REVIEW

The usefulness of C-reactive protein for the prediction of post-infarct left ventricular systolic dysfunction and heart failure

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Abstract

Acute myocardial infarction (MI) provokes a systemic inflammatory response that may contribute to the development of left ventricular systolic dysfunction (LVSD) and heart failure (HF). Patients with post-infarct HF with concomitant LVSD have the most unfavourable long-term prognosis. Measurement of C-reactive protein (CRP) concentration reflecting an involvement of inflammatory pathways in post-infarct myocardial damage offers an attractive strategy to improve risk stratification and clinical decision-making for early management of high-risk patients. Despite growing evidence for the prognostic value of CRP both as a single factor and as a component of multi-marker approach in MI, CRP measurement is not yet incorporated into current guidelines. This may be due to conflicting results reported in existing studies related to various limitations in study designs, such as retrospective case control design, prior myocardial damage, CRP measurement with low-sensitivity assays, non-homogenous populations with acute coronary syndromes, different treatment strategies, small sample sizes, and the lack of left ventricular ejection fraction assessment and long-term clinical and echocardiographic monitoring. As a result, previous studies have not provided conclusive evidence of the prognostic value of CRP for post-infarct LVSD or HF. Future studies with an adequate design including upstream mediators of inflammation as inflammatory markers are needed to identify the best biomarker-based strategies for identifying high-risk patients. Further clinical trials involving anti-inflammatory therapies targeting different pathways of inflammatory activation in MI should test the inflammatory hypothesis of post-infarct LVSD and HF. Identifying high-risk patients with persistent post-infarct inflammatory response may allow incorporation of pathophysiological guidance for implementation of personalised treatment approaches.

Key words: acute myocardial infarction, left ventricular function, heart failure, echocardiography, C-reactive protein, inflammation

Kardiol Pol 2018; 76, 5: 821–829

INTRODUCTION

Despite the progressive decline of mortality in patients with myocardial infarction (MI) due to frequent use of reperfusion therapies including primary percutaneous coronary intervention (PCI) and other potent evidence-based management, post-infarct left ventricular systolic dysfunction (LVSD) and heart failure (HF) are still common complications [1–8]. Depending on the time point of assessment, diagnostic criteria, and therapeutic approach, the prevalence of LVSD post-infarct has been estimated at between 15% and 60% [2, 3, 5, 6, 9, 10]. LVSD after MI has been identified as a significant marker of poor prognosis associated with at least a three- to four-fold increase in cardiovascular (CV) mortality and risk of HF [2, 4, 6, 9, 10]. Decreased left ventricular ejection fraction (LVEF) present in echocardiography at hospital discharge after MI is a well-recognised marker of early LVSD and an independent prognostic factor of patient outcomes with regard to re-infarction, re-hospitalisation, and cardiac death [2, 4–6, 9, 10]. Moreover, the incidence of post-infarct HF is still approximately 28% [1, 2, 6, 7]. HF following an MI affects both in-hospital and long-term mortality and morbidity [1, 2, 6–8]. Even in the era of commonly used evidence-based therapies,

patients with post-infarct HF with concomitant LVSD have the most unfavourable long-term prognosis [1, 2, 6–8]. Early identification of high-risk patients using proven prognostic factors is of utmost importance because it allows for institution of preventive strategies.

Pathophysiology of post-infarct LVSD and HF is multifactorial and not clearly understood [8, 11–13]. However, it is currently known that the following processes are involved: myocardial injury associated with infarct size, myocardial stress resulting in neurohormonal activation including sympathetic overstimulation and increased levels of natriuretic peptides, left ventricular remodelling (LVR) as a result of myocyte death and abnormal renewal of extracellular matrix, and oxidative stress [11, 12]. Current theories for understanding the mechanism of damage caused by MI also emphasise the role of local and systemic inflammation [12, 14–19]. Acute MI is associated with intense inflammatory response, which is essential for cardiac repair, involving activation of toll-like receptor signalling, complement activation, generation of reactive oxygen species, cytokine and chemokine upregulation, leukocyte and macrophage recruitment, and activation of the fibrosis process [14, 15]. However, overactive or prolonged post-infarct inflammatory response might trigger further cardiac damage, resulting in LVR, progressive LVSD, and possibly the development of HF [14–18, 20].

