Prognostic Impact of Remnant-like Particle Cholesterol in Patients with Differing Glucose Metabolic Status: an Observational Cohort Study from China

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Abstract

**Background:** It is uncertain whether remnant-like particle cholesterol (RLP-C) could predict residual risk in patients under different glucose metabolic status. The study aimed to evaluate the relationship between RLP-C and adverse prognosis in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) undergoing percutaneous coronary intervention (PCI) and identify the potential impact of glucose metabolism on the predictive value of RLP-C.

**Methods:** The study enrolled 2419 patients with NSTE-ACS who underwent PCI at Beijing Anzhen Hospital from January to December 2015. RLP-C was calculated as follows: total cholesterol (TC) minus low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). The primary endpoint was a composite of events as follows: all-cause death, non-fatal myocardial infarction (MI), and ischemia-driven revascularization.

**Results:** RLP-C was significantly associated with adverse prognosis in the total population [hazard ratio (HR) 1.291 per 1-SD increase of RLP-C, 95% confidence interval (CI) 1.119-1.490, p <0.001], independent of confounding risk factors. However, subgroup analysis showed that increasing RLP-C was shown to be associated with higher risk of adverse event only in the diabetic population [HR 1.385 per 1-SD increase of RLP-C, 95% CI 1.183-1.620, p <0.001]. RLP-C failed to be a significant determinant of adverse prognosis in the pre-diabetic and non-diabetic population. The addition of RLP-C to baseline model significantly enhanced the predictive value for adverse event both in total and diabetic population.

**Conclusions:** Higher RLP-C level is a significant and independent predictor of adverse prognosis in diabetic patients with NSTE-ACS who underwent PCI.

Background

As the most serious manifestation of atherosclerotic cardiovascular disease (ASCVD), acute coronary syndrome (ACS) leads to a consistently higher risk of recurrence of cardiovascular events despite use of evidence-based secondary prevention therapies [1,2]. Low-density lipoprotein cholesterol (LDL-C) has been extensively recognized as one of the important risk factors for ASCVD and reduction of serum LDL-C levels with statins is an effective therapy to reduce cardiovascular risks [3]. Despite regulating LDL-C with statins, residual risk for recurrence of cardiovascular events remains in patients with ACS [4-7], which indicates that there are factors other than LDL-C that determine risk. Identification of these residual risk factors is important if we are to tailor risk reduction strategies that match individual risk level and to develop new therapeutic targets.

Studies have reported that the residual risk can be partly ascribed to an increased level of remnant lipoproteins [2,4,8,9]. Remnant lipoproteins are lipoproteins that are rich of triglycerides (TGs), components of which include very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and chylomicron [10]. The cholesterol content of remnant lipoproteins is defined as remnant-like particle cholesterol (RLP-C). Nowadays, the pattern of targeting LDL-C alone has changed, with recent guidelines...
highlighting the important role of non-high-density lipoprotein cholesterol (non-HDL-C), which includes RLP-C, on the pathogenesis of atherosclerosis; and thus its availability as an additional therapeutic target [11]. As a component of non-HDL-C, it is of great significance to further clarify the role of RLP-C in the development of coronary atherosclerosis.

Results from previous studies have revealed that the impact of RLP-C seems to be more prominent in high-risk patient groups such as patients with metabolic syndrome or type 2 diabetes [12-16]. It is worth exploring whether the predictive value of RLP-C for adverse outcomes varies among populations with different glucose metabolic states. This study therefore aimed to evaluate the relationship between RLP-C and adverse prognosis in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) undergoing percutaneous coronary intervention (PCI) and identify the potential impact of glucose metabolism on the predictive value of RLP-C.

Methods

Study population

This study retrospectively screened patients with NSTE-ACS who underwent PCI at Beijing Anzhen Hospital (Beijing, China) from January to December 2015. NSTE-ACS was composed of non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA), definitions of which were determined by appropriate guidelines [17]. The exclusion criteria were: (1) missing clinical, laboratory, and angiographic data; (2) history of cardiogenic shock, chronic inflammatory disease, or neoplasm; (3) evidence of active infection; (4) chronic renal failure with estimated glomerular filtration rate (eGFR) <30 mL/(min*1.73 m2) and significant hepatic disease; (5) other serious diseases; and (6) PCI failure, PCI-related complications, and in-hospital death. Ultimately, 2419 patients who met the inclusion criteria were enrolled. The enrolled patients’ demographic and clinical characteristics, laboratory investigations, and coronary procedural results were retrieved and collected from the medical record system.

Written informed consent was obtained from each participant, and the study protocol was approved by the Clinical Research Ethics Committee of Beijing Anzhen Hospital, Capital Medical University.

