Elevated Remnant Cholesterol is Associated with Adverse Cardiovascular Outcomes in Patients with Acute Coronary Syndrome

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**Aims:** This study aimed to investigate the association of elevated RC levels with adverse cardiovascular outcomes in acute coronary syndrome (ACS) patients with and without diabetes.

**Methods:** We analyzed data from 1716 patients with ACS undergoing percutaneous coronary intervention. RC was calculated as total cholesterol minus high-density lipoprotein cholesterol minus low-density lipoprotein cholesterol. RC >75th percentile of the cohort (>0.79 mmol/L) was defined as abnormally elevated RC. Cox-regression models and Kaplan-Meier analyses were used to assess the relationship between RC >0.79 mmol/L and major adverse cardiovascular events (MACE).

**Results:** During a median follow-up of 927 days, a total of 354 patients had at least one event. In the overall population, compared with those with RC ≤ 0.79 mmol/L, patients with RC >0.79 mmol/L had a significantly higher risk of MACE after adjustment for potential confounders (hazard ratio: 1.572, 95% confidence interval: 1.251-1.975, P<0.001). In addition, RC >0.79 mmol/L was associated with an increased risk of MACE of 66.7% (P=0.001) and 50.1% (P=0.022) in the diabetic and non-diabetic subgroups (P for interaction=0.073), respectively. The addition of RC significantly improved the predictive ability of baseline models for MACE in diabetic patients (all P<0.05), but not in non-diabetic patients (all P>0.05).

**Conclusion:** Abnormally elevated RC was significantly associated with worse prognosis in both diabetic and non-diabetic patients with ACS; however, the prognostic value of RC might be superior among diabetic patients.

**Key words:** Remnant cholesterol, Acute coronary syndrome, Diabetes, Major adverse cardiovascular events

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**Introduction**

Atherogenic dyslipidemia, a lipid disorder related to increased risk of atherosclerotic cardiovascular disease (ASCVD), is a well-established major cause for lipid-dependent residual risk, independent of low-density lipoprotein cholesterol (LDL-C)1-4. The lipid profiles of atherogenic dyslipidemia have the following characteristics: an excess of circulating triglycerides containing very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and their remnants; low concentrations of high-density lipoprotein cholesterol (HDL-C); high concentrations of small dense low-density lipoprotein cholesterol. In atherogenic dyslipidemia, triglyceride-rich lipoproteins (TRLs) are larger and can carry more cholesterol per particle than LDL-C5. Cholesterol contained in TRLs is more easily absorbed by macrophage cells, thereby promoting massive cholesterol load, causing foam cell formation, and inducing a cascade of events leading to...
Remnant cholesterol (RC) refers to the cholesterol component of the TRLs, which consists of VLDL and IDL in the fasting state and chylomicron remnants in the postprandial state. Circulating VLDL can be hydrolyzed by the lipoprotein lipase enzyme into IDL and LDL-C, both of which enrich cholesterol and are highly atherogenic. Triglycerides in TRLs include chylomicrons and VLDL, which are synthesized and secreted from intestinal epithelial cells and liver, respectively, and metabolized in plasma. Non-fasting triglycerides and RC are part of the same lipoprotein and therefore are highly correlated. Emerging epidemiologic and genetic analyses suggest that elevated levels of triglycerides and RC serve as independent markers of increased risk of ischemic events. However, the cholesterol content of particles, rather than triglycerides themselves, is likely to constitute the causal moiety contained in the atherogenic lipid profiles. RC shares the potential to constitute the causal moiety contained in the atherogenic lipid profiles. RC shares the potential to constitute the causal moiety contained in the atherogenic lipid profiles. RC shares the potential to constitute the causal moiety contained in the atherogenic lipid profiles. RC shares the potential to constitute the causal moiety contained in the atherogenic lipid profiles. RC shares the potential to constitute the causal moiety contained in the atherogenic lipid profiles. RC shares the potential to constitute the causal moiety contained in the atherogenic lipid profiles. RC shares the potential to constitute the causal moiety contained in the atherogenic lipid profiles. RC shares the potential to constitute the causal moiety contained in the atherogenic lipid profiles. RC shares the potential to constitute the causal moiety contained in the atherogenic lipid profiles. RC shares the potential to constitute the causal moiety contained in the atherogenic lipid profiles. RC shares the potential to constitute the causal moiety contained in the atherogenic lipid profiles. RC shares the potential to constitute the causal moiety contained in the atherogenic lipid profiles. RC shares the potential to constitute the causal moiety contained in the atherogenic lipid profiles. RC shares the potential to constitute the causal moiety contained in the atherogenic lipid profiles. RC shares the potential to constitute the causal moiety contained in the atherogenic lipid profiles.

Diabetes has been shown to be highly associated with atherosclerosis. Patients with diabetes have a two- to four-fold increased risk of developing ASCVD compared with normal subjects. Diabetic individuals without prior myocardial infarction (MI) had the same risk of coronary events as non-diabetic individuals with prior MI. Additionally, serum RC levels have been shown to be elevated in diabetic patients, and are partially involved in platelet activation in diabetic patients without obstructive coronary artery disease (CAD).

To date, the association of RC with clinical outcomes in patients with acute coronary syndrome (ACS) has not been fully determined, and the prognostic value of RC in the diabetic and non-diabetic subgroups remains controversial. In this study, we aimed to investigate the combined effect of RC and the presence or absence of diabetes on the clinical outcomes in ACS patients.

**Methods**

**Study Design and Follow-Up**

This study was a retrospective analysis derived from a single-center prospective observational study (ChiCTR1800017417) which recruited 1,770 patients who underwent coronary angiography for ACS and were treated with primary or elective percutaneous coronary intervention (PCI) at our cardiovascular center from June 2016 to November 2017. In the present study, we ultimately included 1,716 patients after excluding patients with definite or probable familial hypercholesterolemia, prior coronary artery bypass graft surgery, cardiogenic shock, left ventricular ejection fraction < 30%, renal failure with creatinine clearance < 15 ml/min, and known cancer history. The diagnosis of definite or probable familial hypercholesterolemia relied on Dutch Lipid Clinic Network criteria including family history, clinical history of premature ASCVD, physical examination for xanthomas and corneal arcus, very high LDL-C on repeated measurements, and/or a causative mutation detected by molecular genetics. Creatinine clearance was calculated by CKD-EPI formula. Four patients were also excluded because of missing follow-up data despite at least 4 separate attempts to contact them. The date of the first recruited participant was June 2016, and the end of the follow-up was December 2019.

This study complied with the “Helsinki Declaration of Human Rights” and was approved by the Institutional Review Committee of Beijing Anzhen Hospital, Capital Medical University. All patients were followed up at 1, 6, 12, 18, 24, 30, and 36 months after hospital discharge. The occurrence of cardiovascular events was confirmed by checking medical records, PCI reports, laboratory results, imageological examinations, and electrocardiograms from Beijing Anzhen Hospital or other hospitals during outpatient follow-up or telephone follow-up.

**Outcome Ascertainment**

The primary endpoint was a composite of major adverse cardiovascular events (MACE), including all-cause death, non-fatal MI, non-fatal stroke, or unplanned repeat revascularization. MI was defined as an increase in cardiac troponin or creatine kinase levels, accompanied by ischemic symptoms or electrocardiograph changes suggesting ischemia. The appearance of new pathological Q waves in ≥ 2 consecutive electrocardiograph leads was also diagnosed as MI. Stroke was defined as an ischemic cerebral infarction, with evidence of neurological dysfunction, requiring hospitalization, and clinically documented lesions on brain computed tomography or magnetic resonance imaging. Unplanned repeat revascularization was defined as any non-stage revascularization after index PCI. Staged revascularization was defined as planned revascularization of residual stenotic lesions within 90 days after index PCI, or where the revascularization status was urgent.
emergency, or salvage. If >1 event occurred during follow-up (death > stroke > MI > revascularization), the most severe endpoint event was selected for the primary endpoint analysis.

