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INTERLEUKIN-6 AND HIGH-SENSITIVITY C-REACTIVE PROTEIN IN CHRONIC CORONARY SYNDROMES: PATHOPHYSIOLOGICAL RATIONALE AND CLINICAL INTERPRETATION IN STABLE ANGINA

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ИНТЕРЛЕВКИН-6 И ВИСОКОЧУВСТВИТЕЛЕН С-РЕАКТИВЕН ПРОТЕИН ПРИ ХРОНИЧНИ КОРОНАРНИ СИНДРОМИ: ПАТОФИЗИОЛОГИЧНА ОБОСНОВКА И КЛИНИЧНА ИНТЕРПРЕТАЦИЯ ПРИ СТАБИЛНА АНГИНА

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Abstract. Chronic coronary syndromes (CCS) are driven by atherosclerosis in which inflammation contributes to plaque progression and adverse events. Interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) are linked, non-equivalent biomarkers along the IL-6 → hepatic acute-phase response → CRP axis. This narrative review summarizes the biological rationale and clinical evidence on IL-6 and hs-CRP as diagnostic and prognostic biomarkers in CCS, emphasizing stable cohorts assessed with invasive coronary angiography or coronary CT angiography. Available data suggest IL-6 is more consistently associated with the presence and burden of coronary atherosclerosis, whereas hs-CRP is more robustly validated for prognostic risk stratification but shows heterogeneous associations with anatomic stenosis severity. Both markers are nonspecific and influenced by metabolic comorbidity and background therapy; therefore, they should be interpreted as adjuncts rather than standalone diagnostic tests. Standardized studies with uniform angiographic endpoints are needed to define incremental diagnostic value and clinically relevant thresholds.

Key words: chronic coronary syndrome; stable angina; interleukin-6; high-sensitivity C-reactive protein; coronary angiography

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Резюме. Хроничните коронарни синдроми (CCS) се дължат основно на коронарна атеросклероза, при която възпалението допринася за прогресията на плаката и изява на нежелани събития. Интерлевкин-6 (IL-6) и високочувствителният С-реактивен протеин (hs-CRP) са свързани, но неекивалентни биомаркери по оста IL-6 → чернодробен острофазов отговор → CRP. Настоящият обзор обобщава биологичната обосновка и клиничните данни за IL-6 и hs-CRP като диагностични и прогностични биомаркери при CCS, с акцент върху стабилни кохорти, оценявани чрез инвазивна коронарна ангиография или КТ коронарна ангиография. Наличните данни показват, че IL-6 се асоциира силно с наличие и тежест на коронарна атеросклероза, докато hs-CRP е по-добре валидиран за прогностична рискова стратификация, но връзката му с анатомичната тежест на стенозите е хетерогенна. И двата маркера са неспецифични и се влияят от метаболитна коморбидност и терапия, поради това следва да се интерпретират като допълващи, а не като самостоятелни диагностични тестове. Необходими са стандартизирани проучвания с унифицирани ангиографски крайни точки за определяне на допълнителната диагностична стойност и клинично значимите прагове.

Ключови думи: хроничен коронарен синдром, стабилна ангина пекторис, интерлевкин-6, високо-чувствителен С-реактивен протеин, коронарна ангиография

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Introduction

Chronic coronary syndromes (CCS) encompass stable angina and related clinical phenotypes caused mainly by coronary atherosclerosis. Contemporary diagnostic pathways combine clinical risk assessment with functional and anatomic testing, while invasive coronary angiography (ICA) is reserved for selected scenarios and remains a key reference standard for defining anatomic obstructive coronary artery disease (CAD) [1]. Despite major advances in imaging and physiology-guided decision-making, a central challenge in stable disease is the imperfect alignment between symptoms, ischemia, and anatomic stenosis severity, and the limited ability of lumenography alone to reflect plaque biology [1-4].

Inflammation is a core driver of atherosclerosis and contributes to endothelial activation, leukocyte recruitment, cytokine signaling, and extracellular matrix remodeling within plaques [2-5]. This biology provides a rationale for studying systemic inflammatory biomarkers as adjuncts to refine phenotyping and risk stratification in stable CAD. Among many candidates, interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) are particularly appealing because they lie on a coherent inflammatory axis (Fig. 1): IL-6 is an upstream cytokine and a major driver of hepatic acute-phase protein synthesis, including CRP, whereas hs-CRP represents a downstream and analytically robust readout of the acute-phase response [6-11].