Demographic and clinical data collection

Data of demographic and clinical characteristics, including age, sex, weight, height, heart rate, blood pressure (BP) [systolic blood pressure (SBP) and diastolic blood pressure (DBP)], smoking, drinking, medical history, family history, and medical treatment were extracted from the medical record system of Beijing Anzhen Hospital. Body mass index (BMI) was calculated as follows: weight in kilograms divided by the square of the height in meters. Participants previously diagnosed with diabetes (treated with diet, insulin, or oral agents) or whose glycosylated hemoglobin A1c (HbA1c) level ≥6.5% were considered to have diabetes. Non-diabetes was defined as a HbA1c level <5.7% and pre-diabetes was defined as a HbA1c level ≥5.7 but < 6.5% [18].
Laboratory measurements

Venous blood samples were drawn after an overnight fast on the day of the baseline coronary procedure. Routine hematology and biochemical parameters, including lipid profiles [triglyceride (TG), total cholesterol (TC), LDL-C, HDL-C], high-sensitivity C-reactive protein (hs-CRP), creatinine, uric acid (UA), fasting blood glucose (FBG), HbA1c, and other biomarkers, were measured by standard laboratory methods. Concentrations of TC, HDL-C, and TG were quantified by standard enzymatic techniques. LDL-C was determined by homogeneous direct method. Left ventricular ejection fraction (LVEF) was evaluated by two-dimensional modified Simpson's method using an ultrasonic cardiogram (Philips Company, Eindhoven, The Netherlands).

RLP-C levels were calculated as follows: TC minus LDL-C and HDL-C, which was recommended by relevant dyslipidemia guidelines [20,21]. The eGFR was calculated as follows: eGFR [mL/(min*1.73m2)] = 186*serum creatinine (mg/dl)-1.154*age-0.203 (*0.742 if female) [22].

Coronary procedure

Coronary angiogram data were analyzed and recorded by at least two experienced cardiologists, and visual measurements of coronary artery lesion characteristics were obtained. A multi-vessel lesion was defined as more than two main branches with extent of stenosis ≥ 50%. A chronic total occlusion lesion was defined as a total occlusion [thrombolysis in myocardial infarction (TIMI) flow grade 0] and an occlusion time ≥ 3 months, which was judged from the medical history or previous coronary angiogram results. A diffuse lesion was defined as a single stenotic lesion with a length of ≥ 20 mm. A bifurcation lesion was defined as stenosis occurring adjacent to and/or involving the origin of a significant side branch that has too much functional value and so cannot be lost during the interventional procedure. PCI was performed according to current practice guidelines in China, and strategies were selected by experienced interventional cardiologists.

Follow-up

After baseline PCI, all patients were followed up by trained professionals who were blinded to the baseline information at 3, 6, and 12 months and then annually for up to 36 months. The information about adverse prognostic events was obtained from patients or their family members by telephone questionnaire. The information was further confirmed by careful verification of corresponding medical records if necessary. The primary observational endpoint was defined as a composite of events including all-cause death, non-fatal myocardial infarction (MI) and ischemia-driven revascularization. The secondary observational endpoints are each component of the composite primary endpoint. For patients who had multiple adverse outcomes during the follow-up, only the most severe event (all-cause death > non-fatal MI > ischemia-driven revascularization) was selected to perform our analyses. If the same event occurs multiple times, only the first occurrence was used for analysis.

Statistical analysis
Continuous variables with normal distribution were presented as mean ± standard deviation (SD), and differences between two groups were examined by independent-sample t-test. Data distributed nonnormally were presented as median (25th and 75th percentiles: P25, P75) and differences between two groups were tested by the Mann-Whitney U test. Categorical variables were expressed as counts and percentages and compared by Chi-square test (χ² test) or Fisher's exact test. The Spearman's rank correlation test or Pearson correlation test was used for evaluating the correlations between variables when appropriate. The participants were divided into two groups according to the median of RLP-C level. The Kaplan-Meier survival analysis was used to assess adverse prognosis in the two groups, and differences between groups were evaluated by the log-rank test. The determinants of adverse events were assessed by univariate Cox proportional hazards analyses. Variables that were significant (P < 0.05) in the univariate analysis were introduced into the multivariate analysis to determine the independent predictors of adverse prognosis. Both univariate and multivariate Cox proportional hazards analyses examined 1-SD increment in continuous variables except for age, heart rate, SBP, and number of stents. The results were presented as hazard ratio (HR) and 95% confidence intervals (95% CI).

C-statistics including receiver-operating characteristic (ROC) curve analysis were performed to examine the incremental effects of RLP-C on the predictive potential of the baseline model that including traditional risk factors. DeLong's test was used to compare the area under the curve (AUC) from each of the models. We also calculated category-free net reclassification improvement (NRI) and integrated discrimination improvement (IDI) to determine the extent to which the addition of RLP-C improves the predictive power of existing baseline model.

