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Remnant cholesterol and coronary atherosclerotic plaque burden assessed by computed tomography coronary angiography

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HIGHLIGHTS

- A substantial residual cardiovascular event risk exists in statin-treated patients.
- Part of this risk may be attributable to elevated levels of remnant cholesterol.
- Computed tomography angiography non-invasively quantifies coronary plaque burden.
- Remnant cholesterol levels predict significant total coronary plaque burden.
- This relationship persists in patients with optimal low-density lipoprotein levels.

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ABSTRACT

Background and aims: There remains a substantial residual risk of ischaemic heart disease (IHD) despite optimal low-density lipoprotein cholesterol (LDLC) reduction. Part of this risk may be attributable to remnant cholesterol, which is carried in triglyceride-rich lipoproteins. We evaluated the relationship between remnant cholesterol and coronary atherosclerotic plaque burden assessed non-invasively by computed tomography coronary angiography (CTCA) in patients with suspected coronary artery disease (CAD).

Methods and results: This was a multicentre study of 587 patients who had a CTCA and fasting lipid profile within 3 months. Calculated remnant cholesterol was total cholesterol minus LDLC minus high-density lipoprotein cholesterol (HDLC). Significant coronary atherosclerotic burden was defined as CT-Leaman score > 5 (CT-LeSc), an established predictor of cardiac events. Mean age was 61 ± 12 years and mean pretest probability of CAD was 23.2 ± 19.8%. LDLC levels were < 1.8 mmol/L in 134 patients (23%), of whom 82% were statin-treated. Patients with CT-LeSc > 5 had higher mean remnant cholesterol than those with CT-LeSc ≤5 (0.76 ± 0.36 mmol/L *vs.* 0.58 ± 0.33 mmol/L, $p = 0.01$). On univariable analysis, remnant cholesterol ($p = 0.01$), LDLC ($p = 0.002$) and HDLC ($p < 0.001$) levels predicted CT-LeSc > 5, whilst triglycerides ($p = 0.79$) had no association with CT-LeSc > 5. On multivariable analysis in the subset of patients with optimal LDLC levels, remnant cholesterol levels remained predictive of CT-LeSc > 5 (OR 3.87, 95% confidence interval 1.34–7.55, $p = 0.004$), adjusted for HDLC and traditional risk factors.

Conclusions: Remnant cholesterol levels are associated with significant coronary atherosclerotic burden as assessed by CTCA, even in patients with optimal LDLC levels. Future studies examining whether lowering of remnant cholesterol can reduce residual IHD risk are warranted.

1. Introduction

There is strong evidence that lowering low-density lipoprotein cholesterol (LDLC) significantly reduces ischaemic heart disease (IHD) risk [1]. However, a large residual risk for recurrent cardiovascular (CV) events remains in statin-treated patients despite optimal LDLC

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reduction [2–4]. Part of this residual risk may be explained by increased concentrations of remnant cholesterol.

Remnant cholesterol is defined as the cholesterol content of a subset of the triglyceride-rich lipoproteins (TRLs) called remnants [5], which have increased in prevalence due to the global obesity and metabolic syndrome epidemic [6]. In the nonfasting state, remnants are comprised of chylomicron remnants, very low-density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL); and in the fasting state, VLDL and IDL. Recent genetic studies suggest a causal association between elevated remnant cholesterol and IHD [7–9]. Moreover, remnant cholesterol levels have been shown to predict incident IHD in large, diverse primary prevention cohorts [10]. Elevated remnant cholesterol concentrations are also associated with increased all-cause mortality, both in the general population [11] and in patients with IHD [12].

The atherogenicity of remnant cholesterol has been demonstrated in many experimental studies, with potential mechanisms including the retention of remnants in the arterial intima [13], their direct uptake by macrophages [14], and the induction of an inflammatory state [8,15]. However, the relationship between remnant cholesterol levels and coronary atherosclerotic plaque burden has yet to be defined by clinical measures.