C-reactive protein (CRP) is the most extensively studied biomarker of inflammation in atherosclerotic cardiovascular diseases (CVDs) [17–30]. CRP is an acute phase protein that is released predominantly by hepatocytes in response to inflammatory cytokines such as interleukin (IL)-6 and tumour necrosis factor α (TNF-α) [18, 20, 21, 23]. It has become the preferred inflammatory biomarker due to its long half-life, standardised laboratory assays, and prognostic data based on the results of observations from stratifying patients with, or at risk of, CVD [13, 17–30]. CRP measurement reflecting the involvement of inflammatory pathways of myocardial damage offers an attractive strategy to improve risk stratification and clinical decision-making for management of post-infarct patients with the highest risk for adverse outcomes [16, 17, 20, 21, 31]. However, despite growing evidence for the prognostic value of CRP in acute coronary syndromes (ACSs), CRP measurement is not yet incorporated into current guidelines when defining the standard of care for treatment post-MI.

CRP FOR CV RISK ASSESSMENT

There is evidence that inflammation plays a critical role in atherogenesis and subsequent atherosclerotic CV events [18]. Low-grade inflammation precedes the onset of vascular events [24, 27]. Given that even a slightly elevated CRP concentration (≥ 2 mg/L) can reveal lower levels of inflammation, it may be useful for determining further CV risk [24–28, 30]. The results of existing studies have shown that CRP concentration is associated with the long-term risk of a first atherosclerotic

CV event in a general population without known CVD and with recurrent CV events in patients with established disease [22, 24–28, 30, 32].

The JUPITER trial confirmed that men and women with elevated high-sensitivity CRP concentration (hsCRP) ≥ 2 mg/L but with low concentration of low-density lipoprotein cholesterol (LDL-C) are at substantial vascular risk [24]. Based on the meta-analysis by Buckley et al. [26], the evidence strongly indicates that CRP is associated with events of coronary heart disease (CHD). In addition, consistent evidence suggests that adding CRP to risk prediction models improves risk stratification, particularly among patients who are at intermediate risk based on traditional risk factors alone [26]. In a comprehensive meta-analysis of more than 50 prospective studies encompassing more than 160,000 subjects without any known history of CVD, elevated hsCRP was associated with an increase in risk of CHD and CV mortality [30]. Moreover, the magnitude of risk associated with one standard deviation in hsCRP elevation was similar to that observed for such elevation in blood pressure or total cholesterol level.

Based on this evidence, current United States CV screening guidelines suggest evaluation of hsCRP when additional risk information may be needed before the initiation of statin therapy [33]. The American College of Cardiology recommends testing hsCRP as class IIa for men > 50 years and women > 60 years of age with LDL-C < 130 mg/dL, without chronic kidney disease, diabetes, or hormone replacement therapy, and class IIb in asymptomatic intermediate-risk patients. Current guidelines of the European Society of Cardiology give hsCRP a class IIb recommendation, stating that hsCRP may be measured as part of refined risk assessment in patients with unusual or moderate CV risk profiles [34].

There is compelling evidence for an association between the elevated hsCRP and the long-term (follow-up of 4.8 years) risk of acute CV events such as CV death, MI, or stroke in patients with stable CHD [28]. Preprocedural hsCRP predicts long-term (up to 10-year follow-up) CV outcomes such as mortality, MI, stroke, and stent thrombosis in patients with stable CHD undergoing PCI with coronary artery stenting [29, 32].

