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Residual Inflammatory Risk in Patients With Established Atherosclerotic Cardiovascular Disease and Low-Density Lipoprotein Cholesterol at Target: A Systematic Review and Meta-Analysis

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Abstract

Intensive lowering of low-density lipoprotein cholesterol (LDL-C) reduces recurrent events in atherosclerotic cardiovascular disease (ASCVD), yet many patients who reach guideline LDL-C targets still experience events. Residual inflammatory risk (RIR), defined by high-sensitivity C-reactive protein (hs-CRP) ⩾2 mg/L, is a candidate driver, but its prognostic impact has not been quantified in the LDL-at-target population. We performed the first systematic review and meta-analysis of RIR restricted to patients with established ASCVD and LDL-C <70 mg/dL. We searched PubMed, Cochrane CENTRAL, and EMBASE from inception to May 2026 for cohorts and prespecified analyses comparing hs-CRP ⩾2 versus <2 mg/L within an LDL-C <70 mg/dL stratum. Adjusted hazard ratios (HRs) for major adverse cardiovascular events (MACE) and mortality were pooled using random-effects models, and certainty was rated with GRADE. Seven studies were eligible, and five contributed adjusted estimates. RIR prevalence was 29-47%. RIR was independently associated with higher hazards of MACE (pooled adjusted HR 1.48, 95% CI 1.16-1.88) and all-cause mortality (HR 2.13, 95% CI 1.27-3.57), whereas associations for myocardial infarction, stroke, and repeat revascularization were not statistically significant. Certainty of evidence was low, downgraded for residual confounding and inconsistency. Among patients with established ASCVD and well-controlled LDL-C, RIR was independently associated with higher risks of MACE and all-cause mortality, identifying inflammation as a distinct, potentially modifiable therapeutic target beyond LDL-C lowering. These hypothesis-generating findings support trials enrolling patients with both LDL-C <70 mg/dL and hs-CRP ⩾2 mg/L. The review was registered in PROSPERO (CRD420261381858).

Categories: Cardiology
Keywords: atherosclerotic cardiovascular disease, high-sensitivity c-reactive protein, inflammation, ldl-cholesterol, meta-analysis, residual inflammatory risk, secondary prevention

Introduction And Background

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and disability worldwide, causing approximately 18 million deaths annually across high- and low-to-middle-income countries. Intensive low-density lipoprotein cholesterol (LDL-C) lowering with statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has substantially reduced recurrent cardiovascular events, reinforcing the "lower-is-better" paradigm endorsed by major guidelines and supported by landmark trials, including Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22), Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER), and ODYSSEY OUTCOMES [1-4]. Yet even among patients with established ASCVD who achieve guideline-recommended LDL-C targets (<70 mg/dL, or <55 mg/dL in very high-risk subgroups), a substantial burden of recurrent major adverse cardiovascular events (MACE) persists, indicating that LDL-C reduction, while necessary, is insufficient to eliminate cardiovascular risk [5-8].

Residual cardiovascular risk is multifactorial, encompassing persistent cholesterol burden, elevated triglycerides, prothrombotic states, and systemic inflammation, each contributing independently to recurrent events [9,10]. Among these, residual inflammatory risk has emerged as a particularly actionable

target, commonly defined by a high-sensitivity C-reactive protein (hs-CRP) level ⩾2 mg/L despite optimized lipid-lowering therapy and well-controlled LDL-C [11]. Such elevations reflect persistent vascular inflammation driven by NLRP3 inflammasome activation and downstream interleukin-1β and interleukin-6 signaling, independent of cholesterol burden [12]. This phenotype is highly prevalent: approximately one-third of statin-treated patients in PROVE-IT TIMI 22 and IMPROVE-IT retained hs-CRP >2 mg/L despite LDL-C <70 mg/dL, and a large population-based study of patients with established ASCVD in Spain reported hs-CRP ⩾2 mg/L in nearly 58% [13,14]. Given that hundreds of millions of people live with ASCVD worldwide, these proportions imply that residual inflammatory risk affects a very large, and largely underrecognized, share of otherwise optimally treated patients.

In statin-treated patients, hs-CRP predicts MACE and cardiovascular mortality at least as strongly as, and in contemporary analyses more strongly than, LDL-C. In a pooled analysis of 31,245 patients from the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients With Diabetes (PROMINENT), Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial (REDUCE-IT), and Long-Term Outcomes Study to Assess Statin Residual Risk With Epanova in High Cardiovascular Risk Patients With Hypertriglyceridemia (STRENGTH) trials, residual inflammatory risk was significantly associated with incident MACE (adjusted HR 1.31, 95% CI 1.20-1.43), cardiovascular mortality (adjusted HR 2.68, 95% CI 2.22-3.23), and all-cause mortality (adjusted HR 2.42, 95% CI 2.12-2.77), whereas residual cholesterol risk was not associated with MACE across LDL-C quartiles in the same cohort [5]. Accordingly, the 2025 ACC (American College of Cardiology) Scientific Statement on Inflammation and Cardiovascular Disease recognized hs-CRP as a predictor of recurrent vascular events comparable to LDL-C and endorsed its use for risk stratification in secondary prevention [15]. Anti-inflammatory trials extend this association beyond prognosis toward causality: the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) showed that canakinumab, a monoclonal antibody targeting interleukin-1β, reduced cardiovascular events in patients selected for hs-CRP ⩾2 mg/L independently of any LDL-C change, and the Colchicine Cardiovascular Outcomes Trial (COLCOT) and Low-Dose Colchicine 2 (LoDoCo2) trial subsequently showed that low-dose colchicine reduced MACE by 23% and 31%, respectively [16-18]. Low-dose colchicine has since been endorsed as an adjunctive option for chronic coronary disease in current guidelines and is available as a low-cost generic, making residual inflammatory risk a directly treatable target rather than merely a prognostic marker [8].

Despite these data, no systematic review or meta-analysis has comprehensively synthesized the prevalence or quantified the prognostic impact of residual inflammatory risk on MACE, cardiovascular mortality, and all-cause mortality specifically in patients with established ASCVD who have achieved LDL-C <70 mg/dL. The largest existing synthesis pooled randomized-trial participants irrespective of lipid status [5], leaving the independent prognostic significance of hs-CRP in the real-world, LDL-at-target secondary-prevention population, the group clinicians actually face, unquantified; cohorts enrolled irrespective of LDL-C conflate residual cholesterol and residual inflammatory risk, and heterogeneity in hs-CRP thresholds, LDL-C targets, background lipid-lowering regimens, and underlying ASCVD populations has further precluded definitive estimates [5,13]. Current guidelines also do not yet incorporate hs-CRP into routine secondary-prevention treatment decisions [15]. We therefore undertook a systematic review and meta-analysis anchored to a uniform hs-CRP threshold ⩾2 mg/L and an LDL-C target <70 mg/dL, with two prespecified objectives: (1) to estimate the pooled prevalence of residual inflammatory risk, thereby quantifying the proportion of optimally treated ASCVD patients who remain candidates for anti-inflammatory therapy, and (2) to quantify its association with MACE, cardiovascular mortality, and all-cause mortality. By isolating this dual-biomarker phenotype, the review aims to provide population-level estimates to inform risk stratification and guide evidence-based anti-inflammatory therapeutic strategies in lipid-controlled ASCVD.

Review

Materials and methods

Study Design and Registration

This systematic review and meta-analysis was conducted in accordance with Cochrane guidance, reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [19], and registered in PROSPERO (CRD420261381858).

Eligibility Criteria

Eligible studies enrolled adults with established ASCVD (secondary-prevention populations) and evaluated residual inflammatory risk, defined as high-sensitivity C-reactive protein (hs-CRP) ⩾2 mg/L, among patients with LDL-C at target, with an extractable stratum of LDL-C <70 mg/dL (<1.8 mmol/L). Studies had to include a comparator with hs-CRP <2 mg/L within the same LDL-C stratum; report at least one outcome of interest (MACE, individual MACE components, cardiovascular death, all-cause mortality, or the prevalence of hs-CRP ⩾2 mg/L); and be observational cohorts or prespecified secondary analyses of randomized controlled trials (RCTs). hs-CRP had to be measured outside the acute-phase window, before the event, ⩾48 h after percutaneous coronary intervention (PCI), or as a delayed/persistent measurement. We excluded post hoc RCT analyses, primary-prevention or mixed cohorts without isolated ASCVD data, studies using

conventional rather than high-sensitivity CRP, and studies lacking an extractable LDL-C <70 mg/dL plus hs-CRP ⩾2 mg/L stratum.

Search Strategy and Study Selection

We searched PubMed, Cochrane CENTRAL (Cochrane Central Register of Controlled Trials), and EMBASE from inception to May 2026 without language restrictions, combining Boolean concept blocks for hs-CRP/inflammation, LDL-C/lipid control, residual risk, MACE/mortality, and ASCVD (full strategy in the Appendices). Reference lists of included studies and previous reviews, grey literature, and trial registries were hand-searched for additional or unpublished studies. Two reviewers independently screened titles, abstracts, and full texts, resolving disagreements by consensus.

Data Extraction

Two reviewers independently extracted data using a standardized form, capturing study design, source cohort, population characteristics, ASCVD subtype, LDL-C and hs-CRP thresholds, hs-CRP timing and assay, stratum sample sizes, follow-up duration, outcome definitions, event counts, effect estimates with 95% confidence intervals (CIs), and model covariates. When multiple reports shared a source cohort, data were extracted once per outcome to avoid double-counting.

