Heart failure (HF) affects 5.1 million people in the USA, with an estimated cost of $32 billion each year [1]. Despite pharmacological advancements and interventional therapy, morbidity and mortality rates remain markedly high. Given that half of those who develop HF die within 5 years of diagnosis, effective prognostic and management strategies become even more critical.

HF is traditionally defined as a hemodynamic disorder caused by a dysfunction in ventricular filling or reduced ejection fraction. However, recent data suggest a more complex syndrome involving genetic, neurohormonal and biochemical changes acting on both cardiac myocytes and interstitium [2]. Moreover, growing evidence now supports inflammation as a key factor in the progression of chronic HF. The association between HF and inflammation was first reported in 1956, demonstrating a positive correlation between levels of C-reactive protein (CRP), a nonspecific acute phase protein produced by hepatocytes at times of inflammation, and severity of HF [3]. Since that first observation, additional inflammatory cytokines such as IL-1, IL-6 and TNF-α have all been linked to HF [4,5]. Several hypotheses have been proposed to explain the underlying mechanism of inflammation involved in HF. One such hypothesis explores the role of endotoxins and its release into circulation by bacteria translocated from the gut caused by bowel wall edema [4]. Endotoxin, also known as lipopolysaccharide, has been shown to induce TNF-α and other proinflammatory mediators in a dose-dependent manner in mild-to-moderate HF [5]. The cytokine hypothesis proposes that ischemic cardiac injury triggers a stress response resulting in release of proinflammatory cytokines (TNF-α, IL-1, IL-6, IL-18) by the damaged myocardium, leading to such detrimental effects as myocyte apoptosis and necrosis. IL-6 has been shown to induce myocyte hypertrophy, myocardial dysfunction and muscle wasting; whereas TNF-α has been shown to cause left ventricular dysfunction, left ventricular remodeling and myocyte apoptosis (Figure 1) [4]. Consequently, hypoperfused skeletal muscle and ischemia as a result of reduced cardiac output enhance the detrimental effects by releasing more of the same proinflammatory cytokines and causing further cell damage to the myocardium. Thus, a
Elevated CRP has been closely associated with rheumatological conditions in addition to atherosclerosis and cardiovascular risk. CRP is primarily synthesized in the liver in response to a rise in proinflammatory cytokine IL-6 at times of major infections, trauma, surgery and other inflammatory conditions. However, there is also evidence of local CRP production in extrahepatocytes, including vascular smooth muscle, respiratory epithelial cells, renal epithelium and neuronal cells, where CRP may impair the expression of nitric oxide synthase, reduce nitric oxide release and upregulate endothelial expressions of chemokines.

Since the discovery of CRP as an important mediator of inflammation and worsening HF, studies have investigated therapeutic modalities to modulate clinical outcomes in patients with HF. Traditional assays of CRP have been used but did not have the capability to detect basal levels. High-sensitivity CRP (hsCRP) is currently used, which more accurately measures basal concentrations to better stratify cardiovascular risk.

**Prognostic implications**

Elevated CRP has been associated with worse outcomes and is imputed to be a predictor of future development of HF in high-risk populations. Elderly patients with the highest concentrations of CRP were found to be at 2.64-times greater risk for developing HF when compared to the lowest. The Val-HeFt study demonstrated a direct correlation between elevated plasma CRP level and heart failure severity. Patients with CRP above 3.23 mg/l had greater indices of HF severity: lower left ventricular ejection fraction, higher heart rate, higher prevalence of atrial fibrillation and NYHA classes III or IV. Furthermore, increasing risk of death and first morbid event (defined as death, sudden death with resuscitation, hospitalization for HF or administration of an intravenous inotropic or vasodilator drug for 4 h or more without hospitalization) was also observed in patients with rise in CRP over time.