**Determination of Lipid Profiles**

Blood samples for the standard lipid profiles were collected after an overnight fast and the biochemical analysis was carried out in the local laboratory. RC was calculated from the standard lipid profiles with the formula: RC = total cholesterol – HDL-C – LDL-C. RC > 75th percentile of the cohort (>0.79 mmol/L) was defined as abnormally elevated RC. According to the lipid alteration characteristics of atherogenic dyslipidemia corresponding to higher cardiovascular risk in ACS patients, we set groups of triglycerides >1.69 mmol/L, HDL-C <1.03 mmol/L, and LDL-C >1.80 mmol/L when analyzing the baseline lipid profiles.

**Statistical Analysis**

Continuous variables were presented as means ± standard deviations (normal distribution) which were compared between groups by independent-sample t-test or ANOVA test or shown as median and interquartile range (IQR) (non-normal distribution) which were compared between groups by Mann-Whitney U test or Kruskal–Wallis H test. Categorical variables were expressed as counts and percentages which were compared between groups by Chi-squared test or Fisher's exact test. The Kaplan-Meier method was used to derive the event rate and plot the time-survival curve. The unadjusted and adjusted Cox proportional hazards models were used to assess the association between baseline RC levels and MACE. The results of Cox analysis were interpreted using hazard ratio (HR) and 95% confidence intervals (95%CI). Adjustments were made for multiple confounders including clinically relevant risk factors, and variables with statistical significance: sex, age, body mass index (BMI), current smoking, hypertension, diabetes, past MI, past PCI, chronic kidney disease (CKD), admission diagnosis with ST segment elevation myocardial infarction, GRACE risk score, high sensitive C-reactive protein (hs-CRP), left-main/multi-vessel disease, complete revascularization, and discharged with aspirin, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers and β-blockers. The interaction effect was examined by the likelihood ratio test, and the proportional hazard assumption was tested by demonstrating no importance of variables multiplied by time as time-dependent variables. The incremental predictive values of adding RC to four baseline models were analyzed by calculating C-statistics, net reclassification improvement (NRI) and integrated discrimination improvement (IDI). The 2-sided significance level was set at P<0.05. All statistical analyses were performed with the IBM SPSS Statistics version 26.0 (IBM Corporation, Chicago, IL) and R Software version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

**Baseline Characteristics**

Over a median follow-up of 927 days (IQR: 927 to 1,109 days), a total of 354 patients had at least one event, and fifty-two of them suffered more than one event. The baseline characteristics of 1,716 participants stratified by MACE are shown in Table 1. Baseline lipid profiles showed that MACE was highly related to elevated levels of RC, triglycerides, total cholesterol, LDL-C and non-HDL-C, and lower levels of HDL-C (all P values <0.001). Compared with those without MACE, patients with MACE had higher levels of fasting plasma glucose, glycosylated hemoglobin, and hs-CRP, and had higher rates of diabetes, past MI, past PCI, and CKD. The higher rate of left main or multi-vessel disease and lower rate of complete revascularization were also related to MACE. Of the 1716 patients with ACS undergoing PCI, 1409 (82.1%) patients treated with DES, 97 (5.7%) patients with BRS, 111 (27.2%) patients with DCB. 1 of them use both DES and BRS, 27 of them use both DES and DCB, and 2 of them use both BRS and DCB.

The baseline characteristics stratified by presence vs. absence of diabetes are shown in Table 2. Of the total of 354 events, 195 occurred in the diabetic cohort (n=791) and 159 in the non-diabetic cohort (n=925). Compared with those without diabetes, patients with diabetes were older and had higher levels of triglycerides, and BMI. In the diabetic cohort, patients had more comorbidities such as hypertension, dyslipidemia, and CKD, more complex coronary lesions, and a lower rate of complete revascularization. Data on baseline characteristics of the study population grouped by RC of ≤ 0.79 vs. >0.79 mmol/L are detailed in Supplementary Table 1. Of the 354 patients with MACE, 118 were in the high RC group (n=428) and 237 were in the low RC group (n=1288). Patients with abnormally elevated RC levels were younger and had higher levels of BMI, fasting plasma glucose, and hs-CRP.

**Predictive Role of RC for MACE**

Kaplan-Meier analyses showed that elevated RC
Table 1. Baseline characteristics of study subjects by MACE

| Variable | All subjects (n=1716) | With MACE (n=354) | Without MACE (n=1362) | P value |
|----------|------------------------|-------------------|-----------------------|---------|
| **Lipid Profile** | | | | |
| RC -mmol/L | 0.58 (0.43-0.79) | 0.62 (0.44-0.96) | 0.58 (0.42-0.77) | 0.001 |
| RC | | | | <0.001 |
| Low (≤ 0.79 mmol/L) | 1288 (75.1) | 236 (66.7) | 1052 (77.2) | | |
| High (>0.79 mmol/L) | 428 (24.9) | 118 (33.3) | 310 (22.8) | | |
| TG -mmol/L | 1.45 (1.01-2.06) | 1.62 (1.11-2.28) | 1.42 (0.98-2.01) | <0.001 |
| TC -mmol/L | 4.14 ± 0.98 | 4.28 ± 0.99 | 4.11 ± 0.98 | 0.004 |
| LDL-C -mmol/L | 2.44 ± 0.80 | 2.55 ± 0.78 | 2.41 ± 0.80 | 0.004 |
| HDL-C -mmol/L | 1.03 ± 0.23 | 0.99 ± 0.21 | 1.04 ± 0.24 | <0.001 |
| Non-HDL-C -mmol/L | 3.11 ± 0.94 | 3.29 ± 0.97 | 3.06 ± 0.93 | <0.001 |
| TG >1.69 mmol/L + HDL-C <1.03 mmol/L | 463 (27.0) | 128 (36.2) | 335 (24.6) | <0.001 |
| LDL-C and RC groups | | | | |
| LDL-C <1.8 mmol/L and RC ≤ 0.79 mmol/L | 332 (19.3) | 50 (14.1) | 282 (20.7) | 0.007 |
| LDL-C <1.8 mmol/L and RC >0.79 mmol/L | 65 (3.8) | 13 (3.7) | 52 (3.8) | 1.000 |
| LDL-C ≥ 1.8 mmol/L and RC ≤ 0.79 mmol/L | 956 (55.7) | 186 (52.5) | 770 (56.5) | 0.198 |
| LDL-C ≥ 1.8 mmol/L and RC >0.79 mmol/L | 363 (21.2) | 105 (29.7) | 258 (18.9) | <0.001 |
| **Demographics** | | | | |
| Male -n (%) | 1316 (76.7) | 275 (77.7) | 1041 (76.4) | 0.670 |
| Height -m | 1.68 ± 0.07 | 1.67 ± 0.07 | 1.68 ± 0.07 | 0.313 |
| Weight -kg | 73 ± 12 | 72 ± 11 | 73 ± 12 | 0.069 |
| BMI -kg/m² | 25.7 ± 3.1 | 25.5 ± 3.2 | 25.8 ± 3.1 | 0.108 |
| **Risk Factors** | | | | |
| Current smokers -n (%) | 759 (44.2) | 168 (47.5) | 591 (43.4) | 0.189 |
| Hypertension -n (%) | 1093 (63.7) | 228 (64.4) | 865 (63.5) | 0.802 |
| Dyslipidemia -n (%) | 1374 (80.1) | 297 (83.9) | 1077 (79.1) | 0.051 |
| Diabetes -n (%) | 791 (46.1) | 195 (55.1) | 596 (43.8) | <0.001 |
| Past MI -n (%) | 328 (19.1) | 92 (26.0) | 236 (17.3) | <0.001 |
| Past PCI -n (%) | 340 (19.8) | 97 (27.4) | 243 (17.8) | <0.001 |
| CKD -n (%) | 53 (3.1) | 22 (6.2) | 31 (2.3) | <0.001 |
| **Type of ACS** | | | | |
| NSTE-ACS -n (%) | 1494 (87.1) | 308 (87.0) | 1186 (87.1) | 0.992 |
| STEMI -n (%) | 222 (12.9) | 46 (13.0) | 176 (12.9) | | |
| **GRACE variables** | | | | |
| Age -years | 60 ± 10 | 60 ± 11 | 60 ± 10 | 0.253 |
| HR -bpm | 69 ± 9 | 71 ± 10 | 68 ± 9 | <0.001 |
| SBP -mmHg | 130 ± 16 | 132 ± 17 | 130 ± 16 | 0.017 |
| Creatinine -μmol/L | 70.3 (62.2-79.7) | 72.0 (63.5-83.0) | 69.7 (61.6-78.9) | 0.003 |
| Heart failure -n (%) | 467 (28.5) | 108 (32.0) | 359 (27.6) | 0.134 |
| ST-segment deviation-n (%) | 306 (17.8) | 74 (20.9) | 232 (17.0) | 0.106 |
| Elevated cardiac enzymes/markers-n (%) | 443 (25.8) | 91 (25.7) | 352 (25.8) | 1.000 |
| Cardiac arrest -n (%) | 2 (0.1) | 2 (0.6) | 0 (0.0) | 0.057 |
| **GRACE risk score** | 104 ± 39 | 107 ± 41 | 103 ± 38 | 0.043 |
| **GRACE risk** | | | | 0.004 |
| Low | 1106 (64.5) | 214 (60.5) | 892 (65.5) | | |
| Intermediate | 287 (16.7) | 52 (14.7) | 235 (17.3) | | |
| High | 323 (18.8) | 88 (24.9) | 235 (17.3) | | |
| **Laboratory Measurements** | | | | |
| FPG -mmol/L | 5.78 (5.23-6.93) | 6.24 (5.45-8.02) | 5.72 (5.20-6.75) | <0.001 |
| Glycosylated hemoglobin -% | 6.1 (5.6-7.1) | 6.4 (5.7-7.5) | 6.0 (5.5-7.0) | <0.001 |
| hs-CRP -mg/L | 1.4 (0.7-3.5) | 2.2 (0.9-5.3) | 1.2 (0.6-3.1) | <0.001 |
In univariate analysis, RC > 0.79 mmol/L was associated with a 60.7% increased risk of MACE in the overall population (Fig. 3). Multivariate Cox proportional hazards regression models, as shown in Fig. 3, demonstrated that RC > 0.79 mmol/L was associated with an extra 57.2% risk of MACE in the overall population. Moreover, RC > 0.79 mmol/L was associated with an increased risk of MACE of 66.7% and 50.1% in the diabetic and non-diabetic subgroups (P for interaction = 0.073), respectively. The predictive value of RC for MACE is primarily associated with an increase in unplanned repeat revascularization, independent of the presence of diabetes (Table 3).