The clinical roles of IL-6 and hs-CRP differ. hs-CRP is widely available, standardized, and supported by extensive prognostic literature, while IL-6 may capture more proximate inflammatory signaling related to plaque biology and has shown consistent associations with anatomic disease burden in several angiographic and imaging cohorts [12-14]. However, both biomarkers are nonspecific, can be influenced by comorbidity and background therapy, and are not recommended as standalone diagnostic tests for obstructive CAD in current CCS guidelines [1, 12, 15].

This review summarizes the pathophysiological rationale and clinical evidence for IL-6 and hs-CRP as diagnostic and prognostic biomarkers in CCS, with emphasis on stable populations evaluated by invasive angiography or contemporary anatomic imaging. Particular attention is given to (I) biological plausibility along the IL-6→CRP axis, (II) associations with anatomic CAD presence and burden, and (III) how these markers might complement established diagnostic algorithms in research and clinical practice [1, 12, 15].

This perspective is particularly relevant for stable angina patients referred for invasive coronary angiography.

Inflammation and atherosclerosis

Atherosclerosis is now understood as a chronic inflammatory disease of the arterial wall rather than a purely lipid-storage disorder [2-5]. Early lesion development is initiated by endothelial dysfunction and retention of atherogenic lipoproteins, followed by recruitment of monocytes and lymphocytes and differentiation of macrophages that perpetuate local inflammation [2-4]. Within plaques, inflammatory mediators promote oxidative stress, smooth muscle cell phenotypic switching, extracellular matrix degradation, and the formation of a necrotic core, thereby contributing to plaque growth and vulnerability [2-4].

A key implication is that clinical events may arise from plaques that are not necessarily the most stenotic on angiography. Plaque vulnerability depends on inflammatory cell content, fibrous cap thickness, and thrombogenicity, which may be only partially captured by lumenography [2-4]. Accordingly, anatomic stenosis severity and biological plaque activity can be discordant, and the inflammatory milieu may help explain heterogeneity in outcomes among patients with similar anatomic findings [2-4, 14].

The IL-1β/IL-6/CRP axis provides a useful framework linking local plaque inflammation to systemic biomarkers. Upstream cytokines such as IL-1β and IL-6 stimulate hepatic acute-phase responses, increasing circulating CRP, fibrinogen, and other proteins measurable by routine assays [6-11]. Because CRP integrates multiple upstream signals, hs-CRP is an attractive marker for “residual inflammatory risk”, a concept describing persistent inflammation despite optimal LDL lowering and guideline-directed therapy [12, 16].

Randomized trials targeting inflammation in atherosclerotic disease provide clinical proof that inflammatory pathways are modifiable and clinically relevant. In CANTOS, IL-1β inhibition reduced cardiovascular events without affecting LDL cholesterol, supporting risk reduction through inflammation lowering independent of lipid lowering [17]. Similarly, low-dose colchicine reduced ischemic events in chronic coronary disease and after myocardial infarction in LoDoCo2 and COLCOT, respectively, reinforcing inflammation as a therapeutic target [18-19]. These trials do not establish IL-6 or hs-CRP as diagnostic tests for stenosis; rather, they strengthen the biological rationale for using inflammatory biomarkers to characterize risk phenotypes and to interpret variation across stable cohorts [16-19].

In stable CCS, the potential diagnostic contribution of inflammatory biomarkers is nuanced. Biomarkers are unlikely to replace imaging or physiological assessment but may add incremental information when used alongside anatomic reference standards (ICA or CCTA), especially in borderline or intermediate-risk scenarios where additional biological context could refine risk estimation [1, 13]. Therefore, evaluating IL-6 and hs-CRP in stable populations referred for angiography is clinically relevant and aligns with current interest in improving phenotyping beyond stenosis severity alone [1-4, 16].

IL-6: Biology and clinical relevance

IL-6 is a pleiotropic cytokine produced by immune cells (monocytes/macrophages and lymphocytes) and by vascular and metabolic tissues including endothelium, smooth muscle cells, and adipose tissue [6-9]. IL-6 signals through a receptor complex involving IL-6 receptor (IL-6R) and gp130, activating intracellular pathways such as JAK/STAT and MAPK. Importantly, IL-6 operates via both classical signaling (membrane IL-6R) and trans-signaling (soluble IL-6R), which expands the range of IL-6-responsive cells and may amplify vascular inflammatory responses [8-9].

