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

Qi Zhao

Capital Medical University Affiliated Anzhen Hospital

Ting-Yu Zhang

Capital Medical University Affiliated Anzhen Hospital

Yu-Jing Cheng

Capital Medical University Affiliated Anzhen Hospital

Yue Ma

Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital

Ying-Kai Xu

Capital Medical University Affiliated Anzhen Hospital

Jia-Qi Yang

Capital Medical University Affiliated Anzhen Hospital

Yujie Zhou (✉ azzyj12@163.com)

Capital Medical University

Research

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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 (NSTEMI-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 NSTEMI-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 NSTEMI-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 (NSTEMI) 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 NSTEMI who underwent PCI at Beijing Anzhen Hospital (Beijing, China) from January to December 2015. NSTEMI 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 $\times$ 1.73 m 2) 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 $\geq 6.5\%$ 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: $\text{eGFR [mL/(min*1.73m}^2\text{)]} = 186 * \text{serum creatinine (mg/dl)}^{-1.154} * \text{age}^{-0.203} (*0.742 \text{ if female})$ [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 $\geq 50\%$. 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 $\pm$ standard deviation (SD), and differences between two groups were examined by independent-sample t-test. Data distributed non-normally 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 (χ^2 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, pre-diabetic, 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 NSTEMI-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 NSTEMI-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

IVUS [32]. 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 hypertriglyceridemia 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 NSTEMI-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]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 administered, 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 NSTEMI-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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References

- [1] Fox KA, Carruthers KF, Dunbar DR, et al. Underestimated and under-recognized: The late consequences of acute coronary syndrome (GRACE UK-Belgian Study). *Eur Heart J*, 2010, 31(22): 2755-2764.
- [2] Schwartz GG, Abt M, Bao W, et al. Fasting triglycerides predict recurrent ischemic events in patients with acute coronary syndrome treated with statins. *J Am Coll Cardiol*, 2015, 65(21): 2267-2275.
- [3] Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*, 2010; 376(9753): 1670-1681.
- [4] Miller M, Cannon CP, Murphy SA, et al. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol*, 2008, 51(7): 724-730.
- [5] Mora S, Wenger NK, Demicco DA, et al. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the treating to new targets (TNT) study. *Circulation*, 2012, 125(16): 1979-1987.
- [6] Sabatine MS, Giugliano RP, Keech AC, et al. FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*, 2017, 376(18): 1713-1722.
- [7] Cannon CP, Blazing MA, Giugliano RP, et al. IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*, 2015, 372(25): 2387-2397.
- [8] Miller M, Ginsberg HN, Schaefer EJ. Relative atherogenicity and predictive value of non-high-density lipoprotein cholesterol for coronary heart disease. *Am J Cardiol*, 2008, 101(7): 1003-1008.
- [9] Khetarpal SA, Rader DJ. Triglyceride-rich lipoproteins and coronary artery disease risk: new insights from human genetics. *Arterioscler Thromb Vasc Biol*, 2015, 35(2): e3-9.
- [10] Chapman MJ, Ginsberg HN, Amarenco P, et al. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J*, 2011, 32(11): 1345-1361.

- [11] Mach F, Baigent C, Catapano AL, et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*, 2019, pii: ehz455.
- [12] Fukushima H, Sugiyama S, Honda O, et al. Prognostic value of remnant-like lipoprotein particle levels in patients with coronary artery disease and type II diabetes mellitus. *J Am Coll Cardiol*, 2004; 43(12): 2219-2224.
- [13] Nguyen SV, Nakamura T, Uematsu M, et al. Remnant lipoproteinemia predicts cardiovascular events in patients with type 2 diabetes and chronic kidney disease. *J Cardiol*, 2017, 69(3):529-535.
- [14] Qin Z, Zhou K, Li YP, et al. Remnant lipoproteins play an important role of in-stent restenosis in type 2 diabetes undergoing percutaneous coronary intervention: a single-centre observational cohort study. *Cardiovasc Diabetol*, 2019, 18(1): 11.
- [15] Nakamura T, Obata JE, Takano H, et al. High serum levels of remnant lipoproteins predict ischemic stroke in patients with metabolic syndrome and mild carotid atherosclerosis. *Atherosclerosis*, 2009, 202(1): 234-240.
- [16] Nakamura T, Takano H, Umetani K, et al. Remnant lipoproteinemia is a risk factor for endothelial vasomotor dysfunction and coronary artery disease in metabolic syndrome. *Atherosclerosis*, 2005, 181(2): 321-327.
- [17] Roffi M, Patrono C, Collet JP, et al. ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*, 2016, 37(3): 267-315.
- [18] American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*, 2014, 37(Suppl 1): S81-90.
- [19] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*, 1972, 18: 499–502.
- [20] Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel Members. An International atherosclerosis society position paper: global recommendations for the management of dyslipidemia–full report. *J Clin Lipidol*, 2014, 8(1): 29-60.
- [21] Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1-full report. *J Clin Lipidol*, 2015, 9(2):129-169.
- [22] Levey AS, Coresh J, Greene T, et al. Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for