CRP FOR PREDICTION OF ADVERSE OUTCOMES IN ACS

Rapidly accumulating evidence demonstrated the important role of CRP concentration for clinical risk stratification in patients with ACS with regard to mortality, recurrent MI, in-stent restenosis, and composite clinical endpoints [20, 21, 29, 31, 32, 35–44]. A meta-analysis by He et al. [36] indicated that higher early CRP concentration (within the first 72 h of ACS onset) increases long-term risk of recurrent CV events (including MI) or death, and may be a valuable prognostic predictor after ACS, including homogenous populations with MI. The finding by Schiele et al. [39] that a high CRP concentration combined with the GRACE risk score improves the

risk classification represents a useful contribution to clinical management of patients with ACS. Recently, Klingenberg et al. [40] found an improvement of 9% (or 11% in ST-segment elevation myocardial infarction [STEMI] patients) in identifying the risk of long-term mortality in patients with ACS referred for coronary angiography by applying a multi-marker approach. This approach included hsCRP as opposed to the GRACE score alone. According to a meta-analysis by Mincu et al. [37], preprocedural hsCRP could be a valuable predictor of global CV risk in patients with STEMI undergoing PCI and with up to 36 months of follow-up. The clinical endpoints in that study included in-hospital or follow-up all-cause mortality, recurrent MI, in-hospital target vessel revascularisation, as well as in-hospital or follow-up composite endpoints including death, target vessel revascularisation, recurrent MI, and stent-related complications. The levels of hsCRP and LDL-C have been shown to be independently related to the risk of recurrent events in several randomised trials focusing on conservative versus intensive statin therapy in patients post ACS [44]. In the TIMI 22 PROVE-IT trial, hsCRP measured 30 days after ACS was independently associated with the risk of CV death [44].

CRP FOR PREDICTION OF POST-INFARCT LVSD

There is currently some convincing evidence that evaluation of CRP concentration in patients with ACS, including those with MI, provides prognostic value in predicting the risk of developing LVSD in short-term and long-term follow-up [35, 37, 39, 41, 43, 45–48].

Several studies found a robust relationship between in-hospital CRP concentration and the presence of LVSD defined as LVEF < 40% at hospital discharge after ACS [35, 45, 46]. Lim et al. [35] found LVSD at discharge in 32% of patients with low-sensitivity CRP concentration measured on day 3 after admission in the third tertile of CRP compared to 8% with CRP in the first tertile of CRP (p < 0.001). This study involved a non-homogenous group of 754 patients with ACS, in which 54% of patients had STEMI but only 70% of them were treated with PCI. Aggelopoulos et al. [45] showed that an increase of 10 mg/L in CRP concentration during 12 h after admission for ACS independently predicted a 6% increase of risk for LVSD at discharge. However, this study has limitations that should be taken into consideration, such as inclusion of patients with unstable angina (22% of cases), retrospective case control design, prior symptoms of CHD in about 50% of patients, exclusion of patients with LVEF between 40% and 50%, and use of low-sensitivity assay for CRP measurement. In a study of 204 patients with STEMI, Swiatkiewicz et al. [46] demonstrated that the prevalence of LVSD at hospital discharge increased from low to higher tertiles of hsCRP at discharge (14.7% vs. 23.5% vs. 45.6%, p < 0.001). They concluded that the measurement of hsCRP at hospital discharge is a useful marker of LVSD at discharge with a greater discriminating value for early LVSD detection

than B-type natriuretic peptide (BNP) concentration. In contrast to earlier studies, the study of Swiatkiewicz et al. [46] was performed in a homogenous population with a first STEMI undergoing early successful PCI and discharged with guideline therapies. It was also based on rigorous selection criteria and excluded confounding factors that could affect cardiac injury and inflammatory response, including prior myocardial damage, active inflammatory process, and ongoing anti-inflammatory therapy.

In addition, other studies showed significant inverse correlations between early CRP concentration and LVEF assessed as a continuous variable during hospitalisation for ACS [39, 41]. Suleiman et al. [41] observed significantly lower LVEF at hospital discharge along with increasing quartiles of hsCRP within 12 to 24 h of symptom onset in 1044 patients hospitalised for an acute MI. However, factors such as inclusion of patients with various types of MI (70% of patients had STEMI), prior MI in 20% of patients, and application of reperfusion therapy (thrombolysis or PCI) only in half of the entire study group may have biased the results of this study. Similarly, in the study including a non-homogenous population of 1901 patients with ACS (STEMI was diagnosed in 50% of patients and only 30% underwent PCI), Schiele et al. [39] found lower LVEF assessed during angiography in patients with CRP concentration on admission in the fourth quartile compared to lower quartiles (p < 0.001).

