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REMNANT CHOLESTEROL IN ATHEROSCLEROTIC CARDIOVASCULAR DISEASE: CLINICAL AND THERAPEUTIC RELEVANCE

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SUMMARY

Background. Lowering low-density lipoprotein cholesterol (LDL-C) remains central to the prevention of atherosclerotic cardiovascular disease (ASCVD), yet clinically relevant residual risk persists in many patients despite attainment of recommended LDL-C goals. Remnant cholesterol (RC), which reflects the cholesterol carried by triglyceride-rich lipoproteins (TRLs) and their remnants, has therefore attracted interest as a complementary marker of lipid-related risk, particularly in hypertriglyceridemia and metabolic disease.

Methods. This narrative review synthesizes evidence from 40 publications identified through a comprehensive search of PubMed, Embase, Web of Science, and Scopus up to April 12, 2026. The search focused on peer-reviewed prospective studies, clinical trials, Mendelian randomization analyses, meta-analyses, and guidelines published in English between 2018 and 2026, alongside selected landmark studies required for clinical context. The review addresses RC metabolism and atherogenic mechanisms, methods of estimation, epidemiological and genetic associations with cardiovascular outcomes, and the implications of currently available and emerging lipid-lowering therapies.

Results. Remnant lipoproteins can be retained within the arterial wall and taken up by macrophages without obligatory prior oxidative modification, providing a biologically plausible link between RC and atherosclerosis. Prospective cohorts consistently associate higher RC with cardiovascular events, while Mendelian randomization studies support a causal contribution of remnant-related pathways. Repeated or cumulative RC exposure may add prognostic information in selected populations, including patients with metabolic dysfunction, chronic kidney disease (CKD), and metabolic dysfunction-associated steatotic liver disease (MASLD). Several lipid-lowering therapies reduce RC together with other apolipoprotein B (apoB)-containing lipoproteins; however, their cardiovascular benefit should not be interpreted as proof of an RC-specific treatment effect. High-dose icosapent ethyl has demonstrated outcome benefit in appropriately selected patients with elevated triglycerides.

Conclusions. RC is a clinically relevant complementary marker of residual lipid-related risk, especially in patients with hypertriglyceridemia and metabolic disorders. LDL-C remains the primary evidence-based therapeutic target. RC measurement may refine risk assessment in selected patients, but standardized thresholds and randomized outcome evidence for therapies directed specifically at RC are still needed before RC can be considered an independent routine treatment target.

Keywords: remnant cholesterol, ASCVD, MACE, residual risk

Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death worldwide despite major advances in prevention and lipid-lowering therapy [1]. The clinical success of low-density lipoprotein cholesterol (LDL-C) reduction is unequivocal, but it does not eliminate cardiovascular events. This persistent burden has shifted attention toward other atherogenic apolipoprotein B (apoB)-containing particles that may contribute to residual risk.

Residual cardiovascular risk is particularly relevant in patients who continue to experience major adverse cardiovascular events (MACE) despite achieving LDL-C goals and receiving treatment for conventional risk factors. Among the candidate contributors, cholesterol carried by triglyceride-rich lipoproteins (TRLs) and their remnants has shown associations with ASCVD that are not fully captured by triglyceride or LDL-C concentrations alone [2, 3].

Plasma triglyceride concentrations are a practical marker of the abundance of TRLs, including intestinal chylomicrons and hepatic very-low-density lipoproteins (VLDL). During lipolysis, these particles become progressively smaller and cholesterol-enriched, generating remnant lipoproteins with recognized atherogenic potential [1, 3].

TRL metabolism is dynamic. Lipoprotein lipase (LPL) hydrolyzes triglycerides in apoB-48-containing chylomicrons and apoB-100-containing VLDL, producing chylomicron remnants and VLDL remnants; VLDL metabolism may also proceed through intermediate-density lipoproteins (IDL) toward LDL. Although specialized assays can quantify remnant-like particle cholesterol, calculated remnant cholesterol (RC) is more readily applicable in clinical practice [4]:

RC = total cholesterol - HDL-C - LDL-C [4]

Interest in RC has also been reinforced by therapies that modify TRL metabolism. Agents targeting angiopoietin-like protein 3 (ANGPTL3) or apolipoprotein C-III (apoC-III) can markedly lower triglycerides and remnant-related lipoproteins [5–7]. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors also reduce RC, but their established cardiovascular benefit is principally attributed to lowering LDL-C and the overall burden of apoB-containing particles rather than to a proven RC-specific effect [8–10].