At the vascular level, IL-6 signaling is associated with endothelial activation, upregulation of adhesion molecules, and chemokine expression that facilitate leukocyte recruitment into the arterial wall, thereby perpetuating inflammatory plaque remodeling [2-4, 6-9]. IL-6 can also interact with prothrombotic and metabolic pathways, linking systemic inflammation to hemostatic balance and cardiometabolic risk factors that cluster in CCS populations [6-9, 12].

A central downstream effect of IL-6 is induction of hepatic acute-phase proteins, including CRP and fibrinogen, linking local vascular inflammation to systemic inflammatory readouts [10, 11]. Because IL-6 sits upstream of CRP, it may capture more proximate inflammatory signaling relevant to plaque biology, whereas hs-CRP integrates upstream cytokine activity into a stable acute-phase response [6-11].

Genetic and epidemiological evidence supports a potentially causal role of the IL-6 pathway in CAD. In a large collaborative meta-analysis, genetic variation in IL6R (Asp358Ala; rs2228145) was associated with altered IL-6 signaling and a lower risk of coronary heart disease, consistent with the hypothesis that downregulation of IL-6R signaling may be protective [20]. Such findings strengthen biological plausibility for IL-6 as a relevant marker of inflammatory activity in atherosclerosis and provide context for ongoing interest in upstream anti-inflammatory strategies [16-20].

Evidence for IL-6 in CCS

Clinical studies in stable angina suggest that low-grade inflammatory activation is measurable even in stable presentations. Early work reported elevated pro-inflammatory cytokines, including IL-6, in chronic stable angina and demonstrated modulation with antiplatelet/anti-inflammatory therapy [21]. Similarly, Gabriel et al. reported measurable IL-6 activity in patients with stable angina pectoris, supporting the concept of persistent low-grade inflammation even in clinically stable presentations [22].

Across angiography-based studies, IL-6 has been associated with the presence and severity of CAD, although endpoints differ across cohorts. In observational angiography cohorts, IL-6 has been linked to markers of disease burden such as multi-vessel disease and angiographic severity measures, suggesting that higher systemic IL-6 levels may reflect greater atherosclerotic burden in stable disease [23-25].

Several studies specifically examined IL-6 in relation to angiographic scoring systems or quantitative severity assessments. While cutoffs and analytic approaches vary, these reports support a graded relationship between IL-6 levels and angiographic severity, motivating ROC-based analyses to explore diagnostic discrimination for significant CAD in stable patients referred for ICA [24-25]. Importantly, such diagnostic evaluations should be interpreted in the context of established clinical likelihood models, and should report incremental value (e.g., changes in AUC, calibration, and net reclassification) rather than relying on single cut points [1, 12].

Contemporary imaging data are concordant: in PROMISE, higher IL-6 levels were associated with CTA-defined stenosis and higher CAD-RADS categories in patients evaluated for stable chest pain, supporting an anatomic link between IL-6 and coronary atherosclerosis in a modern diagnostic pathway [13]. Notably, this association emphasizes that IL-6 may relate to overall atherosclerotic burden rather than solely to symptom status, reinforcing the concept that biomarkers can reflect biological disease activity beyond clinical presentation [13].

Beyond anatomic associations, IL-6 has demonstrated prognostic relevance in stable CAD. In an elective coronary angiography cohort, higher IL-6 levels were associated with an increased risk of long-term cardiovascular events [26]. Similarly, in STABILITY (stable coronary heart disease), IL-6 was independently associated with major adverse cardiovascular events, supporting IL-6 as a marker of residual inflammatory risk in chronic stable disease [14]. Together, these findings suggest that IL-6 may have dual relevance: as a marker related to anatomic burden in stable cohorts, and as a prognostic marker reflecting inflammatory risk [13-14, 26].

Hs-CRP: biology and clinical relevance

CRP is a pentraxin acute-phase protein synthesized predominantly by hepatocytes in response to cytokine stimulation, especially IL-6 [10-11]. High-sensitivity assays enable reliable quantification at low concentrations typical of chronic, low-grade inflammation, making hs-CRP the most widely used inflammatory biomarker in cardiovascular medicine [12, 15]. CRP also plays roles at sites of inflammation and infection, and its circulating concentration reflects an integrated acute-phase response to diverse stimuli, including subclinical inflammation relevant to atherosclerotic disease [10-11, 27].

An ongoing debate is whether CRP is merely a marker or also a mediator of atherosclerosis. Experimental observations suggest potential interactions with

complement activation and endothelial function, but in clinical practice hs-CRP is primarily used as a risk marker rather than a direct treatment target [10, 12, 15, 27].