Outcomes and Subgroup Analyses

The primary outcome was MACE as defined in each study. Secondary outcomes were individual MACE components, cardiovascular death, all-cause mortality, and the prevalence of residual inflammatory risk (hs-CRP ⩾2 mg/L among patients with LDL-C <70 mg/dL/<1.8 mmol/L). Adjusted hazard ratios (HRs) with 95% CIs were preferentially extracted for time-to-event outcomes. Prespecified subgroup analyses examined LDL-C threshold (<70 vs. more intensive targets such as <55 mg/dL), population type (PCI, registry, RCT secondary analysis, stroke, and MINOCA (myocardial infarction with nonobstructive coronary arteries) cohorts), and follow-up duration, with subgroup differences tested by χ^2 when sufficient studies were available. Sensitivity analyses excluded high-risk-of-bias studies, applied leave-one-out analysis, and ensured each source cohort contributed once per outcome.

Studies Included Versus Studies Contributing to Synthesis

Eligibility for the review depended solely on the selection criteria and reporting of a prespecified outcome, independent of whether data could be quantitatively pooled; eligible studies were therefore retained even when they did not contribute to a given meta-analysis. Of the seven included studies, five (Bay et al. (2025) [20], Di Muro et al. (2026) [21], Mazhar et al. (2026) [22], Zhang et al. (2024) [23], and Gao et al. (2025) [24]) provided directly extractable adjusted HRs for the residual-inflammatory-risk versus no-inflammatory-risk comparison and contributed to the pooled analyses. Two eligible studies were not pooled: Bohula et al. (2015) [25] (IMPROVE-IT) reported HRs only against a common "neither-target" referent, precluding recovery of a valid comparison HR and CI, whereas Zhang et al. (2022) [26] (CNSR-III, Third China National Stroke Registry) reported recurrent ischemic stroke in a dedicated stroke cohort, with a different design and endpoint from the incident stroke pooled from PCI cohorts. All seven studies informed the review (study-selection flow, characteristics tables, risk-of-bias assessment, narrative synthesis, and GRADE judgments). Bohula et al. (2015) [25] additionally contributed target-achievement and leave-one-out findings, and Zhang et al. (2022) [26] contributed its recurrent-stroke association (adjusted HR 1.50, 95% CI 1.07-2.12) to the narrative synthesis. Reporting included and contributing study counts separately follows PRISMA and avoids selection bias from excluding studies based on data availability or results.

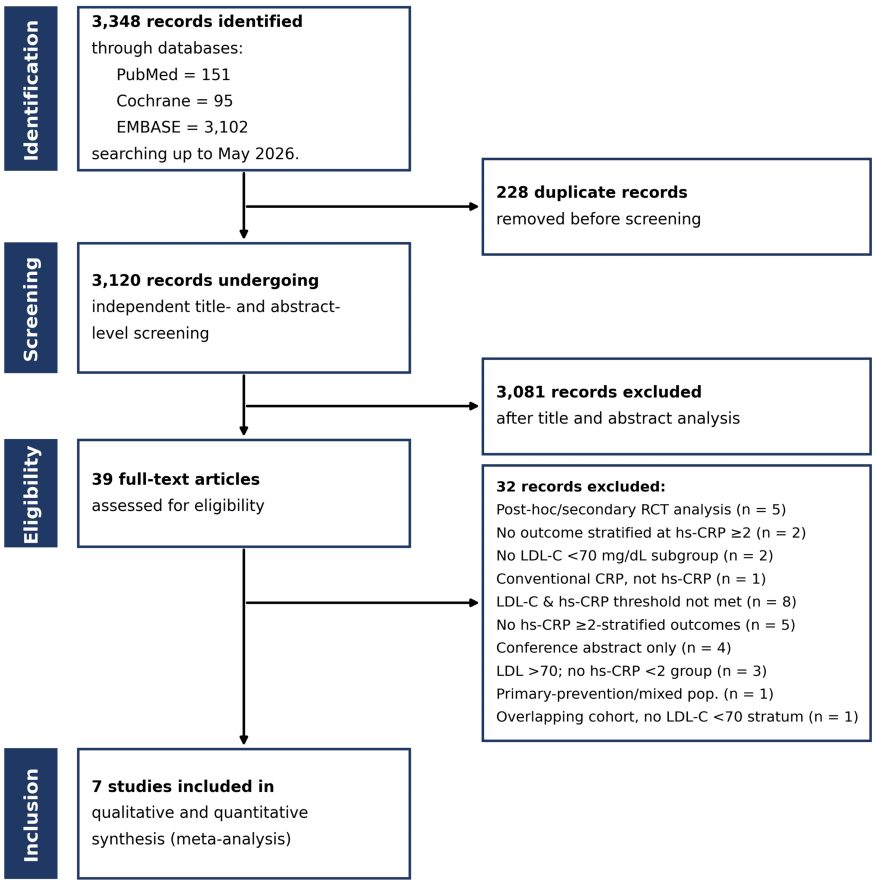

FIGURE 1: PRISMA flow diagram of the study selection

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: randomized controlled trial; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; CRP: C-reactive protein.

Risk of Bias and Certainty of Evidence

Two reviewers independently assessed risk of bias using the Quality In Prognosis Studies (QUIPS) tool [27], appropriate for the prognostic question of hs-CRP-defined residual inflammatory risk, evaluating the six QUIPS domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting, with particular attention to confounder adjustment, hs-CRP assay and timing, and LDL-C/hs-CRP stratum definitions. Disagreements were resolved by consensus. The certainty of evidence for each outcome was rated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [28] and summarized in a summary-of-findings table.

Statistical Analysis

Analyses used R with the meta and metafor packages. Adjusted HRs with 95% CIs were pooled on the log scale by the generic inverse-variance method; unadjusted estimates, used only when adjusted ones were unavailable, were considered separately. The prevalence of residual inflammatory risk was pooled as proportions using a variance-stabilizing transformation. Random-effects models with restricted maximum likelihood estimation were applied throughout, given anticipated clinical and methodological heterogeneity; heterogeneity was assessed with Cochran's Q, I^2, and τ^2. A two-sided $p < 0.05$ was considered statistically significant.

Assessment of Publication Bias

Because each meta-analysis included fewer than 10 studies, funnel-plot asymmetry and Egger's test were not performed, as these methods are underpowered and unreliable with few studies (Cochrane Handbook); small-study effects and publication bias were instead considered qualitatively and acknowledged as a limitation. Several factors suggest limited distortion: several cohorts were derived from large registry- or

population-based sources (e.g., Stockholm Creatinine Measurements (SCREAM), CNSR-III) rather than small, selectively published studies, and the prognostic association was directionally consistent across cohorts of differing size, design, and geography. Nonetheless, the influence of unpublished or selectively reported data cannot be formally excluded, and pooled estimates should be interpreted with this limitation in mind.

Results

Study Selection

The systematic search identified 3,348 records (PubMed, n = 151; Cochrane Library, n = 95; EMBASE, n = 3,102) published up to May 2026. After removal of 228 duplicates, 3,120 records underwent independent title and abstract screening, of which 3,081 were excluded. Thirty-nine full-text articles were assessed for eligibility, and 32 were excluded, most commonly because outcomes were not stratified at the high-sensitivity C-reactive protein (hs-CRP) ⩾2 mg/L threshold, the combined LDL-C <70 mg/dL and hs-CRP criteria were not jointly met, no hs-CRP ⩾2 mg/L-stratified outcomes were reported, or the report was a post hoc or secondary randomized-trial analysis (full reasons in Figure *1*). Seven studies satisfied all eligibility criteria and were included in the qualitative and quantitative synthesis. Five cohort studies (Bay et al. (2025) [20], Di Muro et al. (2026) [21], Mazhar et al. (2026) [22] (SCREAM), Zhang et al. (2024) [23], and Gao et al. (2025) [24]) provided adjusted time-to-event estimates and contributed to the meta-analyses; two further eligible studies, Bohula et al. (2015) [25] (a prespecified analysis of IMPROVE-IT) and Zhang et al. (2022) [26] (CNSR-III registry), were included but were not poolable and are summarized narratively.

Characteristics of Included Studies

The included studies enrolled patients with established ASCVD managed to an LDL-C target of <70 mg/dL and examined residual inflammatory risk, defined by an hs-CRP concentration ⩾2 mg/L. Populations spanned coronary artery disease undergoing percutaneous coronary intervention (PCI), routine-care ASCVD cohorts, in-stent restenosis, stabilized post-acute coronary syndrome, MINOCA, and ischemic stroke or transient ischemic attack (TIA). Most studies were prospective or retrospective cohort studies, with one prespecified randomized trial analysis (IMPROVE-IT). Median or mean follow-up ranged from about one to six years (Table *1*).