Higher CRP is also associated with worse prognosis in the setting of acute decompensated HF. There is a positive correlation between risk of death and HF readmissions within 3 months (hazard ratio [HR] 2.46; 95% CI: 1.29–4.70) in patients with CRP >12 mg/l compared to those with lower levels; reducing these levels could theoretically reverse remodeling and improve prognosis in patients with HF. Multiple studies supporting an association between CRP elevations and severity of HF, the modulation of CRP levels and therapeutic effect on clinical outcomes has become an important topic of current and future interest. Whether CRP has a role beyond prognosis and can be used in the management of HF will be further discussed.

**Experimental studies**

Interventional animal studies have been conducted to explore the inflammatory pathophysiology of CRP in HF and to evaluate potential treatment options for future HF therapy. Of particular interest has been the question whether CRP contributes to the inflammatory pathophysiology or is merely a marker of disease. Unfortunately, direct evaluation of the role of CRP in animals has been limited by species-specific differences in CRP activity. In humans, CRP exists primarily as a pentamer of five identical polypeptide subunits, each containing 206 amino acid residues. The murine version of CRP, however, exists at different concentrations.

The murine version of CRP, however, exists at different concentrations. The murine version of CRP, however, exists at different concentrations. The murine version of CRP, however, exists at different concentrations. However, murine CRP interacts with low-density lipoproteins (LDL) and complement to accelerate the progression of atherosclerotic lesions. Conversely, mice have functionally different LDL particles and murine CRP may be unable to interact with complement. In a study of genetically modified mice that lacked the CRP gene, investigators actually observed a trend toward increased atherosclerotic lesions, suggesting a potential protective role of endogenous CRP in the mouse.

Concentrations of human CRP increase up to 1000-fold within 24–48 h of tissue injury and represent a sensitive, but a nonspecific marker of inflammation. However, murine CRP does not appear to behave as an acute phase reactant and

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**Figure 1. The cytokine hypothesis of heart failure.**

CRP: C-reactive protein; IL-1: Interleukin-1; IL-6: Interleukin-6; IL-18: Interleukin-18; TNF-α: Tumor necrosis factor-α.

Adapted from [2].
becomes only modestly elevated to values approaching the upper limit of normal in human patients (2 mg/l) in models of severe inflammatory injury [18]. Therefore, evaluations of CRP in mouse models have traditionally been confined to administration of exogenous human CRP or to transgenic expression of human CRP. In either case, these models may not accurately reflect the pathophysiology of endogenous CRP activity in mice – let alone be translatable to human pathophysiology.

Given the limitations of murine CRP evaluations, numerous investigators have taken to rabbit experiments. Rabbit CRP behaves as an acute phase reactant (similar to human CRP) and demonstrates similar interactions between LDL, complement and atherosclerotic lesions [20]. However, in a study of rabbits that were genetically modified to express increasing amounts of human CRP, investigators found no association between CRP concentration and coronary atherosclerosis [20]. Subsequent evaluations of CRP overexpression in rabbits undergoing surgical coronary ligation found no association between CRP concentration, infarct size or plasma markers of cardiac injury [21]. These findings dampen the enthusiasm for CRP as a target for pharmacological intervention and support the notion that CRP may indeed be only a marker of systemic inflammation.

Another approach to preclinical evaluation of the role of CRP in HF pathophysiology involves targeting upstream stimulators of CRP. IL-1 is an apical proinflammatory cytokine that regulates CRP activity via induction of IL-6. In preclinical models of experimental myocardial infarction (by surgical ligation of the left coronary artery), genetically modified mice that lack the IL-1 receptor experienced reduced cardiomyocyte apoptosis and reduced cardiac remodeling, whereas genetically modified mice with enhanced IL-1 activity experienced increased apoptosis, contractile dysfunction and cardiac remodeling [22]. A separate series of investigations confirmed that pharmacologic blockade of the IL-1 receptor ameliorated cardiac remodeling following surgical coronary ligation [23–25]. These results led to the design and conduct of two pilot clinical trials in patients with ST-segment elevation myocardial infarction, combined n = 40 patients) in which 14 days of treatment with recombinant IL-1 receptor antagonist (anakinra, KINERET®) led to a marked reduction of CRP and a reduction in new-onset HF at 12 weeks after ST-segment elevation myocardial infarction [26,27]. Similar treatment regimen in 182 patients with non-ST-segment elevation myocardial infarction also observed a significant reduction in the primary endpoint of CRP area under the curve [28]. Additional pilot studies of IL-1 blockade in patients with HF show a preliminary benefit in aerobic exercise capacity (peak VO₂) accompanied by significant CRP reduction [12,29,30].

