.755\)), though insignificantly.

4. Discussion

Our study totally enrolled 832 patients diagnosed with coronary artery disease who were eligible for stent placement after coronary angiography examination, and the results showed that (1) after stent placement, rather than an independent predictor, the predictive value of Lp(a) elevation on cardiovascular outcomes, especially coronary revascularization, was dependent on baseline LDL-C level; (2) in the subgroup of baseline LDL-C ≥ 1.8 mmol/L, patients with high Lp(a) level have increased incidence of MACE than patients with low Lp(a) level, and the between-group difference was mainly derived from coronary revascularization. Nevertheless, in the subgroup of baseline LDL-C < 1.8 mmol/L, the incidence of MACE after stent placement was comparable between high and low Lp(a) level groups; (3) moreover, in comparison to patients with low Lp(a) level, patients with high Lp(a) level more often presented with acute coronary syndrome and three vessel stenoses.

Currently, percutaneous coronary intervention is broadly applied in patients with significant coronary artery stenosis, and this reperfusion strategy has profoundly improved cardiovascular outcomes in the past two decades. However, accumulating evidence from retrospective and perspective studies shows that, despite stent placement and strictly adhering to contemporary guideline recommended medications, a substantial number of patients still have a high residual cardiovascular risk, especially target vessel restenoses which necessitate revascularization. With respect to these findings, many strategies aiming to reduce residual cardiovascular risk have been introduced, and more aggressive LDL-C lowering is considered as one of the most attractive and promising strategies. In the PROVE IT-TIMI 22 trial \[6\], Cannon CP and colleagues observed that in patients with acute coronary syndrome, intensive therapy (80 mg of atorvastatin daily) conferred greater benefits of mortality and MACE than those of standard therapy (40 mg of pravastatin daily), which was believed attributed to further reduction of LDL-C by intensive lipid lowering therapy (LDL-C 1.60 mmol/L versus 2.46 mmol/L, \(P < 0.001\)). However, after nearly 2 years’ followup, the incidence of revascularization in intensive therapy group was still up to 16.3%. Additionally, in the IDEAL and TNT trials, after approximately 5 years’ follow-up, 12.0% and 8.7% of MACE were observed, respectively, \[7, 8\]. Findings of these large clinical trials consistently show
Finally, our current study shows that, in the subgroup of high LDL-C level, the incidence of coronary revascularization after stent placement is positively associated with Lp(a) level. Accordingly, Lp(a) is capable of impairing tissue growth factor beta (TGF-β) activity which results in smooth muscle cells’ proliferation and migration [25]. Furthermore, the results from Bruneck study support the notion that fibrinolysis attenuation by Lp(a) is crucial for stabilizing atheroma-attached fibrin thrombi [26]. Lastly, Lp(a) elevation promotes endothelial dysfunction which also contributes to the restenosis progress [27]. The higher percentage of patients presented with acute coronary syndrome and three vessel stenoses also indicates that the thrombi burden in high Lp(a) groups is greater than that in low Lp(a) group. Taken together, it is reasonable to make a conclusion that in patients with stent placement, high Lp(a) level may portend a high restenosis rate.

In conclusion, our current study reveals that, in patients with stent placement, Lp(a) elevation is positively associated with coronary restenosis which requires revascularization. In patients with baseline level of LDL-C $\geq 1.8$ mmol/L, the incidence of MACE and coronary revascularization is significantly higher in high Lp(a) group than low Lp(a) group, indicating that, after stent placement, in patient with both baseline levels of LDL-C and Lp(a) elevation, more aggressive LDL-C reduction may mitigate the adverse effects imposed by Lp(a) elevation.

Conflict of Interests

All authors declare that there is no conflict of interests.

Acknowledgments

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