Computed tomography coronary angiography (CTCA) has become widely available and adopted, due to its high predictive accuracy in detecting obstructive coronary artery disease (CAD) [16]. It also demonstrates the presence and extent of non-obstructive CAD in the entire coronary artery tree, enabling non-invasive quantification of the total coronary atherosclerotic burden. Several CTCA plaque burden scores have recently been developed and prognostically validated, including the CT-adapted Leaman score (CT-LeSc), for which a high (> 5) score is an independent long-term predictor of hard cardiac events [17,18].

This study aimed to determine the relationship between remnant cholesterol and total coronary atherosclerotic burden assessed non-invasively by CTCA. To evaluate its role in residual CV risk, we also specifically examined the impact of elevated remnant cholesterol on plaque burden in patients with optimal LDLC levels.

2. Materials and methods

2.1. Study population

We retrospectively studied consecutive patients ≥18 years of age who underwent a clinically indicated CTCA for suspected CAD from September 2010 to September 2016 at MonashHeart (Monash Health, Melbourne, Australia) and Mildura Base Hospital (Mildura, Victoria, Australia). Only patients who had a full fasting lipid profile performed within 3 months prior to the CTCA were included. Fig. 1 describes the patient selection and study design. The study was approved by the Human Research and Ethics Committee of both institutions.

2.2. CTCA acquisition and interpretation

All CTCAs were performed on a 320-detector-row scanner (Aquilion Vision, Toshiba, Japan) at MonashHeart or a 128-detector-row scanner (Somatom Definition, Siemens Medical, Germany) at Mildura Base Hospital. The studies were performed according to established guidelines [19] and departmental protocol [20]. Image data sets were analysed using axial and multiplanar reconstructions. We excluded 18 scans (3%) deemed uninterpretable due to artefact or heavy calcification. All scans were simultaneously evaluated by two expert readers unaware of patients' lipid results. Studies were interpreted according to current guidelines [21] using a 16- segment model. Each coronary segment > 2 mm in diameter was analysed for the presence of plaque and each lesion was visually graded as non-obstructive (< 50% estimated obstruction of coronary luminal diameter) or obstructive (≥50% of luminal diameter) stenosis. Plaque composition was classified as non-calcified, calcified, or mixed.

2.3. Quantification of coronary atherosclerotic burden

The primary measure of total coronary atherosclerotic burden was the CT-LeSc, calculated using three sets of weighting factors: 1) location of coronary plaques, accounting for dominance; 2) type of plaque, with a multiplication factor of 1 for calcified plaques and 1.5 for non-calcified and mixed plaques; and 3) degree of stenosis, with a multiplication factor of 1 for obstructive (≥50% stenosis) and 0.615 for non-obstructive (< 50% stenosis) lesions [22]. The total CT-LeSc was calculated as the sum of the scores of all evaluable coronary segments. Two alternative CT plaque burden scores, the segment involvement score (SIS) and segment stenosis score (SSS), were also evaluated. SIS was calculated as the total number of coronary segments with plaque, irrespective of the degree of luminal stenosis within each segment (range 0–16). SSS was calculated by grading each coronary segment as having no to severe plaque (scores 0 to 3) based on stenosis severity, with the scores of all 16 segments being summed to yield a total score (range 0–48) [23]. A significant coronary atherosclerotic burden was defined using prognostically validated cutoffs: CT-LeSc > 5 [17,18], SIS > 4 [24], or SSS > 5 [23].