In the overall population, compared with four baseline models, the addition of RC had significant increases in C-statistics (all P-values < 0.05), and significant improvement in reclassification as assessed by NRI (all P-values < 0.05) and IDI (all P-values < 0.05) (Table 4). Moreover, the model performance after the addition of RC to the baseline models were significantly improved in the diabetic subgroup (all P-values < 0.05), but not in the non-diabetic subgroup levels corresponded to a higher probability of developing MACE in the overall population (log-rank P < 0.001, Fig. 1A) and the diabetic subgroup (log-rank P < 0.001, Fig. 1B), but not in the non-diabetic subgroup (log-rank P = 0.070, Fig. 1C). Fig. 2 described Kaplan-Meier curves derived from a combination of four potential LDL-C and RC cutoff levels. Regardless of LDL-C levels, elevated RC levels identified patients at a higher risk of MACE compared with those at lower RC levels in the overall population (log-rank P < 0.001, Fig. 2A). This difference was mainly derived from the diabetic subgroup, where elevated RC levels were related to a significantly higher risk of MACE, even though LDL-C was well controlled (log-rank P < 0.001). Diabetic patients with plasma levels of LDL-C < 1.8 mmol/L and RC > 0.79 mmol/L seemed to have a worse prognosis than those with plasma levels of LDL-C > 1.8 mmol/L and RC < 0.79 mmol/L (Fig. 2B). In the non-diabetic subgroup, the incidence of MACE showed no differences among groups with various levels of LDL-C and RC (log-rank P = 0.083, Fig. 2C).

MACE indicates major adverse cardiovascular events; RC: remnant cholesterol; TG: triglycerides; TC: serum total cholesterol; LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; BMI: body mass index; CAD: coronary artery disease; MI: myocardial infarction; PCl: percutaneous coronary; ACS: acute coronary syndrome; CKD: chronic kidney disease; NST-ACS: non-ST segment elevation acute coronary syndrome; STEMI: ST segment elevation myocardial infarction; GRACE: Global Registry of Acute Coronary Events; HR: heart rate; SBP: systolic blood pressure; FPG: fasting plasma glucose; hs-CRP: high sensitive C-reactive protein; LVEF: left ventricular ejection fraction; LM: left-main artery; LAD: left anterior descending artery; DES: drug eluting stent; BRS: bioresorbable scaffold; DCB: drug coated balloon; ACEI: angiotensin converting enzyme inhibitor; ARB-angiotensin II receptor blocker.

(Cont. Table 1)

| Variable                          | All subjects (n=1716) | With MACE (n=354) | Without MACE (n=1362) | P value |
|-----------------------------------|-----------------------|-------------------|-----------------------|---------|
| **Angiographic Findings**         |                       |                   |                       |         |
| LM/multi-vessel disease - n (%)   | 1456 (84.8)           | 323 (91.2)        | 1133 (83.2)           | <0.001  |
| Proximal LAD stenosis - n (%)     | 861 (50.2)            | 193 (54.5)        | 668 (49.0)            | 0.076   |
| **Procedural Results**            |                       |                   |                       |         |
| DES - n (%)                       | 1409 (82.1)           | 278 (78.5)        | 1131 (83.0)           | 0.058   |
| BRS - n (%)                       | 97 (5.7)              | 23 (6.5)          | 74 (5.4)              | 0.520   |
| DCB - n (%)                       | 111 (27.2)            | 33 (33.7)         | 78 (25.2)             | 0.128   |
| Complete revascularization - n (%)| 1052 (61.3)           | 151 (42.7)        | 901 (66.2)            | <0.001  |
| **Medications before admission**  |                       |                   |                       |         |
| Aspirin - n (%)                   | 1256 (73.2)           | 266 (75.1)        | 990 (72.7)            | 0.389   |
| P2Y12 inhibitors - n (%)          | 700 (40.8)            | 151 (42.7)        | 549 (40.3)            | 0.459   |
| Statins - n (%)                   | 1230 (71.7)           | 260 (73.4)        | 970 (71.2)            | 0.446   |
| ACEI/ARBs - n (%)                 | 488 (28.4)            | 115 (32.5)        | 373 (27.4)            | 0.067   |
| β-blockers - n (%)                | 634 (36.9)            | 118 (33.3)        | 516 (37.9)            | 0.129   |
| **Medications at discharge**      |                       |                   |                       |         |
| Aspirin - n (%)                   | 1700 (99.1)           | 344 (97.2)        | 1356 (99.6)           | <0.001  |
| P2Y12 inhibitors - n (%)          | 1716 (100.0)          | 354 (100.0)       | 1362 (100.0)          | NA      |
| Statins - n (%)                   | 1716 (100.0)          | 354 (100.0)       | 1362 (100.0)          | NA      |
| ACEI/ARBs - n (%)                 | 829 (48.3)            | 182 (51.4)        | 647 (47.5)            | 0.211   |
| β-blockers - n (%)                | 1203 (70.1)           | 231 (65.3)        | 972 (71.4)            | 0.030   |

