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Association Between High-Sensitivity C-Reactive Protein (hs-CRP) Levels and Cardiovascular Disease

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ABSTRACT

Aim – This review aims to systematically evaluate the prognostic and clinical utility of high-sensitivity C-reactive protein (hs-CRP) across the full spectrum of cardiovascular diseases, from coronary artery disease and heart failure to stroke, arrhythmias, valvular disease, cardiomyopathies, and infectious cardiac conditions. **Background** – Cardiovascular disease (CVD) remains the leading cause of global

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mortality, with chronic low-grade inflammation increasingly recognized as a central driver alongside traditional risk factors. hs-CRP, an acute-phase reactant synthesized under interleukin-6 stimulation, offers a widely available and reproducible window into systemic inflammatory burden. Its associations with atherosclerosis, endothelial dysfunction, myocardial fibrosis, and adverse vascular remodeling have generated substantial clinical interest across diverse cardiac conditions. **Review Results** – Elevated hs-CRP independently predicts major adverse cardiovascular events in coronary artery disease, acute myocardial infarction, and unstable angina, with prognostic gradients persisting after lipid adjustment. In ischemic stroke, admission hs-CRP forecasts recurrence and 3-month functional outcomes, whereas associations with hemorrhagic stroke are weak and non-causal. In heart failure, raised hs-CRP correlates with worse remodeling, higher hospitalization rates, and increased mortality across both HFrEF and HFpEF phenotypes. Co-elevation with hypertension confers synergistic cardiovascular mortality risk. In peripheral artery disease, the CRP-to-albumin ratio outperforms hs-CRP alone for predicting limb and cardiovascular outcomes. Modest but significant associations are observed in atrial fibrillation and TAVI candidates. In myocarditis and pericarditis, serial hs-CRP monitoring guides disease activity assessment and therapy duration. Mendelian randomization studies consistently position CRP as a downstream inflammatory marker rather than an independent causal agent. **Conclusion** – hs-CRP provides clinically meaningful prognostic information across virtually the entire cardiovascular disease spectrum. Its signal is strongest in ischemic and inflammatory disorders, moderate in heart failure and peripheral artery disease, and modest in hemorrhagic stroke and atrial fibrillation. It functions as an adjunctive prognostic biomarker reflecting downstream cytokine-driven pathology rather than a causal mediator. **Clinical Significance** – As a low-cost, broadly available biomarker, hs-CRP can meaningfully refine cardiovascular risk stratification when integrated into multimarker clinical frameworks. Serial monitoring adds prognostic value in myocarditis, pericarditis, and heart failure. Future research should prioritize validated condition-specific cut-points, multimarker panel strategies, and interventional trials targeting inflammatory signaling to determine whether reducing hs-CRP translates to improved patient outcomes.

Keywords: Cardiovascular disease (CVD), Heart failure (HF), Chronic inflammation, High-sensitivity C-reactive protein
(hs-CRP), Tumor necrosis factor-alpha (TNF-α), Interleukin-6 (IL-6), Oxidative stress, Endothelial dysfunction.

Introduction

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide. Increasing evidence indicates that chronic low-grade inflammation plays a central role in the development and progression of CVD. Heart failure (HF), in particular, is increasingly recognized as a chronic inflammatory condition characterized by sustained activation of immune pathways. Inflammation is a key component in the pathophysiology of incident HF. The heart's inability to maintain adequate cardiac output may trigger an inflammatory response marked by elevated concentrations of pro-inflammatory cytokines, including tumor necrosis factor-alpha

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(TNF-α) and interleukin-6 (IL6) [1]. These cytokines contribute to myocardial remodeling, fibrosis, and ultimately decreased cardiac function. Furthermore, chronic inflammation may lead to a self-perpetuating cycle that exacerbates HF symptoms [2]. Studies have shown that oxidative stress results from an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defenses. In HF, increased oxidative stress is linked to ischemia, inflammation, and neurohormonal activation. Excess ROS may cause cellular damage, apoptosis, and contribute to myocardial dysfunction [1]. C-reactive protein (CRP) is a marker of systemic inflammation and has been shown to impair endothelial function. Elevated CRP levels are associated with reduced endothelial vasodilator capacity, suggesting its role in endothelial dysfunction, a recognized precursor of CVD. Research has indicated that CRP may promote vascular stiffness and tight junction formation, leading to an increase in vascular inflammation and contributing to the pathogenesis of hypertension and atherosclerosis [3]. CRP has also been reported to influence vascular reactivity through nitric oxide (NO)-dependent pathways.

Moreover, CRP interacts with inflammatory biomarkers such as IL-6 and tumor necrosis factor-alpha (TNF-α). Elevated CRP levels correlate positively with IL-6 and TNF-α in patients with essential hypertension, suggesting that CRP not only reflects systemic inflammation but may also participate in inflammatory cascades that exacerbate endothelial activation and promote vascular injury [4].Although CRP serves as a general marker of inflammation, other biomarkers such as IL-6, galectin-3, and soluble ST2 provide additional insight into inflammatory and remodeling processes associated with HF. IL-6 has demonstrated high reported sensitivity and specificity in predicting HF in selected cohorts [5]. Galectin-3 concentrations correlate with higher IL-6 and CRP levels, highlighting its involvement in inflammatory pathways leading to HF. Elevated galectin-3 levels have been associated with an increased risk of incident HF and mortality, independent of traditional risk factors [6].