Characteristic	Bay, 2025 [20]	Di Muro, 2026 [21][a]	Mazhar, 2026 [22][b]	Zhang, 2024 [23]	Bohula, 2015 [25][c]	Zhang, 2022 [26][d]	Gao, 2025 [24]
Study design	Prospective cohort (PCI registry)	Retrospective cohort (PCI)	Retrospective cohort (SCREAM)	Retrospective cohort (single center)	Prespecified RCT analysis (IMPROVE-IT)	Prospective registry (CNSR-III)	Prospective cohort (single center)
Country/setting	USA (single center)	USA (single center)	Sweden (Stockholm)	China (Fuwai, Beijing)	Multinational	China (multicentre)	China (Fuwai, Beijing)
Enrolment period	2012-2022	2012-2022	2007-2021	2017-2018	2005-2010	2015-2018	2015-2019
Follow-up period	366 days (median)	1 year	4.5 years (median)	36 months (median)	~6 years (trial)	1 year	41.7 months (median)
Population	CAD undergoing PCI (statin-treated)	CAD/PCI, LDL-C <70 (well-controlled)	ASCVD (routine care)	CAD/PCI for in-stent restenosis	Stabilized post-ACS	Ischaemic stroke/TIA	MINOCA
Total patients, N	15,494	9,446	39,638	2,079	15,179	10,499	1,062

TABLE 1: Design and characteristics of the included studies

Total patients, N is the size of the full source cohort. Studies contributing to the pooled analyses: [20-24].

[a]Di Muro et al. (2026) [21]: four-group design stratified by triglycerides × hs-CRP; N is the full cohort.

[b]Mazhar et al. (2026) [22]: SCREAM cohort; only the LDL-C <70 mg/dL strata are used in this analysis, and this is the sole SCREAM source.

[c]Bohula et al. (2015) [25]: prespecified analysis of IMPROVE-IT; groups defined by 1-month achieved LDL-C and hs-CRP targets after randomization. Not included in the pooled analyses because hazard ratios were reported only against a common "neither-target" referent.

[d]Zhang et al. (2022) [26]: CNSR-III; baseline data available only for the entire cohort (all LDL-C levels). Not included in the pooled analyses because it reported recurrent ischemic stroke in a dedicated stroke cohort, a different design and endpoint from the incident stroke pooled from PCI cohorts.

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CNSR-III, Third China National Stroke Registry; hs-CRP, high-sensitivity C-reactive protein; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol; MINOCA, myocardial infarction with non-obstructive coronary arteries; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SCREAM, Stockholm Creatinine Measurements project; TIA, transient ischemic attack.

Crucially, the analytic contrast was internally consistent across studies: median or mean LDL-C was <70 mg/dL in both inflammatory strata within each cohort, whereas hs-CRP differed markedly between the low-inflammation (<2 mg/L; typically, ≈0.7-0.9 mg/L) and high-inflammation (≥2 mg/L; typically, ≈3.8-5.1 mg/L) groups, confirming that the comparison isolated the residual inflammatory phenotype rather than residual cholesterol burden. Patients with residual inflammatory risk tended to have a higher body mass index and a greater burden of diabetes mellitus, chronic kidney disease, dialysis dependence, and peripheral and cerebrovascular disease, reflecting a higher baseline comorbidity burden that was addressed through multivariable adjustment in contributing studies (Table *2*).

Characteristics	Bay, 2025 [20]		Di Muro, 2026 [21]		Mazhar, 2026 [22][a]		Zhang, 2024 [23]		Bohula, 2015 [25]		Zhang, 2022 [26][b]		Gao, 2025 [24]	
	hs-CRP <2 mg/L	hs-CRP ≥2 mg/L	hs-CRP <2 mg/L	hs-CRP ≥2 mg/L	hs-CRP <2 mg/L	hs-CRP ≥2 mg/L	hs-CRP <2 mg/L	hs-CRP ≥2 mg/L	hs-CRP <2 mg/L	hs-CRP ≥2 mg/L	hs-CRP <2 mg/L	hs-CRP ≥2 mg/L	hs-CRP <2 mg/L	hs-CRP ≥2 mg/L
Sample size and demographics														
n	4621	2624	5339[c]	3009[c]	5,351	4,751	464	187	5,995	5,045	5,598	4,901	212	164
Age, years	66.9 ± 10.6	67.1 ± 10.9	67.5 ± 10.7	68.3 ± 11.2	68 ± 11	70 ± 11	61.0 ± 10.0	61.2 ± 10.0	64 ± 10	64 ± 10	61 (53-68)	64 (56-72)	56.5 ± 11.7	55.6 ± 11.7
BMI, kg/m²	27.5 ± 4.5	30.0 ± 6.0	27.4 ± 4.5	29.6 ± 5.9	NR	NR	25.4 ± 2.7	25.8 ± 3.2	28 ± 5	30 ± 6	24.3 (22.5-26.3)	24.6 (22.7-26.8)	25.3 ± 3.7	24.8 ± 3.7

Female sex	905 (19.6%)	725 (27.6%)	1073 (20.1%)	871 (29.0%)	1412 (26%)	1534 (32%)	81 (17.5%)	41 (21.9%)	20%	26%	1,698 (30.3%)	1,626 (33.2%)	46 (21.7%)	46 (28.1%)
Medical history														
Current smoker	399 (8.6%)	308 (11.7%)	428 (8.0%)	325 (10.8%)	NR	NR	298 (64.2%)	115 (61.5%)	27%	36%	NR	NR	NR	NR
Diabetes mellitus	2319 (50.2%)	1503 (57.3%)	2511 (47.0%)	1608 (53.4%)	1679 (31%)	2023 (43%)	211 (45.5%)	89 (47.6%)	24%	32%	1,241 (22.2%)	1,270 (25.9%)	42 (19.8%)	26 (15.8%)
Insulin dependent	657 (28.3%)	590 (39.3%)	720 (28.7%)	624 (38.8%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hypertension	4392 (95.1%)	2528 (96.3%)	5051 (94.6%)	2886 (95.9%)	3925 (73%)	3862 (81%)	293 (63.3%)	136 (72.7%)	57%	64%	3,423 (61.2%)	3,183 (65.0%)	119 (56.1%)	87 (53.0%)
Dyslipidaemia/hyperlipidaemia	NR	NR	5130 (96.1%)	2841 (94.4%)	4717 (88%)	3966 (83%)	NR	NR	NR	NR	NR	NR	129 (60.8%)	91 (55.4%)
Peripheral artery disease	333 (7.2%)	298 (11.4%)	376 (7.0%)	360 (12.0%)	360 (6.7%)	618 (13%)	7 (1.5%)	8 (4.3%)	3.50%	6.80%	NR	NR	NR	NR
Cerebrovascular disease	421 (9.1%)	321 (12.2%)	487 (9.1%)	371 (12.3%)	1448 (27%)	1498 (32%)	4 (0.9%)	1 (0.5%)	5.60%	7.40%	1,554 (27.8%)[d]	1,590 (32.4%)[d]	NR	NR
Atrial fibrillation	342 (7.4%)	294 (11.2%)	393 (7.4%)	388 (12.9%)	927 (17%)	1216 (26%)	NR	NR	NR	NR	NR	NR	NR	NR
Chronic kidney disease	1099 (23.8%)	913 (34.8%)	1213 (22.7%)	1012 (33.7%)	932 (17%)[e]	1316 (28%)[e]	2 (0.4%)	3 (1.6%)	NR	NR	NR	NR	NR	NR
Dialysis	65 (1.4%)	182 (6.9%)	67 (1.3%)	176 (5.8%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Prior PCI	2547 (55.1%)	1435 (54.7%)	3191 (59.8%)	1710 (56.8%)	2510 (47%)	1783 (38%)	ISR cohort	ISR cohort	75%[f]	70%[f]	NR	NR	NR	NR
Prior MI	1255 (27.2%)	765 (29.2%)	1375 (25.8%)	816 (27.1%)	2391 (45%)	1917 (40%)	NR	NR	18%	19%	NR	NR	13 (6.1%)	14 (8.5%)
Family history of CAD	959 (20.8%)	508 (19.4%)	1098 (20.6%)	531 (17.6%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Medications														
Statins	4621 (100%)	2624 (100%)	100% (incl.)	100% (incl.)	4380 (82%)[g]	3616 (76%)[g]	446 (96.1%)	176 (94.1%)	100%[f]	100%[f]	5,230 (93.5%)[h]	4,479 (91.8%)[h]	204 (96.2%)	159 (96.9%)
PCSK9 inhibitors	14 (0.3%)	6 (0.2%)	NR	NR	incl. in LLT	incl. in LLT	NR	NR	0	0	NR	NR	NR	NR
DAPT	4379 (94.8%)	2425 (92.5%)	NR	NR	2128 (40%)	1592 (34%)	448 (96.6%)	176 (94.1%)	NR	NR	NR	NR	195 (91.9%)	151 (92.0%)
Beta-blocker	3759 (81.4%)	2157 (82.3%)	NR	NR	3715 (69%)	3411 (72%)	391 (84.3%)	163 (87.2%)	NR	NR	NR	NR	146 (68.9%)	116 (70.7%)
RAAS inhibitors	3081 (66.7%)	1758 (70.0%)	NR	NR	3828 (72%)	3428 (72%)	258 (55.6%)	122 (65.2%)	NR	NR	NR	NR	144 (67.9%)	103 (60.8%)
Laboratory values														
LDL-C, mg/dL	54.2 (46.0-62.2)	55.6 (46.6-62.8)	<70 (all)	<70 (all)	55 (46-62)[i]	56 (46-62)[i]	56.1 ± 9.9	56.0 ± 9.7	48 ± 13[f]	49 ± 13[f]	88 (65-113)[j]	92 (68-118)[j]	<70	<70
hs-CRP, mg/L	0.8 (0.4-1.2)	3.8 (2.7-5.7)	0.9 ± 0.5	4.4 ± 2.1	0.9 (0.9-1.0)	4.0 (2.7-7.3)	0.65	4.12	0.9 (0.6-1.3)[f]	4.2 (2.8-7.9)[f]	0.86 (0.55-1.25)	5.10 (3.06-11.21)	<2	≥2
Total cholesterol, mg/dL	110 (99-121)	112 (100-123)	109.4 ± 16.5	109.9 ± 15.9	NR	NR	115.9 ± 21.4	118.3 ± 36.0	162 ± 26	162 ± 26	NR	NR	119.5 ± 18.6[k]	119.5 ± 19.3[k]

