Serial Measurements of C-Reactive Protein After Acute Myocardial Infarction in Predicting One-Year Outcome

Olivera DIMITRIJEVIĆ,1 BS, Blagica Djorić STOJIĆEVSKI,2 MD, Svetlana IGNJATOVIC,3 PhD, and Nada Majkić SINGH,3 PhD

SUMMARY

Systemic markers of inflammation are considered reliable predictors of future coronary events in patients with acute myocardial infarction (AMI). The aim of this study was to evaluate the prognostic relevance of serial C-reactive protein (CRP) measurements in patients with ST-elevation AMI (STEMI) on one-year outcome. In 31 patients with STEMI, serial measurements of CRP were obtained, and for each patient, the following values were determined: (i) values at admission, up to 12 hours after symptom onset, (ii) maximal values obtained 24-72 hours after symptom onset (early acute values), and (iii) late acute values (96-120 hours after symptom onset). The combined endpoint was any new cardiovascular event, including death.

Early and late acute CRP levels were the only parameters found to be significantly higher in patients with an adverse outcome than in patients with a good outcome. A significantly higher rate of endpoint events was found in patients with elevated early (Hazard ratio [HR] 5.54, 95% CI 2.05-25.40; \( P = 0.007 \)) and late acute CRP (HR 9.01, 95% CI 1.66-19.56; \( P = 0.005 \)). Multiple logistic regression analysis identified only early acute CRP as an independent predictor of an unfavorable outcome (Odds ratio 8.00, 95% CI 1.15-55.60; \( P = 0.04 \)), after adjustment for established risk factors.

CRP level measured 24-72 hours after symptom onset is an independent predictor of one-year outcome in patients with STEMI. Values obtained later in the setting of STEMI do not add further prognostic information. CRP at admission is not related to long-term prognosis. (Int Heart J 2006; 47: 833-842)

Key words: Systemic markers of inflammation, C-reactive protein, ST-elevation acute myocardial infarction, Risk markers, Outcome

The acute coronary syndromes (ACS), which comprise unstable angina, myocardial infarction without ST-segment elevation, and myocardial infarction with ST-segment elevation, are multifactor diseases involving both thrombotic and inflammatory processes.1-4) Numerous studies have identified elevated levels of markers of inflammation as risk indicators for future cardiovascular events in
patients with acute myocardial infarction (AMI). Of these markers, C-reactive protein (CRP) has been the most widely studied, but other biochemical parameters that have also been proposed for risk stratification include white blood cell count, fibrinogen, cellular adhesion molecules, cytokines, and components of the complement system.\(^5,6\)

The data from several studies indicate that CRP is an important risk marker in patients with ST-segment elevation acute myocardial infarction (STEMI). The predictive value of CRP has been examined in different settings, including the short-term risk, long-term risk, and risk after revascularisation procedures.\(^7\)-\(^13\) Careful timing of sampling relative to the onset of symptoms was not performed routinely in some of the studies, and a broad range of cutoff values has been reported, concerning mostly the major endpoint events, which all may have implications for the interpretation of the results. CRP is synthesized in the liver as part of the acute phase response stimulated by interleukin-6, and a lag period before CRP levels begin to rise in the circulation was about 12 hours after the onset of pain in most of the AMI patients.\(^14\) CRP levels on admission, therefore, represent baseline CRP levels, ie, levels that are not the result of myocardial necrosis. As these levels are higher in individuals with recognized risk factors for ACS,\(^15\)-\(^23\) indicating that low-grade inflammation may play an important role in AMI onset, it might be of interest to investigate separately the possible prognostic values of inflammatory marker levels at admission, and levels when the acute phase response is fully developed.

The aim of this study was to establish cutoff points that best stratify STEMI patients into low and high risk groups for the recurrence of any new vascular event, including death, for CRP (i) at admission, (ii) during the early (24-72 hours after symptom onset) and (iii) during the late (96-120 hours after symptom onset) stage of AMI setting, and to evaluate their independent prognostic relevancies in terms of one-year outcome.