**MicroRNA, inflammatory cytokines & HF**

Emerging evidence suggests micro-RNAs (miRNA), short non-coding mRNAs, to have important regulatory role in the pathogenesis of HF. Binding of miRNA to its complementary mRNA results in the inhibition of target gene expression and preventing mRNA translation [31]. Animal models, particularly mice studies involving transverse aortic constriction–induced hypertrophy, have shown to have a dysregulation of a specific group of miRNA [31,32]. In addition, alterations of miRNA and mutations in miRNA processing enzyme (dicer) have been associated with the progression of HF and abnormal cardiovascular development, respectively [32]. Although there is evidence of abundant expression of certain miRNA in the heart, T-cells, B-cells, monocytes and miRNA upregulation on activation of NF-kB (an important transcription factor for the increased expression of TNF-α, IL-1 and IL-6) [33], there are currently no data to suggest a correlation between miRNA with CRP levels. Data to support miRNA and its role in the inflammatory process are preliminary. Further research is still needed to elucidate the relationship between miRNA and proinflammatory cytokines in HF.

### Clinical Studies

#### Standard therapies

Angiotensin-converting enzymes inhibitors, angiotensin receptor blockers and β-blockers are all evidence-based therapies for the management of HF [34]. However, their effect on inflammation has only recently been studied. The role of CRP was first evaluated in patient samples from Val-HeFT to determine the anti-inflammatory effects of angiotensin-converting enzymes inhibitors and angiotensin receptor blockers on plasma CRP and long-term outcome in patients with HF [14]. A significant reduction in CRP was observed in patients with HF treated with valsartan alone for 12 months, in contrast to those receiving angiotensin-converting enzymes inhibitors in combination with valsartan. These findings suggest no additional benefit with combination therapy. More importantly, the modulation of CRP was not found to be predictive of patient outcomes.

β-blockers have also been evaluated for their potential anti-inflammatory role. The anti-inflammatory properties of carvedilol have been explored in ischemic cardiomyopathy, using inflammatory and hemodynamic stress markers to predict treatment outcomes in patients with chronic HF [35]. In β-blocker-naïve patients with left ventricular ejection function <40%, carvedilol was initiated for 12 months to assess its effect on biomarkers, risk of CHF exacerbation and long-term mortality. In addition to observing a decrease of inflammatory biomarkers, CRP was found to be inversely related to left ventricular function. A reduction in CRP from baseline with carvedilol therapy was associated with improved left ventricular function. Given the modest sample size of this study, more data are needed to determine the treatment effect of β-blockers on CRP in HF.

#### Statins

Beyond lipid lowering, statins also reduce inflammation through its pleiotropic effects [Table 1]. Statins have been extensively studied in patients with coronary artery disease and other atherosclerotic-related diseases, but not HF. Because the JUPITER trial demonstrated that patients on rosuvastatin [36] achieving hsCRP <2 mg/l had a 62% decrease in cardiovascular event, a similar approach to CRP was also explored in patients with HF.