estimating glomerular filtration rate. *Ann Intern Med*, 2006, 145(4): 247-254.

[23] Varbo A, Benn M, Tybjaerg-Hansen A, et al. Remnant cholesterol as a causal risk factor for ischemic heart disease. *J Am Coll Cardiol*, 2013, 61(4): 427-436.

[24] Jørgensen AB, Frikke-Schmidt R, West AS, et al. Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. *Eur Heart J*, 2013, 34(24): 1826-1833.

[25] Joshi PH, Khokhar AA, Massaro JM, et al. Remnant lipoprotein cholesterol and incident coronary heart disease: the jackson heart and Framingham offspring cohort studies. *J Am Heart Assoc*, 2016, 5(5): e002765.

[26] Kugiyama K, Doi H, Takazoe K, et al. Remnant lipoprotein levels in fasting serum predict coronary events in patients with coronary artery disease. *Circulation*, 1999, 99(22): 2858-2860.

[27] Jepsen AM, Langsted A, Varbo A, et al. Increased remnant cholesterol explains Part of residual risk of all-cause mortality in 5414 patients with ischemic heart disease. *Clin Chem*, 2016, 62(4): 593-604.

[28] Nguyen SV, Nakamura T, Kugiyama K. High Remnant Lipoprotein Predicts Recurrent Cardiovascular Events on Statin Treatment After Acute Coronary Syndrome. *Circ J*, 2014, 78(10): 2492-2500.

[29] Fujihara Y, Nakamura T, Horikoshi T, et al. Remnant Lipoproteins Are Residual Risk Factor for Future Cardiovascular Events in Patients with Stable Coronary Artery Disease and On-Statins Low-Density Lipoprotein Cholesterol Levels <70 mg/dL. *Circ J*, 2019, 83(6):1302-1308.

[30] Lin A, Nerlekar N, Rajagopalan A, et al. Remnant cholesterol and coronary atherosclerotic plaque burden assessed by computed tomography coronary angiography. *Atherosclerosis*, 2019, 284: 24-30.

[31] Puri R, Nissen SE, Shao M, et al. Non-HDL Cholesterol and Triglycerides: Implications for Coronary Atheroma Progression and Clinical Events. *Arterioscler Thromb Vasc Biol*, 2016, 36(11): 2220-2228.

[32] Matsuo N, Matsuoka T, Onishi S, et al. Impact of remnant lipoprotein on coronary plaque components. *J Atheroscler Thromb*, 2015, 22(8): 783-795.

[33] Krauss RM. Lipids and lipoproteins in patients with type 2 diabetes. *Diabetes Care*, 2004, 27(6): 1496-1504.

[34] Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. *Circ Res*, 2016, 118(4): 547-563.

[35] Goliasch G, Wiesbauer F, Blessberger H, et al. Premature myocardial infarction is strongly associated with increased levels of remnant cholesterol. *J Clin Lipidol*, 2015, 9(6): 801-806.