2.4. Laboratory analyses

Lipid profiles were obtained in all patients within 3 months prior to the CTCA; 159 (27%) of these samples were measured within 7 days of the scan. Lipid profiles were obtained after an 8–12 h fast from one of two laboratories (Monash Pathology, Victoria; Barratt & Smith Pathology, Victoria). Total cholesterol (TC), high density lipoprotein cholesterol (HDLC) and triglycerides (TGs) were measured using standard enzymatic assays (Beckman Coulter, California, US). LDLC was calculated using the Friedewald equation when plasma triglycerides were ≤4.5 mmol/L and otherwise measured directly (Roche, Indianapolis, US) in a third laboratory (Dorevitch Pathology, Victoria) in 11 patients (2%). Fasting remnant cholesterol was calculated as fasting TC minus LDLC minus HDLC. Non-HDLC, calculated as TC minus HDLC, was a combined measure of the cholesterol content of atherogenic apolipoprotein B-containing lipoproteins (LDL, lipoprotein (a), chylomicrons, TRLs and their remnants).

2.5. Ascertainment of risk factors

Hypertension was defined as a systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg at the time of CTCA, or diagnosis/treatment of hypertension. Diabetes mellitus was defined by a haemoglobin A1c ≥ 6.5% or use of diabetic medications. Dyslipidaemia was defined as either TC > 6.2 mmol/L, LDLC > 4.1 mmol/L, HDLC < 1.0 mmol/L, serum TG > 1.7 mmol/L [25] or diagnosis/treatment of dyslipidaemia. Family history of premature CAD was defined as any first-degree family member with IHD before 60 years of age. Smokers were both active or former smokers. Obesity was defined as BMI ≥30 kg/m^2. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) 30–59 mL/min/1.73 m^2; as per CKD guidelines (eGFR < 60 mL/min/1.73 m^2) [26] and with the exclusion of patients with eGFR < 30 mL/min/1.73 m^2 from CTCA. Existing statin therapy and intensity was documented at the time of the CTCA. Optimal LDLC level was defined by the guideline-recommended treatment target of < 1.8 mmol/L for patients at very high-risk of CV disease [25,27]. A low HDLC level of < 1.0 mmol/L was used to indicate increased CV risk [27]. The Framingham risk score was used to estimate the 10-year absolute risk of CV disease [28]. The pretest probability of obstructive CAD in symptomatic patients was calculated with the CAD Consortium clinical score [29].