Methods

To synthesize current evidence on the clinical and therapeutic relevance of RC in ASCVD, we performed a structured literature search across four primary databases: PubMed/MEDLINE, Embase, Web of Science, and Scopus. The search covered publications indexed from January 1, 2018, to April 12, 2026, alongside selected historical landmark papers necessary to contextualize clinical concepts. The final search verification was completed on April 12, 2026.

To ensure full reproducibility, the database-specific search strings and logical operators were configured as follows:

• **PubMed/MEDLINE:** ("remnant cholesterol"[Title/Abstract] OR "remnant-like particle cholesterol"[Title/Abstract] OR "triglyceride-rich lipoproteins"[Title/Abstract] OR "VLDL remnants"[Title/Abstract]) AND ("atherosclerosis"[MeSH Terms] OR "atherosclerotic cardiovascular disease"[Title/Abstract] OR "ASCVD"[Title/Abstract] OR "major adverse cardiovascular events"[Title/Abstract] OR "residual risk"[Title/Abstract]) AND ("2018/01/01"[Date - Publication] : "2026/04/12"[Date - Publication])

Filters applied: Species (Humans), Language (English), Text availability (Full text).

• **Embase:** ('remnant cholesterol'/exp OR 'remnant cholesterol':ti,ab OR 'triglyceride rich lipoprotein'/exp OR 'triglyceride rich lipoprotein':ti,ab) AND ('cardiovascular disease'/exp OR 'atherosclerosis'/exp OR 'major adverse cardiovascular event':ti,ab OR 'residual risk':ti,ab) AND [2018-2026]/py

Filters applied: Human, English language, Article / Review journal types.

• **Web of Science (Core Collection):** TS=("remnant cholesterol" OR "remnant-like particle cholesterol" OR "triglyceride-rich lipoproteins") AND TS=("atherosclerotic cardiovascular disease" OR "ASCVD" OR "residual cardiovascular risk" OR "MACE")

Filters applied: Publication Years: 2018–2026; Document Types: Articles, Review Articles; Languages: English.

• **Scopus:** TITLE-ABS-KEY ("remnant cholesterol" OR "triglyceride-rich lipoproteins" OR "remnant lipoproteins") AND TITLE-ABS-KEY ("atherosclerotic cardiovascular disease" OR "ASCVD" OR "residual risk" OR "MACE") AND PUBYEAR > 2017 AND PUBYEAR < 2027

Filters applied: Document Type: Article, Review; Language: English; Source Type: Journal.

We focused our selection on peer-reviewed prospective cohort studies, randomized clinical trials, Mendelian randomization analyses, systematic reviews, and international clinical guidelines published in English. Non-peer-reviewed preprints, conference abstracts without detailed methodology, experimental animal models, and studies lacking comprehensive lipid panel reporting were excluded.

Title, abstract, and full-text evaluations were conducted independently by two reviewers (A.G. and E.A.). Any disagreement regarding study inclusion was resolved through discussion and consensus with the senior co-authors (V.O. and V.C.). A final total of 40 representative publications met all criteria and were included in this narrative review.

Results

Pathophysiological Mechanisms of Remnant Cholesterol in Atherogenesis

Unlike native LDL, which generally requires modification before substantial scavenger-receptor-mediated uptake, remnant lipoproteins can enter the arterial wall and be taken up by macrophages without obligatory prior oxidative modification [1, 11]. This process promotes foam-cell formation and expansion of the intimal lipid core [1, 11]. Because each remnant particle can carry more cholesterol than an LDL particle, arterial retention and accumulation of remnants may contribute substantially to atherogenesis [1, 12].

Epidemiological Evidence and Cardiovascular Outcomes

Across prospective cohorts, higher RC levels are consistently associated with cardiovascular events across diverse clinical settings. However, because the magnitude and independence of these associations vary according to population characteristics, estimation methods, covariate adjustments, and background lipid-lowering therapy, these epidemiological observations are best interpreted as complementary to established lipid markers rather than a replacement for them.

