ABSTRACT

BACKGROUND: There is a paucity of data on the prognostic role of C-reactive protein (CRP) measured after myocardial infarction. We prospectively examined the association of CRP with heart failure and death among patients with myocardial infarction in the community.

METHODS AND RESULTS: All Olmsted County residents who had a myocardial infarction meeting standardized criteria were prospectively enrolled to measure CRP on admission and followed for heart failure and death. A total of 329 consecutive patients (mean age 69 ± 16 years, 52% men) were enrolled. At 1 year, 28% of patients experienced heart failure and 20% died. There was a strong positive graded association between CRP and the risk of developing heart failure, as well as dying over the period of follow-up (P < .001). Compared with patients in the first tertile, patients in the third tertile of the CRP distribution had a markedly increased risk of heart failure and death independently of age, sex, troponin T, Q wave, comorbidity, previous myocardial infarction, and recurrent ischemic events (adjusted hazard ratio 2.47 [95% confidence interval, 1.27-4.82] for heart failure and 3.96 [95% confidence interval, 1.78-8.83] for death).

CONCLUSIONS: These prospective data indicate that among contemporary community subjects with myocardial infarction, heart failure and death remain frequent complications. CRP is associated with a large increase in the risk of heart failure and death, independently of age, sex, myocardial infarction severity, comorbidity, previous myocardial infarction, and recurrent ischemic events. These data suggest that inflammatory processes may play a role in the development of heart failure and death after myocardial infarction independently of other conventional prognostic indicators. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: C-reactive protein; Community; Death; Heart failure; Myocardial infarction; Prognosis
heart failure.\(^{15,16}\) Finally, most studies published on CRP after myocardial infarction evaluated only early outcomes\(^{14}\) or consisted of case series\(^{12,13,17,18}\) or post hoc analyses of clinical trials,\(^{8-11,19}\) with their inherent selection biases and the inconsistent control they have over important characteristics such as comorbidity.

We prospectively addressed these gaps in knowledge among all consecutive patients presenting with myocardial infarction from a geographically defined community by examining whether CRP was associated with an increased risk of heart failure and death after myocardial infarction, independently of other predictors of these outcomes.

**METHODS**

**Study Population**

Olmsted County, Minnesota, is relatively isolated from other urban centers, and nearly all medical care in virtually every specialty is delivered to residents by a few providers,\(^{20}\) which include the Mayo Clinic and its affiliated hospitals; the Olmsted Medical Center and its affiliated community hospital; local nursing homes; and a few private practitioners. Each provider in the community uses 1 medical record, whereby all medical information for each individual is in a single file. Through the Rochester Epidemiology Project, medical diagnoses, surgical interventions, and other key information from the dossier are abstracted and coded, thereby allowing the linkage of medical records from all sources of care. This provides a unique infrastructure to analyze disease outcomes. The county population was 106,479 in 1990\(^{20}\) and increased to 124,277 in 2000 while becoming ethnically more diverse.

**Patient Enrollment**

All Olmsted County residents hospitalized between November 2002 and December 2004 and presenting with a troponin T value greater than or equal to 0.03 ng/mL (upper limit of normal defined using the value at which the coefficient of variation is <10%) were prospectively identified within 12 hours of the blood draw through the electronic files of the Department of Laboratory Medicine. Consent was sought from patients (or the next of kin) to measure CRP in unused serum initially stored for additional clinical need. Three patients did not have serum available in which to measure CRP; thus, they were not included in the analyses.

Of the approached patients, 82% consented for the study. Cases were classified using published recommendations,\(^{21}\) and definite or probable myocardial infarction was included as defined by the combination of cardiac pain, biomarkers, and Minnesota coding of electrocardiograms.\(^{22}\) The reliability of this methodology is excellent.\(^{1,23}\)

**CLINICAL SIGNIFICANCE**

- Our research revealed a strong, graded association between CRP and the development of heart failure after myocardial infarction.
- Patients with the highest levels of CRP had a 4-fold increase in risk of death after myocardial infarction.