The study population was divided into three subgroups according to glycometabolic status: diabetic, prediabetic, and non-diabetic group. Similar statistical analyses were performed in subgroups. Statistical tests were performed with SPSS 23.0 (SPSS Inc., Chicago, Illinois, USA), The R Programming Language (version 3.5.1) and MedCalc version 19.1 (MedCalc Software, Belgium). A two-tail P value < 0.05 was regarded as statistically significant.

Results

A total of 2419 patients (mean age: 60.08±8.97 years; 71.8% men) were divided into two groups: with-event group and without-event group. During the 36-month follow-up period, thirty-nine patients (1.6% of total population) were lost to follow-up, and 454 (18.8%) patients experienced an adverse event, which comprised 21 (0.9%) all-cause deaths, 117 (4.8%) non-fatal MI, and 316 (13.1%) of ischemia-driven revascularization.

Baseline characteristics

The baseline characteristics of the study population are summarized in Table 1. RLP-C was significantly higher in patients with worse prognosis compared with those without. Patients with an adverse event exhibited higher age, BMI, heart rate, and SBP. These patients also appeared to have more previous comorbidities and more severe coronary artery disease. Disparities were also observed between the two
groups in terms of TG, TC, HDL-C, hs-CRP, creatinine, eGFR, FBG, HbA1c, LVEF and RLP-C. RLP-C level was significantly higher in patients with diabetes than pre-diabetes (0.74±0.51 vs 0.68±0.36, P=0.003) and non-diabetes (0.74±0.51 vs 0.66±0.37, P<0.001). However, there was no significant difference in RLP-C level between pre-diabetic and non-diabetic populations (0.68±0.36 vs 0.66±0.37, P=0.339) (Figure 1). RLP-C level was positively correlated with TG (r=0.853, P<0.01), TC (r=0.455, P<0.01) and LDL-C (r=0.112, P<0.01), while negatively correlated with HDL-C (r=-0.173, P<0.01).

**Predictive value of RLP-C in total population**

The study population were stratified into two groups according to the median of RLP-C level. Kaplan-Meier curves for incidence of the composite and each component of endpoint events according to the median of RLP-C were shown in Figure 2. Compared with patients with lower median of RLP-C, those with higher median of RLP-C presented with a significantly higher incidence of composite endpoint event (Figure 2A, Log-rank P value <0.001). The difference was mainly driven by the increased incidence of non-fatal MI (Figure 2C, Log-rank P value =0.002) and ischemia-driven revascularization (Figure 2D, Log-rank P <0.001). Kaplan-Meier curves for all-cause death between the lower and higher RLP-C group failed to reach statistical significance (Figure 2B, Log-rank P =0.260).

Multivariate Cox proportional hazard analysis including variables that had statistical significance (P < 0.05, details shown in Table S1) were constructed to evaluate the predictive potential of RLP-C for composite and endpoint event. After adjusting for confounding variables, higher RLP-C levels remained to be an independent risk predictor of composite endpoint event, non-fatal MI and ischemia-driven revascularization, despite of regarding RLP-C as nominal or continuous variable (Table 2).

The addition of RLP-C had a significant incremental effect on the AUC obtained with baseline risk model that consisted of traditional risk factors including age, sex (female), smoking, hypertension, prior MI, prior PCI, eGFR, HbA1c, TC, HDL-C, LVEF, left main disease and multi-vessel disease (AUC: baseline model, 0.798 vs. baseline model + RLP-C, 0.811, P for comparison < 0.001) (Table 3). Moreover, adding RLP-C to the baseline model significantly improved the reclassification and discrimination ability with a category-free NRI of 0.084 and an IDI of 0.017 (both p < 0.05) (Table 3).

**Predictive value of RLP-C in subgroups with various glycometabolic statuses**

The predictive value of RLP-C was further evaluated in subgroups with various glycometabolic status [non-diabetic population (n =926), pre-diabetic population (n =645), diabetic population (n =848)]. Kaplan-Meier curves for incidence of the composite and each component of endpoint event according to the median of RLP-C in various subgroups were summarized in Figure 3. In patients with diabetes, the incidence of composite endpoint event, non-fatal MI and ischemia-driven revascularization in higher RLP-C group was significantly higher than that in lower RLP-C group [Figure 3(i-l)]. The difference was not found in pre-diabetic [Figure 3(e-h)] and non-diabetic [Figure 3(a-d)] patients.
In multivariate Cox proportional hazard analysis, increasing RLP-C levels were shown to be significantly associated with higher risk of adverse event in the diabetic population. However, RLP-C failed to be a significant determinant of adverse prognosis in the pre-diabetic and non-diabetic populations (Table 4).

In diabetic population, the AUC increased significantly after adding RLP-C to the baseline model (AUC: baseline model, 0.788 vs. baseline model + RLP-C, 0.836, P for comparison < 0.001). In contrast, the addition of RLP-C did not have a significant incremental effect on AUC in pre-diabetic and non-diabetic population (Table 5, Figure 4). Furthermore, the addition of RLP-C significantly improved the reclassification and discrimination ability beyond the baseline model with a category-free NRI of 0.155 and an IDI of 0.040 (both p < 0.05) in diabetic population but not in pre-diabetic and non-diabetic population (Table 5).