The clinical spectrum of RC-associated vascular damage encompasses both coronary and peripheral territories. Prospective population data link elevated RC concentrations with incident myocardial infarction and a markedly increased risk of peripheral artery disease [13]. A systematic review corroborated these findings, demonstrating a positive association between RC levels and both the presence and

severity of coronary artery disease (CAD), though marked heterogeneity in study design and analytical methodologies limits direct quantitative comparisons across cohorts [14]. Crucially, the atherogenic impact of remnant lipoproteins is apparent early in the life course. In a prospective cohort of 5,939 young adults followed for a median of 22 years, each 0.5 mmol/L increase in RC was associated with an adjusted 30% increase in the risk of incident cardiovascular events (adjusted HR 1.3, 95% CI 1.1–1.5) [12]. This finding is particularly notable given that the cohort baseline age was approximately 30 years, a life stage when conventional short-term risk scoring systems typically underestimate long-term atherogenic trajectory.

To distinguish genuine causal involvement from passive biomarker association, Mendelian randomization (MR) analyses provide critical mechanistic insights into remnant-related metabolic pathways [11, 13]. Large-scale genomic studies demonstrate that lifelong genetically predicted elevations in non-fasting RC are directly and causally linked to an increased susceptibility to ischemic heart disease [11, 13]. Nevertheless, because MR estimates reflect cumulative, lifelong exposure to elevated lipoprotein burdens, their quantitative effect sizes cannot be extrapolated directly to predict the immediate clinical impact of short-term pharmacological reductions in RC [13].

Beyond primary manifestation, remnant lipoproteins contribute substantially to residual cardiovascular risk in treated populations. Observational analyses indicate that patients with elevated RC retain a persistent excess risk of events even when LDL-C targets are achieved, a phenomenon particularly pronounced in the context of obesity, type 2 diabetes (T2D), or metabolic dysfunction [15, 16]. Similarly, in statin-treated patients with established stable CAD who achieved LDL-C levels below 70 mg/dL, elevated remnant lipoprotein concentrations remained independently predictive of recurrent cardiovascular events and restenosis-related complications [17]. Collectively, these data emphasize the imperative of evaluating the comprehensive apoB-containing lipoprotein profile rather than relying solely on isolated lipid parameters.

Cumulative Exposure and Visit-to-Visit Variability

A key methodological and clinical consideration in interpreting epidemiological data is that reliance on single baseline measurements may substantially underestimate an individual's cumulative vascular exposure to atherogenic lipoproteins over time [18, 19]. Beyond absolute concentrations, the dynamic nature of lipid parameters provides incremental prognostic information. Long-term visit-to-visit RC variability has been independently associated with an increased risk of ischemic stroke in general population cohorts [19], as well as with MACE in high-risk populations, such as individuals with T2D [20].

This cumulative atherogenic burden appears particularly critical in secondary prevention and older age groups. In a retrospective analysis of adults aged 75 years and older with established ASCVD, cumulative time-weighted exposure to RC served as an independent predictor of recurrent MACE [18]. Notably, this excess risk persisted even among patients who had achieved target LDL-C control under potent statin therapy, further highlighting the residual risk mediated by prolonged exposure to remnant lipoproteins [18].

Cerebrovascular Impact and Carotid Remodeling

The epidemiological link between RC and overt clinical events is strongly mirrored in studies evaluating subclinical vascular disease across diverse age groups. These imaging findings are biologically coherent with the propensity of remnant particles to penetrate and become entrapped within the arterial wall. However, observational imaging studies alone cannot definitively establish a direct causal relationship between RC elevation and vascular remodeling, necessitating an integrated synthesis of pediatric, adult, and mechanistic data.

Vascular alterations associated with elevated remnant lipoproteins manifest early in life. In pediatric and adolescent cohorts, elevated serum RC concentrations correlate directly with increased carotid intima-media thickness (cIMT), indicating that subclinical structural changes initiate long before clinical cardiovascular disease becomes apparent [16]. In adult populations, this structural impact displays a clear continuous pattern. Qian et al. demonstrated a robust, dose-dependent relationship between RC levels and carotid structural remodeling, where each increment of ≥ 1 mmol/L in RC was associated with a 28% increase in the risk of abnormal mean cIMT and a 25% increase in maximum cIMT [21].