Moreover, several studies demonstrated an inverse relationship between in-hospital CRP measurement and LVEF assessment after a long period of observation post-MI [42, 47, 48]. Ørn et al. [47] observed in 42 patients with first STEMI treated by PCI that CRP measured on day 2 and week 1 after admission significantly predicted LVEF in cardiac magnetic resonance imaging at two months. In 48 patients with STEMI undergoing PCI, Mather et al. [48] found hsCRP on day 7 to be the strongest independent predictor of LVEF at three months assessed by cardiac magnetic resonance imaging. Swiatkiewicz et al. [42] observed significantly higher hsCRP 24 h after admission and lower LVEF six months after hospital discharge post-STEMI in the group of patients with LVR at six months after discharge compared to patients without LVR.

The lack of correlation between in-hospital CRP concentration and LVEF reported in some studies [49, 50] could be caused by the presence of confounding factors such as heterogeneity of the investigated population and early timing of both CRP concentration measurements and LVEF assessment. However, the elevated CRP concentration was associated with left ventricular (LV) diastolic dysfunction after MI, suggesting that inflammation is related to post-infarct LVR independently of LVSF [49].

CRP FOR PREDICTION OF POST-INFARCT HF

There are data indicating a positive relationship between elevated CRP levels and the long-term risk of developing

new HF in different populations [12, 13, 19]. CRP also has a prognostic value in predicting adverse outcome in patients with existing HF [12, 13, 19, 51–53]. In addition, a few studies demonstrated an association between CRP levels and the risk of HF in patients with stable CHD [28, 54]. In the PEACE trial involving patients with stable CHD, partly after MI and receiving modern medical therapy, an elevated hsCRP was an independent predictor of new HF over a mean follow-up of 4.8 years, even after adjusting for baseline characteristics and treatments [28]. In the Heart and Soul Study, increased hsCRP was a risk factor for hospitalisation due to HF during a three-year follow-up of elderly outpatients with stable CHD, including those after MI [54]. This association was independent of concurrent CHD severity and appeared to be at least partially explained by abnormal LV diastolic function and increased filling pressures.

There is some evidence for an association between elevated CRP levels and incidence of HF after ACS, indicating that CRP may predict hospitalisation for HF [36, 38, 41, 44, 55]. A meta-analysis by He et al. [36] indicated that early CRP concentration may have prognostic value for long-term risk of HF assessed as a component of composite clinical endpoint after ACS. In the PROVE IT-TIMI 22 trial, the patients with ACS, including those with MI and hsCRP > 2 mg/L 30 days after ACS stabilisation, had a two-fold higher risk of developing new or worsening HF in the follow-up of 24 months [44].

Studies assessing the prognostic value of CRP in homogenous populations with MI focused mainly on adverse outcomes other than HF, such as mortality or recurrent MI. However, some studies have examined the relationship between in-hospital CRP concentration and risk of development of HF after acute MI [36, 38, 41, 55]. Moreover, only a few studies demonstrated an association between CRP and the occurrence of HF post-MI as a single clinical endpoint [38, 41, 55]. Suleiman et al. [41] showed that early hsCRP is a significant marker of long-term development of HF (defined as readmission to hospital for the management of HF during 23 months of follow-up) in 1044 patients with acute MI. In addition, hsCRP was shown to add remarkable prognostic information compared to conventional risk factors, including known clinical predictors of HF, pre-discharge LVEF, and recurrent MI during follow-up. Bursi et al. [55] found that hsCRP on admission for MI is associated with a significant increase in the risk of HF in a one-year follow-up, independently of factors such as age, MI severity, comorbidity, previous MI, and recurrent ischaemic events. Because hsCRP was not correlated with conventional measures of infarct size (such as Q waves, ST elevation, and troponin T or peak creatine kinase MB levels), its effect was unlikely to be mediated by these parameters. The findings of Bursi et al. [55] indicate that inflammatory processes play an independent role in the development of HF, and hsCRP measurement may assist in risk stratification after MI. Unfortunately, in-hospital LVEF was

not assessed in their study. Another study [38] that exclusively included STEMI patients concluded that hsCRP measurement has a minimal impact in predicting post-infarct HF. However, it was a retrospective analysis of a relatively short one-year follow-up of non-optimally treated patients (therapy with angiotensin convertase inhibitors was applied in less than half of the study population) with only a single-point hsCRP measurement on hospital admission.