Discussion

In the present study, we found a strong and independent relationship between fasting RLP-C levels and adverse prognosis in patients with NSTE-ACS treated with PCI. Further subgroup analyses elucidated that RLP-C showed a better predictive value in the diabetic population. However, RLP-C failed to be a significant determinant of adverse prognosis in the pre-diabetic and non-diabetic populations. Addition of RLP-C level had a significant incremental effect on the predictive value for adverse events.

It has been widely demonstrated that LDL-C is one of the most significant risk indicators for ASCVD, and reduction of serum LDL-C levels with statins is a well-established therapy to reduce the ASCVD risk. However, many patients whose LDL-C levels are well controlled by statins continue to suffer recurrent cardiovascular events [3-7]. In recent years, factors related to obesity and metabolic syndrome such as triglycerides rich lipoproteins (TRLs) have been considered as potential metabolism-related risk factors for cardiovascular diseases and the cause of residual risks other than LDL-C. As the cholesterol component of the subset of TRLs, RLP-C has been demonstrated to be a causal risk factor for ischemic heart disease (IHD) [23-25]. Clinical studies also revealed that higher RLP-C levels showed favorable predictive value for the risk of recurrent cardiovascular events in patients with either stable coronary artery disease (SCAD) or ACS, regardless of the baseline treatment of statins and level of LDL-C [12,26-29]. The current analyses extend these findings to a cohort of patients with NSTE-ACS treated with PCI and indicates that elevated RLP-C is significantly associated with adverse prognosis.

Previous studies have also demonstrated the significant association of RLP-C with plaque characteristics of the coronary arteries, such as plaque burden, composition and vulnerability. Lina et al revealed that RLP-C levels were significantly related to coronary atherosclerotic burden evaluated by computed tomography coronary angiography (CTCA), even in patients with optimal LDL-C levels [30]. Puri et al. demonstrated that non-HDL-C levels were closely correlated with progression and regression of atherosclerotic plaque burden assessed by intravascular ultrasound (IVUS), independent of LDL-C levels [31]. Matsuo et al. found that in statin treated patients, RLP-C levels, as opposed to LDL-C levels, were strongly associated with the proportion of plaque necrosis (a marker of plaque vulnerability) evaluated by
These findings provide important confirmation and interpretation of previous results from clinical studies, suggesting that high RLP-C level is one of the risk factors for cardiovascular events. Additionally, this correlation between RLP-C and plaque characteristics was observed in the statin-treated and optimal LDL-C level group, indicating that high RLP-C levels may be a residual risk factor in the statin-treated population.

In this study, LDL-C level did not show predictive value for poor prognosis, which is consistent with previous studies [5,13,29]. The underlying causes can be complex. Firstly, most participants enrolled in the present study underwent statin therapy, whose lipid-lowering and other effects may have potential impacts on the association of LDL-C levels with adverse events. Moreover, patients with complex coronary lesions or clinical conditions may be inclined to receive more intensive lipid-lowering therapy. Such treatment selection bias or so called “confounding by indication” may have a certain influence on the predictive ability of LDL-C or even lead to a paradox phenomenon, such as the phenomenon that the use of angiotensin converting enzyme inhibitor (ACEI) could predict adverse events, which was present in our study. The present study revealed that RLP-C levels remained a predictor of adverse prognosis despite the probable influence of statin treatment on RLP-C levels, which indicated that RLP-C may have greater atherogenicity than other serum lipid parameters. TG, TC, and HDL-C lost their predictability in the multivariate Cox proportional hazard analysis using covariates, including RLP-C, in the present study; which can partly be attributed to the strong correlation between them and RLP-C levels.

Results from previous studies have revealed that the impact of RLP-C seems to be more prominent in patients with high-risk, such as metabolic syndrome or type 2 diabetes [12-16]. Our study also shows that RLP-C has predictive value for poor outcomes only in patients with diabetes, which indicates that there is significant interaction of glycometabolic status and RLP-C level on the risk of adverse prognosis. Diabetic patients have more complex lipid metabolism disorders than non-diabetic patients characterized by increased TG levels and decreased HDL-C levels [33]. Therefore, in addition to LDL-C, other lipid-metabolic indicators may also have a certain impact on the cardiovascular risk of diabetic patients. Studies have proved that hypertriglycerideremia and high TRLs play an important role in the development of coronary artery disease (CAD) [2,4,9]. TG is predominantly carried by TRLs, which binds to arterial endothelium, where lipoprotein lipase initiates TG hydrolysis, finally leading to the production of remnant lipoproteins. Thus, the concentrations of TG are closely related to the cholesterol content of remnant lipoproteins, that is, RLP-C [34,35]. The association of RLP-C with TG level was also verified in the present study. Studies have also shown that RLP-C levels increased in patients with diabetes compared with non-diabetic patients [12,26,35], which was consistent with our study. These phenomena may magnify the predictive value of RLP-C for adverse prognosis in patients with recognized diabetes.