Beyond localized carotid remodeling, elevated RC is strongly associated with cerebrovascular outcomes. Prospective data from the Copenhagen General Population Study, encompassing over 100,000 individuals, confirmed a strong positive association between non-fasting RC concentrations and incident ischemic stroke [22]. Moreover, long-term intra-individual fluctuations in RC levels appear to compound this risk, with high RC variability conferring an additional 9% increase in ischemic stroke incidence per 1-SD increment [19]. At the tissue level, these clinical and radiological observations are biologically compatible with mechanisms involving lipid retention, oxidative processes, cholesterol crystal formation, inflammation, and macrophage injury within atherosclerotic plaques; however, these mechanisms should not be interpreted as evidence that RC alone directly determines plaque instability [22, 23].

Efficacy of Pharmacological Interventions

Intervention studies provide crucial insights into how established lipid-modifying therapies alter apoB-containing lipoproteins and triglyceride-rich particles, indirectly impacting RC levels. Importantly, most landmark clinical outcome trials were not intentionally designed to test RC lowering as a primary or isolated therapeutic strategy. Consequently, observed reductions in RC must be interpreted within the broader framework of overall atherogenic lipoprotein modification rather than as an independent pharmacodynamic target.

Standard lipid-lowering modalities exert variable, yet substantial, effects on remnant particle kinetics. HMG-CoA reductase inhibitors (statins) upregulate hepatic LDL receptor-mediated endocytosis, thereby accelerating the clearance of multiple circulating apoB-containing fractions [9, 10]. Integrated analyses incorporating data from trials such as STELLAR and PREVAIL demonstrated substantial reductions in remnant-like particle cholesterol (RLP-C) following statin initiation; however, these changes reflect a global reduction in apoB-containing lipoproteins and should not be construed as evidence of an RC-specific reduction in cardiovascular events [10, 24]. Similarly, ezetimibe inhibits intestinal cholesterol absorption by targeting the Niemann-Pick C1-Like 1 (NPC1L1) transporter, providing additive lowering of both LDL-C and broader apoB-containing fractions when combined with baseline statin therapy [25]. In the landmark IMPROVE-IT trial, the primary composite cardiovascular endpoint occurred in 32.7% of patients in the simvastatin-ezetimibe arm versus 34.7% in the simvastatin monotherapy group; nevertheless, this clinical benefit was directly proportional to the incremental lowering of LDL-C and overall atherogenic particle burden, preventing a definitive attribution to RC reduction per se [26].

More potent biological therapies demonstrate pronounced effects on remnant clearance pathways. PCSK9 inhibitors markedly increase LDL receptor availability. In clinical evaluations, evolocumab achieved a 44% reduction in fasting RC levels among patients with severe mixed dyslipidemias, such as familial dysbetalipoproteinemia [27]. Likewise, alirocumab administration has been consistently associated with significant reductions in serum RC across hyperlipidemic cohorts [28]. However, as with oral agents, the demonstrated reduction in cardiovascular events in large-scale outcome trials with PCSK9 inhibition is fundamentally interpreted through the drastic clearance of circulating LDL-C and total apoB particles.

Parallel to LDL-receptor-centric pathways, targeted triglyceride-lowering strategies provide complementary evidence regarding remnant particle modulation. In the REDUCE-IT trial, high-dose icosapent ethyl (4 g/day) significantly reduced the primary cardiovascular composite endpoint to 17.2% compared to 22.0% in the placebo arm ($p < 0.001$) among statin-treated patients with elevated triglycerides [29]. Mechanistically, the EVAPORATE trial corroborated these clinical findings by demonstrating a 17% regression in coronary low-attenuation plaque volume over an 18-month period following icosapent ethyl administration [30]. Although these outcomes confirm robust clinical and anatomical benefits in high-risk patients with persistent hypertriglyceridemia, they do not isolate RC reduction as the sole mediator of vascular protection, given the multi-factorial anti-inflammatory, antithrombotic, and membrane-stabilizing properties of purified eicosapentaenoic acid.

Discussion

Impact of RC on Multimorbidity and Chronic Disease Progression

1. Chronic Kidney Disease (CKD)

The relationship between dyslipidemia and progressive renal impairment extends beyond atherosclerotic renal artery stenosis [31, 32]. Clinical data demonstrate that elevated RC levels independently predict new-onset CKD and accelerate diabetic nephropathy progression [31–33].