Time to presentation was defined as the interval from the self-reported onset of symptoms to the first electrocardiogram in hours. Killip class was assessed within 24 hours of admission. Comorbidity was measured by the Charlson index.\(^{24}\) Clinical diagnoses were used to ascertain hypertension, diabetes, hyperlipidemia, family history of coronary disease (defined as coronary disease in first-line male descendants aged <55 years and in first-line female descendants aged <65 years), and smoking. The extent of angiographic coronary disease was measured as the number of vessels with stenosis greater than 50%; multivessel disease was defined as at least 2 vessels with greater than 50% stenosis. Recurrent ischemic events included recurrent myocardial infarction or unstable angina and were defined by physicians’ diagnoses.

**Biomarkers**

Patients who undergo a clinically indicated blood draw have blood stored to allow for tests without additional phlebotomy. These samples are stored at −70°C and held for 6 days. All patients potentially experiencing a myocardial infarction or next of kin were contacted for permission to use these samples for measurement of CRP.

CRP was measured on serum from the first draw after symptom onset using a latex-enhanced immunoturbidimetric assay on a Hitachi 912 automated analyzer (Hitachi Ltd, Fukushima, Japan) and reagents from Diasorin (Stillwater, Minn). The reference interval for the assay was 0.20 to 0.8 mg/L. The interassay and intra-assay coefficients of variation of the high-sensitivity CRP method were less than 10% for the lower limit and less than 5% for the upper limit; interassay precision was 8.5% at a mean CRP of 1.0 mg/L, 4.6% at a mean CRP of 2.3 mg/L, and 3.4% at a mean CRP of 52.0 mg/L.

Venous samples for troponin T were obtained at the time of admission and 6 to 9 hours after the symptom onset. Serum stored from clinically indicated draws was used to measure creatine kinase-MB (CKMB) with the Elecsys 2010 automated immunochemistry analyzer (Roche Diagnostic, Indianapolis, Ind). Peak troponin T and CKMB values were used in the analyses. Biomarkers were measured in the Immunochromical Core Laboratory of Mayo Medical Laboratories, where all quality control and quality assurance procedures are in place.

**Follow-up**

The complete (inpatient and outpatient) medical record for each participant was reviewed by abstractors who were unaware of the CRP value. This process yields information that is complete, because more than 90% of the population...
Table 1  Baseline Characteristics According to Tertiles of C-Reactive Protein

<table>
<thead>
<tr>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>CRP &lt; 3 mg/L</td>
<td>CRP = 3-15 mg/L</td>
<td>CRP &gt; 15 mg/L</td>
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<tr>
<td>N = 112</td>
<td>N = 109</td>
<td>N = 108</td>
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<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
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<tr>
<td>Age, mean ± SD</td>
<td>68 ± 14</td>
<td>67 ± 16</td>
<td>72 ± 17</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>59.8</td>
<td>46.8</td>
<td>49.1</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>70.5</td>
<td>71.6</td>
<td>75.9</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>10.7</td>
<td>31.2</td>
<td>38.0</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>17.0</td>
<td>24.8</td>
<td>15.7</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>59.8</td>
<td>71.6</td>
<td>54.6</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>27.2 ± 4.4</td>
<td>29.7 ± 6.5</td>
<td>27.3 ± 6.3</td>
</tr>
<tr>
<td>Familial history of CAD, %</td>
<td>21.8</td>
<td>13.3</td>
<td>10.4</td>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>2.7</td>
<td>4.6</td>
<td>9.3</td>
</tr>
<tr>
<td>Comorbidity index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, %</td>
<td>47.3</td>
<td>27.5</td>
<td>13.0</td>
</tr>
<tr>
<td>1-2, %</td>
<td>34.8</td>
<td>39.5</td>
<td>25.9</td>
</tr>
<tr>
<td>≥3, %</td>
<td>17.9</td>
<td>33.0</td>
<td>61.1</td>
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<tr>
<td>Myocardial infarction characteristics</td>
<td></td>
<td></td>
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<tr>
<td>Q wave, %</td>
<td>52.9</td>
<td>56.7</td>
<td>54.6</td>
</tr>
<tr>
<td>ST segment elevation, %</td>
<td>23.2</td>
<td>22.9</td>
<td>12.0</td>
</tr>
<tr>
<td>Killip class &gt;1, %</td>
<td>15.2</td>
<td>31.2</td>
<td>39.8</td>
</tr>
<tr>
<td>Time from symptoms to CRP measurement, median (25th-75th percentile)</td>
<td>7.2 (3.1-10.2)</td>
<td>6.3 (1.9-26.6)</td>
<td>3.0 (0.6-9.7)</td>
</tr>
<tr>
<td>Peak troponin T, median (25th-75th percentile)</td>
<td>0.91 (0.19-2.54)</td>
<td>0.75 (0.23-2.91)</td>
<td>0.40 (0.13-1.38)</td>
</tr>
<tr>
<td>Peak CKMB, median (25th-75th percentile)</td>
<td>17.2 (7.1-90.8)</td>
<td>17.7 (8.3-114.4)</td>
<td>9.9 (4.5-23.1)</td>
</tr>
</tbody>
</table>