Triglycerides, mg/dL	73 (51-106)	85 (60-122)	73.6 ± 30.7	80.4 ± 30.7	NR	NR	103.7	121.4	115 (82-165)	128 (90-183)	122 (91-167)[j]	120 (91-165)[j]	101.9 (79.7-156.8)[k]	110.7 (83.3-154.1)[k]
HDL-C, mg/dL	38 (31-46)	36 (30-44)	40.5 ± 12.2	39.0 ± 11.7	NR	NR	42.5 ± 11.6	38.4 ± 11.4	43 ± 13	40 ± 13	42 (36-51)[j]	41 (34-48)[j]	42.9 ± 12.4[k]	38.7 ± 11.6[k]
HbA1c, %	6.8 (6.1-7.8)	7.0 (6.2-8.2)	NR	NR	NR	NR	6.5 ± 1.1	6.7 ± 1.2	NR	NR	NR	NR	NR	NR
eGFR, mL/min	76.8 (61.6-92.1)	70.7 (51.7-88.4)	NR	NR	≥60 in 83%	≥60 in 72%	NR	NR	82 ± 25[f]	85 ± 30[f]	NR	NR	NR	NR
Serum creatinine, mg/dL	NR	NR	1.3 ± 1.41	1.5 ± 1.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

TABLE 2: Baseline demographics, medical history, medications, and laboratory values of patients with LDL-C <70 mg/dL, stratified by hs-CRP

Restricted to LDL-C <70 mg/dL unless indicated; hs-CRP <2 vs. ≥2 mg/L defines no-RIR vs. RIR strata. Values are n (%), mean ± SD, or median (IQR).

[a]SCREAM cohort; LDL-C <70 mg/dL strata only; BMI, smoking, lipids other than LDL-C, and HbA1c not captured.

[b]Entire stroke/TIA cohort, all LDL-C levels (median ≈88–92 mg/dL); LDL-C <70 mg/dL subgroup not published; interpret with caution.

[c]Triglyceride <150 mg/dL strata of a triglyceride × hs-CRP four-group design.

[d]Prior cardio-/cerebrovascular disease.

[e]eGFR <60 mL/min/1.73 m².

[f]IMPROVE-IT: groups defined by 1-month achieved LDL-C and hs-CRP; all on simvastatin ± ezetimibe; prior PCI and lipids at index ACS; eGFR by Cockcroft–Gault; percentages only.

[g]Any lipid-lowering therapy.

[h]Lipid-lowering drugs (mostly statins).

[i]Converted from mmol/L (1.43 and 1.45 mmol/L).

[j]Converted from mmol/L.

[k]Converted from mmol/L (cholesterol × 38.67; triglycerides × 88.57).

ACS: acute coronary syndrome; BMI: body mass index; CAD: coronary artery disease; DAPT: dual antiplatelet therapy; eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin; HDL-C: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; IQR: interquartile range; ISR: in-stent restenosis; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction; NR: not reported; PCI: percutaneous coronary intervention; PCSK9: proprotein convertase subtilisin/kexin type 9; RAAS: renin–angiotensin–aldosterone system; RIR: residual inflammatory risk; SD: standard deviation; TIA: transient ischemic attack.

Primary Outcome: Major Adverse Cardiovascular Events

Five studies (26,722 patients; 10,735 with and 15,987 without residual inflammatory risk) reported adjusted hazard ratios (HRs) for MACE. Residual inflammatory risk was associated with a significantly higher hazard of MACE (pooled adjusted HR 1.48, 95% CI 1.16-1.88; random-effects REML (restricted maximum likelihood) model with Knapp-Hartung confidence intervals; Figure *2*). The direction of effect was consistent across all five cohorts: Bay et al. (2025) [20] (HR 1.78, 95% CI 1.36-2.33), Di Muro et al. (2026) [21] (1.82, 1.42-2.33), Gao et al. (2025) [24] (1.51, 1.16-1.96), Zhang et al. (2024) [23] (1.34, 1.03-1.75), and Mazhar et al. (2026) [22] (1.18, 1.05-1.33), although the magnitude varied, producing substantial statistical heterogeneity (I^2 = 69%, τ^2 = 0.028, Q p = 0.004). The 95% prediction interval (0.88-2.48) crossed unity, indicating that in a future setting, the effect could plausibly be null even though the pooled estimate is clearly positive. In absolute terms, applying the pooled HR to an assumed baseline risk of 50 per 1,000 corresponded to 73 per 1,000 (58-92). Crude event rates were concordant (9.1% vs. 5.0%; rate ratio 1.82; Tables *3*, *4*).

Outcome/Study	Follow-up	RIR (hs-CRP ≥2), n/N (%)	No inflammatory risk (hs-CRP <2), n/N (%)	Crude rate ratio

MACE composite				
Bay et al., 2025 [20]	~1 yr	82/2624 (3.1%)	69/4621 (1.5%)	2.09
Di Muro et al., 2026 [21]	~1 yr	153/3009 (5.1%)	133/5339 (2.5%)	2.04
Mazhar et al., 2026 [22]	~4.5 yr	655/4751 (13.8%)	486/5351 (9.1%)	1.52
Zhang et al., 2024 [23]	~3 yr	50/187 (26.7%)	90/464 (19.4%)	1.38
Gao et al., 2025 [24]	~3.5 yr	37/164 (22.6%)	23/212 (10.8%)	2.08
Crude pooled		977/10735 (9.1%)	801/15987 (5.0%)	1.82
All-cause mortality				
Bay et al., 2025 [20]	~1 yr	67/2624 (2.6%)	42/4621 (0.9%)	2.81
Di Muro et al., 2026 [21]	~1 yr	91/3009 (3.0%)	53/5339 (1.0%)	3.05
Mazhar et al., 2026 [22]	~4.5 yr	1228/4751 (25.8%)	649/5351 (12.1%)	2.13
Zhang et al., 2024 [23]	~3 yr	9/187 (4.8%)	10/464 (2.2%)	2.23
Gao et al., 2025 [24]	~3.5 yr	6/164 (3.7%)	1/212 (0.5%)	7.76
Crude pooled		1401/10735 (13.1%)	755/15987 (4.7%)	2.76
Spontaneous/nonfatal MI				
Bay et al., 2025 [20]	~1 yr	48/2624 (1.8%)	58/4621 (1.3%)	1.46
Di Muro et al., 2026 [21]	~1 yr	66/3009 (2.2%)	76/5339 (1.4%)	1.54
Zhang et al., 2024 [23]	~3 yr	11/187 (5.9%)	7/464 (1.5%)	3.9
Gao et al., 2025 [24]	~3.5 yr	12/164 (7.3%)	4/212 (1.9%)	3.88
Crude pooled		137/5984 (2.3%)	145/10636 (1.4%)	1.68
Repeat revascularization (any)				
Bay et al., 2025 [20]	~1 yr	253/2624 (9.6%)	311/4621 (6.7%)	1.43
Di Muro et al., 2026 [21]	~1 yr	190/3009 (6.3%)	325/5339 (6.1%)	1.04
Zhang et al., 2024 [23]	~3 yr	41/187 (21.9%)	80/464 (17.2%)	1.27
Gao et al., 2025 [24]	~3.5 yr	9/164 (5.5%)	4/212 (1.9%)	2.91
Crude pooled		493/5984 (8.2%)	720/10636 (6.8%)	1.22
Stroke (incident)				
Bay et al., 2025 [20]	~1 yr	9/2624 (0.3%)	13/4621 (0.3%)	1.22
Di Muro et al., 2026 [21]	~1 yr	12/3009 (0.4%)	14/5339 (0.3%)	1.52
Zhang et al., 2024 [23]	~3 yr	1/187 (0.5%)	4/464 (0.9%)	0.62
Gao et al., 2025 [24]	~3.5 yr	3/164 (1.8%)	1/212 (0.5%)	3.88
Crude pooled		25/5984 (0.4%)	32/10636 (0.3%)	1.39

TABLE 3: Outcome event rates (prevalence) by residual inflammatory risk status

Values are author-reported events/N (crude %) within each hs-CRP stratum; all patients had LDL-C <70 mg/dL.

RIR was defined as hs-CRP ≥2 mg/L, whereas no inflammatory risk was defined as hs-CRP <2 mg/L.

Crude rate ratio = RIR % ÷ no-IR % (unadjusted; for orientation only; use adjusted hazard ratios for inference).

Crude pooled = Σevents ÷ ΣN across studies; dominated by the largest cohort and mixes differing follow-up durations (1–4.5 years), so it is descriptive only.