Table 1: ***Pathophysiological Role of CRP and Inflammation in Cardiovascular Disease***

Component	Key Findings	Pathophysiological Impact
Systemic inflammation	HF and CVD trigger inflammatory responses with ↑ TNF-α and IL-6 [1,7]	Drives myocardial remodeling, fibrosis, reduced cardiac output [1,2]
Chronic inflammation	Persistent cytokine activation forms self-perpetuating inflammatory cycle [2]	Accelerates HF progression and symptom severity [2]
Oxidative stress	Imbalance between ROS production and antioxidant defense in HF [1,2]	Cellular damage, apoptosis, myocardial dysfunction [1]
CRP (general role)	Acute-phase reactant synthesized under IL-6 stimulation [3,7]	Reflects systemic inflammatory burden [13]

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Component	Key Findings	Pathophysiological Impact
Endothelial function	CRP reduces nitric oxide (NO) bioavailability [4,47]	Impaired vasodilation → endothelial dysfunction [4]
Vascular remodeling	CRP promotes vascular stiffness and tight junction formation [3]	Contributes to hypertension and atherosclerosis [3,47]
Cytokine interaction	CRP positively correlates with IL-6 and TNF-α [4,7]	Enhances endothelial activation and vascular injury [4]
HF biomarkers	IL-6, Galectin-3, soluble ST2 provide additional specificity [5,6]	Identify remodeling, fibrosis, and prognosis [5,6]

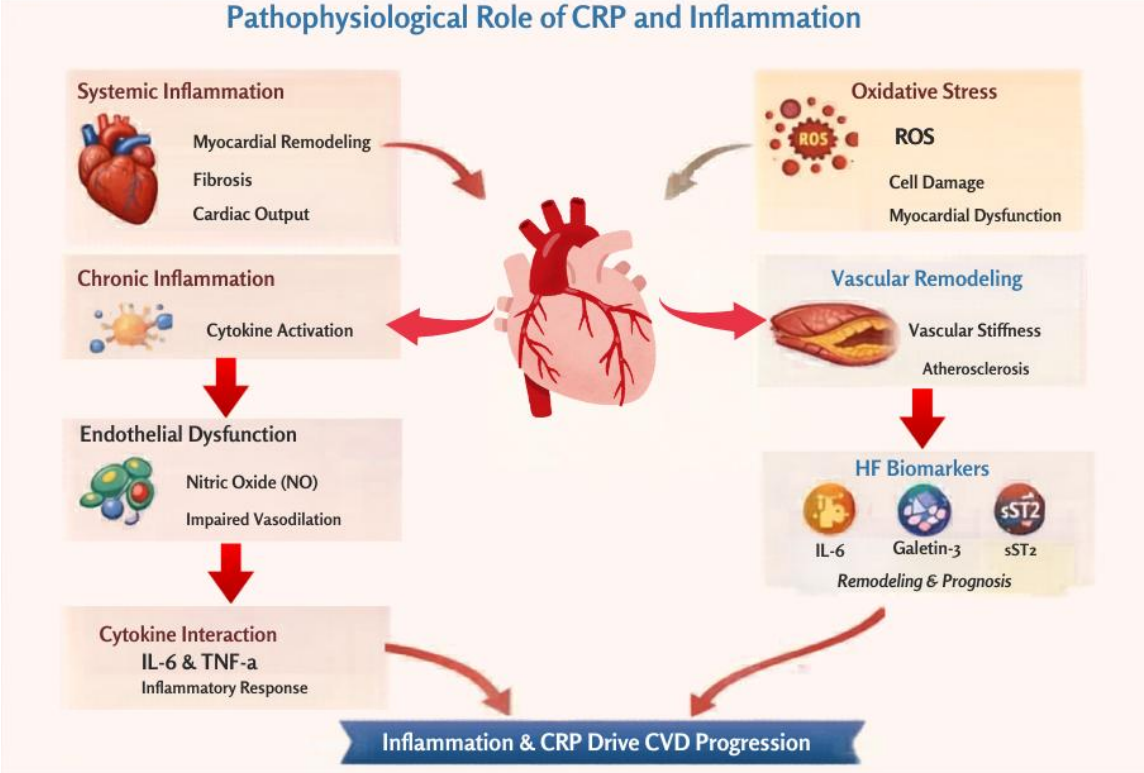


Figure 1. Pathophysiological role of CRP and inflammation in cardiovascular disease. CRP amplifies the inflammatory cycle through cytokine interaction, endothelial dysfunction, oxidative stress, and vascular remodeling.

1. CRP and Coronary Artery Disease (CAD):

High-sensitivity C-reactive protein (hs-CRP) is a well-established biomarker of inflammation in coronary artery disease (CAD), reflecting immune activation within atherosclerotic plaques. Elevated hs-CRP levels are associated with greater plaque burden and endothelial dysfunction, both central to atherogenesis **[7].** Prospective data indicate that individuals with hs-CRP ≥ 2 mg/L have a significantly higher risk

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of major adverse cardiovascular events compared with those with levels < 1 mg/L, even after lipid adjustment [8]. Intracoronary imaging studies using optical coherence tomography have demonstrated that patients in the highest hs-CRP tertile more frequently exhibit thin-cap fibro atheroma and lipid-rich plaques [9]. In acute coronary syndrome cohorts, elevated hs-CRP has been linked to a 1.5–2-fold increase in recurrent myocardial infarction risk [10]. Current European guidelines recognize hs-CRP as a risk modifier in intermediate-risk patients [11], and recent reviews confirm its incremental prognostic value beyond LDL cholesterol [12]. However, because hs-CRP may rise in non-cardiac inflammatory states, it should be interpreted as an indicator of residual inflammatory risk within a comprehensive clinical assessment.