Large-scale epidemiologic studies have consistently linked CRP to cardiovascular risk, supporting its role in risk stratification and as an enrichment tool for clinical trials [12, 28]. In primary prevention, hs-CRP measurement was used to identify individuals who might benefit from statin therapy; in JUPITER, statin therapy reduced events among participants with elevated hs-CRP despite low LDL cholesterol, highlighting that lowering inflammation and lipid pathways together can translate to clinical benefit [29-30].

In CCS, hs-CRP is attractive because it is standardized, relatively stable, and readily available. Consensus cut points (e.g., < 1, 1-3, and > 3 mg/L) have been used for broad risk categorization, although interpretation should account for comorbidities, intercurrent illness, and background therapy [12, 15]. These properties make hs-CRP a pragmatic marker for residual inflammatory risk, but they do not guarantee anatomic diagnostic specificity for obstructive CAD in stable populations [12, 31-33].

Evidence for hs-CRP in CCS

In stable CAD, hs-CRP has repeatedly been associated with future cardiovascular events, supporting a consistent prognostic signal. In AtheroGene, CRP and fibrinogen provided prognostic information among patients with stable angina [34]. In PEACE and CLARICOR, hs-CRP contributed to risk stratification in stable CAD populations, particularly in multivariable or multibiomarker contexts [35-36]. STABILITY further supports inflammation as a prognostic domain in stable coronary heart disease, with hs-CRP and IL-6 showing graded associations with cardiovascular outcomes [14].

In contrast, associations between hs-CRP and anatomic stenosis burden on angiography are heterogeneous. Some angiography-based studies reported associations between CRP levels and the presence or extent of coronary stenosis, whereas others found weak or absent correlations with severity scores in stable cohorts [31-32]. This heterogeneity is consistent with the concept that hs-CRP reflects systemic inflammatory activity and residual inflammatory risk rather than providing a direct measure of luminal stenosis severity [12, 16].

Metabolic factors may further modify these associations. In stable angina, obesity elevates baseline hs-CRP and can attenuate the relationship between CRP and stenosis burden, complicating diagnostic interpretation in overweight or obese populations [33]. Consequently, studies assessing diagnostic discrimination for obstructive CAD using hs-CRP should consider stratification by BMI and other metabolic covariates and should report incremental value beyond standard clinical predictors [12, 33]. Key clinical studies in CCS are summarized in Table 1.

Table 1. Key clinical studies of IL-6 and hs-CRP in CCS

Study	Population	Biomarker	Reference standard	Endpoint	Key finding
Ikonomidis 1999	Chronic stable angina	IL-6	Clinical stable CAD context	Inflammatory profile	Elevated cytokines; reduced with aspirin.
Gabriel 2000	Stable angina	IL-6	Clinical stable CAD context	Biomarker profile	Measurable IL-6 activity in stable angina.
Gotsman 2008	Angiography cohort	IL-6	ICA	CAD severity	IL-6 associated with CAD severity.
Gerin 2017	Patients undergoing ICA	IL-6	ICA	Severity scores	IL-6 related to CAD severity; ROC reported.
Wainstein 2017	Intermediate-risk overweight	IL-6, hs-CRP	ICA	Significant CAD	IL-6 predictive of CAD in angiography cohort.
Ferencik 2022 (PROMISE)	Stable chest pain evaluation	IL-6	CCTA	Stenosis, CAD-RADS	Higher IL-6 associated with CTA stenosis/ CAD-RADS.
Mossmann 2022	Elective angiography cohort	IL-6	ICA	Long-term outcomes	Higher IL-6 predicts long-term events.
Sinning 2006 (AtheroGene)	Stable angina	CRP (hs)	Clinical stable CAD	Prognosis	CRP associated with adverse prognosis.
Sabatine 2007 (PEACE)	Stable CAD	hs-CRP	Trial cohort	Outcomes	hs-CRP cut points predict events.
Taniguchi 2005	Stable CAD	hs-CRP	ICA	Presence/extent	hs-CRP linked to stenosis presence/extent.
Ulucay 2007	Stable angina	hs-CRP	ICA	Severity	Variable association with stenosis severity.
Aronson 2006	Stable angina	CRP	ICA	Stenosis burden	Obesity modifies CRP–stenosis relationship.

