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Original Article

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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.

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

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-C[5]. 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

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ASCVD[5].

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[6]. Circulating VLDL can be hydrolyzed by the lipoprotein lipase enzyme into IDL and LDL-C, both of which enrich cholesterol and are highly atherogenic[7]. Triglycerides in TRLs include chylomicrons and VLDL, which are synthesized and secreted from intestinal epithelial cells and liver, respectively, and metabolized in plasma[8]. 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[6, 9-14]. However, the cholesterol content of particles, rather than triglycerides themselves, is likely to constitute the causal moiety contained in the atherogenic lipid profiles[5]. RC shares the potential with LDL-C to penetrate the arterial intima and cause atherosclerosis by delivering cholesterol content[8]. In addition, elevated RC but not LDL-C levels have been shown to be causally associated with low-grade inflammation and ASCVD, providing mechanistic support for TRLs as a trigger for atherothrombotic events[15].

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[16]. Additionally, serum RC levels have been shown to be elevated in diabetic patients[17, 18], and are partially involved in platelet activation in diabetic patients without obstructive coronary artery disease (CAD)[19].

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[20, 21]. 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[22]. 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 then 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/m^2	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				0.992
NSTE-ACS -n (%)	1494 (87.1)	308 (87.0)	1186 (87.1)	
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

(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

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; PCI: 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.

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**).

In univariate analysis, RC >0.79mmol/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

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)	575 (72.7)	741 (80.1)	<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/m^2	25.7 ± 3.1	26.0 ± 3.2	25.5 ± 3.0	0.001
Risk Factors				
Current smokers -n (%)	759 (44.2)	322 (40.7)	437 (47.2)	0.008
Hypertension -n (%)	1093 (63.7)	540 (68.3)	553 (59.8)	<0.001
Dyslipidemia -n (%)	1374 (80.1)	661 (83.6)	713 (77.1)	0.001
Past MI -n (%)	328 (19.1)	170 (21.5)	158 (17.1)	0.024
Past PCI -n (%)	340 (19.8)	191 (24.1)	149 (16.1)	<0.001
CKD -n (%)	53 (3.1)	36 (4.6)	17 (1.8)	0.002
Type of ACS				<0.001
NSTE-ACS -n (%)	1494 (87.1)	722 (91.3)	772 (83.5)	
STEMI -n (%)	222 (12.9)	69 (8.7)	153 (16.5)	
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)	69.3 (61.3-79.5)	71.2 (62.7-80.0)	0.037
Heart failure -n (%)	467 (28.5)	189 (24.7)	278 (31.9)	0.001
ST-segment deviation-n (%)	306 (17.8)	111 (14.0)	195 (21.1)	<0.001
Elevated cardiac enzymes/markers-n (%)	443 (25.8)	170 (21.5)	273 (29.5)	<0.001
Cardiac arrest -n (%)	2 (0.1)	2 (0.3)	0 (0.0)	0.412
GRACE risk score	104 ± 39	103 ± 39	105 ± 38	0.283
GRACE risk				0.184
Low	1106 (64.5)	528 (66.8)	578 (62.5)	
Intermediate	287 (16.7)	124 (15.7)	163 (17.6)	
High	323 (18.8)	139 (17.6)	184 (19.9)	
Laboratory Measurements				
FPG -mmol/L	5.78 (5.23-6.93)	7.10 (6.23-8.25)	5.32 (4.98-5.72)	<0.001
Glycosylated hemoglobin -%	6.1 (5.6-7.1)	7.2 (6.6-8.1)	5.6 (5.4-5.9)	<0.001
hs-CRP -mg/L	1.4 (0.7-3.5)	1.4 (0.7-3.7)	1.3 (0.6-3.2)	0.056

(Cont. Table 2)