Bay et al. [20] counts are 1-year Kaplan–Meier-derived. Gao et al. [24] (death, MI, revascularization, stroke) and Zhang et al. [23] (stroke) are count-only outcomes. Bohula et al. [25] and Zhang et al. [26] are not included (no RIR-vs.-no-IR event split in the LDL-C <70 mg/dL stratum).

N: number of patients; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; RIR: residual inflammatory risk; IR: inflammatory risk; MI: myocardial infarction.

Outcome	Reference	Studies (k)	Pooled HR (95% CI)	I^2	τ^2	95% prediction interval
MACE (CV death, MI, stroke)	[20-24]	5	1.48 (1.16-1.88)	69%	0.028	0.88-2.48
All-cause mortality	[20-23]	4	2.13 (1.27-3.57)	78%	0.098	0.69-6.53
Spontaneous/nonfatal MI	[20,21,23]	3	1.59 (0.44-5.80)	67%	0.120	0.22-11.44
Repeat revascularization (any)	[20,21,23]	3	1.02 (0.83-1.25)	0%	0.000	—
Stroke (incident)	[20,21]	2	1.26 (0.59-2.69)	0%	0.000	n/a (k=2)

TABLE 4: Pooled meta-analysis of adjusted hazard ratios (RIR vs no inflammatory risk)

Random-effects model (restricted maximum likelihood (REML) estimator) with Knapp-Hartung confidence intervals; HR = hazard ratio; I^2 = proportion of variability attributable to heterogeneity; τ^2 = between-study variance; prediction intervals reported where ≥3 studies contributed. Bohula et al. [25] and Zhang et al. [26] were not pooled (synthesized narratively).

k: number of studies; HR: hazard ratio; CI: confidence interval; MACE: major adverse cardiovascular events; CV: cardiovascular; MI: myocardial infarction; RIR: residual inflammatory risk; REML: restricted maximum likelihood; I^2: proportion of variability attributable to heterogeneity; τ^2: between-study variance; n/a: not applicable.

Secondary Outcomes

All-cause mortality: Four studies (26,346 patients; 10,571 with and 15,775 without residual inflammatory risk) contributed adjusted estimates for all-cause mortality (Gao et al. (2025) [24] did not provide an adjusted mortality estimate). Residual inflammatory risk was associated with approximately a doubling of the hazard of death (pooled adjusted HR 2.13, 95% CI 1.27-3.57; Figure *3*), with study-level HRs ranging from 1.47 to 2.81. Heterogeneity was substantial (I^2 = 78%, τ^2 = 0.098), and the 95% prediction interval was wide and crossed unity (0.69-6.53). Modeled on a baseline of 48 per 1,000, this corresponded to 99 per 1,000 (61-161); crude mortality was 13.1% vs. 4.7% (rate ratio 2.76).

Spontaneous or nonfatal myocardial infarction: Three studies could be pooled. The point estimate favored higher risk with residual inflammatory risk but was imprecise and not statistically significant (pooled adjusted HR 1.59, 95% CI 0.44-5.80; I^2 = 67%, τ^2 = 0.120; prediction interval 0.22-11.44; Figure *4*). Crude rates were 2.3% vs. 1.4% (rate ratio 1.68).

Repeat revascularization: Three studies reported adjusted estimates for repeat revascularization (any definition). No statistically significant association was detected (pooled adjusted HR 1.02, 95% CI 0.83-1.25), with no statistical heterogeneity (I^2 = 0%, τ^2 = 0; Figure *5*), despite a modestly higher crude rate in the residual-inflammatory-risk group (8.2% vs. 6.8%; rate ratio 1.22).

Incident stroke: Two studies contributed adjusted estimates for incident stroke. The pooled estimate was elevated but imprecise and not statistically significant (pooled adjusted HR 1.26, 95% CI 0.59-2.69; I^2 = 0%; Figure *6*); with only two contributing studies, a prediction interval was not estimable. Crude rates were 0.4% vs. 0.3% (rate ratio 1.39). Figure *7* provides an overview of pooled HRs across all outcomes.

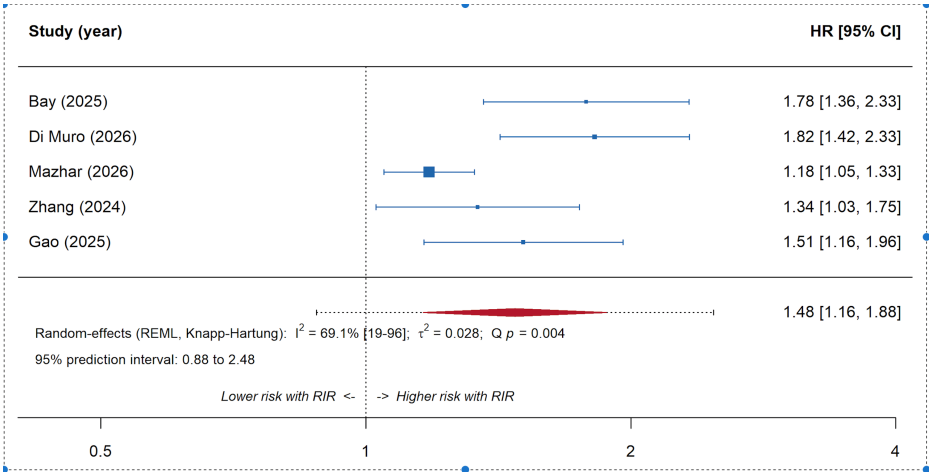

FIGURE 2: Forest plot of the association between residual inflammatory risk and major adverse cardiovascular events

Pooled hazard ratio for MACE comparing patients with hs-CRP-defined residual inflammatory risk (RIR) versus those without RIR despite LDL-C control. Studies included were Bay et al. [20], Di Muro et al. [21], Mazhar et al. [22], Zhang et al. [23], and Gao et al. [24]. Blue squares represent study-specific hazard ratios and are sized in proportion to each study's weight. Horizontal lines indicate the corresponding 95% confidence intervals. The red diamond represents the pooled hazard ratio from the random-effects model (REML with Knapp-Hartung adjustment), and its width indicates the 95% confidence interval. The dotted line through the diamond indicates the 95% prediction interval. The vertical dotted line marks the line of no effect (HR = 1).

MACE: major adverse cardiovascular events; hs-CRP: high-sensitivity C-reactive protein; RIR: residual inflammatory risk; LDL-C: low-density lipoprotein cholesterol; REML: restricted maximum likelihood; HR: hazard ratio.

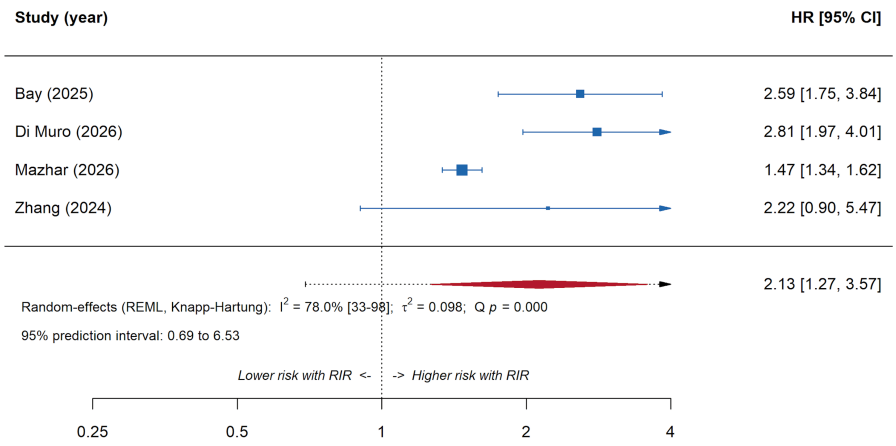

FIGURE 3: Forest plot of the association between residual inflammatory risk and all-cause mortality

Pooled hazard ratio for all-cause mortality comparing patients with versus without hs-CRP-defined RIR. Studies: Bay et al. [20], Di Muro et al. [21], Mazhar et al. [22], and Zhang et al. [23]. Blue squares are study-specific hazard ratios, sized in proportion to each study's weight. Horizontal lines show their 95% confidence intervals. Arrows indicate that the intervals extend beyond the plotted axis. The red diamond is the pooled hazard ratio from the random-effects model (REML with Knapp-Hartung adjustment), and the dotted line through it is the 95% prediction interval. The vertical dotted line marks HR = 1.

hs-CRP: high-sensitivity C-reactive protein; RIR: residual inflammatory risk; REML: restricted maximum likelihood; HR: hazard ratio.