Table 1: Characteristics of study participants with and without major adverse cardiovascular events (MACE). Levels corresponded to a higher probability of developing MACE in the overall population (log-rank P < 0.001, Fig. 1A) and the diabetic subgroup (log-rank P < 0.001, Fig. 1B), but not in the non-diabetic subgroup (log-rank P = 0.070, Fig. 1C).
Table 2. Baseline characteristics of study subjects by diabetes

| Variable | All subjects (n=1716) | Diabetes (n=791) | Non diabetes (n=925) | P value |
|----------|-----------------------|-----------------|---------------------|---------|
| MACE     | 354 (20.6)            | 195 (24.7)      | 159 (17.2)          | <0.001  |
| Lipid Profile |                      |                 |                     |         |
| RC -mmol/L | 0.58 (0.43-0.79) | 0.57 (0.42-0.79) | 0.59 (0.43-0.80) | 0.642   |
| RC       |                       |                 |                     | 0.930   |
|          | Low (≤ 0.79 mmol/L)   | 1288 (75.1)     | 595 (75.2)          | 693 (74.9) |
|          | High (>0.79 mmol/L)   | 428 (24.9)      | 196 (24.8)          | 232 (25.1) |
| TG -mmol/L | 1.45 (1.01-2.06) | 1.50 (1.08-2.08) | 1.40 (0.95-2.04) | 0.022   |
| TC -mmol/L | 4.14 ± 0.98          | 4.12 ± 1.00     | 4.16 ± 0.96         | 0.442   |
| LDL-C -mmol/L | 2.44 ± 0.80 | 2.42 ± 0.79     | 2.45 ± 0.81         | 0.398   |
| HDL-C -mmol/L | 1.03 ± 0.23          | 1.02 ± 0.22     | 1.04 ± 0.25         | 0.146   |
| Non-HDL-C -mmol/L | 3.11 ± 0.94 | 3.10 ± 0.96     | 3.12 ± 0.92         | 0.661   |
| TG >1.69 mmol/L + HDL-C <1.03 mmol/L | 463 (27.0) | 219 (27.7) | 244 (26.4) | 0.580 |
| LDL-C and RC groups |                      |                 |                     |         |
| LDL-C <1.8 mmol/L and RC ≤ 0.79 mmol/L | 332 (19.3) | 163 (20.6) | 169 (18.3) | 0.246 |
| LDL-C <1.8 mmol/L and RC >0.79 mmol/L | 65 (3.8) | 26 (3.3) | 39 (4.2) | 0.380 |
| LDL-C ≥ 1.8 mmol/L and RC ≤ 0.79 mmol/L | 956 (55.7) | 432 (54.6) | 524 (56.6) | 0.426 |
| LDL-C ≥ 1.8 mmol/L and RC >0.79 mmol/L | 363 (21.2) | 170 (21.5) | 193 (20.9) | 0.797 |
| Demographics |                      |                 |                     |         |
| Male -n (%) | 1316 (76.7) | 741 (80.1) | 675 (72.7) | <0.001 |
| Height -m   | 1.68 ± 0.07  | 1.67 ± 0.08     | 1.68 ± 0.07         | 0.001   |
| Weight -kg  | 73 ± 12      | 73 ± 12         | 72 ± 11             | 0.335   |
| BMI -kg/m²  | 25.7 ± 3.1   | 26.0 ± 3.2      | 25.5 ± 3.0          | 0.001   |
| Risk Factors |                      |                 |                     |         |
| Current smokers -n (%) | 759 (44.2) | 437 (47.2) | 322 (40.7) | 0.008 |
| Hypertension -n (%) | 1093 (63.7) | 553 (59.8) | 540 (68.3) | <0.001 |
| Dyslipidemia -n (%) | 1374 (80.1) | 713 (77.1) | 661 (83.6) | 0.001 |
| Past MI -n (%) | 328 (19.1) | 158 (17.1) | 170 (21.5) | 0.024 |
| Past PCI -n (%) | 340 (19.8) | 149 (16.1) | 191 (24.1) | <0.001 |
| CKD -n (%)   | 53 (3.1)     | 17 (1.8)        | 36 (4.6)            | 0.002   |
| Type of ACS  |                      |                 |                     | <0.001 |
| NSTE-ACS -n (%) | 1494 (87.1) | 772 (83.5) | 722 (91.3) |         |
| STEMI -n (%) | 222 (12.9) | 153 (16.5) | 69 (8.7) |         |
| GRACE variables |                      |                 |                     |         |
| Age -years | 60 ± 10       | 61 ± 10         | 59 ± 11             | <0.001 |
| HR -bpm    | 69 ± 9        | 70 ± 9          | 68 ± 9              | <0.001 |
| SBP -mmHg  | 130 ± 16      | 132 ± 17        | 128 ± 16            | <0.001 |
| Creatinine -μmol/L | 70.3 (62.2-79.7) | 71.2 (62.7-80.0) | 69.3 (61.3-79.5) | 0.037 |
| Heart failure -n (%) | 467 (28.5) | 278 (31.9) | 189 (24.7) | 0.001 |
| ST-segment deviation-n (%) | 306 (17.8) | 195 (21.1) | 111 (14.0) | <0.001 |
| Elevated cardiac enzymes/markers-n (%) | 443 (25.8) | 273 (29.5) | 170 (21.5) | <0.001 |
| Cardiac arrest -n (%) | 2 (0.1) | 0 (0.0) | 2 (0.3) | 0.412 |
| GRACE risk score | 104 ± 39 | 105 ± 38 | 103 ± 39 | 0.283 |
| GRACE risk   |                      |                 |                     | 0.184   |
| Low         | 1106 (64.5)   | 578 (62.5)      | 528 (66.8)          |         |
| Intermediate | 287 (16.7) | 163 (17.6) | 124 (15.7) |         |
| High        | 323 (18.8)   | 184 (19.9)      | 139 (17.6)          |         |
| Laboratory Measurements |                  |                 |                     |         |
| FPG -mmol/L | 5.78 (5.23-6.93) | 5.32 (4.98-5.72) | 7.10 (6.23-8.25) | <0.001 |
| Glycosylated hemoglobin -% | 6.1 (5.6-7.1) | 5.6 (5.4-5.9) | 7.2 (6.6-8.1) | <0.001 |
| hs-CRP -mg/L | 1.4 (0.7-3.5) | 1.3 (0.6-3.2) | 1.4 (0.7-3.7) | 0.056 |
predictive ability for MACE in the diabetic subgroup, but not in the non-diabetic subgroup. It has been well-established that LDL-C is a vital risk factor for ASCVD, but many patients continue to experience recurrent cardiovascular events even with statin-controlled LDL-C levels. A growing number of genetic and observational studies suggest that RC may contribute to this residual risk. RC, consisting of smaller VLDL, IDL, and chylomicron remnants, is small enough to enter directly into the subintimal space, get trapped, and cause plaque formation. Moreover, experimental studies have shown that elevated RC levels correspond to a higher probability of developing MACE in the overall population and the diabetic subgroup, but not in the non-diabetic subgroup.

**Discussion**

In the present study, we investigated the association of elevated RC levels with MACE in 1716 ACS patients. Abnormally elevated RC (>0.79 mmol/L) was associated with an extra 57.2% risk of MACE in the overall population, and with 66.7% and 50.1% higher adjusted risk of MACE in the diabetic and non-diabetic subgroups, respectively. Adding RC to the baseline models significantly improved the predictive ability for MACE in the diabetic subgroup, but not in the non-diabetic subgroup.

It has been well-established that LDL-C is a vital risk factor for ASCVD, but many patients continue to experience recurrent cardiovascular events even with statin-controlled LDL-C levels. A growing number of genetic and observational studies suggest that RC may contribute to this residual risk. RC, consisting of smaller VLDL, IDL, and chylomicron remnants, is small enough to enter directly into the subintimal space, get trapped, and cause plaque formation. Moreover, experimental studies have shown that elevated RC levels correspond to a higher probability of developing MACE in the overall population and the diabetic subgroup, but not in the non-diabetic subgroup.
As the cholesterol component of the TRLs, RC is over yielded in insulin-resistant state and play a crucial role in the pathogenesis of CAD in diabetic individuals\(^2^9\). In a cross-sectional study comparing lipoprotein profile in individuals with normal and impaired glucose metabolism, diabetic participants showed higher large and small VLDL concentrations\(^3^0\). Using nuclear magnetic resonance for detailed analyses of lipoprotein subclass sizes and particle concentrations, Garvey et al. concluded that as insulin resistance becomes more severe, the mean particle size of VLDL increased, solely due to an increase in the number of large VLDL particles produced primarily by the liver, while the concentration of medium and small VLDL particles did not change significantly\(^3^1\). Large VLDL particles may confer more cardiovascular disease risk\(^3^2, 3^3\).