2.6. Statistical analysis

Continuous variables are presented as mean ± SD when normally

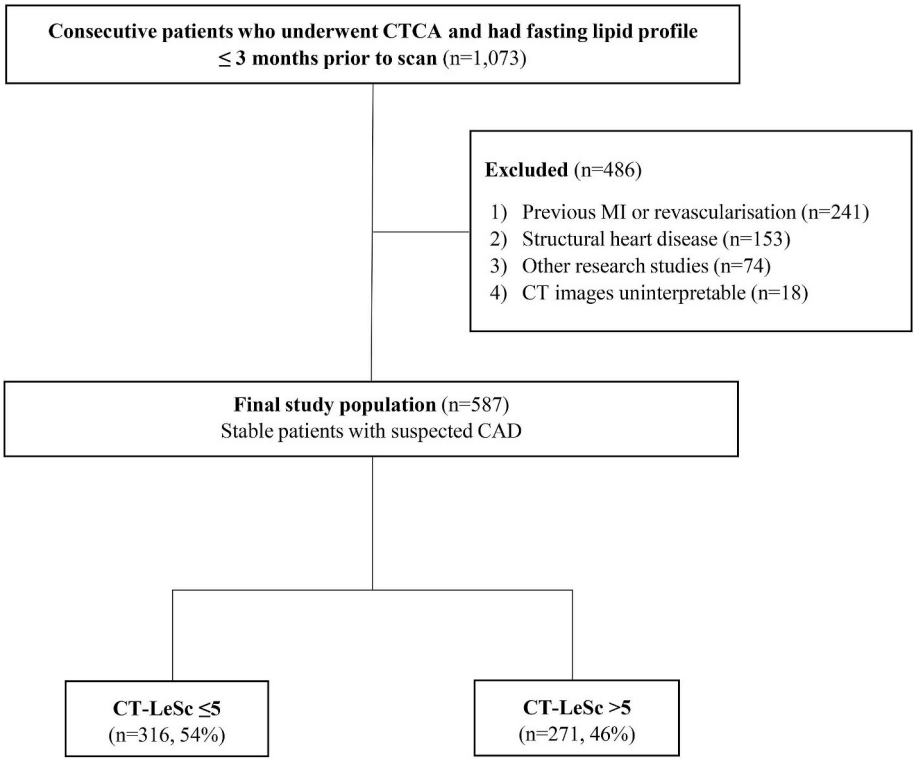

Fig. 1. Patient selection and study design.
Flow chart demonstrating study inclusion and exclusion criteria. CTCA, computed tomography coronary angiography; MI, moycardial infarction; CAD, coronary artery disease; CT-LeSc, CT-adapted Leaman score.

distributed, or median (interquartile range) in cases of non-normal distribution. Categorical variables are expressed as frequencies with percentages. For assessment of baseline characteristics, patients were divided into two groups based on remnant cholesterol levels above or below the median of 0.60 mmol/L, defined as 'high' or 'low' remnant cholesterol, respectively. Differences between groups were evaluated using the Chi square or Fisher exact test for categorical variables, and unpaired *t*-test or Mann-Whitney *U* test for continuous variables as appropriate. Statistical significance was defined as $p < 0.05$ (2 tailed).

The correlation between lipid parameters was assessed using the Spearman's rank correlation coefficient (rs). Univariable analysis (binary logistic regression model) was performed to identify predictors of CT-LeSc > 5 among the demographic, clinical and lipid variables. To specifically assess the role of remnant cholesterol in residual CV risk, multivariable logistic regression was performed in the subset of patients with optimal LDLC levels, using clinical variables previously shown to independently predict a high CT-LeSc [22], along with low HDLC. Statistical analysis was performed using SPSS version 25.0 (IBM Corp, Armonk, NY).

3. Results

3.1. Patient characteristics

The study population comprised 587 patients, with mean age 61 ± 12 years and 55% males. Baseline patient characteristics according to high and low remnant cholesterol levels are presented in Table 1. 241 (41%) were on statins at the time of the CTCA, of whom 112 (46%) had a dose equivalent to atorvastatin 10–20 mg and 85 (35%) had a dose equivalent to atorvastatin 40–80 mg [30]. The prevalence of existing statin therapy was significantly higher in patients with CT-LeSc > 5 compared to those with low CT-LeSc ≤5 (58% *vs.* 38%, $p < 0.001$). The mean 10-year risk of CV disease was 13.8 ± 8.9%, and the mean pretest probability of obstructive CAD was 23.2 ± 19.8%.

3.2. Lipid parameters

The mean values of TC, LDLC, HDLC and remnant cholesterol were 4.8 ± 1.2 mmol/L, 2.8 ± 1.0 mmol/L, 1.2 ± 0.4 mmol/L and 0.72 ± 0.46 mmol/L, respectively. The median values of TG and non-HDLC cholesterol were 1.3 (0.9–1.8) mmol/L and 3.4 (2.7–4.3) mmol/L, respectively. Remnant cholesterol levels were highly correlated with fasting TG levels (rs = 0.98, $p < 0.001$), inversely correlated with HDLC (rs = −0.39, $p < 0.001$), and poorly correlated with LDLC levels (rs = 0.07, $p < 0.001$). LDLC levels were optimal in 134 patients (23%), of whom 110 patients (82%) were on a statin. Patients with CT-LeSc > 5 had a higher mean remnant cholesterol level than those with CT-LeSc ≤5 (0.76 ± 0.36 mmol/L *vs.* 0.58 ± 0.33 mmol/L, $p = 0.01$).

3.3. CTCA results

Overall, the median CT-LeSc was 4.5 (IQR 0–9.0). Of patients with CAD (n = 428; 73%), those with obstructive plaque (n = 260; 44%) had a median CT-LeSc of 9.5 (6.1–12.7), whilst those with non-obstructive plaque (n = 168; 29%) had a median CT-LeSc of 3.7 (2.2–6.0). The number of patients with a significant coronary atherosclerotic burden as evaluated by the CT-LeSc, SSS, and SIS was 271 (46%), 201 (34%), and 130 (22%), respectively.