Variable	All subjects (n=1716)	Diabetes (n=791)	Non diabetes (n=925)	P value
Angiographic Findings				
LM/multi-vessel disease -n (%)	1456 (84.8)	713 (90.1)	743 (80.3)	<0.001
Proximal LAD stenosis -n (%)	861 (50.2)	399 (50.4)	462 (49.9)	0.876
Procedural Results				
DES-n (%)	1409 (82.1)	660 (83.4)	749 (81.0)	0.206
BRS-n (%)	97 (5.7)	32 (4.0)	65 (7.0)	0.010
DCB-n (%)	111 (27.2)	56 (27.2)	55 (27.2)	1.000
Complete revascularization-n (%)	1052 (61.3)	464 (58.7)	588 (63.6)	0.042
Medications before admission				
Aspirin -n (%)	1256 (73.2)	591 (74.7)	665 (71.9)	0.207
P2Y12 inhibitors -n (%)	700 (40.8)	315 (39.8)	385 (41.6)	0.480
Statins -n (%)	1230 (71.7)	585 (74.0)	645 (69.7)	0.060
ACEI/ARBs -n (%)	488 (28.4)	259 (32.7)	229 (24.8)	<0.001
β-blockers -n (%)	634 (36.9)	304 (38.4)	330 (35.7)	0.259
Medications at discharge				
Aspirin -n (%)	1700 (99.1)	783 (99.0)	917 (99.1)	0.950
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)	398 (50.3)	431 (46.6)	0.136
β-blockers -n (%)	1203 (70.1)	572 (72.3)	631 (68.2)	0.073

Abbreviations as in Table 1.

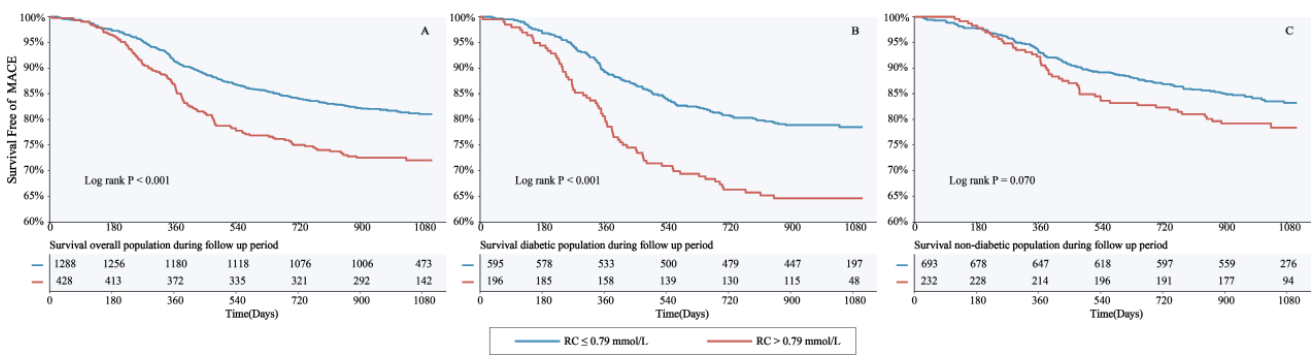

Fig. 1. Survival curves of MACE based on dichotomous RC Levels in ACS patients with or without diabetes

Kaplan-Meier curves showed that elevated RC levels corresponded to a higher probability of developing MACE in the overall population (A) and the diabetic subgroup (B), but not in the non-diabetic subgroup (C). MACE: major adverse cardiovascular events; RC: remnant cholesterol.

(all P-values >0.05).