These anti-inflammatory effects and the potential downregulation of CRP associated with statins were examined in patients...
<table>
<thead>
<tr>
<th>Study of year</th>
<th>Therapy/intervention</th>
<th>CHF etiology</th>
<th>Study design</th>
<th>Sample size</th>
<th>Study duration</th>
<th>Main outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>White et al. (2006)</td>
<td>Dobutamine vs milrinone</td>
<td>ADHF</td>
<td>Prospective, randomized, double-blind, placebo-controlled</td>
<td>29</td>
<td>72 h</td>
<td>IL-6, IL-18, CRP – Improved 6MWT</td>
<td>[55]</td>
</tr>
<tr>
<td>Chow et al. (2011)</td>
<td>Nitroglycerin versus Nesiritide</td>
<td>ADHF</td>
<td>Open-label, prospective, randomized trial</td>
<td>66</td>
<td>48 h</td>
<td>IL-6 with NES No significant Δ in CRP, TNF-α between groups</td>
<td>[54]</td>
</tr>
<tr>
<td>Inder S. Anand (Val-HeFT) (2005)</td>
<td>Valsartan</td>
<td>Heart failure (HF) NYHA Class II-IV, LVEF &lt;40%</td>
<td>Retrospective analysis</td>
<td>5010</td>
<td>12 months</td>
<td>CRP w/Valsartan – no significant change seen in pts ACEI and Valsartan</td>
<td>[14]</td>
</tr>
<tr>
<td>Sola et al. (2006)</td>
<td>Atorvastatin</td>
<td>Non ischemic HF, EF &lt;35%</td>
<td>Prospective, randomized, placebo-controlled</td>
<td>108</td>
<td>12 months</td>
<td>CRP, TNF-α, IL-6, E-SOD</td>
<td>[37]</td>
</tr>
<tr>
<td>Bleske et al. (2006)</td>
<td></td>
<td>Nonischemic cardiomyopathy</td>
<td>Prospective, randomized, placebo-controlled</td>
<td>15</td>
<td>12 weeks</td>
<td>LDL Non-significant reductions in CRP, BNP</td>
<td>[38]</td>
</tr>
<tr>
<td>Mc Murray et al. (2009)</td>
<td>Rosuvastatin</td>
<td>Congestive HF</td>
<td>Retrospective analysis of CORONA</td>
<td>4961</td>
<td>Median follow-up 2.7 years</td>
<td>Significant Δ CRP in patients with elevated baseline CRP &gt;2 mg/L.</td>
<td>[40]</td>
</tr>
<tr>
<td>GISSI Investigators (2008)</td>
<td>Chronic HF, NYHA Class II-IV</td>
<td>Prospective, randomized, placebo-controlled</td>
<td></td>
<td>4574</td>
<td>Median follow-up 3.9 years</td>
<td>No significant difference in time to death, or admission to hospital for cardiovascular event</td>
<td>[41]</td>
</tr>
<tr>
<td>Nessler et al. (2013)</td>
<td>Carvedilol</td>
<td>Chronic HF</td>
<td>Prospective</td>
<td>86</td>
<td>12 months, total follow up period of 9 ± 3 years from baseline</td>
<td>CRP were associated with LVEF improvement – Higher BNP was associated with increased mortality – Increase of TNF associated with frequent admissions</td>
<td>[35]</td>
</tr>
<tr>
<td>Moreira et al. (METIS) Trial (2009)</td>
<td>Methotrexate</td>
<td>Ischemic HF</td>
<td>Randomized double-blind</td>
<td>50</td>
<td>12 weeks</td>
<td>No significant improvement in 6MWT, CRP, or NYHA Class</td>
<td>[45]</td>
</tr>
</tbody>