2. Acute Myocardial Infarction (AMI) and hs-CRP:

Acute myocardial infarction (AMI) and acute coronary syndromes (ACS) are driven not only by coronary plaque rupture but also by an intense inflammatory response that amplifies myocardial injury. High-sensitivity C-reactive protein (hs-CRP), produced by hepatocytes under interleukin-6 stimulation, rises within hours after myocardial necrosis and typically peaks within 48–72 hours [13]. The 2023 guidelines of the European Society of Cardiology emphasize that inflammation plays a fundamental role in ACS pathophysiology, although hs-CRP is not recommended as a diagnostic marker; instead, it may assist in risk stratification [14].Large cohort studies published between 2022 and 2024 demonstrate that elevated hs-CRP at hospital admission independently predicts 30-day major adverse cardiovascular events (MACE), including death, recurrent infarction, and heart failure, even after adjustment for troponin and clinical risk factors [15],[16]. Patients in the highest hs-CRP quartile show approximately a twofold higher short-term mortality risk compared with those in the lowest quartile [15]. Serial measurements provide additional prognostic value. Persistent elevation or further rise of hs-CRP after primary percutaneous coronary intervention (PCI) correlates with larger infarct size, reduced left ventricular ejection fraction, and early adverse remodeling. Imaging-based studies confirm that higher inflammatory burden is associated with impaired ventricular recovery during follow-up [17]. Mechanistically, CRP reflects systemic inflammatory activation rather than acting as a direct causal factor in plaque rupture. Mendelian randomization analyses indicate no independent causal link between genetically elevated CRP levels and myocardial infarction risk [2]. However, clinical trials targeting inflammation demonstrate improved outcomes when inflammatory pathways are suppressed. Updated analyses of anti-inflammatory strategies confirm reductions in recurrent cardiovascular events when inflammatory signaling is modulated [18, 19]. Despite its prognostic relevance, hs-CRP has limitations. It lacks specificity and may be elevated in infection, trauma, or chronic inflammatory diseases. Timing of sampling influences interpretation, and standardized acute-phase cutoff values remain inconsistent across studies [15],[17]. Therefore, hs-CRP should be considered a complementary prognostic biomarker rather than a replacement for cardiac troponin in AMI management. Overall, contemporary evidence supports hs-CRP as an independent indicator of short-term risk following AMI, primarily reflecting the magnitude of post-infarction inflammatory activity that contributes to myocardial damage and early complications.

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3. Stable and Unstable Angina and hs-CRP:

Stable angina results from fixed, hemodynamically significant atherosclerotic stenosis with limited active inflammation. In this setting, circulating CRP concentrations are usually within normal limits or only mildly elevated, reflecting low-grade chronic vascular inflammation rather than acute plaque activity [14]. Because of this modest inflammatory profile, hs-CRP has limited diagnostic or short-term prognostic value in stable angina [12]. In contrast, unstable angina is characterized by plaque rupture or erosion with superimposed thrombosis and amplified inflammatory signaling. Multiple contemporary studies (2022–2024) report significantly higher hs-CRP levels in unstable angina compared with stable disease, linking elevated values to plaque instability and recurrent ischemic symptoms [20, 21]. Importantly, CRP elevation in unstable angina may occur before detectable myocardial necrosis, as cardiac troponin can remain within normal range in the absence of infarction. This supports the concept that hsCRP reflects systemic inflammatory activation rather than the extent of ischemic injury itself [12],[22]. Prospective cohort analyses demonstrate that patients with unstable angina in the highest hs-CRP categories have increased risk of progression to myocardial infarction and early adverse cardiovascular events [21],[23]. Recent data also show that composite inflammatory indices incorporating CRP—such as the CRP-to-albumin ratio—correlate independently with clinical severity and short-term outcomes in acute coronary syndromes [24]. These findings reinforce that CRP functions primarily as a marker of inflammatory burden. Mechanistic investigations and genetic analyses confirm that CRP is unlikely to be a direct causal mediator of plaque rupture; rather, it is a downstream acute-phase reactant induced by cytokine signaling during vascular inflammation [22]. Therefore, current evidence supports hs-CRP as a prognostic indicator in unstable angina but not as a standalone diagnostic tool. Its interpretation must consider confounding factors such as infection or systemic inflammatory disorders, which can falsely elevate levels. Overall, the distinction is clear: stable angina shows minimal inflammatory activation with limited CRP utility, whereas unstable angina demonstrates significant inflammatory involvement in which elevated hs-CRP provides independent prognostic information regarding disease severity and early complications.

4. Ischemic Stroke and Transient Ischemic Attack (TIA) and hs-CRP:

Ischemic stroke is strongly linked to vascular inflammation, and high-sensitivity C-reactive protein (hs-CRP) reflects this inflammatory burden. Large prospective cohorts show that individuals with elevated baseline hs-CRP have a significantly higher risk of future ischemic stroke, independent of age, hypertension, diabetes, and smoking [25],[13]. Data from population-based analyses such as the UK Biobank demonstrate that persistently rising CRP levels over time are associated with increased incident ischemic stroke, supporting CRP as a marker of chronic vascular inflammation rather than an acute fluctuation [26]. In patients with established ischemic stroke, admission hs-CRP independently predicts short-term mortality, recurrent stroke, and poor functional recovery at 3 months, even after adjustment for stroke severity and comorbidities [27],[28]. Studies published in journals affiliated with the American Heart Association confirm that patients in the highest

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hs-CRP categories have significantly greater risk of unfavorable neurological outcomes compared with those in lower categories [27]. The prognostic association is biologically plausible. Elevated CRP reflects activation of cytokine-mediated inflammatory pathways that contribute to endothelial dysfunction, plaque instability, and microvascular injury [13]. However, genetic and mechanistic evidence indicates that CRP itself is unlikely to be a direct causal factor; it is primarily a downstream inflammatory biomarker [29]. In transient ischemic attack (TIA), evidence is less robust. While elevated hs-CRP does not reliably diagnose TIA, higher levels may predict early recurrence or progression to stroke, suggesting a prognostic rather than diagnostic role [25],[28]. Recent meta-analyses (2022– 2024) show that composite inflammatory indices incorporating CRP—such as the CRP-to-albumin ratio— improve risk stratification. Higher ratios are consistently associated with increased mortality and greater post stroke disability [30]. Despite these associations, hs-CRP lacks disease specificity and may be elevated in infection or systemic inflammatory conditions, limiting its standalone clinical utility. Therefore, hs-CRP should be interpreted as an adjunctive prognostic marker reflecting inflammatory activity, not as a diagnostic test for ischemic stroke or TIA. Overall, contemporary evidence supports hs-CRP as an independent predictor of ischemic stroke risk and outcome, with stronger prognostic value in stroke than in TIA.