3.4. Predictors of coronary atherosclerotic burden

In the univariable analysis, a significant atherosclerotic burden defined by CT-LeSc > 5 was associated with age, male gender, hypertension, diabetes and dyslipidaemia. Remnant cholesterol, TC, LDLC

Table 1
Clinical, lipid and CTCA characteristics according to high and low remnant cholesterol levels.

	Low remnant cholesterol (< 0.6 mmol/L)	High remnant cholesterol (≥ 0.6 mmol/L)	Total	*p* value
	(n = 281)	(n = 306)	(n = 587)	
Clinical				
Age (years)	61.1 ± 12.2	60.4 ± 12.3	60.8 ± 12.3	0.51
Male	149 (53)	174 (57)	323 (55)	0.45
Hypertension	136 (48)	176 (58)	312 (53)	0.09
Diabetes mellitus	39 (13)	66 (22)	105 (18)	0.02
Dyslipidaemia	142 (51)	259 (85)	401 (68)	< 0.001
Smoking	80 (29)	119 (39)	199 (34)	0.006
Family history of CAD	122 (43)	127 (42)	249 (42)	0.8
Obesity	63 (22)	108 (35)	171 (29)	0.003
Chronic kidney disease	20 (7)	26 (9)	46 (8)	0.42
Existing statin therapy	90 (32)	149 (47)	239 (41)	0.008
Framingham risk score	12.4 ± 8.2	15.1 ± 9.2	13.8 ± 8.9	0.02
CAD Consortium score	21.2 ± 19.1	24.9 ± 20.2	23.2 ± 19.8	0.03
Lipids (mmol/L)				
Total cholesterol	4.47 ± 1.00	5.02 ± 1.28	4.76 ± 1.20	< 0.001
LDL cholesterol	2.74 ± 0.88	2.92 ± 1.13	2.83 ± 1.02	0.03
HDL cholesterol	1.36 ± 0.46	1.14 ± 0.38	1.24 ± 0.43	< 0.001
Remnant cholesterol	0.40 ± 0.11	1.08 ± 0.53	0.72 ± 0.46	< 0.001
Triglycerides	0.9 (0.7-1.1)	1.8 (1.5-2.4)	1.3 (0.9-1.8)	< 0.001
Non-HDL cholesterol	3.1 (2.5-3.7)	3.7 (3.0-4.7)	3.4 (2.7-4.3)	< 0.001
Symptoms				0.38
Typical chest pain	39 (14)	49 (16)	88 (15)	
Atypical chest pain	190 (68)	200 (65)	390 (66)	
Dyspnea	17 (6)	21 (7)	38 (6)	
Asymptomatic	19 (7)	29 (10)	48 (8)	
Unknown	13 (5)	7 (2)	20 (3)	
CTCA results				0.14
No CAD	84 (30)	75 (25)	159 (27)	
Non-obstructive CAD	81 (29)	87 (28)	168 (29)	
Obstructive CAD	116 (41)	144 (47)	260 (44)	
Technical data				
Heart rate (bpm)			56.8 ± 6.9	
Contrast dose (ml)			89.1 ± 36.8	
Radiation dose (DLP)			291.1 ± 182.6	
Plaque burden score				
SIS	2 (0-5)	2.5 (0-5)	2 (0-5)	0.42
SIS > 4	84 (30)	97 (32)	181 (31)	0.56
SSS	3 (0-7)	3.0 (0-8)	3 (0-8)	0.15
SSS > 5	92 (33)	109 (36)	201 (34)	0.32
CT-LeSc	3.7 (0-8.9)	5.2 (0.6-9.0)	4.5 (0-9)	0.03