In shown that RC is involved in the formation and progression of atherosclerosis by activating monocytes, upregulating proinflammatory cytokines, and increasing pro-thrombotic factors\(^1^5, 2^7\). In a clinical study including 60,608 individuals with ischemic heart disease, researchers observed a causal relationship between elevated RC levels and low-grade inflammation, as defined by CRP, and an increased risk of ischemic heart disease\(^1^5\). In the present study, we found that hs-CRP was significantly raised in patients with elevated RC levels, and RC was closely correlated with hs-CRP (Spearman’s \(R=0.101, P<0.001\)).

TRLs are of particular importance in diabetic populations when compared with non-diabetic populations because insulin resistance increases hepatic VLDL production and decreases clearance of TRLs\(^2^8\). As the cholesterol component of the TRLs, RC is over yielded in insulin-resistant state and play a crucial role in the pathogenesis of CAD in diabetic individuals\(^2^9\). In a cross-sectional study comparing lipoprotein profile in individuals with normal and impaired glucose metabolism, diabetic participants showed higher large and small VLDL concentrations\(^3^0\). Using nuclear magnetic resonance for detailed analyses of lipoprotein subclass sizes and particle concentrations, Garvey et al. concluded that as insulin resistance becomes more severe, the mean particle size of VLDL increased, solely due to an increase in the number of large VLDL particles produced primarily by the liver, while the concentration of medium and small VLDL particles did not change significantly\(^3^1\). Large VLDL particles may confer more cardiovascular disease risk\(^3^2, 3^3\).
Table 3. Relationships between each endpoint and RC as a categorical variable in the overall population, diabetes, and non-diabetes

|                          | Crude Model | Adjusted Model* |
|--------------------------|-------------|-----------------|
|                          | HR (95%CI)  | P value         | HR (95%CI)  | P value         |
| **Overall population**   |             |                 |             |                 |
| MACE                     | 1.607 (1.288-2.004) | <0.001 | 1.572 (1.251-1.975) | <0.001 |
| All-cause death          | 0.885 (0.437-1.791) | 0.734 | 1.015 (0.452-2.007) | 0.477 |
| Non-fatal MI             | 1.618 (0.898-2.913) | 0.109 | 1.425 (0.774-2.623) | 0.256 |
| Non-fatal Stroke         | 1.810 (0.792-4.136) | 0.159 | 1.940 (0.798-4.719) | 0.144 |
| Unplanned repeat revascularization | 1.695 (1.330-2.160) | <0.001 | 1.629 (1.269-2.090) | <0.001 |
| **Diabetes**             |             |                 |             |                 |
| MACE                     | 1.862 (1.388-2.498) | <0.001 | 1.667 (1.222-2.276) | 0.001 |
| All-cause death          | 0.871 (0.287-2.646) | 0.807 | 0.105 (0.581-3.234) | 0.415 |
| Non-fatal MI             | 1.152 (0.451-2.944) | 0.768 | 0.458 (0.125-1.681) | 0.239 |
| Non-fatal Stroke         | 1.683 (0.622-4.551) | 0.305 | 1.572 (0.480-5.151) | 0.455 |
| Unplanned repeat revascularization | 1.921 (1.395-2.646) | <0.001 | 1.809 (1.293-2.530) | 0.001 |
| **Non-diabetes**         |             |                 |             |                 |
| MACE                     | 1.364 (0.974-1.909) | 0.071 | 1.501 (1.060-2.125) | 0.022 |
| All-cause death          | 0.892 (0.358-2.220) | 0.805 | 1.545 (0.586-4.070) | 0.379 |
| Non-fatal MI             | 2.079 (0.965-4.479) | 0.062 | 2.055 (0.923-4.572) | 0.078 |
| Non-fatal Stroke         | 2.194 (0.491-9.805) | 0.304 | 1.924 (0.105-10.347) | 0.505 |
| Unplanned repeat revascularization | 1.467 (1.031-2.128) | 0.034 | 1.463 (1.011-2.158) | 0.045 |

*Adjusted model including sex, age, BMI, current smoking, hypertension, diabetes, past MI, past PCI, CKD, statins on admission, discharged with aspirin, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers and β-blockers, complete revascularization, STEMI, hs-CRP, GRACE risk score, left main or multi-vessel disease. cNRI: continuous net-reclassification index; IDI: integrated discrimination improvement. Other abbreviations as in Table 1.

Table 4. Model performance after the addition of classified RC to baseline models in the overall population and diabetic subgroups

|                          | C-Statistic (95%CI) | P value | NRI (95%CI) | P value | IDI (95%CI) | P value |
|--------------------------|---------------------|---------|-------------|---------|-------------|---------|
| **Overall population**   |                     |         |             |         |             |         |
| model 1 + RC             | 0.575 (0.544-0.605) | 0.009   | 0.099 (0.045-0.150) | <0.001 | 0.012 (0.003-0.024) | <0.001 |
| model 2 + RC             | 0.620 (0.590-0.650) | 0.021   | 0.099 (0.048-0.150) | <0.001 | 0.011 (0.003-0.026) | <0.001 |
| model 3 + RC             | 0.621 (0.598-0.660) | 0.020   | 0.099 (0.048-0.151) | <0.001 | 0.011 (0.002-0.025) | <0.001 |
| model 4 + RC             | 0.676 (0.650-0.724) | 0.009   | 0.099 (0.034-0.146) | <0.001 | 0.009 (0.002-0.022) | <0.001 |
| **Diabetic subgroup**    |                     |         |             |         |             |         |
| model 1 + RC             | 0.585 (0.543-0.638) | 0.003   | 0.156 (0.071-0.235) | <0.001 | 0.025 (0.006-0.054) | <0.001 |
| model 2 + RC             | 0.638 (0.600-0.676) | 0.005   | 0.156 (0.086-0.235) | <0.001 | 0.020 (0.005-0.051) | <0.001 |
| model 3 + RC             | 0.659 (0.621-0.675) | 0.013   | 0.156 (0.048-0.234) | <0.001 | 0.012 (0.001-0.041) | 0.020 |
| model 4 + RC             | 0.688 (0.655-0.721) | 0.033   | 0.156 (0.024-0.251) | <0.001 | 0.011 (0.001-0.035) | 0.020 |
| **Non-diabetic subgroup**|                     |         |             |         |             |         |
| model 1 + RC             | 0.574 (0.529-0.619) | 0.291   | 0.050 (-0.022-0.129) | 0.209 | 0.004 (0.000-0.015) | 0.119 |
| model 2 + RC             | 0.581 (0.536-0.625) | 0.460   | 0.050 (-0.040-0.129) | 0.199 | 0.004 (0.000-0.016) | 0.159 |
| model 3 + RC             | 0.599 (0.549-0.653) | 0.397   | 0.051 (-0.028-0.162) | 0.211 | 0.004 (0.000-0.019) | 0.161 |
| model 4 + RC             | 0.678 (0.619-0.738) | 0.310   | 0.062 (-0.055-0.189) | 0.302 | 0.005 (-0.001-0.025) | 0.238 |

Model 1: sex, age, BMI, current smoking;
Model 2: sex, age, BMI, current smoking, hypertension, diabetes, past MI, past PCI, CKD;
Model 3: sex, age, BMI, current smoking, hypertension, diabetes, past MI, past PCI, CKD, statins on admission, discharged with aspirin, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers and β-blockers;
Model 4: sex, age, BMI, current smoking, hypertension, diabetes, past MI, past PCI, CKD, statins on admission, discharged with aspirin, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers and β-blockers, complete revascularization, STEMI, hs-CRP, GRACE risk score, left main or multi-vessel disease.
NRI: continuous net-reclassification index; IDI: integrated discrimination improvement. Other abbreviations as in Table 1.
patients with type 2 diabetes, a setting of abnormal TRLs metabolism and increased cardiovascular risk, Prenner et al. found that VLDL was associated with coronary artery calcification independent of established cardiovascular risk factors, and may have value even beyond apolipoprotein B levels\(^ {28} \). Therefore, we speculated that in the present study, RC was more strongly associated with poorer prognosis in ACS patients with diabetes due to the significant increase in VLDL, compared with those without diabetes.