5. Hemorrhagic Stroke and hs-CRP:

Hemorrhagic stroke, including intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), differs fundamentally from ischemic stroke in pathophysiology. The primary event is vessel rupture rather than atherosclerotic plaque instability. Consequently, the association between high-sensitivity C-reactive protein (hsCRP) and hemorrhagic stroke is weaker and less consistent than in ischemic stroke [31]. Large prospective datasets such as the UK Biobank show that elevated or rising CRP strongly predicts ischemic stroke but demonstrates only modest or statistically non-significant associations with intracerebral hemorrhage after adjusting for hypertension, anticoagulant use, and other confounders [32]. Observational cohort studies (2022–2024) indicate that higher admission hs-CRP in ICH patients correlates with hematoma expansion, early neurological deterioration, and short-term mortality; however, effect sizes are smaller compared with ischemic stroke [33],[34]. Mendelian randomization analyses published in recent cardiovascular research journals report no convincing causal relationship between genetically elevated CRP levels and risk of spontaneous intracerebral bleeding [35]. This supports the interpretation that CRP elevation represents a secondary inflammatory response to tissue injury rather than a precipitating factor for hemorrhage.

Histopathological and clot-based investigations further demonstrate variable CRP expression within hematoma tissue, with no consistent pattern across hemorrhagic subtypes [36]. These findings reinforce that CRP reflects systemic inflammatory activation following vascular rupture and blood–brain barrier disruption. Meta-analyses conducted between 2022 and 2024 conclude that although elevated CRP is associated with worse functional outcome and higher mortality in ICH, its predictive value is moderate and inferior to established prognostic indicators such as hematoma volume and Glasgow Coma Scale score [37]. Importantly, CRP lacks specificity. Infection, trauma, or chronic inflammatory disorders may confound interpretation in

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hemorrhagic stroke patients. Therefore, hs-CRP should not be considered a diagnostic marker or causal mediator in hemorrhagic stroke. Overall, current evidence indicates that CRP has limited and mainly prognostic relevance in hemorrhagic stroke, with substantially weaker predictive strength compared with ischemic stroke.

6. Heart Failure (HFrEF and HFpEF) and hs-CRP:

Heart failure (HF), including reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF), is increasingly recognized as an inflammatory-mediated syndrome in addition to a hemodynamic disorder. Elevated high-sensitivity C-reactive protein (hs-CRP) reflects systemic inflammatory activation that contributes to myocardial remodeling and disease progression **[38].** Large population studies demonstrate that individuals with higher baseline hs-CRP have an increased long-term risk of developing incident heart failure, independent of hypertension, diabetes, and coronary artery disease **[39].** In established HF, elevated hs-CRP at baseline independently predicts short-term mortality and re-hospitalization. Contemporary cohort analyses (2022–2024) report that patients in the highest hs-CRP categories have significantly greater 6-month mortality compared with those in lower categories, even after adjusting for natriuretic peptides and left ventricular ejection fraction **[40].** A recent prognostic meta-analysis confirms that hs-CRP is associated with adverse cardiovascular events across both HFrEF and HFpEF, with consistent risk gradients for hospitalization and death. Importantly, the association persists in HFpEF, a phenotype strongly linked to systemic inflammation and metabolic dysfunction **[41].** Longitudinal evaluations show that persistently elevated CRP levels correlate with worsening functional class, impaired exercise tolerance, and reduced overall survival **[42].** These findings suggest that sustained inflammatory activity parallels ongoing myocardial injury and fibrosis. Mechanistic data indicate that CRP itself is unlikely to be a primary causal driver; rather, it serves as a downstream biomarker of cytokine-mediated inflammatory pathways involved in ventricular remodeling **[43].** Despite its prognostic value, hs-CRP lacks disease specificity and can be elevated by infection, obesity, or chronic inflammatory disorders. Therefore, it should complement—not replace—established HF biomarkers such as natriuretic peptides. Overall, current evidence supports hs-CRP as a reliable prognostic marker in both HFrEF and HFpEF, reflecting inflammatory burden and identifying patients at higher risk of hospitalization and mortality.

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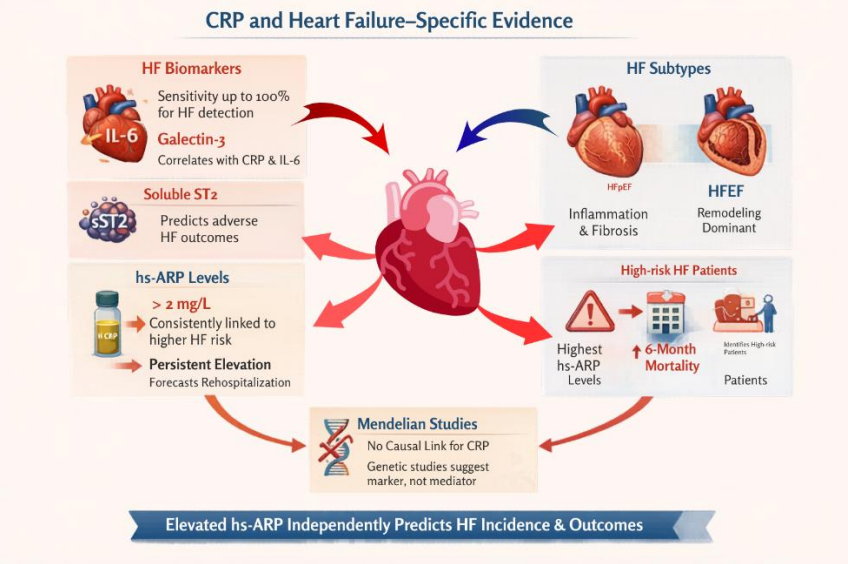


Figure 2. CRP and heart failure–specific evidence. Elevated hs-CRP independently predicts HF incidence and adverse outcomes across both HFrEF and HFpEF phenotypes, with Mendelian studies confirming its role as a prognostic marker rather than a causal mediator.