Values are expressed as n(%), mean ± SD or median (IQR).
CAD, coronary artery disease; CTCA, computed tomography coronary angiography; SIS, segment involvement score; SSS, segment stenosis score; CT-LeSc, CT-adapted Leaman score.

and HDLC levels were predictors of CT-LeSc > 5, whilst TG levels had no association with CT-LeSc > 5 (Table 2). Remnant cholesterol levels also predicted significant atherosclerotic burden evaluated by the SSS and SIS: OR 1.60 per 1 mmol/L increase (95% CI 1.03–2.77, $p = 0.04$) for SSS > 5, and OR 1.53 (95% CI 1.02–3.23, $p = 0.04$) for SIS > 4.

On multivariable analysis performed in the subset of patients with optimal LDLC levels (n = 134), increasing remnant cholesterol levels were an independent predictor of CT-LeSc > 5 (OR 3.87, 95% CI 1.34–7.55 per 1 mmol/L increase, $p = 0.004$), as was HDLC < 1.0 mmol/L (OR 3.00, 95% CI 1.22–5.83 per 1 mmol/L increase, $p = 0.03$) (Fig. 2).

4. Discussion

The present analysis is the first to demonstrate a relationship between remnant cholesterol and total coronary atherosclerotic plaque burden assessed by CTCA. We found that remnant cholesterol levels predict significant coronary atherosclerotic burden, and that this was independent of traditional CV risk factors in patients with optimal LDLC levels.

The association of remnant cholesterol with increased atherosclerotic burden in this study is supported by experimental evidence that remnants contribute to arterial intimal cholesterol deposition, vascular inflammation and subsequent plaque formation. While large chylomicrons and VLDL particles fail to cross the endothelial barrier, their smaller remnants not only penetrate the arterial intima but may be bound and retained by connective tissue matrix [13]. Remnant particles are larger than LDL and carry up to 40 times more cholesterol per particle, which may render them more atherogenic than LDL [31]. Unlike LDL, remnants do not require oxidation to be taken up by macrophages to cause foam cell formation [14]. Remnant cholesterol is also causally associated with low-grade inflammation, with a near three-fold higher C- reactive protein level for each 1 mmol/L increase in remnant cholesterol [8]. In addition, Moens et al. showed elevated levels of remnant cholesterol to elicit arterial wall inflammation and a multilevel cellular immune response [15]. This combination of local intimal infiltration and inflammation is a likely explanation for the effect of remnant cholesterol on atherogenesis.

Consistent with current evidence, we found no association between fasting TG levels and total atherosclerotic burden. Whilst both fasting and non-fasting TG levels may predict future CV risk [32], the exact role of TGs in mediating atherosclerosis continues to be debated [33]. TGs are predominantly carried by TRLs, and concentrations of TGs are highly correlated with the cholesterol content of TRL remnants, that is, remnant cholesterol. Most cells in the body can readily metabolise TGs but not cholesterol, and unlike cholesterol, TGs do not accumulate in

Table 2
Univariable analysis - predictors of significant coronary atherosclerotic burden (CT-LeSc > 5) in the study population (n = 587).

	OR	95% CI	*p* value
Age	1.07	1.05–1.08	< 0.001
Male gender	3.33	2.36–4.69	< 0.001
Hypertension	2.26	1.62–3.16	< 0.001
Diabetes mellitus	1.46	1.15–1.77	< 0.001
Dyslipidaemia	1.88	1.31–2.70	0.001
Smoking	1.26	0.89–1.78	0.2
Family history of CAD	0.82	0.59–1.13	0.23
Obesity	1.02	0.71–1.45	0.93
Chronic kidney disease	1.87	0.79–4.38	0.16
Chest pain	1.12	0.68–1.56	0.22
Framingham risk score	1.07	1.04–1.09	< 0.001
CAD Consortium score	1.12	1.10–1.14	< 0.001
Total cholesterol	1.38	1.20–1.60	< 0.001
LDL cholesterol	1.31	1.11–1.56	0.002
HDL cholesterol	0.45	0.29–0.68	< 0.001
Remnant cholesterol	1.29	1.08–1.52	0.01
Triglycerides	1.65	1.15–2.14	0.79
Non-HDL cholesterol	1.23	1.06–1.43	0.007