CRP IN MULTI-MARKER APPROACH FOR PREDICTION OF POST-INFARCT HF

Currently available biomarkers reflecting several pathobiological processes that lead to post-infarct LVSD and HF help to identify the specific pathways involved in individual patients [12, 13, 19, 53]. Measurements of biomarkers, even those that are not independent predictors of risk, may be of clinical value because they provide information on the pathogenesis of LV damage and HF, and can aid in guiding management of treatment. The following biomarkers reflect different ongoing processes in injured myocardium: BNP (neurohormonal activation), soluble FMS-like tyrosine kinase receptor (vascular remodelling), hsCRP (inflammation), ST2 (myocyte stretch), cardiac-specific troponin I (myocyte injury), uric acid (oxidative stress), and creatinine (renal function) [12, 53]. In the PROVE IT-TIMI 22 trial, the patients with evidence of both persistent inflammation (increased hsCRP) and haemodynamic stress (elevated BNP) were at the highest risk for future HF post-ACS [44]. Thus, the two biomarkers, hsCRP and BNP, which reflect the different pathways in LV damage, yield complementary information regarding future risk. However, even among patients with low BNP, an increased hsCRP identified a sizeable high-risk subgroup within a patient population (40.6%) that would otherwise be deemed low-risk for HF or CV death. Therefore, combined use of both biomarkers may be useful in selecting patients for targeted novel treatments to prevent HF after ACS [44].

CRP INVOLVEMENT IN MI

Acute MI provokes an intense inflammatory response that contributes to cardiac repair; however, an overactivated inflammatory response may be involved in an extension of myocardial injury that is essential in the pathogenesis of post-infarct LVR, LVSD, and possibly HF [14–18, 20]. In response to myocardial necrosis, the inflammatory reaction involves the activation of chemokine and cytokine synthesis, the adhesion molecule expression on vascular endothelial cells, the complement cascade stimulating proinflammatory cytokines release (such as transforming growth factor-α, IL-1, and IL-6), and the recruitment of leukocytes. Then, the secretion of anti-inflammatory cytokines (such as IL-10, transforming growth factor-β) and the modulation of cardiac macrophages towards an anti-inflammatory phenotype play an important role in suppressing post-infarct inflammatory

response. Finally, activation of myofibroblasts and deposition of matrix proteins promote the healing from myocardial infarct, preserving the integrity and geometry of LV. A defect in the regulation of the post-infarct inflammatory response contributes to the temporal prolongation or spatial expansion of the inflammatory reaction, resulting in progressive LVR and worsening of LV function. In addition to demonstrating the level of inflammation, CRP is a useful biomarker because its increased levels indicate an aggravated inflammatory response that may predict adverse outcomes post-MI [15–17, 20, 21]. In fact, CRP seems to represent both a marker and a mediator of inflammatory reaction following MI [15–17, 20, 21].