Table 2: ***CRP and Heart Failure–Specific Evidence.***

Aspect	Evidence Summary	Clinical Implication
IL-6	Sensitivity 100%, specificity 75.35% for HF in selected cohorts [5]	Strong predictive biomarker [5]
Galectin-3	Positively correlates with CRP and IL-6 [6]	Predicts incident HF and mortality [6]
Soluble ST2	Independent predictor of adverse HF outcomes [43]	Superior prognostic value in chronic HF [43]
hs-CRP and incident HF	Independent association across populations [39]	Risk stratification marker [39]
HF subtypes	HFpEF: inflammation & fibrosis-driven; HFrEF: remodeling-dominant [41,43]	Different inflammatory pathways require tailored monitoring [38,43]
Serial CRP levels	Persistent elevation associated with rehospitalization [40,42]	Prognostic monitoring tool [40]
Highest hs-CRP categories	Significantly increased 6-month mortality [40]	Identifies high-risk patients [40]
hs-CRP ≥ 2 mg/L	Associated with highest HF risk, particularly in HFpEF [41]	Threshold for elevated cardiovascular risk [8,41]

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Aspect	Evidence Summary	Clinical Implication
Mendelian randomization	No strong genetic causal link for CRP itself [2,43]	Suggests downstream marker rather than mediator [2]

7. Hypertensive Heart Disease / Chronic Hypertension and hs-CRP:

Chronic hypertension is associated with persistent low-grade systemic inflammation, reflected by modest but sustained elevations in high-sensitivity C-reactive protein (hs-CRP). This inflammatory activity contributes to vascular remodeling and hypertensive end-organ damage **[44]**. Population-based analyses published between 2022 and 2024 show that elevated hs-CRP alone confers only a moderate increase in cardiovascular risk; however, when combined with uncontrolled or long-standing hypertension, the risk of cardiovascular and all-cause mortality rises substantially **[7],[45]**. Large cohort data indicate a synergistic interaction: individuals with both high blood pressure and elevated hs-CRP have significantly poorer survival compared with those who exhibit either abnormality in isolation **[45]**. This interaction persists after adjustment for age, smoking, diabetes, and lipid levels. Longitudinal studies further demonstrate that concurrent increases in CRP and systolic blood pressure predict future coronary artery disease and broader cardiovascular events more strongly than either marker alone **[46]**. Mechanistic investigations suggest that CRP is linked to endothelial dysfunction, partly through reduced nitric oxide bioavailability and promotion of vascular inflammation, processes that accelerate arterial stiffness and left ventricular hypertrophy in hypertensive patients **[47]**.

Experimental and clinical research supports the concept that inflammatory activation amplifies blood-pressure– related vascular injury, thereby worsening hypertensive heart disease progression **[48]**. Despite these associations, Mendelian randomization and mechanistic reviews indicate that CRP is unlikely to be a primary causal agent in hypertension; rather, it reflects inflammatory signaling that modifies cardiovascular risk **[49]**. Clinically, hs-CRP should therefore be interpreted as an adjunctive risk stratification tool. Its greatest predictive value appears when evaluated alongside blood pressure control status rather than as an isolated biomarker. Overall, contemporary evidence supports a moderate but consistent role for hs-CRP as an inflammatory modifier that magnifies cardiovascular risk in patients with chronic hypertension and hypertensive heart disease.

8. Peripheral Artery Disease (PAD) and hs-CRP:

Peripheral artery disease (PAD) is a manifestation of systemic atherosclerosis in which inflammation contributes to plaque progression and thrombotic risk. High-sensitivity C-reactive protein (hs-CRP) reflects this inflammatory burden and has prognostic relevance in PAD, although it does not directly measure the anatomical severity of arterial stenosis **[50]**. Recent cohort studies (2022–2024) demonstrate that elevated hs-CRP levels independently predict major adverse cardiovascular events (MACE), including myocardial infarction, stroke, and cardiovascular death, in patients with established PAD **[51, 52]**. Importantly, inflammatory markers based on CRP appear more useful for predicting outcomes than for assessing the degree of limb ischemia or angiographic narrowing.

Composite indices such as the CRP-to-albumin ratio (CAR) have shown stronger

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prognostic performance than CRP alone. Contemporary analyses report that higher CAR values are independently associated with increased risk of limb-related events, including acute limb ischemia, need for revascularization, and amputation **[53]**.
Peri-procedural data indicate that patients with elevated CRP levels around the time of endovascular or surgical PAD interventions experience higher rates of early restenosis and limb complications **[54]**. Meta-analyses published between 2022 and 2024 confirm that CRP-related inflammatory indices consistently correlate with long-term mortality and limb loss in PAD populations **[55]**. These associations remain significant after adjustment for diabetes, smoking status, renal function, and ankle–brachial index. Mechanistically, CRP elevation reflects systemic inflammatory activation contributing to endothelial dysfunction, plaque instability, and thrombogenicity, rather than acting as a direct causal factor **[56]**.
Despite its prognostic utility, hs-CRP lacks specificity and can be elevated in infection or chronic inflammatory states. Therefore, it should complement established risk markers such as ankle–brachial index and clinical staging. Overall, contemporary evidence supports hs-CRP and derived ratios such as CAR as practical tools for identifying PAD patients at higher risk of cardiovascular and limb-related complications, rather than for quantifying stenosis severity.

9. Atrial Fibrillation (AF) and hs-CRP:

Atrial fibrillation (AF) is increasingly understood as a condition influenced by structural remodeling, electrical instability, and inflammatory activation. High-sensitivity C-reactive protein (hs-CRP) reflects systemic inflammation that may contribute to atrial fibrosis and conduction abnormalities **[57]**. Prospective cohort studies and pooled analyses published from 2022 onward report that individuals with elevated CRP have a modest but statistically significant higher risk of incident AF, with relative risk estimates generally between 1.2 and 1.3 after adjustment for conventional risk factors **[58, 59]**.This association supports the concept that inflammation participates in atrial substrate modification, although the magnitude of risk increase remains moderate rather than strong **[57, 58]**.
Among patients with established AF, higher hs-CRP concentrations are linked to increased rates of all-cause mortality and major adverse cardiovascular events (MACE), including stroke and heart failure hospitalization. However, effect sizes are modest compared with established predictors such as age, left atrial size, and comorbidity burden [60]. In the interventional setting, elevated pre-procedural CRP or CRP-based inflammatory indices independently predict AF recurrence after catheter ablation [61]. Patients with higher inflammatory markers show greater likelihood of arrhythmia persistence during follow-up. Mechanistic reviews indicate that CRP itself is unlikely to directly trigger AF; rather, it serves as a downstream marker of cytokine-mediated inflammatory pathways contributing to atrial remodeling [49]. Genetic evidence does not support a strong causal relationship. Importantly, hs-CRP lacks disease specificity and may be elevated due to infection, obesity, or systemic inflammatory disorders. Therefore, it should be considered an adjunctive prognostic biomarker rather than a diagnostic or causal factor in AF. Overall, contemporary evidence indicates that CRP provides modest prognostic information in AF, reflecting inflammatory activity that influences arrhythmia development and recurrence, but with limited standalone predictive strength.