SD = standard deviation; BMI = body mass index; CAD = coronary artery disease; CRP = C-reactive protein; CKMB = creatine kinase-MB.

The baseline characteristics were examined according to the tertiles of the distribution of CRP (Table 1). Tertile 1 includes patients with CRP less than 3 (n = 112), tertile 2 includes patients with CRP between 3 and 15 (n = 109), and tertile 3 includes patients with CRP greater than 15 mg/L (n = 108). Kaplan-Meier curves estimated survival according to CRP tertiles and were compared using the log-rank test. For survival free from heart failure, the analysis was repeated treating death as a competing risk. Cox proportional hazards regression estimated the hazard ratio (HR) and 95% confidence interval (CI) for death and heart failure. Recurrent ischemic events were analyzed as a time-dependent covariate. Analyses were performed using SAS statistical software, version 8 (SAS Institute Inc, Cary, NC). The institutional review board approved the study.

RESULTS

We included 329 subjects with a mean age of 69 ± 16 years; 52% were men, 269 patients had definite myocardial infarction, and 60 patients had probable myocardial infarction. CRP was measured a median of 6.1 hours (25th-75th percentile 1.2-11.0 hours) after symptom onset. The median CRP was 5.7 mg/L (25th-75th percentile 2.0-31.0 mg/L). The baseline characteristics were examined according to the tertiles of the distribution of CRP (Table 1). Tertile 1 includes patients with CRP less than 3 (n = 112), tertile 2 includes patients with CRP between 3 and 15 (n = 109), and tertile 3 includes patients with CRP greater than 15 mg/L (n = 108). The CRP value that identifies patients in the third tertile (CRP < 3 mg/L) matches the published cutoff for high risk. Kaplan-Meier curves estimated survival according to CRP tertiles and were compared using the log-rank test. For survival free from heart failure, the analysis was repeated treating death as a competing risk. Cox proportional hazards regression estimated the hazard ratio (HR) and 95% confidence interval (CI) for death and heart failure. Recurrent ischemic events were analyzed as a time-dependent covariate. Analyses were performed using SAS statistical software, version 8 (SAS Institute Inc, Cary, NC). The institutional review board approved the study.
familial coronary disease, but no association was found between CRP and other cardiovascular risk factors. Elevated CRP was positively associated with greater comorbidity (P < .001).

Ninety-four patients (29%) were in Killip class greater than I at presentation, and greater Killip class was associated with increased CRP.

There was no association between CRP and Q waves on the electrocardiogram and no positive association between CRP and the presence of ST elevation or other biomarkers. Indeed, there was no association between CRP and troponin T at the time of hospitalization (r = 0.005, P = .74) and only a weak inverse correlation with peak troponin T (r = -0.177, P < .01) and peak CKMB (r = -0.291, P < .01).

**C-Reactive Protein, Heart Failure, and Death After Myocardial Infarction**

The mean follow-up was 1.0 ± 0.6 years. At 1 year, 63 patients had died and 182 were still alive, whereas 84 had less than 1 year of follow-up. On the basis of Kaplan-Meier estimates, at 1 year 28% of patients (95% CI, 23%-33%) had experienced heart failure and 20% of patients (95% CI, 15%-24%) had died; 103 recurrent ischemic events occurred.