Fukushima et al. found that diabetic patients with CAD had higher RC levels than those without CAD, and that elevated RC was an independent predictor of future coronary events in patients with CAD and diabetes\(^ {34} \). A cross-sectional study suggested that the association between disorders of triglyceride and RC metabolism might account for the risk of CAD in patients with diabetes\(^ {34} \). Qin et al. reported that elevated RC (≥ 0.505 mmol/L) was associated with in-stent restenosis in type 2 diabetes undergoing PCI\(^ {35} \). Elevated RC was also regarded as an independent risk factor in menopausal women with CAD and diabetes\(^ {36} \). Calculated RC was significantly associated with MACE in diabetic patients with non-ST segment elevation ACS undergoing PCI, as opposed to in the pre-diabetic and non-diabetic subgroups\(^ {37} \). Similarly, in the present study, elevated RC represented a significantly higher risk of MACE in ACS patients with diabetes after adjusting for potential confounders. Differently, we found that RC was a significant and independent predictor of MACE in non-diabetic patients as well.

Kaplan-Meier analyses demonstrated that the prognosis of patients with plasma levels of LDL-C < 1.8 mmol/L and RC > 0.79 mmol/L was poorer than those with plasma levels of LDL-C > 1.8 mmol/L and RC < 0.79 mmol/L in patients with diabetes. Similar to our finding, in overweight or obese subjects at high cardiovascular risk, levels of triglycerides and remnant-C, but not LDL-C, were associated with cardiovascular outcomes independent of other risk factors\(^ {22} \). In US individuals free of ASCVD, the discordant high RC/low LDL-C group, but not the low RC/high LDL-C group, was associated with increased ASCVD risk compared to the concordant group\(^ {38} \). Varbo et al. found the non-fasting RC concentrations were associated stepwise with increased all-cause mortality in general Danish population, concentrations of LDL cholesterol were not\(^ {36} \). These findings may suggest that enhanced RC represents an additional risk factor beyond LDL-C for ASCVD. Therefore, the potential value of targeted RC-lowering needs further investigation. A post hoc analysis of the TNT trial showed that intensive lipid-lowering therapy significantly reduced cardiovascular risk among patients with elevated RC levels\(^ {39} \). There is a lack of randomized controlled trials to explore whether lowering RC levels confers cardiovascular benefits in patients at high risk of ASCVD. It is worth looking forward to an ongoing randomized controlled trial that aims to reduce cardiovascular events by lowering TRLs in patients with diabetes and dyslipidemia\(^ {8} \). Of note, all participants in this trial will be tested for directly measured RC.

Several limitations of our study need to be noted. First, RC was calculated using cholesterol measured on admission and the on-treatment RC may be more clinically relevant. Second, calculated remnant cholesterol may not be as accurate as directly measured remnant cholesterol, and the specific components of it, such as VLDL and chylomicron remnants, were not known. However, calculated remnant cholesterol can be readily obtained from baseline lipid profiles and several studies have shown that calculated RC and measured RC predict MACE risk with similar confidence\(^ {40, 41} \). Third, all enrolled patients in our CV center were discharged with statin therapy according to the guidelines for secondary prevention of ACS, but we did not focus on the adjustment of lipid-lowering regimen during follow-up. Fourth, all patients in the present study were Chinese, so the results should be interpreted and generalized to other ethnic groups with caution since dissimilar metabolic levels exist among different races. Fifth, the determination of causality was limited by the nature of the observational study design, partly due to the possibility of residual confounding.

**Conclusion**

Abnormally elevated RC was significantly and strongly associated with worse prognosis in both diabetic and non-diabetic patients with ACS; however, the prognostic value of RC might be superior among diabetic patients. Randomized clinical trials are warranted to examine whether lowering RC in such patients can reduce future cardiovascular risk.

**Abbreviations**

ASCVD: atherosclerotic cardiovascular disease; ACS: acute coronary syndrome; BMI: body mass index; NRI: net reclassification improvement; CAD: coronary artery disease; CKD: chronic kidney disease; GRACE: Global Registry of Acute Coronary Events; HDL-C: high-density lipoprotein cholesterol; HR: hazard ratio; IDI: integrated discrimination
improvement; IDL: intermediate-density lipoprotein; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; MACE: major adverse cardiovascular events; MI: myocardial infarction; PCI: percutaneous coronary intervention; RC: remnant cholesterol; TRLs: triglyceride-rich lipoproteins; VLDL: very low-density lipoprotein; 95% CI: 95% confidence interval.

Data Availability
The datasets used during the current study are available on reasonable request.

Conflicts of Interest
The authors declare that they have no conflict of interest.

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Not applicable.

Ethics Approval and Consent to Participate
This study was approved by the institutional review board of Beijing Anzhen Hospital, Capital Medical University.

Authors’ Contribution
All authors were involved in the conception and design of the study and the collection, analysis, and interpretation of the data. All authors reviewed the final manuscript. All authors read and approved the final manuscript.

References
1) Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH and Witztum JL: Lipoprotein Management in Patients With Cardiometabolic Risk. J Am Coll Cardiol, 2008; 51: 1512-1524
2) Chapman MJ, Ginsberg HN, Amarenco P, Andreotti F, Borén J, Catapano AL, Descamps OS, Fisher E, Kovanen PT, Kuivenhoven JA, Lesnik P, Masana L, Nordestgaard BG, Ray KK, Reiner Z, Taskinen M-R, Tokgözoglu L, Tybjærg-Hansen A and Watts GF: 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: 1345-1361
3) Joshi PH, Khokhar AA, Massaro JM, Lirette ST, Griswold ME, Martin SS, Blaha MJ, Kulkarni KR, D’Agostino RB, Jones SR and Toth PP: Remnant Lipoprotein Cholesterol and Incident Coronary Heart Disease: The Jackson Heart and Framingham Offspring Cohort Studies. J Am Heart Assoc, 2016; 5
4) Varbo A and Nordestgaard BG: Nonfasting Triglycerides, Low-Density Lipoprotein Cholesterol, and Heart Failure Risk: Two Cohort Studies of 113 554 Individuals. Arterioscler Thromb Vasc Biol, 2018; 38: 464-472
5) Nordestgaard BG and Varbo A: Triglycerides and cardiovascular disease. Lancet, 2014; 384: 626-635
6) Varbo A, Benn M, Tybjærg-Hansen A, Jørgensen AB, Frikke-Schmidt R and Nordestgaard BG: Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol, 2013; 61: 427-436
7) Varbo A and Nordestgaard BG: Remnant Cholesterol and Triglyceride-Rich Lipoproteins in Atherosclerosis Progression and Cardiovascular Disease. Arterioscler Thromb Vasc Biol, 2016; 36: 2133-2135
8) Pradhan AD, Paynter NP, Everett BM, Glynn RJ, Amarenco P, Elam M, Ginsberg H, Hiatt WR, Ishibashi S, Koenig W, Nordestgaard BG, Fruchart J-C, Libby P, Libby P: Rationale and design of the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study. Am Heart J, 2018; 206: 80-93
9) Libby P: Triglycerides on the rise: should we swap seats on the seesaw? Eur Heart J, 2015; 36: 774-776
10) Klempfner R, Erez A, Sagit BZ, Goldenberg I, Fisman E, Kopel E, Shlomo N, Israel A and Tenenbaum A: Elevated Triglyceride Level Is Independently Associated With Increased All-Cause Mortality in Patients With Established Coronary Heart Disease: Twenty-Two-Year Follow-Up of the Bezafibrate Infarction Prevention Study and Registry. Circ Cardiovasc Qual Outcomes, 2016; 9: 100-108
11) Nichols GA, Philip S, Reynolds K, Granowitz CB and Fazio S: Increased Cardiovascular Risk in Hypertriglyceridemic Patients With Statin-Controlled LDL Cholesterol. J Clin Endocrinol Metab, 2018; 103: 3019-3027
12) Toth PP, Granowitz C, Hull M, Liassou D, Anderson A and Philip S: High Triglycerides Are Associated With Increased Cardiovascular Events, Medical Costs, and Resource Use: A Real-World Administrative Claims Analysis of Statin-Treated Patients With High Residual Cardiovascular Risk. J Am Heart Assoc, 2018; 7: e008740
13) Nichols GA, Philip S, Reynolds K, Granowitz CB and Fazio S: Increased residual cardiovascular risk in patients with diabetes and high versus normal triglycerides despite
stain-controlled LDL cholesterol. Diabetes Obes Metab, 2019; 21: 366-371