Several pathophysiologic mechanisms may account for the association between high RLP-C levels and the increased prevalence of recurrent adverse events which we observed in current study. (1) RLP-C can upregulate the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells, which further induce the migration of monocytes into the arterial wall [36]. (2) RLP-C increases the generation of tissue factor (TF), which is essential for the
formation of thrombus in vessels [36]. (3) There is evidence that RLP-C can enhance the aggregation of platelets [37]. (4) RLP-C promotes the propagation of smooth muscle cells independently of the impact of oxidative stress [38]. (5) RLP-C is causally related to low-grade inflammation, with a near three-fold higher CRP levels for each 1 mmol/L increase in RLP-C [39]. (6) RLP-C was demonstrated to be a risk indicator for endothelial vasomotor dysfunction [16,40]. (7) High concentrations of RLP-C were proved to be correlated to inflammation in the arterial wall in case of endothelial injury [41]. The pro-inflammatory and pro-atherothrombotic roles of RLP-C listed above may be the explanation for the relationship between high RLP-C levels and future adverse prognosis observed in the current study.

Studies have shown that less than a quarter of patients exhibited an LDL-C level below the guideline recommended target, despite remaining on statin therapy during the secondary prevention period [28,42]. This so called “treatment gap” between target value and clinical practice is common in the real world. In this context, while regarding LDL-C as the primary target, the exploration of residual risk factors can also provide complementary therapeutic strategies for reducing cardiovascular risk. The relationship we have showed between high RLP-C levels and increased incidence of recurrent adverse events in diabetic patients with NSTE-ACS treated with PCI demonstrates that RLP-C may be a complementary risk predictor and therapeutic target.

Previous reports showed that lipid-lowering agents, such as fibrates, ezetimibe, and statins, as well as diet adaptation, proper aerobic exercise, and obesity reduction may effectively decrease RLP-C levels to varying degrees [26,43,44], thus enabling RLP-C as a therapeutic target. However, in addition to statin treatment for LDL-C, it is uncertain whether RLP-C should be a therapeutic target in recognized CAD patients. Clinical trials of non-statin lipid-lowering treatments have shown significant benefit in reducing residual risk, but none have specifically targeted RLP-C. Newer agents, such as potent omega-3 fatty acid derivatives [45] or antisense oligonucleotide to apolipoprotein C-III [46], were proved to have the potential to reduce TRLs significantly and may provide useful tools for answering this question. In JELIS (Japan EPA Lipid Intervention Study), eicosapentaenoic acid (an omega-3 fatty acid derivative) combined with low-dose statins reduced triglycerides by about 5% and coronary events by 19% compared to low-dose statins alone [47]. Novel inhibitors of apolipoprotein C-III, a key regulator of remnant metabolism, have also showed promising results [48]. Furthermore, antibodies to PCSK9, although primarily intended to lower LDL-C concentrations, also proved to reduce cholesterol contained in TRLs to some extent [49].

Nowadays, the pattern of targeting LDL-C alone has changed, with recent guidelines highlighting the important role of non-high-density lipoprotein cholesterol (non-HDL-C), which includes RLP-C, on the pathogenesis of atherosclerosis and thus its availability as an additional therapeutic target [11]. Therefore, it is necessary to develop new therapies targeting RLP-C and conduct randomized trials evaluating whether lowering RLP-C level can regulate plaque morphology and reduce the residual risk of substantial cardiovascular events.

There are some limitations to our study: (1) Remnant lipoproteins mainly contain VLDL and chylomicron remnants. In the fasting state of the present study, VLDL remnants are the major constituent of
circulating remnants, so that the contribution of chylomicron remnants to atherosclerosis and plaque burden may have been underestimated [50]. (2) Although potentially not as accurate as direct measurement, calculated remnant cholesterol as used in our study can be easily performed on a standard lipid profile without any additional cost. (3) Although evidence-based statin treatment was administrated, no specific statin agent or dose was specified. (4) Finally, although sequential surveillance may prove more informative, only baseline lipid profiles before PCI were obtained in our study.

Conclusions

A higher RLP-C level is a significant and independent predictor of adverse prognosis in diabetic patients with NSTE-ACS undergoing PCI, rather than in the subgroup of pre-diabetic and non-diabetic populations. Addition of RLP-C level had a significant incremental effect on the predictive value for adverse events. The current study indicates that the measurement of RLP-C may be important not only for evaluating the risk of adverse prognosis, but also for tailoring treatment to prevent impending cardiovascular events in specific populations.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from each participant, and the study protocol was approved by the Clinical Research Ethics Committee of Beijing Anzhen Hospital, Capital Medical University.