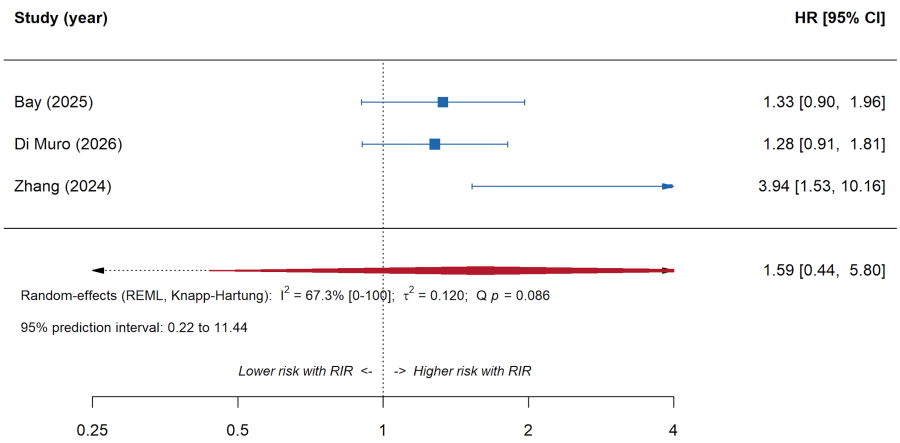

FIGURE 4: Forest plot of the association between residual inflammatory risk and spontaneous or nonfatal myocardial infarction

Pooled hazard ratio for spontaneous/nonfatal MI comparing patients with versus without hs-CRP-defined RIR. Studies: Bay et al. [20], Di Muro et al. [21], and Zhang et al. [23]. Blue squares are study-specific hazard ratios, sized in proportion to each study's weight. Horizontal lines show their 95% confidence intervals. Arrows indicate that the intervals extend beyond the plotted axis. The red diamond is the pooled hazard ratio from the random-effects model (REML with Knapp-Hartung adjustment), and the dotted line through it is the 95% prediction interval. The vertical dotted line marks HR = 1.

MI: myocardial infarction; hs-CRP: high-sensitivity C-reactive protein; RIR: residual inflammatory risk; REML: restricted maximum likelihood; HR: hazard ratio.

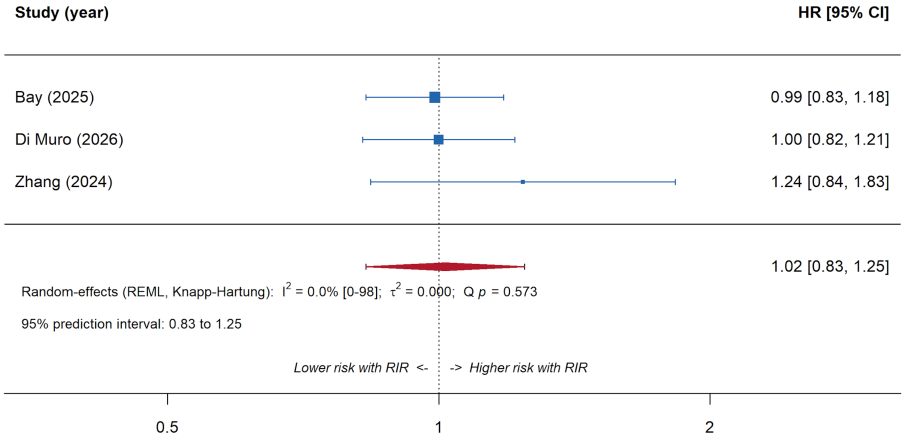

FIGURE 5: Forest plot of the association between residual inflammatory risk and repeat revascularization

Pooled hazard ratio for any repeat revascularization comparing patients with versus without hs-CRP-defined RIR. Studies: Bay et al. [20], Di Muro et al. [21], and Zhang et al. [23]. Blue squares are study-specific hazard ratios, sized in proportion to each study's weight. Horizontal lines show their 95% confidence intervals. The red diamond is the pooled hazard ratio from the random-effects model (REML with Knapp-Hartung adjustment). Its width is the 95% confidence interval, and the 95% prediction interval (0.83–1.25) matches it because the estimated heterogeneity was zero. The vertical dotted line marks HR = 1.

hs-CRP: high-sensitivity C-reactive protein; RIR: residual inflammatory risk; REML: restricted maximum likelihood; HR: hazard ratio.

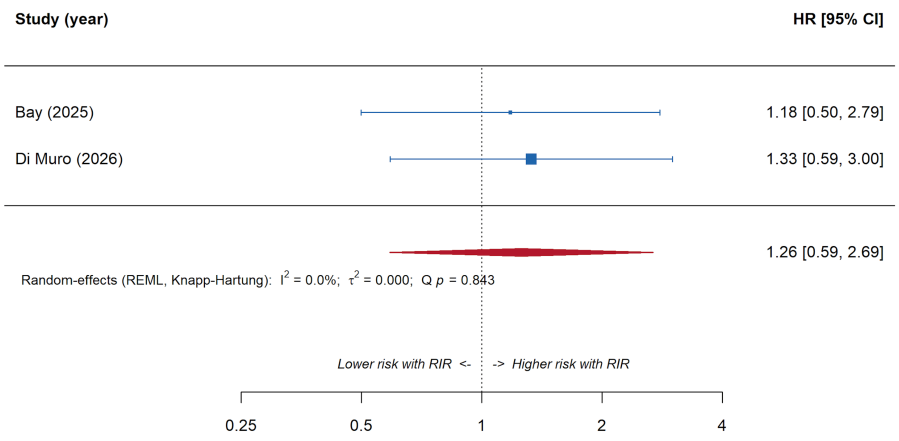

FIGURE 6: Forest plot of the association between residual inflammatory risk and incident stroke

Pooled hazard ratio for incident stroke comparing patients with versus without hs-CRP-defined RIR. Studies: Bay et al. [20] and Di Muro et al. [21]. Blue squares are study-specific hazard ratios, sized in proportion to each study's weight. Horizontal lines show their 95% confidence intervals. The red diamond is the pooled hazard ratio from the random-effects model (REML with Knapp-Hartung adjustment); its width is the 95% confidence interval. No prediction interval is shown because only two studies were pooled. Recurrent ischemic stroke from the CNSR-III stroke cohort, Zhang et al. [26], was not pooled because its design and endpoint differ. The vertical dotted line marks HR = 1.

hs-CRP: high-sensitivity C-reactive protein; RIR: residual inflammatory risk; REML: restricted maximum likelihood; CNSR-III: Third China National Stroke Registry; HR: hazard ratio.

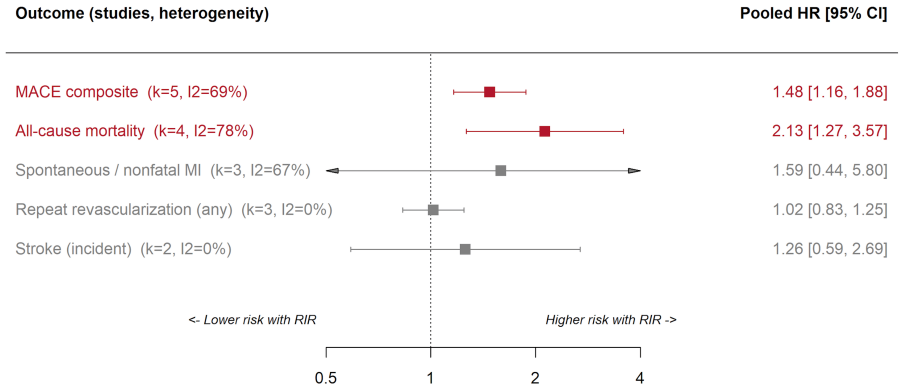

FIGURE 7: Summary forest plot of pooled hazard ratios for all outcomes associated with residual inflammatory risk

Pooled random-effects hazard ratios (REML with Knapp-Hartung adjustment) for each outcome, comparing patients with versus without hs-CRP-defined RIR. Data were pooled from Bay et al. [20], Di Muro et al. [21], Mazhar et al. [22], Zhang et al. [23], and Gao et al. [24]. Red squares represent outcomes with a statistically significant association (95% CI excluding 1): MACE and all-cause mortality. Gray squares represent outcomes with no statistically significant association: spontaneous/nonfatal MI, repeat revascularization, and stroke. Horizontal lines show 95% confidence intervals, and arrows indicate that the intervals extend beyond the plotted axis. k is the number of studies, and I² indicates between-study heterogeneity. The vertical dotted line marks HR = 1.

REML: restricted maximum likelihood; hs-CRP: high-sensitivity C-reactive protein; RIR: residual inflammatory risk; CI: confidence interval; MACE: major adverse cardiovascular events; MI: myocardial infarction; k: number of studies; I²: proportion of variability attributable to heterogeneity; HR: hazard ratio.

Eligible Studies Not Included in the Meta-Analysis

Two eligible studies were summarized narratively rather than pooled. Bohula et al. (2015) [25], in a prespecified analysis of IMPROVE-IT, reported that patients who achieved both LDL-C <70 mg/dL and hs-

CRP <2 mg/L had lower subsequent cardiovascular event rates than those who did not achieve the inflammatory target, directionally supporting the pooled findings; the study was not included in the meta-analysis because its dual-target framing and effect metric were not commensurate with the adjusted HRs from the cohort studies. Zhang et al. (2022) [26] (CNSR-III), in a study conducted in patients with ischemic stroke or TIA, also showed a directionally consistent association but measured hs-CRP in the acute phase (within 24 hours of the index event), which may reflect the acute inflammatory response rather than stable residual inflammation; the study was therefore judged to be at high risk of bias and excluded from pooling.

Risk of Bias Within Studies

Risk of bias was appraised with the Quality in Prognosis Studies (QUIPS) tool across six domains (Table *5*). All five meta-analyzed cohorts were rated moderate overall, and none achieved an overall low rating; the predominant concern was residual confounding, which was judged high in the most heavily weighted cohort (Mazhar et al. (2026) [22]/SCREAM). Among the nonpooled studies, Bohula et al. (2015) [25] was rated moderate overall, whereas Zhang et al. (2022) [26] was rated high overall owing to acute-phase prognostic-factor measurement. Consistent with QUIPS guidance, the two prespecified most important domains were prognostic-factor measurement and study confounding.