Values are expressed as n(%), mean ± SD or median (IQR).
CT-LeSc, CT-adapted Leaman score; CAD, coronary artery disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

atherosclerotic plaque [33]. Hence it is most likely that elevated TGs are a marker of increased levels of remnant cholesterol, and that it is the latter which causes atherosclerosis.

CTCA is unique in its ability to non-invasively identify the presence and extent of non-obstructive plaque, which has prognostic implications [18,24]. Given the heterogeneity and high prevalence [34] of non-obstructive CAD, there is a need for tools to quantify total coronary atherosclerotic burden and improve risk stratification. Coronary artery calcification (CAC) scoring has established utility in CV risk prediction in asymptomatic patients [35], with the extent of CAC being associated with total coronary plaque burden [36]. CT plaque burden scores have also been proposed and prognostically validated, including the SIS and SSS [23,24]. However, the CAC score cannot detect non-calcified plaques [37], which represent an earlier stage of atherosclerosis more prone to rupture [38], and the SIS and SSS do not qualify plaque characteristics. The CT-LeSc is a comprehensive index, incorporating lesion location, stenosis severity and plaque composition, and has shown higher accuracy in predicting long-term cardiac events than the SIS or SSS [17,18]. Hence the CT-LeSc and prognostic cutoff value of > 5 was the optimal method of evaluating total coronary atherosclerotic burden in our analysis.

There has been recent clinical interest into the modulation of coronary plaque characteristics by remnant cholesterol. Puri et al. showed treated levels of non-HDLC to be closely associated with coronary atheroma volume progression and regression on serial intravascular ultrasound (IVUS), independent of LDLC levels [39]. Matsuo et al. found remnant cholesterol levels, and not LDLC levels, to be highly correlated with the percentage of plaque necrosis – a marker of plaque vulnerability – using IVUS in statin-treated patients [40]. Finally, Nakazato et al.demonstrated high non-HDLC to be associated with the extent of non-calcified plaque on CTCA, with a lack of association between LDLC and plaque type [41]. Together, these studies suggest a relationship between remnant cholesterol and plaque characteristics such as volume, vulnerability and composition. The present analysis adds to the evidence by demonstrating the association of remnant cholesterol with the overall burden of coronary plaque.

Among patients with optimal LDLC levels in the present study, most of whom were statin-treated, remnant cholesterol levels were an independent predictor of significant coronary atherosclerotic burden after adjusting for low HDLC and traditional risk factors. This finding lends mechanistic support to the role of remnant cholesterol in residual CV risk. A recurrent event rate of up to 22% exists after optimal LDLC lowering [2–4]. The global metabolic syndrome epidemic is increasing the prevalence of remnants [6], and elevated remnant cholesterol is strongly associated with risk of IHD [7–9] and all-cause mortality [11,12]. There has been a shift from the paradigm of targeting only LDLC, with recent guidelines highlighting non-HDLC, which includes remnant cholesterol, as the major form of atherogenic cholesterol and an additional therapeutic target [25]. Trials of non-statin lipid-lowering therapies in reducing residual risk have failed to show significant benefit [42,43], and none have specifically targeted remnant cholesterol. Recently, omega-3 fatty acids have been shown to reduce remnant cholesterol levels [44], and novel inhibitors of apolipoprotein CIII, a key regulator of remnant metabolism, have had promising results [45]. There is clearly a need for the development of new therapies targeting remnant cholesterol, and randomised trials examining whether lowering remnant cholesterol in those with high concentrations can modulate plaque morphology and reduce CV risk.