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ACDF: Acute decompensated heart failure; BNP: Brain natriuretic peptide; CRP: C-reactive protein; HF: Heart failure; IL-6: Interleukin -6; IL-18: Interleukin -18; LVEF: Left ventricular ejection fraction; 6MWT: Six minute walk test; NT-Pro BNP: N-terminal pro-brain natriuretic peptide; SNRI: Serotonin/norepinephrine reuptake inhibitor; SOD: Erythrocyte superoxide dismutase; SSRI: Selective serotonin reuptake inhibitors; TCA: Tricylic antidepressants; TNF-α: Tumor necrosis factor-α.
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<th>Ref.</th>
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<tr>
<td>Gong et al. (2006)</td>
<td></td>
<td>Congestive HF</td>
<td>Prospective, randomized, placebo-controlled, single blind trial</td>
<td>71</td>
<td>12 weeks</td>
<td>↓ TNF-α ↓ IL-6 ↓ CRP Significant improvements in NYHA, 6MWT, QOL scores</td>
<td>[44]</td>
</tr>
<tr>
<td>Tousoulis et al. (2009)</td>
<td>SSRI versus SNRI versus TCA</td>
<td>Congestive HF</td>
<td>Prospective, placebo-controlled</td>
<td>250</td>
<td>6 months</td>
<td>&gt; of CRP and TNF α in TCA/SNRI compared to SSRI and those without depression ↓ Heart rate in with TCA/SNRI compared with SSRI and without depression</td>
<td>[48]</td>
</tr>
<tr>
<td>Sliwa et al. (2004)</td>
<td>Pentoxifylline</td>
<td>Ischemic HF</td>
<td>Prospective, randomized, double-blind, placebo-controlled</td>
<td>38</td>
<td>6 Months</td>
<td>↓ CRP, NT-pro BNP, TNF-α, Fas/Apo-1 Improvement in functional class, systolic blood pressure, and increase LVED</td>
<td>[47]</td>
</tr>
<tr>
<td>Amin et al. (2013)</td>
<td>Vitamin D supplementations</td>
<td>Congestive HF with Insufficient/Deficient Vitamin D</td>
<td>Prospective</td>
<td>100</td>
<td>4 Months</td>
<td>↓ serum Vit D ↓ pro-BNP ↓ CRP Improved NYHA Improved 6MWT</td>
<td>[49]</td>
</tr>
<tr>
<td>Toblli et al. (2007)</td>
<td>IV Iron</td>
<td>Chronic HF (with anemia and renal failure)</td>
<td>Prospective, randomized, double-blind, placebo-controlled</td>
<td>40</td>
<td>5 Weeks</td>
<td>↓ NT-pro BNP ↓ CRP Improved LVEF, 6MWT and fewer hospitalization with iron</td>
<td>[51]</td>
</tr>
<tr>
<td>Sarafian et al. (2007)</td>
<td>Magnesium</td>
<td>Normomagnesemic Chronic systolic HF</td>
<td>Prospective, randomized, placebo-controlled</td>
<td>35</td>
<td>5 weeks</td>
<td>↓ CRP levels</td>
<td>[50]</td>
</tr>
<tr>
<td>Ma et al. (2013)</td>
<td>Xinmailong (Herb)</td>
<td>Congestive HF</td>
<td>Prospective, randomized, placebo-controlled</td>
<td>121</td>
<td>15 days</td>
<td>↓ CRP levels ↓ Angiotensin II levels ↓ NT-Pro BNP ↓ LVEF</td>
<td>[52]</td>
</tr>
<tr>
<td>Chung et al. (ATTACH). (2003)</td>
<td>Infliximab</td>
<td>Congestive HF</td>
<td>Prospective, randomized, placebo-controlled</td>
<td>150</td>
<td>8-week treatment follow-up 28 weeks</td>
<td>No improvement in clinical outcomes Increased risk for death from any cause or hospitalization</td>
<td>[46]</td>
</tr>
</tbody>
</table>