Study	Participation	Attrition	PF measurement	Outcome measurement	Confounding	Analysis and reporting	Overall
Bay et al., 2025 [20]	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Di Muro et al., 2026 [21]	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Mazhar et al., 2026 [22]	Low	Low	Low	Moderate	High	Moderate	Moderate
Zhang et al., 2024 [23]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Gao et al., 2025 [24]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Zhang et al., 2022 [26]	Low	Low	High	Moderate	Moderate	Moderate	High
Bohula et al., 2015 [25]	Moderate	Low	Moderate	Low	Moderate	Moderate	Moderate

TABLE 5: Risk-of-bias assessment (QUIPS)

Each domain was rated low, moderate, or high by consensus; the overall judgment was based on the two prespecified most important domains (prognostic-factor measurement and study confounding). Zhang et al. [26] was rated high overall owing to acute-phase (within 24 h) hs-CRP measurement.

hs-CRP: high-sensitivity C-reactive protein; QUIPS: Quality in Prognosis Studies (Hayden et al., 2013 [27]).

Certainty of the Evidence

Certainty was assessed with the GRADE framework for prognostic-factor reviews, in which adjusted estimates from observational cohorts begin at high certainty (Table *6*). For both meta-analyzed outcomes, certainty was rated low. MACE was downgraded by one level for risk of bias (residual confounding, with the most influential study at high risk in the confounding domain) and one level for inconsistency (substantial, unexplained statistical heterogeneity); all-cause mortality was downgraded on the same two grounds. The evidence therefore indicates that residual inflammatory risk may increase the risk of MACE and may increase all-cause mortality in patients with established ASCVD and well-controlled LDL-C.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no inflammatory risk (hs-CRP <2 mg/L)	Risk with residual inflammatory risk (hs-CRP ≥2 mg/L)				
MACE (CV death, MI, stroke) follow-up: range 1 to 4.5 years	50 per 1,000	73 per 1,000 (58 to 92)	HR 1.48 (1.16 to 1.88)	26,722 (5 non-randomized studies)	⨁⨁◯◯ Low [a,b]	Residual inflammatory risk may increase the risk of major adverse cardiovascular events.
All-cause mortality follow-up: range 1 to 4.5 years	48 per 1,000	99 per 1,000 (61 to 161)	HR 2.13 (1.27 to 3.57)	26,346 (4 non-randomized studies)	⨁⨁◯◯ Low [a,c]	Residual inflammatory risk may increase all-cause mortality.

TABLE 6: GRADE summary of findings

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Absolute effects are model-based and approximate, as follow-up ranged from 1 to 4.5 years across studies.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different. Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different.

[a]All pooled cohorts were at moderate risk of bias (QUIPS), with none at low risk; chiefly residual confounding, with the most heavily weighted study (Mazhar et al. (2026) [22]/SCREAM) at high risk in the confounding domain. Only adjusted hazard ratios were pooled. Downgraded one level.

[b]Substantial unexplained statistical heterogeneity (I^2 = 69%, Q-test p = 0.004); study hazard ratios ranged from 1.18 to 1.82. Estimates were consistent in direction but varied in magnitude, with too few studies for reliable subgroup or meta-regression exploration. Downgraded one level.

[c]Substantial unexplained statistical heterogeneity (I^2 = 78%, Q-test p < 0.001); study hazard ratios ranged from 1.47 to 2.81. Estimates were consistent in direction (all indicating higher mortality with residual inflammatory risk) but varied materially in magnitude, with too few studies (k = 4) for reliable exploration. Downgraded one level.

CI: confidence interval; hs-CRP: high-sensitivity C-reactive protein; MACE: major adverse cardiovascular events; CV: cardiovascular; MI: myocardial infarction; HR: hazard ratio; GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Publication Bias

Because fewer than 10 studies contributed to any single outcome, formal assessments of small-study effects and publication bias (funnel-plot inspection and Egger's regression test) were not performed, as these methods are underpowered and unreliable below this threshold. The potential for small-study effects and publication bias therefore cannot be excluded and is acknowledged as a limitation.

Discussion

This systematic review found that among patients with established ASCVD who had achieved optimal lipid control (LDL-C <70 mg/dL), residual inflammatory risk (RIR), defined by hs-CRP ⩾2 mg/L, remained independently associated with adverse clinical outcomes. Patients with RIR experienced a 48% higher hazard of major adverse cardiovascular events (MACE; HR 1.48, 95% CI 1.16-1.88; k = 5) and an approximately twofold higher hazard of all-cause mortality (HR 2.13, 95% CI 1.27-3.57; k = 4). All five studies evaluating MACE reported effect estimates above unity, and despite substantial heterogeneity (I^2 = 69%), the direction of association was consistent. In contrast, no statistically significant association was observed for repeat revascularization (HR 1.02), whereas the analyses for myocardial infarction and stroke were limited by imprecision. The certainty of evidence for both outcomes was rated low, reflecting residual confounding and between-study heterogeneity.

These findings are consistent with accumulating evidence supporting the inflammatory theory of atherosclerosis, which holds that persistent vascular inflammation contributes to recurrent cardiovascular events despite optimal lipid lowering. In a collaborative analysis of 31,245 statin-treated patients from the PROMINENT, REDUCE-IT, and STRENGTH trials, hs-CRP was a stronger predictor of stroke, recurrent myocardial infarction (MI), and cardiovascular death than LDL-C, and patients with hs-CRP >2 mg/L retained significant risk even after achieving LDL-C <70 mg/dL, highlighting RIR as an important

determinant of adverse outcomes [5]. The 2025 ACC Scientific Statement recommends broader hs-CRP assessment in both primary and secondary prevention and identifies RIR as a major unmet therapeutic target to be addressed alongside residual cholesterol risk [15]. Analyses of the PROVE-IT and IMPROVE-IT trials similarly showed that patients achieving both hs-CRP <2 mg/L and LDL-C <70 mg/dL had the lowest rates of recurrent events, underscoring that control of both lipids and inflammation is necessary for secondary prevention [29-31]. In REAL-CAD, persistent hs-CRP elevation independently predicted adverse outcomes even among patients meeting guideline-recommended LDL-C targets [32]. Our review adds to this evidence by providing, to our knowledge, the first quantitative synthesis restricted to patients with LDL-C <70 mg/dL, pooling adjusted hazard ratios to distinguish the prognostic contribution of residual inflammation from residual cholesterol risk.

The high prevalence of RIR indicates that it is common among patients receiving contemporary secondary prevention. In PROVE-IT and IMPROVE-IT, approximately one-third of statin-treated patients had persistent hs-CRP >2 mg/L despite achieving LDL-C targets, indicating that a substantial proportion continue to carry inflammatory risk after successful lipid lowering [31]. A large Swedish registry of 84,399 patients with established ASCVD similarly reported that approximately 60% had hs-CRP ⩾2 mg/L despite aggressive contemporary management [32]. Consistent with these observations, 29% to 47% of participants across the cohorts included in this review exhibited RIR, and recent evidence suggests that systemic inflammation (hs-CRP ⩾2 mg/L) affects approximately 38% to 59% of patients with established ASCVD [33]. Collectively, these data indicate that RIR affects roughly one-third to one-half of treated ASCVD patients, underscoring its importance for risk stratification and the development of targeted treatment strategies.

In this review, RIR was associated with MACE and all-cause mortality, whereas evidence for individual nonfatal outcomes was less conclusive. For MACE, all five included studies reported hazard ratios greater than 1 (1.18 to 1.82), supporting a consistent direction of effect. Nevertheless, the prediction interval (0.88 to 2.48) indicates that a future study could observe a near-null association, reflecting substantial between-study heterogeneity. This variability likely reflects differences in study populations, including PCI registries, routine ASCVD cohorts, in-stent restenosis, and MINOCA, as well as geographical differences across the United States, Sweden, and China and follow-up durations of 1 to 4.5 years. All-cause mortality showed the strongest pooled association (HR 2.13), consistent with analyses in which hs-CRP was more strongly associated with cardiovascular death than LDL-C [5]. However, the wide prediction interval (0.69 to 6.53) and substantial heterogeneity (I^2 = 78%) were driven in part by the Mazhar et al. (2026)/SCREAM cohort, which carried the largest statistical weight, had the longest follow-up, and was at higher risk of residual confounding [22]. Nonfatal MI showed an elevated but nonsignificant association (HR 1.59, 95% CI 0.44 to 5.80), largely influenced by the outlying Zhang et al. (2024) estimate (HR 3.94) [23]; with only three studies (k = 3), this finding should be interpreted with caution. Repeat revascularization showed no statistically significant association (HR 1.02; I^2 = 0%), suggesting that reintervention is determined more by anatomical disease burden and symptom severity than by systemic inflammation. Evidence for stroke was limited to two studies (k = 2; HR 1.26, 95% CI 0.59 to 2.69), and the inability to pool the stroke/TIA outcome reported by Zhang et al. (2022) further limits interpretation [26].