**METHODS**

**Study population:** The study population included 31 patients admitted to the intensive care unit of General Hospital Bor for suspected AMI. All patients met the following criteria for AMI diagnosis: prolonged central chest pain, elevated creatine kinase MB (CK-MB) level and ST elevation on electrocardiogram.\(^24\) None of the patients had any sign of interfering noncardiac diseases, such as inflammatory disorders, malignancy, infection, recent surgery, or trauma. Patients admitted up to 12 hours after symptom onset received streptokinase, unless contraindicated. All patients received antiplatelet therapy (aspirin or clopidogrel), unfractionated heparin, GP IIb/IIIa inhibitors, beta-blockers, and, if indi-
cated, oral ACE inhibitors. No anti-inflammatory drugs, except aspirin, were administered.

**Equipment, reagents, and procedures:** Venous blood samples were obtained at admission and then every 24 hours for 4-5 days. Cholesterol and CK-MB were determined immediately after venepuncture by standard methods. Serum samples for CRP determination were stored at -20 °C and assayed in a single batch at the end of the study. CRP was measured by a High Sensitivity CRP test performed on a Behring BN™ II Nephelometer (Dade Behring Marburg GmbH, Germany), using polystyrene particles coated with mouse monoclonal antibodies to CRP. The detection limit of the assay was 0.175 mg/L for measurements performed using a sample dilution of 1:20, and the upper reference limit assigned by the manufacturer was 2.87 mg/L.

For statistical analysis, CRP values were grouped in the following manner: (i) values obtained at admission, up to 12 hours after symptom onset, (ii) maximal values obtained 24-72 hours after symptom onset, when peak CRP is expected (early acute values), and (iii) late acute values (96-120 hours after symptom onset), when CRP tends to decrease.

During the in-hospital stay, the following relevant data (traditional risk factors for occurrence of cardiovascular events) were obtained for each patient: age, sex, smoking status, previous history of unstable angina, hypertension, and diabetes mellitus. All patients provided informed consent for participation in the study.

One-year outcome events were evaluated by direct contact with the patients who survived the AMI, and by examining their medical charts. For patients who died during the study, the date and cause of death were obtained from hospital records. The primary endpoint was the combination of death of any cause and any new vascular event (new episode of unstable angina requiring readmission to hospital, surgical revascularisation of myocardium, and new AMI), whichever came first during the one-year period of follow-up.

**Statistics:** Continuous variables are described as mean or median values, according to the manner of distribution. The degree of univariate association between dichotomous variables and endpoints was examined by Fisher's exact test. Comparisons between the 2 groups for continuous variables were performed with an unpaired t test and Mann-Whitney test, as appropriate. For continuous variables shown to be significantly different between the groups, cutoff points were established via a receiver operator characteristic (ROC) curve. These cutoffs were tested in survival analysis and included in multiple regression models. The Kaplan-Meier technique (log rank test) was applied in survival analysis. The multivariate association between variables (CRP and traditional risk factors: age, sex, smoking, hypercholesterolemia, hypertension, unstable angina, diabetes mellitus) and unfavorable outcome was evaluated with forward stepwise multiple
logistic regression analysis. For all tests, a two-tailed $P$ value $< 0.05$ was considered statistically significant.

**RESULTS**

A total of 31 patients (24 men and 7 women, mean age, 59 years, range, 33-78 years) were enrolled in the study according to the aforementioned criteria for AMI. Of them, 14 (45%) had a history of hypertension, 7 (23%) had a history of unstable angina, 4 (13%) had diabetes mellitus, and 15 (48%) reported being current smokers.

The median time from the onset of chest pain to admission was 9 (range, 1-48) hours. For 10 patients, the interval between symptom onset and admission exceeded 12 hours, and their data on admission were not included in the statistical analysis.

The time course of CRP levels showed 3 different patterns (Figure 1). In 17 (55%) patients (Figure 1a), typical acute phase response was recorded; CRP rose from admission, peaked between 24-72 hours after the onset of pain, and then decreased. In 9 (29%) patients, (Figure 1b) a persistent rise in CRP was observed, and in 5 (16%) patients, (Figure 1c) CRP levels remained normal or slightly elevated during the entire observation period.