Availability of data and materials

The datasets generated and analyzed for this study are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Authors' contributions

QZ (first author) and TYZ (co-first author) made substantial contributions to study design, data collection, data analysis and manuscript writing. YJZ (corresponding author) made substantial contributions to
study design and intellectual direction. They contributed equally to this work. YJC, YM, YKX, JQY made contributions to data collection and analysis. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline clinical characteristics of study population.
|                                | Total population, n=2419 | Without event, n=1965 | With event, n=454 | P value |
|--------------------------------|--------------------------|------------------------|-------------------|---------|
| Age, years                     | 60.08±8.97               | 59.60±8.72             | 62.16±9.70        | <0.001  |
| Male, n (%)                    | 1737 (71.8)              | 1422 (72.4)            | 315 (69.4)        | 0.203   |
| BMI, kg/m²                     | 26.21±3.45               | 26.13±3.40             | 26.55±3.61        | 0.019   |
| Heart rate, bpm                | 69.77±10.15              | 69.44±10.00            | 71.17±10.69       | 0.002   |
| SBP, mmHg                      | 130.30±16.52             | 129.80±15.99           | 132.44±18.50      | 0.005   |
| DBP, mmHg                      | 77.05±9.90               | 77.00±9.68             | 77.25±10.80       | 0.661   |
| Smoking, n (%)                 | 1381 (57.1)              | 1127 (57.4)            | 254 (55.9)        | 0.585   |
| Drinking, n (%)                | 562 (23.2)               | 468 (23.8)             | 94 (20.7)         | 0.157   |
| Family history of CAD, n (%)   | 254 (10.5)               | 203 (10.3)             | 51 (11.2)         | 0.572   |
| Medical history, n (%)         |                          |                        |                   |         |
| Hypertension                   | 1511 (62.5)              | 1210 (61.6)            | 301 (66.3)        | 0.061   |
| Prior MI                       | 527 (21.8)               | 348 (17.7)             | 179 (39.4)        | <0.001  |
| Prior PCI                      | 414 (17.1)               | 280 (14.2)             | 134 (29.5)        | <0.001  |
| Prior CABG                     | 55 (2.3)                 | 23 (1.2)               | 32 (7.0)          | <0.001  |
| Prior stroke                   | 281 (11.6)               | 204 (10.4)             | 77 (17.0)         | <0.001  |
| Prior PAD                      | 84 (3.5)                 | 63 (3.2)               | 21 (4.6)          | 0.137   |
| Glycometabolic status          |                          |                        |                   |         |
| Non-diabetes                   | 926 (38.3)               | 829 (42.2)             | 97 (21.4)         | <0.001  |
| Pre-diabetes                   | 645 (26.7)               | 531 (27.0)             | 114 (25.1)        | 0.406   |
| Diabetes                       | 848 (35.1)               | 605 (30.8)             | 243 (53.5)        | <0.001  |
| Laboratory results             |                          |                        |                   |         |
| TG, mmol/L                     | 1.84±1.32                | 1.69±1.05              | 2.47±2.00         | <0.001  |
| TC, mmol/L                     | 4.17±1.06                | 4.14±1.05              | 4.33±1.07         | 0.001   |
| LDL-C, mmol/L                  | 2.50±0.88                | 2.50±0.89              | 2.50±0.85         | 0.962   |
| HDL-C, mmol/L                  | 0.98±0.23                | 0.99±0.24              | 0.92±0.21         | <0.001  |
| RLP-C, mmol/L                  | 0.69±0.42                | 0.65±0.35              | 0.90±0.61         | <0.001  |
|                              | Value 1 (Range) | Value 2 (Range) | Value 3 (Range) | p-value |
|------------------------------|----------------|-----------------|-----------------|---------|
| hs-CRP, mg/L                 | 1.29 (0.58, 3.31) | 1.22 (0.53, 3.06) | 1.87 (0.77, 4.29) | <0.001  |
| Creatinine, μmol/L           | 76.00±16.95     | 75.68±16.49     | 77.42±18.76     | 0.048   |
| eGFR, ml/(min*1.73m²)        | 93.49±20.36     | 94.09±20.11     | 90.91±21.22     | 0.003   |
| Uric acid, μmol/L            | 346.22±82.64    | 346.45±81.45    | 345.21±87.69    | 0.774   |
| FBG, mmol/L                  | 6.20±1.94       | 6.01±1.71       | 7.03±2.57       | <0.001  |
| HbA1c, %                     | 6.29±1.21       | 6.14±1.08       | 6.96±1.51       | <0.001  |
| LVEF, %                      | 63.92±6.81      | 64.50±6.20      | 61.42±8.56      | <0.001  |
| Initial diagnosis, n (%)     |                |                | 356 (78.4)      | 0.001   |
| UA                           | 2018 (83.4)     | 1662 (84.6)     |                |         |
| NSTEMI                        | 401 (16.6)      | 303 (15.4)      | 98 (21.6)       |         |
| Medical treatment, n (%)     |                |                |                |         |
| ACEI                         | 734 (30.3)      | 577 (29.4)      | 157 (34.6)      | 0.029   |
| ARB                          | 948 (39.2)      | 753 (38.3)      | 195 (43.0)      | 0.068   |
| Aspirin                      | 2417 (99.9)     | 1963 (99.9)     | 454 (100.0)     | 0.496   |
| Clopidogrel                  | 2415 (99.8)     | 1963 (99.9)     | 452 (99.6)      | 0.109   |
| β-Blocker                    | 2199 (90.9)     | 1780 (90.6)     | 419 (92.3)      | 0.255   |
| Statins                      | 2366 (97.8)     | 1922 (97.8)     | 444 (97.8)      | 0.985   |
| Oral hypoglycemic agents     | 437 (18.1)      | 314 (16.0)      | 123 (27.1)      | <0.001  |
| Insulin                      | 232 (9.6)       | 154 (7.8)       | 78 (17.2)       | <0.001  |
| Angiographic data, n (%)     |                |                |                |         |
| Left main disease            | 110 (4.5)       | 64 (3.3)        | 46 (10.1)       | <0.001  |
| Multi-vessel disease         | 1631 (67.4)     | 1225 (62.3)     | 406 (89.4)      | <0.001  |
| Chronic total occlusion      | 345 (14.3)      | 202 (10.3)      | 143 (31.5)      | <0.001  |
| Diffuse lesion               | 605 (25.0)      | 431 (21.9)      | 174 (38.3)      | <0.001  |
Bifurcation lesion