- [36] Doi H, Kugiyama K, Oka H, et al. Remnant lipoproteins induce proatherothrombogenic molecules in endothelial cells through a redox-sensitive mechanism. *Circulation*, 2000, 102(6): 670-676.
- [37] Saniabadi AR, Umemura K, Shimoyama M, et al. Aggregation of human blood platelets by remnant like lipoprotein particles of plasma chylomicrons and very low density lipoproteins. *Thromb Haemost*, 1997, 77(5): 996-1001.
- [38] Zhao D, Letterman J, Schreiber BM. Beta-migrating very low density lipoprotein (beta VLDL) activates smooth muscle cell mitogen-activated protein (MAP) kinase via G protein-coupled receptor-mediated transactivation of the epidermal growth factor (EGF) receptor: effect of MAP kinase activation on beta VLDL plus EGF-induced cell proliferation. *J Biol Chem*, 2001, 276(33): 30579-30588.
- [39] Varbo A, Benn M, Tybjaerg-Hansen A, et al. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. *Circulation*, 2013, 128(12): 1298-1309.
- [40] Kugiyama K, Doi H, Motoyama T, et al. Association of remnant lipoprotein levels with impairment of endothelium-dependent vasomotor function in human coronary arteries. *Circulation*, 1998, 97(25): 2519-2526.
- [41] Bernelot Moens SJ, Verweij SL, Schnitzler JG, et al. Remnant cholesterol elicits arterial wall inflammation and a multilevel cellular immune response in humans. *Arterioscler Thromb Vasc Biol*, 2017, 37(5): 969-975.
- [42] Assmann G, Benecke H, Neiss A, et al. Gap between guidelines and practice: Attainment of treatment targets in patients with primary hypercholesterolemia starting statin therapy. Results of the 4E-Registry (Efficacy Calculation and Measurement of Cardiovascular and Cerebrovascular Events Including Physicians' Experience and Evaluation). *Eur J Cardiovasc Prev Rehabil*, 2006, 13(5): 776-783.
- [43] Packard CJ. Determinants of achieved LDL cholesterol and non-HDL cholesterol in the management of dyslipidemias. *Curr Cardiol Rep*, 2018, 20(8): 60.
- [44] Bozzetto L, Annuzzi G, Corte GD, et al. Ezetimibe beneficially influences fasting and postprandial triglyceride-rich lipoproteins in type 2 diabetes. *Atherosclerosis*, 2011, 217(1): 142-148.
- [45] Ballantyne CM, Braeckman RA, Soni PN. Icosapent ethyl for the treatment of hyper triglyceridemia. *Expert Opin Pharmacother*, 2013, 14: 1409-1416.
- [46] Graham MJ, Lee RG, Bell TA 3rd, et al. Antisense oligonucleotide inhibition of apolipoprotein C-III reduces plasma triglycerides in rodents, nonhuman primates, and humans. *Circ Res*, 2013, 112(11): 1479-1490.
- [47] Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomized open-label, blinded endpoint analysis.

Lancet, 2007, 369(9567): 1090-1098.

[48] TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. N Engl J Med, 2014, 371(1): 22-31.

[49] Dijk W, Le May C, Cariou B. Beyond LDL: What role for PCSK9 in triglyceride-rich lipoprotein metabolism? Trends Endocrinol Metab, 2018, 29(6): 420-434.

[50] Nakamura K, Miyoshi T, Yunoki K, et al. Postprandial hyperlipidemia as a potential residual risk factor. J Cardiol, 2016, 67(4): 335-339.

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/m ²	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
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, $\mu\text{mol/L}$	76.00 $\pm$ 16.95	75.68 $\pm$ 16.49	77.42 $\pm$ 18.76	0.048
eGFR, ml/(min*1.73m ²)	93.49 $\pm$ 20.36	94.09 $\pm$ 20.11	90.91 $\pm$ 21.22	0.003
Uric acid, $\mu\text{mol/L}$	346.22 $\pm$ 82.64	346.45 $\pm$ 81.45	345.21 $\pm$ 87.69	0.774
FBG, mmol/L	6.20 $\pm$ 1.94	6.01 $\pm$ 1.71	7.03 $\pm$ 2.57	<0.001
HbA1c, %	6.29 $\pm$ 1.21	6.14 $\pm$ 1.08	6.96 $\pm$ 1.51	<0.001
LVEF, %	63.92 $\pm$ 6.81	64.50 $\pm$ 6.20	61.42 $\pm$ 8.56	<0.001
Initial diagnosis, n (%)				0.001
UA	2018 (83.4)	1662 (84.6)	356 (78.4)	
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 $\pm$ 1.29	1.87 $\pm$ 1.14	2.33 $\pm$ 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 revascularization	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 revascularization	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 revascularization	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
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
Pre-diabetic 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.

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.

Figures

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.