At the end of the observation period (mean, 13.9 months, range, 12-15 months) one-year outcome was determined, and in 15 patients the following endpoint events were recorded: 4 patients died of cardiovascular causes, 1 had a new AMI, 8 had an episode of unstable angina requiring new admission to hospital,

![Figure 1. Patterns of CRP kinetics during the setting of acute myocardial infarction with ST-elevation: (a) typical acute phase response in 55% of patients, (b) persistently increasing pattern in 29% of patients, and (c) persistently normal or slightly elevated levels in 16% of patients.](image-url)
and 2 patients had undergone percutaneous transluminal coronary angioplasty (PTCA). Of the remaining 16, 14 were found to be free of cardiovascular events and 2 were lost to follow-up. During the follow-up period, all patients received secondary preventive treatment with aspirin or warfarin, statins, and nitrates and calcium-channel blockers, when necessary.

Comparison data for the patients who were free of cardiovascular events (good outcome) and those who had a primary endpoint (adverse outcome) during the follow-up period are presented in Table I. Patients with an adverse outcome had significantly higher median levels of early and late acute CRP. Levels of CRP at admission were not significantly different between the groups. In addition, patients who had a primary endpoint were older than patients who were free of coronary events. The values of other traditional risk factors were not significantly different between the groups. Since the early and late acute CRP levels were the only inflammatory parameters found to be significantly different between the groups, only these 2 values were further analyzed.

Using ROC curve analysis, the cutoff points were established to be 48.3 mg/L (sensitivity 75.0%, specificity 85.7%, area under the curve 0.79 ± 0.09) for early acute CRP and 18.5 mg/L (sensitivity 91.7%, specificity 69.2%, area under the curve 0.79 ± 0.09) for late acute CRP. These cutoffs were tested in survival analysis. It was found that the rate of occurrence of cardiovascular events during the one-year period of follow-up was higher in patients who had early (Hazard ratio [HR] 5.54, 95%CI 2.05-25.40; P = 0.0071) and late (HR 9.01, 95%CI 1.66-19.56; P = 0.0045) acute levels of CRP above the established cutoff points (Table II). Kaplan-Meier survival curves of patients with CRP levels above and below

### Table I. Comparison Data of the Patients With Good and Adverse One-year Outcomes After Acute Myocardial Infarction With ST-elevation

<table>
<thead>
<tr>
<th></th>
<th>Good outcome n = 14</th>
<th>Adverse outcome n = 15</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), years</td>
<td>52.8 (33-78)</td>
<td>64.2 (45-76)</td>
<td>0.0072</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>13 (93)</td>
<td>11 (73)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>10 (71)</td>
<td>5 (33)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>8 (57)</td>
<td>6 (40)</td>
<td>NS</td>
</tr>
<tr>
<td>Unstable angina, n (%)</td>
<td>3 (21)</td>
<td>4 (27)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>1 (6)</td>
<td>3 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Streptokinase reperfusion, n (%)</td>
<td>9 (65)</td>
<td>11 (72)</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol, mean (range), mmol/L</td>
<td>5.87 (4.83-6.65)</td>
<td>5.92 (3.82-8.23)</td>
<td>NS</td>
</tr>
<tr>
<td>CRP, mg/L at admission</td>
<td>3.8 (2.6-8.2)</td>
<td>4.7 (3.5-6.2)</td>
<td>NS</td>
</tr>
<tr>
<td>24-72 h after symptom onset</td>
<td>20.3 (8.0-46.2)</td>
<td>10.6 (49.4-180.5)</td>
<td>0.0075</td>
</tr>
<tr>
<td>96-120 h after symptom onset</td>
<td>14.1 (4.5-25.2)</td>
<td>60.5 (40.8-284.5)</td>
<td>0.0019</td>
</tr>
</tbody>
</table>

Values of CRP are medians (25-75 percentile). NS indicates not significant.
the cutoff points are shown in Figure 2A, for early acute values, and in Figure 2B, for late acute values of CRP. A higher rate of endpoint events was also found in older (>60 years) patients (HR 4.23, 95% CI 1.78-17.33; \( P = 0.031 \)).