Table 2. Comparative characteristics of IL-6 and hs-CRP in CCS

Criterion	IL-6	hs-CRP
Position in inflammatory cascade	Upstream cytokine	Downstream acute-phase protein
Biological meaning	Active cytokine signaling; inflammatory activation	Integrated systemic acute-phase response
Main sources	Immune cells; vascular cells; adipose tissue	Hepatic synthesis (IL-6-driven)
Analytical/clinical availability	Less routine; greater assay variability	Widely available; standardized assays
Association with anatomic CAD in stable CCS	More consistent in several cohorts	Heterogeneous across studies
Principal clinical signal	Potential adjunct diagnostic/phenotyping marker	Risk stratification / prognostic signal

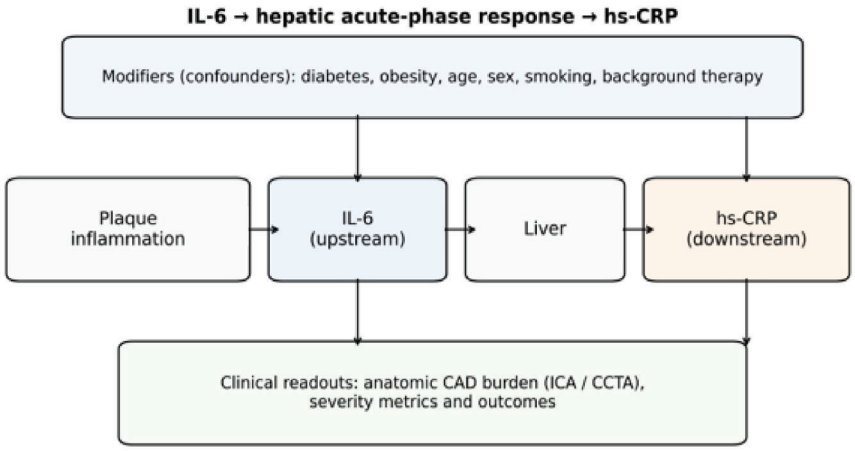

Fig. 1. Conceptual framework: IL-6 → hepatic acute-phase response → hs-CRP

Comparative interpretation and combined use

Because IL-6 and hs-CRP occupy different positions along the same inflammatory pathway, they should be viewed as complementary rather than interchangeable [6-11]. IL-6 may better capture upstream inflammatory signaling relevant to plaque biology and vascular immune activation, while hs-CRP provides an integrated and analytically robust readout of the hepatic acute-phase response [10-12, 15, 27]. Consequently, discordant profiles may occur (e.g., elevated IL-6 with modest hs-CRP, or elevated hs-CRP driven by metabolic inflammation), and such patterns may help contextualize inflammatory burden in stable CCS.

From a diagnostic perspective, neither IL-6 nor hs-CRP is recommended as a standalone test for obstructive CAD; established CCS diagnostic pathways remain anchored in clinical likelihood estimation followed by functional and anatomic evaluation [1]. However, inflammatory biomarkers may add value as adjuncts in research settings – particularly when evaluated against an anatomic reference standard, and when the focus is on incremental discrimination or on defining biological phenotypes associated with higher plaque burden or adverse outcomes [13, 14].

In practical terms, potential utility is greatest where current pathways leave residual uncertainty. For example, in patients with stable chest pain and intermediate clinical likelihood, anatomic imaging (CCTA) or functional testing is used to clarify diagnosis, yet downstream risk can remain heterogeneous even within the same anatomic category [1, 13]. In such settings, inflammatory biomarkers could be evaluated as adjuncts to improve characterization of biological risk (e.g., high vs low inflammatory activity), particularly when combined with an anatomic reference standard and a clear definition of significant CAD. To be clinically meaningful, biomarker models should demonstrate incremental value beyond standard predictors using contemporary performance metrics (change in AUC, calibration, and reclassification), rather than relying on single cut points alone [1, 12].

A practical way to frame combined biomarker use is to consider IL-6 as a proximal signal and hs-CRP as an integrated systemic readout. In stable populations, higher IL-6 may suggest active upstream inflammatory signaling linked to atherosclerotic burden, while elevated hs-CRP may indicate a broader systemic inflammatory state that correlates more consistently with future events [12-14, 34-36]. Such a framework may help guide interpretation when biomarkers are used to complement risk stratification rather than to diagnose stenosis per se.

Evidence from anti-inflammatory outcome trials provides context for biomarker interpretation in CCS. Event reductions with IL-1β inhibition (CANTOS) and with low-dose colchicine (LoDoCo2 and COLCOT) highlight that inflammatory pathways are clinically relevant and modifiable [17-19]. These findings motivate additional work to clarify whether IL-6 and hs-CRP improve phenotyping, decision-making, or prognostication beyond clinical models in stable CCS, and whether clinically meaningful thresholds can be defined for routine interpretation [16-19]. Key differences between IL-6 and hs-CRP are summarized in Table 2.