ACDF: Acute decompensated heart failure; BNP: Brain natriuretic peptide; CRP: C-reactive protein; HF: Heart failure; IL-6: Interleukin-6; IL-18: Interleukin-18; LVEF: Left ventricular ejection fraction; 6MWT: Six minute walk test; NT-Pro BNP: N-terminal pro-brain natriuretic peptide; SNRI: Serotonin/norepinephrine reuptake inhibitor; SOD: Erythrocyte superoxide dismutase; SSRI: Selective serotonin reuptake inhibitors; TCA: Tricyclic antidepressants; TNF-α: Tumor necrosis factor-α.
with nonischemic cardiomyopathy randomized to atorvastatin or placebo. However, preliminary studies showed conflicting results. Although atorvastatin dosed at 20 mg/day demonstrated significant reductions in hsCRP and other markers of inflammation over 12 months, other data suggest that this is dependent on the severity of dyslipidemia at baseline and that moderate lowering of LDL (<160 mg/dl) may not influence hsCRP [37,38].

In an analysis of the CORONA study [39,40], the use of prespecified cut points (hsCRP levels of <2.0 mg/l or >2.0 mg/l) was used to stratify patients with ischemic HF based on risk. Those with CRP >2.0 at baseline demonstrated a 33% reduction with rosuvastatin at 3 months compared with 11.1% with placebo. Moreover, a significant reduction in the primary outcome (cardiovascular death, myocardial infarction and stroke) was observed in this group (unadjusted HR of placebo to rosuvastatin, 0.87; 95% CI: 0.77–0.98; p = 0.024). This was not observed in those with hsCRP <2.0, which demonstrated only modest lowering of CRP (~6%) compared with placebo (27%). Furthermore, stratifying patients by hsCRP did not lower risk of the primary endpoint. Higher nor low hsCRP groups showed any significant reduction in all-cause mortality even though LDL was reduced by 47% in both groups.

Similar to the CORONA study, the larger scale GISSI-HF trial also compared rosuvastatin 10 mg/day with placebo in 4574 patients with chronic HF for a median of 3.9 years [41]. Rosuvastatin significantly reduced hsCRP by 0.45 mg/dl at 3 months (p = 0.019) compared to a nonsignificant reduction of 0.1 mg/dl with placebo. Similarly, changes in hsCRP over time did not translate into improved outcomes. No significant risk reduction in time to death or hospital admission was observed in either group.

Whether the differences in outcomes are related to etiology of HF or age is still unclear; however, certain HF subgroups may influence hsCRP downregulation to varying degrees [42]. In a pooled analysis, statins not only decreased hsCRP (standard mean difference −0.74; 95% CI: -1.16 to −0.32; p = 0.0005), but patients >60 years, HF of ischemic etiology and higher baseline left ventricular ejection function >30% received the greatest benefit from statins through the downregulation of hsCRP. Duration of treatment is also an important factor when modulating hsCRP. The meta-analysis found atorvastatin >12 months to be superior to shorter interval therapy of other statins. This may be because of the ability of statins to reduce hsCRP levels by inhibiting the nuclear-kB pathway [43].

Immunomodulators

Nonspecific immunomodulators were also explored for their potential effects on CRP. Methotrexate was initiated as adjunct to conventional therapy in patients with chronic HF, and effects on CRP were measured at 12 weeks [44]. Patients receiving adjuvant therapy with methotrexate had improvements in NYHA class, 6-min walk test, quality of life general scores, physical health score and accompanied decrease of inflammatory cytokines (TNF-α, IL-6 and CRP) when compared with baseline and control subjects. Although these results appeared to demonstrate that methotrexate, when added to conventional therapy, may provide additional benefits in the downregulation of inflammatory effects resulting in improvement in functional status, results were not consistent [45]. Therefore, results may be too preliminary to determine whether any therapeutic benefit through CRP lowering can be achieved with nonspecific immunomodulators in HF.

A more focused approach has also been explored by targeting specific inflammatory cytokines. Data demonstrating deleterious effects of TNF-α in HF have prompted investigators to study the effects of neutralizing TNF-α on outcomes in the ATTACH trial [46]. The study found that neither dose of 5 mg/kg and 10 mg/kg of infliximab improved clinical status in 14 or 28 weeks, despite reductions of CRP. Furthermore, patients receiving infliximab 10 mg/kg had a worsening in their clinical status and were at an increased risk for mortality and hospitalization caused by HF compared with placebo (HR 2.84; 95% CI: 1.02–7.97). Treatment with both doses of infliximab was associated with a reduction in CRP within the first week; however, levels gradually returned to baseline by the end of the study indicating that compensatory or off-target mechanisms may have counteracted the effects of TNF-α blockade.