C-reactive protein is released as a response to stimulation by IL-6 produced in the ischaemic zone during acute MI; thus, it may indicate the intensity of inflammatory reaction [16, 20, 21, 41, 43, 46, 50]. There is evidence that a rapid increase in CRP concentration during the first hours of MI is the main marker of intensity of inflammation in the infarcted area, which is an important determinant of post-infarct LV damage [16, 20, 21, 41–43, 46, 50]. It has been documented that there is a strong correlation among in-hospital CRP levels, infarct size, and an increase of biochemical markers of myocardial necrosis [20, 21, 41–43, 45, 47, 48, 50]. Ørn et al. [47] found that CRP concentration on day 2 after PCI was significantly correlated with infarct size in cardiac magnetic resonance at two months after STEMI, reflecting the degree of inflammation within the infarcted area. There is also evidence that increased CRP levels may be triggered by the presence of microvasculature obstruction following MI, as defined by an impairment of flow in damaged capillaries in the central infarct zone, resulting in slow diffusion from the necrotic myocardium [47, 48]. Ørn et al. [47] found significantly higher CRP levels in patients with persistent microvascular obstruction in cardiac magnetic resonance on day 2, and especially at week 1 after STEMI. In other studies that included patients with other types of ACS characterised by smaller areas of necrosis (for example, in unstable angina) or a lack thereof, no relationship was found between CRP levels and the markers of myocardial necrosis [49]. In such circumstances, CRP concentration (usually without much elevation) may be related to the presence of low-degree chronic inflammation in the vascular bed in the course of atherosclerosis or vulnerability of unstable plaques rather than the extent of myocardial necrosis.

There is a growing body of basic scientific evidence that CRP may directly contribute to myocardial injury during the infarction due to the pronecrotic and proatherogenic features increasing necrosis expansion [14–18, 21, 56–65]. It was reported that extremely severe inflammatory reaction during MI (with CRP ≥ 20 mg/dL) is an independent predictor of subacute cardiac rupture and ventricular aneurysm [16]. Although the increase in CRP level may be affected by the infarct size, these complications were more often seen in patients with a greater increase of CRP concentration compared to the maximal creatine kinase level, indicating an extensive infarct expansion [16]. In animal studies with an experimental model of MI, when an overexpression of human CRP was created, adverse LVR and LV dysfunction were demonstrated, although the infarct size was similar to the control [56]; whereas the inhibition of exogenous CRP with a specific antagonist or apheresis decreased the myocardial infarct size and cardiac dysfunction [16–18, 57]. CRP binding to phosphocholine groups of necrotic myocardium stimulates complement activation and increases the deposition of complement in the infarcted region, leading to expansion of necrosis in both settings, infarction, and ischaemia-reperfusion injury [15–17, 58, 59]. In vitro studies showed that CRP increases apoptotic rates, macrophage infiltration, expression of chemokines (such as monocyte chemoattractant protein 1) in vascular endothelial cells, and angiotensin II type I receptors in vascular smooth muscle cells [15–17, 60]. CRP also reduces bioavailability of nitric oxide, suppressing angiogenesis, and inhibits the differentiation, function, and survival of endothelial progenitor cells [15–17, 61, 62, 65]. CRP activates various signalling cascades, resulting in an increased expression of inflammatory cytokines, phagocytic activity, production of reactive oxygen species, and promotion of the renin-angiotensin system in the myocardium [15–17, 60, 61]. It becomes clear in a diabetic cardiomyopathy model that overexpression of CRP activates the renin-angiotensin system in the myocardium, enhances inflammation and oxidative stress, promotes fibrosis, and aggravates LV dysfunction [63].

Increased periprocedural CRP levels may be associated with elevated LV end-diastolic pressure in patients undergoing coronary angiography, or PCI with coronary artery stenting, which by itself can provoke an inflammatory response [29, 66]. This suggests that greater LV filling pressure, because of myocyte stretch during acute MI, may contribute to the association of CRP with HF [12, 66]. However, according to current literature, it is unlikely that the rapid increase of CRP level to such a great extent as seen during MI may be caused by the vasculature damage following PCI with an implantation of stents in the setting of acute MI [47].

The timing of hsCRP measurement in MI appears to be important for evaluating its association with subsequent CV outcomes [20, 21, 44]. The increase in hsCRP during MI may represent the acute-phase reaction to the necrosis (when hsCRP is measured within the first 24–72 h of MI), the underlying chronic inflammation that preceded MI (when hsCRP is measured in the early phase of MI), or persistent pro-inflammatory response post-MI (when hsCRP is measured ≥ one month after MI) [20, 21, 44]. HsCRP ≥ 2 mg/L measured ≥ one month after the index MI, by which time the initial necrosis and reactive inflammatory process had resolved, appears to indicate persistent pro-inflammatory activation beyond an acute phase of MI, which may be useful for determining further CV risk [23, 25, 44, 67]. Existing results

show the ability of hsCRP measured one month post-ACS to assess the risk for new HF in stable patients recovering after ACS [28, 44]. However, sufficient convincing evidence that persistent pro-inflammatory response following MI clearly plays a significant role in the development of post-infarct LVSD and HF in long-term follow-up is still lacking [67–72].