|                | 492 (20.3) | 368 (18.7) | 124 (27.3) | <0.001 |
|----------------|------------|------------|------------|--------|

Number of stents

|                | 1.96±1.29  | 1.87±1.14  | 2.33±1.76  | <0.001 |

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; PAD, peripheral arterial disease; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; RLP-C, remnant-like particle cholesterol; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; LVEF, left ventricular ejection fraction; UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2. Multivariate Cox analysis evaluating predictive value of RLP-C for composite and each component of endpoint event in total population.

|                              | RLP-C as a nominal variable* | RLP-C as a continuous variable** |
|------------------------------|------------------------------|----------------------------------|
|                              | HR  | 95% CI          | P value | HR  | 95% CI           | P value |
| Primary endpoint             | 1.960| 1.558-2.465     | <0.001  | 1.291| 1.119-1.490      | <0.001  |
| All-cause death              | 2.207| 0.612-7.959     | 0.226   | 1.829| 0.837-3.995      | 0.130   |
| Non-fatal MI                 | 1.883| 1.195-2.966     | 0.006   | 1.330| 1.002-1.764      | 0.048   |
| Ischemia-driven revascularization | 1.836| 1.395-2.416     | <0.001  | 1.208| 1.016-1.438      | 0.033   |

Multivariate Cox analysis was adjusted for confounders that are significant (P <0.05) in univariate analysis (details shown in Table S1).

* The HR was examined regarding lower median of RLP-C as reference.

** The HR was examined by per 1-SD increase of RLP-C.

RLP-C, remnant-like particle cholesterol; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction.
Table 3. C-statistics for discrimination ability of various predictive model for composite endpoint event in total population.

| ROC curve analysis | Category-free NRI | IDI |
|-------------------|-------------------|-----|
|                   | AUC   | 95% CI | p     | index | p | index | p |
| Baseline model*   | 0.798 | 0.781-0.814 | reference | - | reference | - | reference |
| + RLP-C           | 0.811 | 0.795-0.826 | <0.001 | 0.084 | 0.048 | 0.017 | 0.030 |

* Baseline model includes traditional risk factors: age, sex (female), smoking, hypertension, prior MI, prior PCI, eGFR, HbA1c, TC, HDL-C, LVEF, left main disease and multi-vessel disease.

ROC, receiver operating characteristics; AUC, area under the curve; CI, confidence interval; NRI, net reclassification improvement; IDI, integrated discrimination improvement; RLP-C, remnant-like particle cholesterol.