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10. Valvular Heart Disease (Degenerative Aortic Stenosis / TAVI) and hs-CRP:

Degenerative aortic stenosis is characterized by progressive valvular calcification and fibrosis, processes in which inflammation contributes but is not the sole driver. High-sensitivity C-reactive protein (hs-CRP) reflects systemic inflammatory burden rather than directly mediating valve degeneration **[62].**

In patients undergoing transcatheter aortic valve implantation (TAVI), observational studies from 2022–2024 consistently show that elevated pre-procedural hs-CRP is independently associated with increased 1-year mortality **[63, 64].** This association persists after adjustment for age, left ventricular function, renal status, and procedural variables. Higher baseline CRP levels also correlate with frailty markers and comorbidity burden, suggesting that systemic inflammation partly reflects overall physiological vulnerability rather than valve pathology alone **[62, 63].**

Recent cohort analyses demonstrate that the CRP-to-albumin ratio (CAR), which integrates inflammatory and nutritional status, provides stronger prognostic discrimination than CRP alone for predicting post-TAVI adverse outcomes **[65].** Patients in the highest CAR categories show greater risk of early complications, rehospitalization, and mortality. Meta-analytic data confirm that inflammatory biomarkers measured before TAVI are associated with both short-term and long-term mortality, though the predictive strength is moderate rather than definitive **[66].** Integrating hs-CRP into established procedural risk models improves discrimination for adverse events beyond conventional scores such as surgical risk estimators **[67].** This suggests additive value in pre-procedural risk stratification.

However, mechanistic and genetic analyses do not support a direct causal role for CRP in aortic valve calcification or disease progression **[68].** CRP elevation likely represents systemic inflammatory activation related to aging, comorbidities, and vascular disease. Importantly, CRP lacks disease specificity and may be elevated due to infection or chronic inflammatory conditions, limiting its standalone utility. Therefore, hs-CRP and derived ratios should be considered adjunctive prognostic tools rather than diagnostic or causal indicators in degenerative aortic stenosis.

Overall, contemporary evidence supports CRP-based measures for pre-procedural risk assessment and outcome prediction in TAVI populations, with moderate prognostic value but no proven mechanistic role in valvular degeneration.

11. Cardiomyopathies (Dilated, Hypertrophic, Restrictive) and hs-CRP:

Cardiomyopathies comprise heterogeneous myocardial disorders, including dilated (DCM), hypertrophic (HCM), and restrictive forms, each with distinct mechanisms. The relationship between high-sensitivity C-reactive protein (hs-CRP) and outcomes varies by subtype and underlying etiology **[69].** In dilated cardiomyopathy—particularly non-ischemic and inflammatory variants—elevated hs-CRP is more frequently observed, reflecting cytokine-mediated myocardial injury and adverse ventricular remodeling **[70].** Contemporary reviews (2022– 2024) identify CRP as part of multimarker panels used for risk stratification in DCM, although its standalone specificity remains limited **[71].**

Prospective cardiac magnetic resonance (CMR) studies in non-ischemic DCM show that higher CRP levels correlate with impaired myocardial strain, increased fibrosis markers, and worse clinical outcomes during follow-up **[72].** These findings support

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a prognostic, rather than diagnostic, function. In inflammatory cardiomyopathy, concurrent elevation of CRP and cardiac troponin, together with CMR evidence of edema or late gadolinium enhancement, indicates active myocardial injury and increased risk of heart failure progression or arrhythmia [73].

In hypertrophic cardiomyopathy, associations between hs-CRP and adverse events are weaker and less consistent, with inflammation considered a secondary modifier rather than a central mechanism [74]. Data in restrictive cardiomyopathy are limited, and CRP elevation often reflects systemic comorbidities rather than myocardial pathology itself [69].

Mechanistic analyses indicate that CRP is unlikely to directly cause cardiomyopathy; instead, it acts as a downstream biomarker of inflammatory signaling pathways involved in myocardial remodeling [75].

Importantly, hs-CRP lacks disease specificity and may be elevated in infection, obesity, or systemic inflammatory disorders, limiting its diagnostic value across cardiomyopathy phenotypes.

Overall, current evidence supports hs-CRP as a subtype-dependent prognostic marker—most relevant in inflammatory and non-ischemic DCM—while lacking universal applicability across all cardiomyopathies.

12 Myocarditis:

Myocarditis is an inflammatory disease of the myocardium most commonly triggered by viral infection, immune dysregulation, or systemic inflammatory disorders. The pathological hallmark is myocardial inflammation with associated myocyte injury, which may lead to acute heart failure, arrhythmias, or dilated cardiomyopathy [76].

C-reactive protein (CRP) frequently increases during the acute phase of myocarditis, reflecting systemic inflammatory activation rather than myocardial-specific damage [77]. Contemporary studies published after 2022 confirm that elevated CRP levels correlate with active myocardial inflammation but lack specificity for differentiating myocarditis from acute coronary syndromes or other inflammatory cardiac conditions [78].

Because CRP is synthesized by the liver in response to interleukin-6 and other cytokines, its elevation indicates systemic inflammatory burden rather than direct cardiomyocyte necrosis [77]. High-sensitivity assays detect low-grade inflammation, but they do not distinguish infectious from immune-mediated causes [79].

The 2023 position statement from the European Society of Cardiology emphasizes that CRP should not be used as a standalone diagnostic marker for myocarditis. Diagnosis requires integration of clinical presentation, cardiac troponins, electrocardiographic findings, echocardiography, and particularly cardiac magnetic resonance imaging (CMR) [76].