There was a strong positive graded association between CRP and the long-term development of heart failure. One-year survival free from heart failure was 88% (95% CI, 81%-94%) in the first tertile of CRP, 72% (95% CI, 64%-81%) in the second tertile, and 52% (95% CI, 43%-64%) in the third tertile (P < .01) (Figure 1). These estimates were unchanged after death was analyzed as a competing risk. Compared with patients in the first tertile, patients in the second and third tertiles had a markedly increased risk of heart failure independently of age, sex, and comorbidity. Further adjustment for peak troponin, Q wave, Killip class on admission, previous myocardial infarction, and recurrent ischemic events as a time-dependent covariate did not modify this association (Table 2), nor did further adjustments for cardiovascular risk factors and history of heart failure (data not shown).

During follow-up, 75 deaths occurred. There was a strong positive association between CRP and 1-year survivals. One-year survivals were 93% (95% CI, 88%-98%) among patients in the first CRP tertile, 84% (95% CI, 77%-91%) in the second tertile, and 62% (95% CI, 54%-72%) in the third tertile (P < .01) (Figure 1). Patients in the third tertile had an 8-fold increase in the unadjusted risk of death compared with patients in the first tertile (HR 7.92, 95% CI, 3.75-16.73; P < .01). After further adjustment for age, sex, and comorbidity, patients in the third tertile had a 4-fold increase in the risk of death (adjusted HR 4.28, 95% CI, 1.95-9.38; P < .01) (Table 2). Further adjustment for peak troponin T, Q wave, Killip class, previous myocardial infarction, and recurrent ischemic events as a time-dependent covariate did not modify this association (Table 2). Adjustment for cardiovascular risk factors and history of heart failure did not modify this association (data not shown).

**DISCUSSION**

Heart failure and death remain frequent after myocardial infarction, as shown in this contemporary, geographically defined cohort of patients with rigorously ascertained myocardial infarction. CRP measured on hospital admission for myocardial infarction is associated with a strong, positive

![Figure 1](image_url)  
**Figure 1** Survival free of heart failure (top) and overall survival (bottom) according to CRP tertiles. Hs-CRP = high sensitivity C-reactive protein.
graded increase in the risk of heart failure and death independently of known prognostic factors. Because CRP was not associated with conventional measures of myocardial infarction size (Q waves, ST elevation, troponin T, or peak CKMB), its effect is likely not mediated by these indicators.

**C-Reactive Protein, Heart Failure, and Death After Myocardial Infarction**

Heart failure and death remain frequent during the first year after an acute myocardial infarction, reaffirming data from earlier studies. After myocardial infarction, studies on CRP focused on all-cause and cardiac deaths, which were evaluated mainly in case series and subgroup analysis of data from clinical trials. Yet, studies of patients referred to tertiary centers do not represent the entire spectrum of patients with myocardial infarction, and secondary analyses of clinical trials pertain to selected patients who often have fewer comorbidities. Few studies have investigated the association of postmyocardial infarction heart failure with CRP. Although suggesting a positive association, the studies focused chiefly on short-term risk, used low-sensitivity assays, or considered only patients referred to intensive coronary care units and heart failure episodes that required hospitalization.

The present study pertains to all patients with myocardial infarction within a geographically defined community, which enhances its generalizability. It indicates that elevated CRP is associated with a large increase in the risk of heart failure and death during the first year after myocardial infarction independently of known risk indicators, including other biomarkers, comorbidity, and recurrent ischemic events. To this end, although CRP was higher among subjects with higher Killip class, its predictive value for heart failure during follow-up is independent of Killip class, thus providing incremental information. The graded positive association between CRP and heart failure and death is consistent with a dose-response pattern.

Because few studies have investigated the association of CRP and heart failure, the mechanism for this association is unknown. It is unlikely related to recurrent ischemia because the associations between CRP and heart failure and death were not altered by adjusting for recurrent ischemic events. Alternative explanations include an exaggerated immune response to myocardial injury, as demonstrated by the association of inflammatory cytokines with ventricular remodeling after myocardial infarction, ejection fraction, and heart failure progression. Finally, experimental animal studies showed that CRP may have direct harmful effects on the ischemic myocardium. Griselli et al demonstrated that after coronary ligation, injection of CRP increased infarct size. Barrett et al demonstrated that elevated endogenous CRP is associated with an increase in ischemia/reperfusion injury. All these explanations remain hypothetical and addressing them directly is beyond the scope of this study, which, however, underscores the need of doing so.