Other therapies

Other nontraditional therapies and supplements have been studied in several randomized studies in patients with chronic HF [47–52]. However, despite CRP-lowering effects, a correlation between clinical outcomes and CRP could not be established. More recently, a meta-analysis of randomized clinical trials did not detect any association between baseline CRP concentrations and treatment effect on mortality, readmission or the composite of mortality and readmissions [53]. These data suggest that CRP may be suitable as a marker of prognosis but should not be used to guide therapy in patients with CHF.

Acute HF

Despite the large number of inconclusive clinical trials exploring CRP response to treatment in the setting of chronic HF, even less is known about it in patients with acute HF (AHF). hsCRP concentrations have been found to be as much as 5-times higher on admission in patients with AHF than CHF and decreases with treatment using inotropes and vasodilators with differential effects [54,55]. However, although these therapies reduced CRP in the setting of AHF, any potential treatment effect of CRP on mortality could not be established given limitations in sample size. More data are needed to determine the potential role of CRP in patients with AHF.

Expert commentary & five-year view

Current evidence to support therapeutic response based on CRP levels are lacking in both CHF and AHF, and do not suggest that CRP reductions translate to improved clinical
outcomes. Most clinical trials evaluated a combination of inflammatory and natriuretic peptides to determine treatment effects and associated improvement in clinical status or worsening HF. As a result, it becomes difficult to distinguish whether improved clinical outcomes are a result of CRP lowering, attenuation of the inflammatory cascade, or from therapy itself.

Although CRP levels may not yet hold clinical significance for CRP-targeted therapy, consistent data supporting the association between elevated hsCRP and other inflammatory markers to worsen outcomes in HF suggest future potential as a multimarker panel to better predict prognosis. In advanced chronic HF, the use of multimarkers may be a stronger predictor for risk stratification. Combining hsCRP with natriuretic peptides with or without other prognostic markers could identify those at greatest risk for mortality. Additional investigation is warranted before any recommendations can be made with respect to CRP-guided therapy.

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Key issues

- Heart failure (HF) remains a public health issue with high rates of morbidity and mortality. Half of those who develop HF die within 5 years of diagnosis.
- Traditionally seen as a hemodynamic disorder, recent evidence suggests an inflammatory process involving proinflammatory cytokines (TNF-α, IL-1, IL-6 and IL-18) and the inflammatory marker, C-reactive protein (CRP) on the progression of chronic HF.
- Proinflammatory cytokines have detrimental effects on the myocardium, including myocyte apoptosis and necrosis, myocardial dysfunction, hypertrophy and left ventricular dysfunction.
- Of the biomarkers identified, CRP has been most extensively studied in cardiovascular disease. Recently, more data have come to suggest that elevated CRP levels to be associated with worst outcome and poor prognosis in HF.
- Several interventional studies have been investigated to explore potential treatment effects and health outcomes from CRP modulation.
- Animal studies have been limited due to species-specific differences in CRP molecular size and activity and may not accurately reflect the pathophysiology in humans. Rabbit CRP demonstrates similar activity to human CRP; however, studies in these animal models did not detect an association between elevated concentrations of CRP and atherosclerosis, infarct size and plasma markers of cardiac injury.
- Several interventional clinical trials were able to show improvements in functional status in patients with HF, with an associated decrease in CRP levels and other proinflammatory mediators, such as IL-6, TNF- α and BNP. However, many of the results were inconsistent and preliminary. Additional larger studies are warranted to understand the role of CRP in HF and confirm the results before CRP-targeted therapy may be recommended.
- Consistent data supporting the association of elevated CRP and other inflammatory markers to be stronger predictors of prognosis and outcomes provide implications for multimarker panel to be of greater clinical tool for risk stratification in patients with HF.

References