4.1. Study limitations

There are several limitations related to this report. Firstly, this was a retrospective study on consecutive patients referred for CTCA and our findings may be affected by referral bias. We included only patients with lipid profiles collected within three months prior to their CTCA, and this is reflected in the higher prevalence of dyslipidaemia compared to other studies. Secondly, we used calculated remnant cholesterol on fasting lipid samples. Although possibly not as precise as a direct measurement, calculation of remnant cholesterol can be easily performed on a standard lipid profile at no additional cost. In the fasting state, VLDL and IDL are the major constituents of circulating remnants, however it remains plausible that chylomicron remnants partially contribute to atherosclerosis and plaque burden. Notwithstanding, the

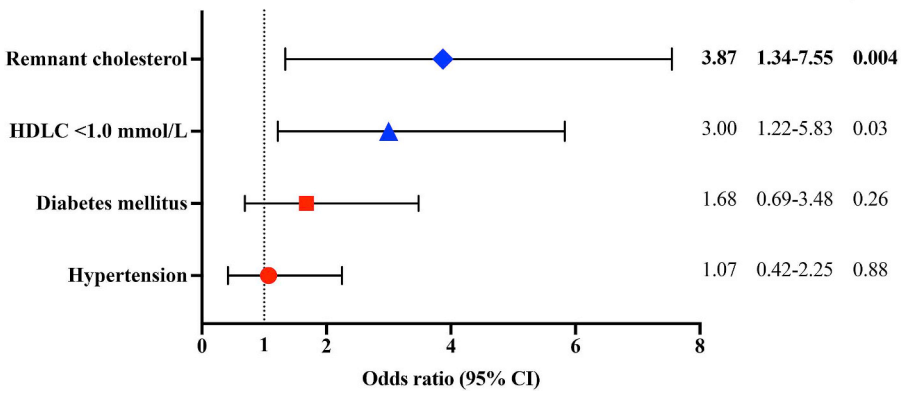

Fig. 2. Predictors of CT-LeSc > 5 in patients with optimal LDL cholesterol levels.
Odds ratio plot showing predictors of CT-LeSc > 5 on multivariable analysis in patients with optimal (< 1.8 mmol/L) LDL cholesterol levels (n = 134). Results for remnant cholesterol are per 1 mmol/L increase. Blue markers represent statistically significant results and red markers represent non-significant results. CT-LeSc, CT-adapted Leaman score; LDL, low-density lipoprotein; HDLC, high-density lipoprotein cholesterol; CI, confidence interval.

impact of remnant cholesterol on coronary atherosclerotic burden, whilst potentially underestimated with the use of fasting samples in our study, was clearly significant. Thirdly, we used a single lipid profile obtained within three months prior to CTCA as a measure of average recent lipid exposure in each patient. Despite the dynamic nature of serum lipid levels, this one-time measurement still captured a strong and consistent association with plaque burden, and represents a clinically relevant approach. Fourthly, given the cross-sectional nature of the study, we were unable to assess for the longitudinal effects of statin therapy on coronary atherosclerotic burden. Finally, we did not perform CAC scoring in this predominantly symptomatic population undergoing CTCA for suspected CAD. Whilst the extent of CAC is associated with total coronary plaque burden, the clinical utility of CAC scoring is derived from asymptomatic populations and hence not applicable to our study cohort.

4.2. Conclusions

There is a significant association between remnant cholesterol levels and total coronary atherosclerotic burden assessed non-invasively by CTCA, which persists in patients with optimal LDLC levels independently of HDLC and traditional CV risk factors. Future studies examining whether lowering of remnant cholesterol can modulate coronary plaque and reduce the substantial residual CV risk seen after LDLC lowering are warranted.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

AL contributed to image analysis, statistical analysis, and writing of the report. NN contributed to writing of the report. AR, JY and RM performed image analysis. SM, RKM, MS and JCD collected clinical and imaging data. SS, SJN and DTW provided scientific direction and contributed to writing of the report.

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