A recent study reported that CRP measured at discharge was not associated with the combined end point of death, myocardial infarction, unstable angina, urgent revascularization, and stroke. Heart failure was not examined as an outcome such that these findings further support our hypothesis that the association between CRP and death is not mediated by ischemia, but rather that heart failure plays an important role.

Previous studies reported conflicting results on whether CRP was associated with myocardial infarction size as assessed by cardiac biomarkers. In acute coronary syndromes, a significant although weak association of CRP with CKMB and troponin was reported. Among community cases that met rigorous criteria for acute myocardial infarction, CRP was not associated with higher troponin, CKMB, or Q waves. Thus, when measured early after

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Hazard Ratios for Heart Failure and Death According to the Tertiles of C-Reactive Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
</tr>
<tr>
<td>CRP tertile 1 (referent)</td>
<td>1</td>
</tr>
<tr>
<td>CRP tertile 2</td>
<td>2.45 (1.30-4.62)</td>
</tr>
<tr>
<td>CRP tertile 3</td>
<td>4.59 (2.53-8.36)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>CRP tertile 1 (referent)</td>
<td>1</td>
</tr>
<tr>
<td>CRP tertile 2</td>
<td>2.39 (1.04-5.50)</td>
</tr>
<tr>
<td>CRP tertile 3</td>
<td>7.92 (3.75-16.73)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval; CRP = C-reactive protein.
*Adjusted for age, sex, comorbidity.
†Adjusted for age, sex, comorbidity, peak troponin T, Q wave, Killip class, previous myocardial infarction, and recurrent ischemic events as time-dependent covariate.
myocardial infarction, CRP does not seem to be related to myocardial injury.\textsuperscript{7,14,42} This is consistent with the fact that CRP provides incremental information over troponin and CKMB to predict death and heart failure, as documented in this article.

These findings provide indirect evidence against the hypothesis that ischemia is the mechanism whereby CRP relates to heart failure and death, an observation further supported by the fact that greater CRP is associated with these outcomes independently of recurrent ischemic events. Indeed, our results resonate with data\textsuperscript{4,43} suggesting that CRP elevation does not reflect plaque inflammation but rather the response of the “downstream myocardium” to the necrosis, and with the report that, compared with other cardiovascular risk predictors, CRP is only a modest predictor of recurrent ischemic events in patients with coronary disease.\textsuperscript{44}

Several predictors of heart failure after myocardial infarction have been examined, such as age, female sex, diabetes, hypertension,\textsuperscript{45,46} brain natriuretic peptide, ejection fraction,\textsuperscript{47} and wall motion score index.\textsuperscript{47,48} Although no study has directly compared CRP with other predictors of heart failure after myocardial infarction, our finding of an almost 4-fold increase in the risk of heart failure was independent of several other known risk markers.

Some potential limitations should be acknowledged to interpret the data. Imaging to quantify myocardial infarction size was not performed, and we relied on electrocardiography and biomarkers, both imperfect surrogate measures.\textsuperscript{49} This may play a role in the lack of association of CRP with angiographic coronary disease or biomarkers. CRP changes dynamically after myocardial infarction, and in most studies, such as the present one, it was measured at only 1 time point;\textsuperscript{34,42,50} this may account for discrepant results observed in other studies.

The strengths of our study include its prospective community-based design, whereby all consecutive patients in a geographically defined population were included and among whom CRP was measured, as recommended,\textsuperscript{50} within 24 hours of admission using a high-sensitivity assay. Additional important strengths include rigorous ascertainment approaches that rely on standardized criteria to define myocardial infarction and heart failure, and the comprehensive nature of the follow-up, which includes all inpatient and outpatient events. These important methodologic strengths optimize the robustness of our findings.

CONCLUSION
These prospective data indicate that in the community, heart failure and death remain frequent after myocardial infarction. CRP is associated with a large increase in the risk of heart failure and death independently of other risk predictors. These data suggest that inflammatory processes play an independent role in the development of heart failure and death after myocardial infarction. Thus, CRP may assist in risk stratification after myocardial infarction.

ACKNOWLEDGMENTS
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References