14) Jørgensen AB, Frikke-Schmidt R, West AS, Grande P, Nordestgaard BG and Tybjærg-Hansen A: Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. Eur Heart J, 2013; 34: 1826-1833

15) Varbo A, Benn M, Tybjærg-Hansen A and Nordestgaard BG: 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: 1298-1309

16) Haffner SM, Lehto S, Rönnemaa T, Pyörälä K and Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med, 1998; 339: 229-234

17) Havel RJ: Remnant lipoproteins as therapeutic targets. Current opinion in lipidology, 2000; 11: 615-620

18) Fukushima H, Sugiyama S, Honda O, Koide S, Nakamura S, Sakamoto T, Yoshimura M, Ogawa H, Fujioka D and Kugiyama K: 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: 2219-2224

19) Koga H, Sugiyama S, Kugiyama K, Fukushima H, Watanabe K, Sakamoto T, Yoshimura M, Jinouchi H and Ogawa H: Elevated levels of remnant lipoproteins are associated with plasma platelet microparticles in patients with type-2 diabetes mellitus without obstructive coronary artery disease. Eur Heart J, 2006; 27: 817-823

20) Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Averna M, Borén J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AFH, Stroes E, Taskinen MR and Tybjærg-Hansen A: Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J, 2013; 34: 3478-3390a

21) Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L and Wiklund O: 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J, 2020; 41: 111-188

22) Castaño O, Pintó X, Subirana I, Amor AJ, Ros E, Hernández A, Martínez-González MA, Corella D, Salas-Salvadó J, Estruch R, Lapetra J, Gómez-Gracia E, Alonso-Gómez AM, Fiol M, Serra-Majem L, Corbella E, Benages D, Soral JV, Ruiz-Canela M, Babió N, Sierra LT, Ortega E and Fito M: Remnant Cholesterol, Not LDL Cholesterol, Is Associated With Incident Cardiovascular Disease. J Am Coll Cardiol, 2020; 76: 2712-2724

23) Helgadottir A, Gretarsdottir S, Thorleifsson G, Hjartarson E, Sigurdsson A, Magnusdottir A, Jonasdottir A, Kristjansson H, Sulem P, Oddsson A, Sveinbjörnsson G, Steinthorsdottir V, Rafnar T, Masson G, Jonsdottir I, Olafsson I, Eyjolfsdóttir SI, Sigurdardottir O, Daneshpour MS, Khalili D, Azifi F, Swinkels DW, Kiemenej L, Quyyumi AA, Levey AI, Patel RS, Hayek SS, Gudmundsdottir IJ, Thorgeirsson G, Thorsteinsdottir U, Gudbjartsson DF, Holm H and Stefansson K: Variants with large effects on blood lipids and the role of cholesterol and triglycerides in coronary disease. Nature genetics, 2016; 48: 634-639

24) Varbo A, Freiberg JJ and Nordestgaard BG: Extreme nonfasting remnant cholesterol vs extreme LDL cholesterol as contributors to cardiovascular disease and all-cause mortality in 90000 individuals from the general population. Clin Chem, 2015; 61: 533-543

25) Elshazly MB, Mani P, Nissen S, Brennan DM, Clark D, Martin S, Jones SR, Quispe R, Donnellan E, Nicholls SJ and Puri R: Remnant cholesterol, coronary atheroma progression and clinical events in statin-treated patients with coronary artery disease. Eur J Prev Cardiol, 2020; 27: 1091-1100

26) Nordestgaard BG, Wootton R and Lewis B: Selective retention of VLDL, IDL, and LDL in the arterial intima of genetically hyperlipidemic rabbits in vivo. Molecular size as a determinant of fractional loss from the intima-inner media. Arterioscler Thromb Vasc Biol, 1995; 15: 534-542

27) Twickler TB, Dallinga-Thie GM, Cohn JS and Chapman MJ: Elevated remnant-like particle cholesterol concentration: a characteristic feature of the atherogenic lipoprotein phenotype. Circulation, 2004; 109: 1918-1925

28) Prenner SB, Mulvey CK, Ferguson JF, Rickels MR, Bhatt AB and Reilly MP: Very low density lipoprotein cholesterol associates with coronary artery calcification in type 2 diabetes beyond circulating levels of triglycerides. Atherosclerosis, 2014; 236: 244-250

29) Schaefer EJ, McNamara JR, Shah PK, Nakajima K, Cupples LA, Ordovas JM and Wilson PW: Elevated remnant-like particle cholesterol and triglyceride levels in diabetic men and women in the Framingham Offspring Study. Diabetes Care, 2002; 25: 989-994

30) Puig-Jóve C, Castelblanco E, Falguera M, Hernández M, Soldevila B, Julián MT, Teis A, Julve J, Barranco-Altirriba M, Franch-Nadal J, Puig-Domingo M, Ortega E, Amigó N, Alonso N and Mauricio D: Advanced lipoprotein phenotype. Circulation, 2004; 109: 1918-1925

31) Garvey WT, Kwon S, Zheng D, Shaughnessy S, Wallace P, Hutto A, Pugh K, Jenkins AJ, Klein RL and Liao Y: Effects of insulin resistance and type 2 diabetes on plasma platelet microparticles in patients with type-2 diabetes mellitus without obstructive coronary artery disease. Eur Heart J, 2006; 27: 817-823

32) Puig-Jóve C, Castelblanco E, Falguera M, Hernández M, Soldevila B, Julián MT, Teis A, Julve J, Barranco-Altirriba M, Franch-Nadal J, Puig-Domingo M, Ortega E, Amigó N, Alonso N and Mauricio D: Advanced lipoprotein profile in individuals with normal and impaired glucose metabolism. Rev Esp Cardiol (Engl Ed), 2021;
33) Grundy SM and Vega GL: Two different views of the relationship of hypertriglyceridemia to coronary heart disease. Implications for treatment. Arch Intern Med, 1992; 152: 28-34

34) Tani S, Yagi T, Atsumi W, Kawauchi K, Matsuo R and Hirayama A: Relation between low-density lipoprotein cholesterol/apolipoprotein B ratio and triglyceride-rich lipoproteins in patients with coronary artery disease and type 2 diabetes mellitus: a cross-sectional study. Cardiovasc Diabetol, 2017; 16: 123

35) Qin Z, Zhou K, Li YP, Wang JI, Cheng WJ, Hu CP, Shi C, He H and Zhou YJ: 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: 11

36) Feng X, Guo Q, Zhou S, Sun T, Liu Y, Zhou Z and Zhou Y: Could remnant-like particle cholesterol become a risk factor in diabetic menopausal women with coronary artery disease? A cross-sectional study of single academic center in China. Lipids Health Dis, 2020; 19: 44

37) Zhao Q, Zhang T-Y, Cheng Y-J, Ma Y, Xu Y-K, Yang J-Q and Zhou Y-J: Prognostic impact of estimated remnant-like particle cholesterol in patients with differing glycometabolic status: an observational cohort study from China. Lipids Health Dis, 2020; 19: 179

38) Quispe R, Martin SS, Michos ED, Lamba I, Blumenthal RS, Saeed A, Lima J, Puri R, Nomura S, Tsai M, Wilkins J, Ballantyne CM, Nicholls S, Jones SR and Elshazly MB: Remnant cholesterol predicts cardiovascular disease beyond LDL and ApoB: a primary prevention study. Eur Heart J, 2021; 42: 4324-4332

39) Vallejo-Vaz AJ, Fayyad R, Boekholdt SM, Hovingh GK, Kastelein JJ, Melamed S, Barter P, Waters DD and Ray KK: Triglyceride-Rich Lipoprotein Cholesterol and Risk of Cardiovascular Events Among Patients Receiving Statin Therapy in the TNT Trial. Circulation, 2018; 138: 770-781