A central threat to the validity of the observed association between RIR and adverse outcomes is residual confounding, because patients with elevated hs-CRP frequently carry a higher comorbidity burden. Across the included cohorts, participants with hs-CRP ⩾2 mg/L consistently showed a higher prevalence of diabetes mellitus, elevated body mass index (BMI), chronic kidney disease (CKD), and peripheral artery disease, all independently associated with worse cardiovascular prognosis. This raises the question of whether hs-CRP is merely a marker of an adverse cardiometabolic phenotype rather than a mediator of disease progression, particularly because adipose tissue is a major source of interleukin-6 (IL-6), the principal stimulus for hepatic CRP production, making obesity a potential confounder [34]. Several lines of evidence, however, argue against residual confounding as the sole explanation. First, we synthesized adjusted rather than crude hazard ratios, reducing the influence of measured confounders. Second, although Mendelian randomization studies do not support a causal role for CRP itself, mechanistic and trial evidence implicates the upstream IL-1β/IL-6 pathway in atherothrombosis, with hs-CRP serving as a marker of this pathway's activity [34,35]. Third, in CANTOS, selective inhibition of IL-1β reduced cardiovascular events without lowering LDL-C, and greater reductions in hs-CRP were associated with greater clinical benefit, supporting inflammation as a mediator of cardiovascular disease [30,31]. Nonetheless, the QUIPS assessment rated most included studies at moderate risk of bias and the Mazhar cohort at high risk of confounding, reducing confidence in the findings. On balance, the evidence supports but does not definitively prove causality.

The association between elevated hs-CRP and adverse cardiovascular outcomes is biologically plausible because inflammation is a fundamental mechanism of atherosclerotic disease progression rather than simply a marker of established disease. The IL-1β→IL-6→CRP pathway provides the mechanistic basis linking systemic inflammation to recurrent events, and randomized trials have shown that targeting this pathway improves outcomes independently of lipid lowering [15,30,31]. CANTOS demonstrated that inhibition of IL-1β with canakinumab reduced MACE by approximately 15% to 17% without altering LDL-C, with the greatest benefit among patients achieving the largest reductions in hs-CRP, supporting inflammation as a modifiable therapeutic target rather than only a prognostic marker [15,30,31].

This concept is reinforced by evidence supporting daily low-dose colchicine (0.5 mg) for secondary

prevention of MACE. Beyond the favorable results of the COLCOT and LoDoCo2 trials, 2025 meta-analyses demonstrated an approximately 25% reduction in MACE with colchicine, supporting the clinical value of inflammation-targeted therapy [36,37]. These findings have shaped contemporary recommendations: the 2023 AHA (American Heart Association)/ACC Chronic Coronary Disease guideline assigns colchicine a Class 2b recommendation for selected high-risk patients, and the 2025 ACC Scientific Statement identifies colchicine as the first FDA-approved anti-inflammatory therapy for ASCVD [8,15]. Ongoing evaluation of IL-6 inhibition, including ziltivekimab, may clarify whether more selective suppression of the inflammatory cascade provides additional cardiovascular benefit [15].

Limitations

The findings of this review should be interpreted in light of several limitations at the study, review, and outcome levels. At the study level, all but one included study (Bohula et al. (2015) [25]) were observational; although adjusted estimates were reported, residual confounding cannot be fully excluded. Most studies also used a single baseline hs-CRP measurement, which may introduce exposure misclassification because hs-CRP varies over time. NHANES (National Health and Nutrition Examination Survey) data show an intra-individual coefficient of variation of approximately 46%, with many participants reclassified on repeat testing, underscoring the limitations of a single measurement for long-term risk stratification [34].

At the review level, the relatively small number of eligible studies (k = 5 to 7) precluded reliable meta-regression and subgroup analyses. Moreover, three of the seven studies were conducted in China, limiting generalizability, and methodological differences were evident across studies, including variations in MACE definitions, follow-up periods, and how pooled event rates were reported.

At the outcome level, the certainty of evidence was low for MACE and mortality and more limited for myocardial infarction, stroke, and revascularization. Because fewer than 10 studies were available, formal assessment of publication bias was not feasible. Collectively, these limitations highlight the need for large-scale studies in geographically diverse populations that incorporate standardized serial hs-CRP measurements [11,34].

Clinical Implications and Future Directions

These findings support measuring hs-CRP alongside LDL-C in patients with established ASCVD rather than relying on LDL-C alone. The 2025 ACC Scientific Statement acknowledges that many patients retain significant RIR despite achieving LDL-C targets (<70 mg/dL) and recommends routine hs-CRP assessment to identify ongoing inflammation despite guideline-directed lipid-lowering therapy [15]. In patients with RIR (hs-CRP ⩾2 mg/L), clinicians should consider adding appropriate anti-inflammatory therapy in line with current evidence and guidelines, rather than focusing solely on further LDL-C reduction [15].

Among currently available therapies, low-dose colchicine (0.5 mg daily) is supported by the most robust evidence [37]. Randomized trials and meta-analyses consistently show that adding colchicine to standard secondary prevention reduces recurrent cardiovascular events [34,37], and the 2023 AHA/ACC Chronic Coronary Disease guideline accordingly assigns it a Class 2b recommendation for selected high-risk patients [8,34].

Future research should prioritize prospective cohorts with repeated hs-CRP measurements, randomized trials specifically enrolling patients with both LDL-C <70 mg/dL and hs-CRP ⩾2 mg/L, and populations beyond the predominant U.S. and Chinese cohorts. Further work is also needed to define the value of emerging biomarkers such as IL-6 and GlycA and imaging approaches such as the perivascular fat attenuation index for inflammatory risk assessment [15].

This review anchored its analytic contrast to LDL-C <70 mg/dL, whereas contemporary guidance increasingly favors a more intensive target of <55 mg/dL in very high-risk ASCVD, as reflected in the 2026 ACC/AHA dyslipidemia guideline [38] and in the first head-to-head randomized comparison of the two thresholds, which reported a lower 3-year risk of major adverse cardiovascular events with intensive (<55 mg/dL) than with conventional (<70 mg/dL) targeting [39]. Achieving <55 mg/dL typically requires escalation to a high-intensity statin plus ezetimibe, with a PCSK9 inhibitor added when needed, and even then a substantial proportion of patients fall short of the goal, considerations that bear directly on feasibility, adherence, and cost-effectiveness [39]. Because the constituent studies did not consistently report an LDL-C <55 mg/dL stratum, we could not directly examine residual inflammatory risk at this lower threshold, and any exploratory analysis at more intensive cutoffs would have been underpowered; we therefore flag this as a limitation and a priority for future work, which should enroll patients meeting both LDL-C <55 mg/dL and hs-CRP ⩾2 mg/L to test whether inflammation retains prognostic weight as residual cholesterol risk is minimized.

Conclusions

This systematic review found that RIR, defined as hs-CRP ⩾2 mg/L, was associated with significantly higher

risks of MACE and death among patients with ASCVD, including those who have reached LDL-C targets. LDL-C reduction alone may therefore be insufficient to address the residual burden of cardiovascular risk, supporting inflammation as a distinct and potentially modifiable therapeutic target. However, given the low certainty of the available evidence, large-scale prospective studies and well-designed randomized trials are needed to confirm these findings before routine clinical application.

Appendices

Search strategy

We searched databases from inception to May 2026 with no language restrictions. We also hand-searched the reference lists of included studies and previous systematic reviews, as well as grey literature and clinical trial registries. The PubMed strategy is shown in full below; equivalent strategies were adapted to database-specific syntax (Emtree headings and field tags) for EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL).

Database (platform)	Date range	Records
PubMed	Inception–May 2026	151
Cochrane CENTRAL	Inception–May 2026	95
EMBASE	Inception–May 2026	3,102
Total records	—	3,348
After duplicate removal (228 removed)	—	3,120

TABLE 7: Databases searched and records retrieved

Set	Concept	Search terms
#1	Established ASCVD (population)	"Atherosclerosis"[Mesh] OR "Coronary Artery Disease"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Stroke"[Mesh] OR "Peripheral Arterial Disease"[Mesh] OR "Carotid Artery Diseases"[Mesh] OR "Ischemic Attack, Transient"[Mesh] OR "Coronary Stenosis"[Mesh] OR Atherosclerosis* OR CAD OR ASCVD OR "secondary prevention" OR "acute coronary syndrome" OR revascularization OR stent*
#2	LDL-C control / lipid-lowering therapy	("Cholesterol, LDL"[Mesh] OR LDL OR "low-density lipoprotein" OR "LDL-C") AND (intensive OR potent OR target OR achieved OR low OR statin OR ezetimibe OR PCSK9)
#3	Inflammation / high-sensitivity CRP	"C-Reactive Protein"[Mesh] OR CRP OR "hs-CRP" OR hsCRP OR inflammation OR "inflammatory risk" OR "residual inflammatory risk"
#4	Outcomes	"MACE"[tiab] OR "Major Adverse Cardiovascular Events"[tiab] OR "CV mortality"[tiab] OR "cardiovascular death"[tiab] OR "incident MI"[tiab] OR "recurrent stroke"[tiab]
#5	Study design	"Cohort Studies"[Mesh] OR cohort OR prospective OR retrospective OR longitudinal OR "Randomized Controlled Trial"[pt] OR placebo[tiab] OR "drug therapy"[sh] OR randomized[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab]
#6	Combined	#1 AND #2 AND #3 AND #4 AND #5

TABLE 8: Search strategy

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CRP, C-reactive protein; hs-CRP, high-sensitivity C-reactive protein; LDL/LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9. Field tags: [Mesh], Medical Subject Heading; [tiab], title/abstract; [pt], publication type; [sh], subheading; asterisk (*) denotes truncation.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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