Recent observational cohorts indicate that higher CRP concentrations are associated with more extensive myocardial edema on CMR and reduced left ventricular ejection fraction during acute presentation [78]. However, the marker does not reliably predict etiology or histopathological subtype [79]. Serial measurement appears more clinically useful than isolated values. Declining CRP levels during hospitalization are generally associated with clinical stabilization and recovery of

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ventricular function. In contrast, persistently elevated CRP may indicate ongoing inflammatory activity or increased risk of adverse remodeling [80]. Importantly, CRP elevation also occurs in systemic infections and autoimmune diseases, limiting its diagnostic precision [77]. Therefore, its value lies primarily in monitoring inflammatory activity and supporting prognostic assessment rather than confirming myocarditis.

Overall, current evidence supports CRP as an adjunctive biomarker in myocarditis management, interpreted alongside imaging findings, cardiac biomarkers, and clinical evolution.

13. Pericarditis:

Acute pericarditis is an inflammatory condition of the pericardial sac, most commonly caused by viral infection, autoimmune disorders, or post-cardiac injury syndromes. The diagnosis is primarily clinical, based on chest pain characteristics, pericardial friction rub, electrocardiographic changes, and imaging evidence of pericardial inflammation or effusion [81].

C-reactive protein (CRP) is a routinely measured biomarker that reflects active pericardial inflammation. Elevated CRP levels are frequently observed during the acute phase and support the diagnosis when interpreted alongside clinical and imaging findings [82]. However, CRP elevation is not specific to pericarditis and must be differentiated from myocardial infarction, systemic infection, or other inflammatory conditions [79].

The 2022–2023 recommendations from the European Society of Cardiology emphasize that CRP measurement is useful both at baseline and during follow-up [81]. Serial CRP testing provides objective evidence of inflammatory activity and treatment response [82]. A progressive decline in CRP concentrations typically parallels symptomatic improvement and resolution of pericardial inflammation [83]. Conversely, persistently elevated CRP after initiation of anti-inflammatory therapy suggests incomplete suppression of inflammation and increased risk of recurrence [83]. Contemporary cohort studies demonstrate that discontinuing therapy before normalization of CRP significantly raises relapse rates, particularly in recurrent pericarditis [84].

CRP normalization is therefore commonly used as a biochemical target to guide duration of nonsteroidal anti-inflammatory drugs (NSAIDs) or colchicine therapy [82]. Nonetheless, clinical judgment remains essential, as symptom resolution and imaging findings must also be considered [81].

Importantly, CRP should not be used in isolation to confirm or exclude pericarditis [79]. Instead, it functions as an adjunctive biomarker that complements physical examination, electrocardiography, echocardiography, and, when necessary, cardiac magnetic resonance imaging [81].

Overall, current evidence supports CRP as a validated and practical marker for monitoring inflammatory activity and guiding therapeutic decisions in pericarditis, while recognizing its lack of disease specificity.

14. Infective Endocarditis:

Infective endocarditis (IE) is a life-threatening infection of the endocardial surface, typically involving cardiac valves and associated with high morbidity and mortality despite advances in antimicrobial therapy. Diagnosis relies on clinical assessment,

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blood cultures, and echocardiographic findings according to contemporary guideline criteria [85].

C-reactive protein (CRP) is commonly elevated in IE due to intense systemic inflammatory activation triggered by microbial invasion [86]. Although CRP lacks specificity for IE diagnosis, elevated levels reflect inflammatory burden and disease severity [87]. Recent multicenter cohort studies published after 2022 demonstrate that higher CRP concentrations at hospital admission are independently associated with increased risk of heart failure, embolic events, and in-hospital mortality [87].

The 2023 scientific update from the European Society of Cardiology indicates that inflammatory markers, including CRP, support clinical assessment but must not replace microbiological confirmation or imaging [85]. Elevated CRP alone cannot distinguish IE from other systemic infections or inflammatory cardiac disorders [86].

Emerging evidence suggests that the CRP-to-albumin ratio improves prognostic stratification by integrating inflammatory intensity and nutritional status [88]. Higher ratios have been linked to greater risk of adverse outcomes, prolonged hospitalization, and mortality [88].

Serial CRP measurement during antimicrobial therapy provides practical monitoring value [89]. A consistent decline in CRP typically correlates with effective infection control and clinical stabilization [89]. In contrast, persistently elevated or rising CRP levels may indicate inadequate antimicrobial response, abscess formation, or metastatic infection [87].

However, CRP trends must be interpreted alongside blood culture results and repeat echocardiography, particularly when complications such as valve destruction or perivalvular extension are suspected [85].

Overall, current evidence supports CRP as a prognostic and monitoring biomarker in infective endocarditis. Its role is complementary, aiding risk assessment and therapeutic evaluation rather than serving as a primary diagnostic criterion.

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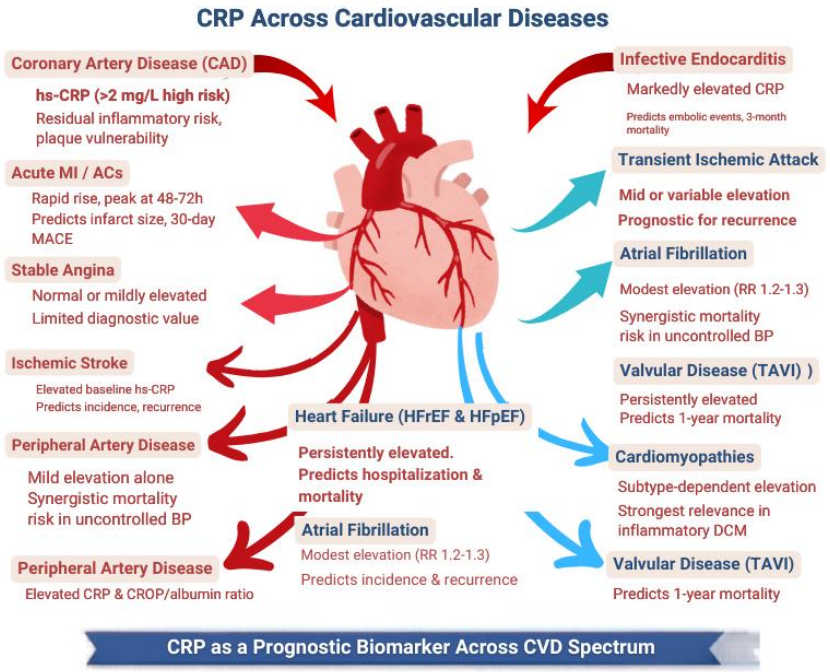