40) Cao Y-X, Zhang H-W, Jin J-L, Liu H-H, Zhang Y, Gao Y, Guo Y-L, Wu N-Q, Hua Q, Li Y-F, Li X-L, Xu R-X, Cui C-J, Liu G, Dong Q, Sun J, Zhu C-G and Li J-J: The longitudinal association of remnant cholesterol with cardiovascular outcomes in patients with diabetes and prediabetes. Cardiovasc Diabetol, 2020; 19: 104

41) Varbo A, Freiberg JJ and Nordestgaard BG: Remnant Cholesterol and Myocardial Infarction in Normal Weight, Overweight, and Obese Individuals from the Copenhagen General Population Study. Clin Chem, 2018; 64: 219-230
### Supplementary Table 1. Baseline characteristics of study subjects by RC categories

| Variable                                      | All subjects (n=1716) | RC ≤ 0.79 mmol/L (n=1288) | RC > 0.79 mmol/L (n=428) | P value |
|-----------------------------------------------|-----------------------|---------------------------|---------------------------|---------|
| **MACE**                                      | 354 (20.6)            | 236 (18.3)                | 118 (27.6)                | <0.001  |
| **Demographics**                              |                       |                           |                           |         |
| Male -n (%)                                   | 1316 (76.7)           | 1003 (77.9)               | 313 (73.1)                | 0.052   |
| Height -m                                     | 1.68 ± 0.07           | 1.68 ± 0.07               | 1.67 ± 0.08               | 0.374   |
| Weight -kg                                    | 73 ± 12               | 72 ± 11                   | 74 ± 12                   | 0.014   |
| BMI -kg/m²                                    | 25.7 ± 3.1            | 25.5 ± 3.0                | 26.2 ± 3.3                | <0.001  |
| **Risk Factors**                              |                       |                           |                           |         |
| Current smokers -n (%)                        | 759 (44.2)            | 558 (43.3)                | 201 (47.0)                | 0.209   |
| Hypertension -n (%)                           | 1093 (63.7)           | 811 (63.0)                | 282 (65.9)                | 0.303   |
| Dyslipidemia                                  | 1374 (80.1)           | 979 (76.0)                | 395 (92.3)                | <0.001  |
| Diabetes-n (%)                                | 791 (46.1)            | 595 (46.2)                | 196 (45.8)                | 0.930   |
| Past MI-n (%)                                 | 328 (19.1)            | 244 (18.9)                | 84 (19.6)                 | 0.810   |
| Past PCI-n (%)                                | 340 (19.8)            | 266 (20.7)                | 74 (17.3)                 | 0.149   |
| CKD -n (%)                                    | 53 (3.1)              | 19 (4.4)                  | 34 (2.6)                  | 0.089   |
| **Type of ACS**                               |                       |                           |                           | 0.236   |
| NSTE-ACS -n (%)                               | 1494 (87.1)           | 1129 (87.7)               | 365 (85.3)                |         |
| STEMI -n (%)                                  | 222 (12.9)            | 159 (12.3)                | 63 (14.7)                 |         |
| **GRACE variables**                           |                       |                           |                           |         |
| Age -years                                    | 60 ± 10               | 60 ± 10                   | 58 ± 11                   | <0.001  |
| HR -bpm                                       | 69 ± 9                | 68 ± 9                    | 69 ± 9                    | 0.033   |
| SBP -mmHg                                     | 130 ± 16              | 130 ± 16                  | 131 ± 17                  | 0.460   |
| Creatinine -μmol/L                           | 70.3 (62.2-79.7)      | 70.2 (62.3-79.4)          | 70.8 (61.3-80.3)          | 0.477   |
| Heart failure -n (%)                          | 467 (28.5)            | 349 (28.1)                | 118 (29.8)                | 0.563   |
| ST-segment deviation -n (%)                   | 306 (17.8)            | 217 (16.8)                | 89 (20.8)                 | 0.076   |
| Elevated cardiac enzymes/markers -n (%)      | 443 (25.8)            | 326 (25.3)                | 117 (27.3)                | 0.444   |
| Cardiac arrest -n (%)                         | 2 (0.1)               | 0 (0.0)                   | 2 (0.5)                   | 0.102   |
| **GRACE risk score**                          | 104 ± 39              | 104 ± 38                  | 103 ± 41                  | 0.625   |
| **GRACE risk**                                |                       |                           |                           | 0.901   |
| Low                                           | 1106 (64.5)           | 834 (64.8)                | 272 (63.6)                |         |
| Intermediate                                  | 287 (16.7)            | 214 (16.6)                | 73 (17.1)                 |         |
| High                                          | 323 (18.8)            | 240 (18.6)                | 83 (19.4)                 |         |
| **Laboratory Measurements**                   |                       |                           |                           |         |
| FPG -mmol/L                                   | 5.78 (5.23-6.93)      | 5.77 (5.23-6.83)          | 5.92 (5.23-7.28)          | 0.038   |
| Glycosylated hemoglobin-%                     | 6.1 (5.6-7.1)         | 6.1 (5.6-7.1)             | 6.2 (5.6-7.2)             | 0.345   |
| hs-CRP -mg/L                                  | 1.4 (0.7-3.5)         | 1.3 (0.6-3.4)             | 1.7 (0.8-3.7)             | 0.001   |
| **Angiographic Findings**                     |                       |                           |                           |         |
| LM/multi-vessel disease -n (%)                | 1456 (84.8)           | 1087 (84.4)               | 369 (86.2)                | 0.405   |
| Proximal LAD stenosis -n (%)                  | 861 (50.2)            | 646 (50.2)                | 215 (50.2)                | 1.000   |
| **Procedural Results**                        |                       |                           |                           |         |
| DES -n (%)                                    | 1409 (82.1)           | 1053 (81.8)               | 356 (83.2)                | 0.553   |
| BRS -n (%)                                    | 97 (5.7)              | 73 (5.7)                  | 24 (5.6)                  | 1.000   |
| DCB -n (%)                                    | 111 (27.2)            | 84 (26.5)                 | 27 (29.7)                 | 0.641   |
| Complete revascularization -n (%)             | 1052 (61.3)           | 802 (62.3)                | 250 (58.4)                | 0.173   |
| **Medications before admission**              |                       |                           |                           |         |
| Aspirin -n (%)                                | 1256 (73.2)           | 949 (73.7)                | 307 (71.7)                | 0.468   |
| P2Y12 inhibitors -n (%)                       | 700 (40.8)            | 533 (41.4)                | 167 (39.0)                | 0.421   |
| Statins -n (%)                                | 1230 (71.7)           | 932 (72.4)                | 298 (69.6)                | 0.305   |
| ACEI/ARBs -n (%)                              | 488 (28.4)            | 365 (28.3)                | 123 (28.7)                | 0.923   |
| β-blockers -n (%)                             | 634 (36.9)            | 480 (37.3)                | 154 (36.0)                | 0.675   |
(Cont. Supplementary Table 1)

| Variable          | All subjects (n=1716) | RC ≤ 0.79 mmol/L (n=1288) | RC > 0.79 mmol/L (n=428) | P value |
|-------------------|-----------------------|---------------------------|--------------------------|---------|
| Medications at discharge |                       |                           |                           |         |
| Aspirin -n (%)    | 1700 (99.1)           | 1277 (99.1)               | 423 (98.8)                | 0.767   |
| P2Y12 inhibitors -n (%) | 1716 (100.0)       | 1288 (100.0)              | 428 (100.0)               | NA      |
| Statins -n (%)    | 1716 (100.0)          | 1288 (100.0)              | 428 (100.0)               | NA      |
| ACEI/ARBs -n (%)  | 829 (48.3)            | 608 (47.2)                | 221 (51.6)                | 0.125   |
| β-blockers -n (%) | 1203 (70.1)           | 891 (69.2)                | 312 (72.9)                | 0.163   |

RC indicates remnant cholesterol. Other abbreviations as in Table 1.