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[6, 23] and observational[22, 24, 25] 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[26]. Moreover, experimental studies have

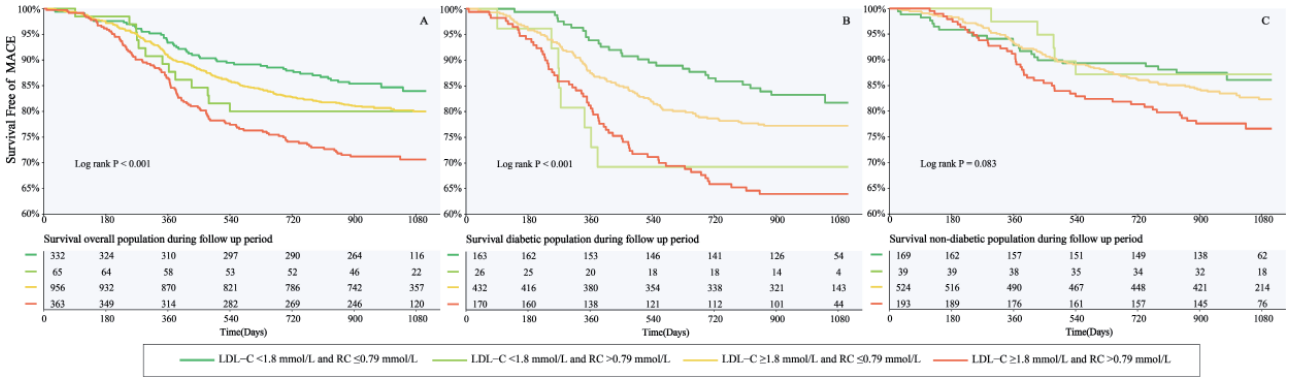

Fig. 2. Survival curves of MACE based on pre-defined categories of RC and LDL-C Levels in ACS patients with or without diabetes

Kaplan-Meier curves showed that elevated RC levels identified patients at a higher risk of MACE compared with those at lower RC levels in the overall population (A). Elevated RC levels were related to a significantly higher risk of MACE in diabetic patients, regardless of LDL-C levels (B). The incidences of MACE showed no differences among groups with various levels of LDL-C and RC in the non-diabetic patients (C). LDL-C: low-density lipoprotein cholesterol; MACE: major adverse cardiovascular events; RC: remnant cholesterol.

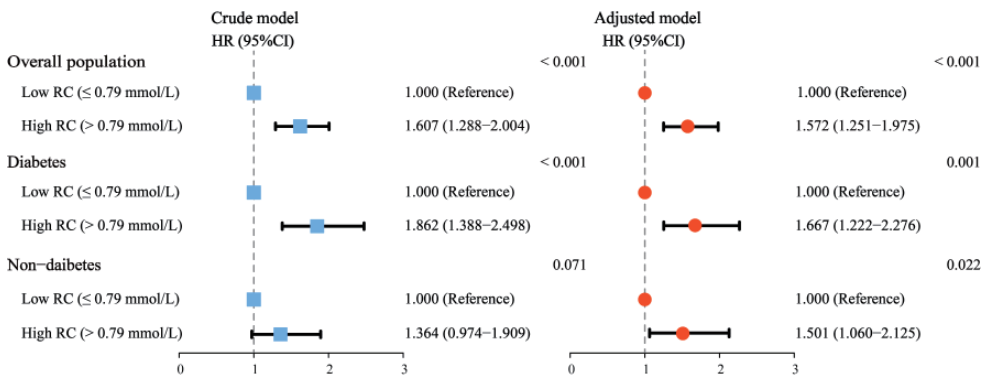

Fig. 3. Remnant cholesterol levels in relation to cardiovascular events in ACS patients with or without diabetes

Crude model demonstrated the univariate analyses for the risk of MACE in the overall population, diabetic population, and non-diabetic population. Adjusted model demonstrated the multivariate analyses for the risk of MACE in the overall population, diabetic population, and non-diabetic population. HR: hazard ratio; RC: remnant cholesterol; 95% CI: 95% confidence interval.

shown that RC is involved in the formation and progression of atherosclerosis by activating monocytes, upregulating proinflammatory cytokines, and increasing pro-thrombotic factors [15, 27]. 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[15]. 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[28]. 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[29]. 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[30]. 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[31]. Large VLDL particles may confer more cardiovascular disease risk[32, 33]. In

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[18]. 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[24]. 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.

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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/m^2	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.