Mechanistically, excess circulating RC particles induce localized renal lipotoxicity [33]. Subendothelial accumulation of remnant lipoproteins within glomerular structures triggers structural impairment of podocytes, mesangial cell proliferation, and proximal tubular cell injury [33]. Glomerular lipid deposition promotes intra-glomerular hypertension, basement membrane thickening, and tubulointerstitial fibrosis through pro-inflammatory cascades, elevated reactive oxygen species (ROS) production, and local downregulation of vasodilatory mediators [33].

Meta-analytic data reported by Karakasis et al. showed that participants in the highest RC category had greater odds of CKD than those in the lowest category (OR 1.46; 95% CI 1.26–1.68). Each 1 mmol/L increase in RC was associated with a mean estimated glomerular filtration rate (eGFR) reduction of 1.43 mL/min/1.73 m^2. In patients with diabetic CKD, each 1-SD increase in RC was associated with a 24% higher risk of progression to end-stage renal disease [33].

2. Metabolic Dysfunction: The Insulin Resistance–T2D Axis

RC is associated with insulin resistance (IR) and T2D, although the available observational evidence does not establish a primary causal role [34, 35]. Cross-sectional data from NHANES 1999–2020 demonstrate nonlinear associations between elevated RC, IR, and the prevalence of T2D [35]. Mediation analysis indicated that IR statistically mediated 54.1% of the association between RC and prevalent T2D; this finding should not be interpreted as proof of a causal biological pathway [35]. Elevated baseline RC has also been associated with post-transplantation diabetes mellitus in kidney transplant recipients [36].

Pathophysiologically, "cholesterol toxicity" drives pancreatic beta-cell decompensation and metabolic dysfunction through two primary mechanisms [34]:

• ***Pro-inflammatory Cascade:*** Lipotoxicity induced by intracellular cholesterol accumulation promotes systemic oxidative stress and activation of inflammatory pathways [34].

• ***Islet Beta-Cell Lipotoxicity:*** Hydrolysis of elevated RC by LPL releases excess free fatty acids, triggering inflammatory cell infiltration into pancreatic islets, systemic elevation of high-sensitivity C-reactive protein (hs-CRP), and ROS-mediated macrophage activation, culminating in progressive beta-cell dysfunction and apoptosis [34].

3. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Visit-to-visit variability of RC has been associated with

incident MASLD [37]. Data from 43,065 participants showed that each 1-SD increase in RC variability, expressed as standard deviation, was associated with an approximately 5% higher risk of MASLD [37].

In a cross-sectional biopsy-based study, directly measured serum RC was associated with the MASLD activity score, including hepatocyte ballooning and lobular inflammation, but not with fibrosis stage; the association was more evident in men [38]. These observational findings suggest a relationship with disease activity but do not demonstrate that remnant accumulation directly causes the reported histological changes [38].

Clinical Synthesis and Therapeutic Strategy

Addressing residual lipid-related risk requires achievement of guideline-recommended LDL-C targets and assessment of other apoB-containing lipoproteins, particularly in patients with hypertriglyceridemia [9, 10]. Statins and ezetimibe remain established therapies for LDL-C lowering [9, 25]. In selected patients with persistent hypertriglyceridemia, high-dose icosapent ethyl provides incremental cardiovascular benefit [29, 30]. ApoC-III inhibitors and ANGPTL3 inhibitors substantially reduce triglyceride-rich lipoproteins through mechanisms involving TRL production and clearance [5–7]. Bempedoic acid acts through ATP-citrate lyase inhibition and is used primarily as an additional LDL-C-lowering therapy; it should not be characterized as an LPL-directed or RC-specific treatment [39, 40].

Conclusions

Taken together, current evidence supports RC as a potentially useful complementary marker of residual atherosclerotic risk. Its greatest clinical relevance may be in patients with hypertriglyceridemia, metabolic syndrome, diabetes, chronic kidney disease, or MASLD, in whom LDL-C alone may not fully describe the burden of atherogenic lipoproteins. Epidemiological and genetic findings are consistent with a biologically important role for remnant-related pathways, but they do not yet establish a universally applicable RC treatment threshold. LDL-C remains the primary evidence-based therapeutic target, while non-HDL-C and apoB provide established measures of the total atherogenic particle burden. Before RC can be adopted as an independent routine treatment target, standardized measurement approaches, clinically validated thresholds, and outcome trials specifically designed around RC-directed strategies are required.

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