Multiple logistic regression analysis was performed to valuate the independent contribution of CRP levels to the risk of death or a new vascular event. Two models were performed, for early and for late acute CRP. It was shown that the only independent predictor of long-term cardiac outcome was the early acute CRP level (Odds ratio [OR] 8.00, 95% CI 1.15-55.60; \( P = 0.036 \)), after adjustment

Figure 2. Kaplan-Meier curves for risk of death or new vascular events after one year of follow-up in patients with CRP levels above and below the cutoff levels (A) 24-72 hours after symptom onset, and (B) 96-120 hours after symptom onset.
for established risk factors. Late acute CRP levels were not independently related to one-year outcome. Significance was lost when variable age was included in the model (unadjusted OR 12.57, 95% CI 1.28-123.49; \( P = 0.030 \), and adjusted OR 6.06, 95% CI 0.51-71.62; \( P = 0.153 \)).

**DISCUSSION**

A growing body of evidence suggests that markers of inflammation may be reliable predictors of outcome in patients with ACS. Several studies have indicated that CRP is an important risk marker in patients with ST segment elevation AMI.\(^7-11\) CRP is the most promising prognostic marker for its analytical properties: CRP has a long half-life, no diurnal variations in concentrations, a rapid acute phase response, and is easily measured by commercially available standardized assays.

In this study, we investigated the prognostic relevancies of CRP in patients with STEMI in terms of one-year outcome. We observed that changes in this inflammatory marker in the setting of AMI had different time-courses. Differences in the individual acute phase response have been observed in the earliest studies on CRP kinetics after AMI.\(^{25,26}\) We showed that changes in CRP levels had 3 distinctive patterns, with possible different prognostic messages (Figure 1): (a) typical acute phase response, with peak CRP levels between 24-72 hours after onset of pain, (b) a persistently increasing pattern, and (c) persistently normal values or slightly elevated pattern of CRP kinetics. Because all patients received similar medical treatment, it could be speculated that the intensity and pattern of the individual inflammatory response may be an independent pathogenic component of AMI.
In accordance with previous studies, we found that AMI patients who had a primary endpoint during the one year of follow-up, had significantly higher median levels of early (peak) and late acute CRP, compared with the patients who were free of cardiovascular events. CRP levels at admission were not significantly different between the groups in our study (Table I). Higher CRP values at admission were found to be predictive of new cardiovascular events in some studies. However, these studies investigated either the predictive value of high CRP on short-term outcome, or when the time interval between the onset of pain and admission exceeded 12 hours, or CRP was not measured using an ultra-sensitive assay.

CRP levels measured 24-72 hours after symptom onset remained a significant prognostic marker of one-year outcome, after correction for established risk factors, in our study. These results are in accordance with the results of others concerning the prognostic relevance of peak CRP levels. Peak CRP level was not an independent prognostic marker in a study that investigated the 3-year outcome after AMI, which, we think, is not necessarily in discordance with our finding, and may suggest that the predictive value of CRP weakens over time. However, in the present study, increased CRP levels measured 4-5 days after symptom onset, although better associated with an unfavorable outcome than peak CRP levels (Table II, Figure 2), were not independently related to long-term prognosis when adjusted for age in a multiple regression model. This finding suggests that persistently high or an increasing pattern of the CRP acute phase response is predominantly associated with older age. Still, the meaning of a continued elevation of CRP levels after AMI needs to be further elucidated, as an understanding of the causes of persistent inflammation may provide additional therapeutic tools.

The cutoff points reported in previous studies differed according to the endpoint events investigated. Berton, et al reported a third day CRP cutoff value of 85 mg/L for one-year total and heart failure mortality, while Anzai, et al found that a peak CRP level greater then 200 mg/L was an independent predictor of cardiac rupture and one-year cardiac death. In the present study, the cutoff values that best discriminated between the patients with good and adverse one-year outcome (combined endpoint: death and any new vascular event) were 48.3 mg/L for early acute and 18.5 mg/L for late acute CRP. The broad range of reported cutoffs in the literature implies that the optimal cutoff for defining high CRP concentrations among patients with AMI remains to be determined.

Although based on a small number of patients, our results confirmed that the inflammatory process, represented by CRP elevation, has an important role in the pathogenesis of future coronary events in patients with STEMI. In these patients, a single measurement of CRP 24-72 hours after symptom onset may be useful as
an independent marker for assessing the likelihood of recurrent events, including death, in the following year.

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REFERENCES