Table 3: ***CRP Across Cardiovascular Diseases: Level Patterns and Clinical Roles.***

Condition	CRP Level Pattern	Main Clinical Role
Coronary artery disease (CAD)	↑ hs-CRP (≥2 mg/L high risk) [8]	Residual inflammatory risk, plaque vulnerability [7,8,9]
Acute MI / ACS	Rapid rise, peak at 48–72 h [13]	Predicts infarct size, 30-day MACE (~2× mortality in highest quartile) [15,16,17]
Stable angina	Normal or mildly elevated [14]	Limited diagnostic value; reflects chronic low-grade inflammation [12,14]
Unstable angina	Markedly elevated [20,21]	Plaque instability and progression to MI; may precede troponin rise [21,22,23]
Ischemic stroke	Elevated baseline hs-CRP [25,26]	Predicts incidence, recurrence, 3-month mortality [27,28,30]
TIA	Mild or variable elevation [25]	Prognostic for early recurrence or progression to stroke [25,28]
Hemorrhagic stroke	Weak/modest association [31,32]	Reflects secondary inflammation; no causal role; moderate prognostic value [33,34,35,37]

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Condition	CRP Level Pattern	Main Clinical Role
Heart failure (HFrEF & HFpEF)	Persistently elevated [39,40]	Strong predictor of hospitalization & mortality in both subtypes [40,41,42]
Hypertension	Mild elevation; synergistic with uncontrolled BP [45,46]	Synergistic mortality risk; amplifies BP-related vascular injury [7,45,46]
Peripheral artery disease (PAD)	Elevated CRP & CRP/albumin ratio [51,52,53]	Predicts MACE, limb ischemia, amputation; CAR outperforms CRP alone [53,54,55]
Atrial fibrillation	Modest elevation (RR 1.2–1.3) [58,59]	Predicts incidence & post-ablation recurrence; modest effect size [58,59,60,61]
Valvular disease (TAVI)	Elevated pre-procedure CRP [63,64]	Predicts 1-year mortality; CAR improves discrimination [63,64,65,66]
Cardiomyopathies	Subtype-dependent elevation [69,70]	Strongest prognostic value in inflammatory and non-ischemic DCM [70,71,72,73]
Myocarditis	Acute elevation; correlates with myocardial edema on CMR [77,78]	Monitoring inflammatory activity; serial decline indicates recovery [77,79,80]
Pericarditis	Elevated during active inflammation [82,83]	Guides NSAID/colchicine therapy duration; normalization = treatment endpoint [81,82,83,84]
Infective endocarditis	Markedly elevated CRP [86,87]	Predicts embolic events, mortality; CAR enhances stratification; serial decline confirms response [87,88,89]

RESEARCH GAPS

Research on High-sensitivity C-reactive protein (hs-CRP) in Cardiovascular Disease shows strong associations with adverse outcomes, but several critical gaps remain. Evidence from Mendelian randomization studies indicates that CRP mainly reflects underlying inflammation rather than acting as a direct causal factor in vascular injury. In addition, measurement practices are inconsistent because sampling time, assay platforms, and study populations differ, preventing universally accepted clinical thresholds. The prognostic value of hs-CRP also varies by disease; it has stronger predictive relevance in Coronary Artery Disease and Ischemic Stroke, but contributes less additional risk information in Atrial Fibrillation and Hemorrhagic Stroke, and few guidelines provide condition-specific algorithms for its use. Global

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clinical integration remains uneven, particularly in low- and middle-income countries where standardized risk models often exclude hs-CRP despite rising cardiovascular burden. Furthermore, most available studies are observational and concentrated in Western populations, while large randomized trials and data from high-risk groups such as South Asians and Africans remain limited.

FUTURE RESEARCH DIRECTIONS

Improving clinical use of High-sensitivity C-reactive protein in Cardiovascular Disease requires progress in several areas. Molecular studies must clarify how inflammatory pathways contribute to endothelial damage, plaque rupture, myocardial fibrosis, and electrical remodeling of the heart. Risk prediction could improve through multimarker panels combining hs-CRP with cytokines such as Interleukin- 6 and Tumor Necrosis Factor- alpha, along with fibrosis indicators like Galectin- 3. Clinical application also requires standardized hs-CRP thresholds and defined testing intervals after events such as Acute Myocardial Infarction or coronary interventions. Large randomized trials targeting inflammatory signaling are necessary to determine whether reducing hs-CRP improves patient outcomes rather than simply lowering a laboratory value. Integration of inflammatory biomarkers into AI-based precision medicine models may help identify patients who benefit most from anti-inflammatory therapies. Finally, long-term cohort studies in underrepresented populations, including South Asia and Sub-Saharan Africa, are required to establish population-specific thresholds and clarify whether persistent hs-CRP elevation predicts future cardiovascular complications more reliably than temporary increases.

CONCLUSION

hs-CRP provides meaningful prognostic information across the full cardiovascular disease spectrum, from coronary artery disease and heart failure to stroke, arrhythmias, and infectious cardiac conditions. Its predictive strength is greatest in ischemic and inflammatory disorders, moderate in heart failure and peripheral artery disease, and modest in hemorrhagic stroke and atrial fibrillation. Mendelian randomization evidence consistently positions CRP as a downstream inflammatory marker rather than a causal disease driver. Composite indices such as the CRP-to-albumin ratio improve prognostic precision by incorporating nutritional status alongside inflammatory burden. As an adjunctive tool, hs-CRP should be interpreted within a full clinical, biochemical, and imaging framework rather than used in isolation. Embedding it in multimarker models and coupling its use with targeted anti-inflammatory trials remains the most promising path toward translating this inflammatory signal into better patient outcomes.

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