CRP AND ANTI-INFLAMMATORY STRATEGIES PREVENTING POST-INFARCT LVSD AND HF

While inflammation contributes significantly to atherosclerosis, an inhibition of inflammation with decreasing CRP concentrations should lower the rates of CV events [23, 25, 67–72]. Based on the results of the JUPITER trial, targeting the "residual inflammatory risk" was recognised as an important factor that should be considered during CV risk assessment in a healthy population [23–25]. The JUPITER study prospectively demonstrated that in a specific population (without pre-existing CVD or diabetes and a baseline LDL-C < 130 mg/dL, but with evidence of ongoing subclinical inflammation, as determined by hsCRP ≥ 2 mg/L), the largest reduction of 65% in the hazard of first-ever CV events (such as MI, stroke, need for arterial revascularisation, and all-cause mortality) after statin therapy was observed in patients who achieved both LDL-C < 70 mg/dL and hsCRP < 2 mg/L [24].

Ultimately, to test the inflammatory hypothesis of atherosclerosis, it is necessary to directly randomise patients to targeted anti-inflammatory therapies and demonstrate that pure inflammation inhibition with decreasing CRP but without lowering LDL-C reduces CV events [23, 25, 67–72]. Currently, it is difficult to advocate CRP as a primary target for therapy because there are no existing drugs that specifically influence CRP alone.

Thus, ongoing trials of inflammatory inhibition are focusing on targeting upstream mediators of inflammation (such as IL-1β, a pro-inflammatory cytokine that plays multiple roles in the atherothrombotic process) as potential treatments for CVD, rather than targeting CRP, the downstream biomarker [22, 67–72]. In this regard, CRP levels are a surrogate biomarker for upstream IL-6 and IL-1 activities.

Presently, several trials of targeted anti-inflammatory therapy in high-risk secondary prevention post-MI are ongoing and other trials are in the planning stages [22, 67–72]. The CANTOS and CIRT trials are the large-scale, hard outcome, randomised, placebo-controlled studies using targeted anti-inflammatory agents that reduce hsCRP and IL-6 (but have no impact on LDL-C) for an improvement of outcome in post-infarct patients [67, 68, 70, 72]. Together, CANTOS and CIRT will enroll more than 20,000 patients worldwide and are expected to provide sufficient evidence for the inflammatory hypothesis of atherothrombosis.

The CANTOS trial was the first study to demonstrate that reducing hsCRP, even in the absence of lipid lowering, prevents CV events in patients with stable CHD after previ-

ous MI, who remained at high vascular risk due to persistent elevations of hsCRP ≥ 2 mg/L despite contemporary secondary prevention strategies [67, 72]. The results of the CANTOS trial showed that decreasing inflammation by canakinumab, a human monoclonal antibody that selectively neutralises IL-1β, significantly reduces recurrent CV events (such as MI, stroke, or CV death) by 15% in 3.7 years of follow-up, with greater risk reduction among patients with larger hsCRP reduction. Moreover, the HsCRP ongoing trial, the sub-study of the CANTOS trial, enrolled patients after prior acute MI, who also had reduced LVEF < 50% and were symptomatic for HF, to prospectively assess exercise capacity, and LVEF and LV diastolic function in echocardiography during a 12-month follow-up [67, 70].