Subgroup considerations

Interpretation of IL-6 and hs-CRP requires attention to comorbidity that can elevate baseline inflammation independently of anatomic CAD. Diabetes, obesity, and smoking are common in CCS and contribute to chronic low-grade inflammation that may influence both biomarkers [12, 16, 33, 37].

In diabetes, chronic inflammation and insulin resistance may increase IL-6 and hs-CRP. In the Veterans Affairs Diabetes Trial, IL-6 was associated with the extent of coronary atherosclerosis, supporting relevance of IL-6 in high-risk metabolic phenotypes [37]. These findings underscore the importance of considering di-

abetes status when evaluating IL-6 associations with anatomic endpoints in stable cohorts.

In obesity, adipose tissue–driven inflammation is a major determinant of hs-CRP and may reduce specificity for anatomic stenosis severity in stable angina. Aronson et al. demonstrated that obesity modifies the relationship between CRP and coronary stenosis burden, illustrating why BMI stratification can be critical in biomarker studies [33].

Age and sex, as well as background therapy (particularly statins), may further modulate biomarker levels and their associations with disease burden and outcomes. Therefore, studies evaluating IL-6 and hs-CRP in stable CCS should incorporate stratified analyses or multivariable adjustment for key covariates to reduce residual confounding and to define subgroups in whom biomarkers may be most informative [1, 12, 33, 37].

Limitations of current evidence and future directions

Across the literature, heterogeneity in patient selection, definitions of significant CAD (e.g., stenosis thresholds), and analytic strategies complicates direct comparison of diagnostic performance for IL-6 and hs-CRP. Many studies are single-center and vary in adjustment for confounding factors such as obesity, diabetes, smoking, and background therapy, which can influence biomarker levels and attenuate associations with anatomic stenosis burden [12, 31-33, 37].

Another important consideration is the choice of reference standard and the clinical question being addressed. Studies anchored to ICA typically focus on luminal stenosis thresholds, whereas CCTA allows characterization of overall plaque burden and distribution, which may align more closely with inflammatory biology [1, 13]. Future diagnostic studies should prespecify whether the aim is to discriminate obstructive stenosis, extensive atherosclerosis, or high-risk plaque features, and should report results in a way that supports clinical translation (including external validation where feasible) [1, 12].

A further methodological issue is that “anatomic CAD” can be defined in multiple ways (presence of any plaque, obstructive stenosis, multi-vessel disease, or quantitative severity scores). Biomarker associations may differ depending on whether the endpoint reflects luminal stenosis, overall plaque burden, or plaque phenotype. Modern CCTA studies, such as PROMISE, highlight the potential value of characterizing disease burden more broadly than stenosis alone, which may better align with inflammatory biology [13].

IL-6 and hs-CRP are nonspecific markers and can be elevated by intercurrent infection or chronic inflammatory disorders. Thus, both markers are most informative when interpreted in a defined clinical context and in conjunction with anatomic and functional assessment rather than as standalone tests [10-12, 15, 27]. In clinical research, rigorous inclusion and exclusion criteria and standardized sampling are important to minimize confounding.

Future studies should focus on well-defined CCS cohorts with standardized sampling, consistent anatomic reference standards (ICA and/or CCTA), and transparent reporting of diagnostic accuracy metrics (including ROC/AUC and calibration where relevant). Given supportive mechanistic and genetic evidence for the IL-6 pathway [6-9, 20], and consistent prognostic data for hs-CRP in stable CAD [14, 34-36], a key goal is to determine whether either marker offers incremental diagnostic value beyond established clinical likelihood models and whether combined biomarker strategies can improve patient phenotyping in stable CCS [1, 16].

Conclusion

IL-6 and hs-CRP reflect distinct yet interconnected components of inflammatory signaling relevant to chronic coronary syndromes. Available evidence suggests that IL-6 is more consistently associated with anatomic CAD presence and burden, whereas hs-CRP is strongly validated for prognostic risk stratification but shows heterogeneous associations with stenosis severity in stable populations. Neither biomarker should be used as a standalone diagnostic test; instead, they may serve as complementary adjuncts that help specify inflammatory burden alongside established clinical and imaging-based assessment. Standardized angiography-based studies in well-defined stable cohorts are needed to clarify incremental diagnostic performance, clinically meaningful thresholds, and potential roles for combined biomarker phenotyping.

No conflict of interest was declared

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