Table 4. Multivariate Cox analysis evaluating predictive value of RLP-C for composite and each component of endpoint event in subgroups with different glycometabolic status.
|                                | RLP-C as a nominal variable* |                          | RLP-C as a continuous variable** |                          |
|--------------------------------|------------------------------|--------------------------|---------------------------------|--------------------------|
|                                | HR   | 95% CI      | P value | HR   | 95% CI      | P value |
| Non-diabetic population        |      |             |         |      |             |         |
| Primary endpoint               | 1.193| 0.681-2.092| 0.538   | 0.957| 0.548-1.670| 0.876   |
| All-cause death                | 0.344| 0.001-229.549| 0.748  | 4.143| 0.240-71.536| 0.328   |
| Non-fatal MI                   | 1.189| 0.382-3.703| 0.766   | 1.092| 0.309-3.855| 0.892   |
| Ischemia-driven revasculariz.  | 1.292| 0.664-2.513| 0.451   | 0.812| 0.421-1.568| 0.535   |
| Pre-diabetic population        |      |             |         |      |             |         |
| Primary endpoint               | 1.335| 0.852-2.092| 0.208   | 0.898| 0.577-1.397| 0.633   |
| All-cause death                | 2.882| 0.337-24.651| 0.334  | 1.132| 0.305-4.202| 0.853   |
| Non-fatal MI                   | 1.346| 0.532-3.404| 0.530   | 1.152| 0.535-2.483| 0.718   |
| Ischemia-driven revasculariz.  | 1.312| 0.750-2.293| 0.341   | 0.725| 0.405-1.297| 0.278   |
| Diabetic population            |      |             |         |      |             |         |
| Primary endpoint               | 4.247| 2.941-6.135| <0.001  | 1.385| 1.183-1.620| <0.001  |
| All-cause death                | 1.571| 0.247-9.996| 0.632   | 0.753| 0.329-1.723| 0.502   |
| Non-fatal MI                   | 6.072| 2.669-13.815| <0.001 | 1.392| 0.975-1.988| 0.069   |
| Ischemia-driven revasculariz.  | 3.683| 2.397-5.657| <0.001  | 1.327| 1.100-1.600| 0.003   |
Multivariate Cox analysis was adjusted for confounders that are significant (P < 0.05) in univariate analysis (details shown in Table S1).

* The HR was examined regarding lower median of RLP-C as reference.

** The HR was examined by per 1-SD increase of RLP-C.

RLP-C, remnant-like particle cholesterol; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction.

Table 5. C-statistics for discrimination ability of various predictive model for composite endpoint event in subgroups with different glycometabolic status.

|                         | ROC curve analysis | Category-free NRI | IDI         |
|-------------------------|-------------------|-------------------|-------------|
|                         | AUC               | 95% CI            | p index     | p index     | p index     |
| **Non-diabetic population** |                   |                   |             |             |             |
| Baseline model*         | 0.836             | 0.810-0.859       | reference   | -           | reference   | -           | reference   |
| +RLP-C                  | 0.838             | 0.813-0.861       | 0.311       | 0.022       | 0.517       | 0.002       | 0.169       |
| **Prediabetic population** |                   |                   |             |             |             |             |             |
| Baseline model*         | 0.781             | 0.747-0.812       | reference   | -           | reference   | -           | reference   |
| +RLP-C                  | 0.781             | 0.747-0.812       | 0.581       | 0.017       | 0.842       | 0.001       | 0.642       |
| **Diabetic population** |                   |                   |             |             |             |             |             |
| Baseline model*         | 0.788             | 0.759-0.815       | reference   | -           | reference   | -           | reference   |
| +RLP-C                  | 0.836             | 0.809-0.860       | <0.001      | 0.155       | 0.010       | 0.040       | <0.001      |

* Baseline model includes traditional risk factors: age, sex (female), smoking, hypertension, prior MI, prior PCI, eGFR, HbA1c, TC, HDL-C, LVEF, left main disease and multi-vessel disease.
ROCS, receiver operating characteristics; AUC, area under the curve; CI, confidence interval; NRI, net reclassification improvement; IDI, integrated discrimination improvement; RLP-C, remnant-like particle cholesterol.

**Figures**

![Figure 1: RLP-C levels in different glycometabolic status.](image)

**Figure 1**

RLP-C levels in different glycometabolic status. RLP-C, remnant-like particle cholesterol.
Figure 2

Kaplan-Meier curves for cumulative event rate according to RLP-C levels in total population. Kaplan-Meier curves for (A) composite endpoint event; (B) all-cause death; (C) non-fatal MI; (D) ischemia-driven revascularization. RLP-C, remnant-like particle cholesterol; PCI, percutaneous coronary intervention; MI, myocardial infarction.
Figure 3

Kaplan-Meier curves for cumulative event rate according to RLP-C levels in various subgroups with different glycometabolic status. Kaplan-Meier curves for cumulative event rate in (a-d) non-diabetic population; (e-h) pre-diabetic population; (i-l) diabetic population. RLP-C, remnant-like particle cholesterol; PCI, percutaneous coronary intervention; MI, myocardial infarction.
Figure 4

ROC curve evaluating predictive value of various models for composite endpoint event in total population and subgroups. (A) Total population; (B) Non-diabetic population; (C) Pre-diabetic population; (D) Diabetic population. Baseline model includes traditional risk factors: age, sex (female), smoking, hypertension, prior MI, prior PCI, eGFR, HbA1c, TC, HDL-C, LVEF, left main disease and multi-vessel disease. RLP-C, remnant-like particle cholesterol.