The ongoing CIRT trial is investigating whether taking low-dose methotrexate (an anti-inflammatory regimen without significant effects on lipid levels) reduces MI, stroke, and CV death (which are the primary clinical endpoints), and also hospitalisation for congestive HF (which is the secondary clinical endpoint) in long-term follow-up of patients with prior MI and either type 2 diabetes or metabolic syndrome known to have high risk on the basis of a persistent pro-inflammatory response [68]. Both observational and mechanistic studies suggest that low-dose methotrexate has clinically relevant anti-atherothrombotic effects and an ability to reduce TNF, IL-6, and CRP levels [68]. The potential clinical impact of CIRT is important because it has sufficient power to directly address HF in the inflammatory hypothesis of post-infarct LV damage. Thus, if this goal is successfully achieved, it will lead to major new directions for personalised CV treatment to decrease the risk of post-infarct HF.

The VCU-ART3 ongoing trial was designed to examine if anakinra, recombinant human IL-1 receptor antagonist, affects LVEF during 12 months after STEMI and if it can prevent new onset of HF in long-term follow-up [69].

If these anti-inflammatory regimens prove to reduce the CV events over an average follow-up period of three to five years, the results of ongoing studies would provide a novel therapeutic approach for the prevention of CV events, including HF, in post-infarct patients.

CONCLUDING REMARKS

Improving risk stratification post-MI is difficult and challenging in clinical practice. Biomarkers offer a desirable strategy in identifying early high-risk patients for adverse outcomes post-MI. Many existing studies show that CRP measurement is useful in predicting post-infarct LVSD or HF. Because CRP reflects inflammation, it provides additional value to conventional risk factors (such as LVEF, natriuretic peptides, troponin, or ST2) representing different pathophysiological processes involved in post-infarct myocardial injury. There is evidence that CRP, both as a single prognostic marker and as a component of a multi-marker strategy, improves risk stratification

for long-term prediction of post-infarct LVSD and HF. The findings of existing studies have important clinical implications because they recommend that patients with elevated CRP concentration during index MI, especially with existing LVSD, should receive more aggressive and personalised medical management.

However, despite the growing evidence of the prognostic value of CRP for the prediction of post-infarct LVSD and HF, the CRP measurement is not yet considered in current guidelines for defining the standards of care treatment in MI. This may be due to conflicting results reported in some studies related to various limitations in study designs, such as retrospective case control design, prior myocardial damage or coronary revascularisation, LVEF assessed as a continuous variable at an early single time point or not measured, single CRP measurement with low-sensitivity assays, non-homogenous populations with ACS, different treatment strategies, small sample sizes, and the lack of neurohormonal activation assessment and long-term clinical and echocardiographic monitoring. As a result, the studies with limitations have not provided sufficient evidence that CRP can serve as an independent predictor, give added value to a suite of multiple predictors, or improve reclassification of the predicted risk of long-term post-infarct LVSD and HF. There is an unmet need for well-designed epidemiological studies aimed at assessing the validity of inflammatory markers to determine the increased risk of post-infarct LVSD and HF in long-term follow-up in homogenous populations with MI after successful early PCI when discharged with guideline therapies.

FUTURE PERSPECTIVES

There is growing evidence that the phrase "lower is better" is true not only for LDL-C but also for biomarkers of inflammation. Thus, identifying high-risk patients with overactive or persistent post-infarct inflammatory response may allow the incorporation of pathophysiological guidance for implementation of personalised treatment approaches modifying inflammatory and fibrotic responses. Future studies with an adequate design and including upstream mediators of inflammation as inflammatory markers are needed to validate the relationship between an overactive and/or prolonged inflammatory activation and adverse outcome post-MI, and to identify the best biomarker-based strategies for identifying high-risk patients. These studies should be prospective observational cohort trials with rigorous selection criteria involving homogenous MI populations treated with guideline therapies, long-term echocardiographic and clinical follow-up, and an adequate sample size with high power calculation. The study design should specifically exclude confounding factors that could affect cardiac injury and inflammatory response, including prior myocardial damage, active inflammatory process, and ongoing anti-inflammatory therapy. Moreover, further clinical trials involving anti-inflammatory therapies

targeting different pathways of inflammatory activation in MI are needed to test the inflammatory hypothesis of long-term post-infarct LVSD and HF.

Conflict of interest: *none declared*

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