Independent Prognostic Value of Elevated C-Reactive Protein in Unstable Angina

Ernesto R. Ferreirós, MD; Carlos P. Boissonnet, MD; Rodolfo Pizarro, MD; Pablo F. García Merletti, MD; Gianni Corrado, MD; Arturo Cagide, MD; Oscar O. Bazzino, MD

Background—There is growing evidence of the prognostic importance of C-reactive protein (CRP) in unstable angina. However, the independent value of CRP relative to other conventional markers at different stages of treatment has not been established. Therefore, we assessed the in-hospital and 90-day prognostic values of serum CRP in unstable angina. We also compared the relation of CRP at admission and discharge with 90-day outcome.

Methods and Results—One hundred ninety-four consecutive patients were included in a derivation (n = 105) and a validation set (n = 89). Serum CRP was measured at admission, at 48 hours, and at hospital discharge. A cutoff point of 1.5 mg/dL for CRP provided optimum sensitivity and specificity for adverse outcome, based on the receiver operator curves. No association was found between CRP on admission and in-hospital outcome. CRP at admission, adjusted for age, ECG findings on admission, silent ischemia, left ventricular wall motion score, and high-risk clinical presentation, was related to the combined end point of refractory angina, myocardial infarction, or death at 90 days (hazard ratio [HR] 1.9, 95% CI 1.2 to 8.3, P = 0.002). CRP at hospital discharge was the strongest independent marker of an adverse outcome (HR 3.16, 95% CI 2.0 to 5.2, P = 0.0001). These results were confirmed in the validation set (CRP at discharge: HR 3.3, 95% CI 2.0 to 7.69, P = 0.0001).

Conclusions—In unstable angina, CRP is a strong independent marker of increased 90-day risk. Compared with CRP at admission, CRP at discharge is better related to later outcome and could be of great utility for risk stratification.

Key Words: angina ■ prognosis ■ proteins

The appearance of a thrombus superimposed on the erosion or fissure of an atherosclerotic plaque is the mechanism involved in the sudden development of acute ischemic syndromes.1–4 According to a newly developed concept, the presence of inflammation at the site of the atherosclerotic lesion might play an important role in the natural history of endothelial injury. This possibility is supported by histological and hematologic evidence.5–9 There is also increased concentration of acute-phase serum reactants such as C-reactive protein (CRP) in patients with unstable angina.10

Selection of a therapeutic strategy for patients with unstable angina may be difficult because of the heterogeneous prognosis of this clinical syndrome.11–13 According to recently published data, many patients admitted with unstable angina and elevated CRP levels have an adverse outcome in the hospital and during the subsequent months.14–16 However, there is no information regarding the independent value of this finding or about the meaning of CRP determinations carried out at different times during the in-hospital evolution.

The aim of this study was to analyze the relation between CRP values measured at admission and discharge and the in-hospital and 90-day outcomes and to compare it with other conventional risk markers such as clinical variables, left ventricular function, or the presence of silent ischemia after admission.

Methods

Patients

We included 194 consecutive patients admitted to the coronary care unit for ischemic chest pain at rest during the 24 hours before admission. Candidates for thrombolysis and those showing abnormal elevation of total serum creatine kinase-MB (CK-MB) on admission or during the first 24 hours were excluded. We also excluded patients with left bundle-branch block or Braunwald type A angina, (angina pectoris subsequent to a precipitating extracardiac cause) or patients with concomitant inflammatory diseases, cancer, or other significant heart diseases. The study was approved by the ethics committee of the Hospital Italiano de Buenos Aires, and all patients gave written informed consent to participate.
Study Design
In this prospective study, 105 patients were included in a derivation set. All results were subsequently validated prospectively in a different group of patients (validation set, n=89). Complete clinical data and blood samples for laboratory measurements were collected at admission. Serum CK-MB level and a baseline ECG were obtained at entry and repeated at 6, 12, and 24 hours and every 24 hours thereafter. A 24-hour Holter monitoring was carried out immediately on admission. A 2D echocardiogram was performed within the initial 24 hours. Serum CRP levels were measured on admission, at 48 hours, and at hospital discharge. CRP measurements, Holter tracings, and 2D echocardiogram tape recordings were analyzed by staff members who were not involved in patient care. Test results were not available to the attending physicians. All patients were followed up for 90 days after admission or until the occurrence of a major event.

Definitions and End Points
The primary end point was the combination of death of any cause, acute myocardial infarction, and/or refractory angina during the 90 days after hospital admission. The definition of refractory angina during initial or subsequent hospitalizations was based on the appearance of ischemic chest pain at rest associated with ST-segment alterations in patients treated with nitroglycerin, aspirin, β-blockers, and intravenous heparin.

Acute myocardial infarction was diagnosed in the presence of chest pain lasting >20 minutes, characteristic ECG alterations, and plasma CK-MB elevation greater than twice the normal or previous elevated value. All end points were validated by a designated committee that was unaware of the CRP results.

Determination of CRP
Blood samples were stored in evacuated tubes at -20°C to be processed within 24 hours by automated microparticle immunoassay (ELISA). The CRP detection range corresponds to values of 0.1 to 12.0 mg/dL, with an interassay variation coefficient of ≤5% (normal values <0.3 mg/dL). Measurements were calibrated according to the 85/506 World Health Organization international reference standard.

Holter Recordings
Modulated frequency recorders (range 0.05 to 40 Hz) were used for this test, according to American Heart Association standards. The recordings were read by 2 independent experienced investigators who were unaware of the clinical data. An ischemic episode was defined as a horizontal or downsloping ST-segment depression, ≥1 mm from baseline and 0.08 seconds from the J point, lasting ≥1 minute. An ischemic event interval of 0.05 to 40 Hz or greater was required for the diagnosis of a new ischemic episode. Tracings were recorded at a speed of 25 mm/s, and for each patient the following parameters were assessed with the Delmar Avionics Dynamic Electrocardiogram scanner Trendsetter Unit: presence or absence of silent ischemia, total number of episodes, and total duration of ischemia (in minutes).

2D Echocardiograms
A 2D echocardiogram was performed on admission to the coronary care unit (median time elapsed since the beginning of pain 12 hours, range 0 to 24 hours). For the analysis of left ventricular function and wall motion abnormalities, we used the segmentation model accepted by the American Society of Echocardiography, which divides the left ventricle into 16 segments and establishes a regional wall motion score for each segment according to the following grading system: 1, normal; 2, hypokinesis; 3, akinesis; and 4, dyskinesis. An acute wall motion alteration was defined by the presence of a score >1 in at least 1 segment. Left ventricular wall motion index (LVWMI) was calculated according to the formula $LVWMI = \frac{2 \times \text{wall motion scores of the 16 segments}}{\text{total number of visualized segments}}$.

Studies were recorded in all conventional ultrasonic windows and independently reviewed by 2 experienced investigators who examined the records without knowledge of the patient’s clinical infor-
The area of the ROC curves relating CRP levels to 90-day outcome, at baseline, 48 hours, and discharge were 0.70±0.069, 0.82±0.058, and 0.84±0.054, respectively. The highest likelihood ratio corresponded to a value of 1.5 mg/dL in the discharge CRP ROC curve (likelihood ratio 5.6, 95% CI 2.3 to 12.1). Baseline characteristics of patients according to CRP levels at admission (above or below 1.5 mg/dL) are compared in Table 1. In patients with elevated CRP, a greater prevalence of prior hypertension (90% versus 67.7%, \( P=0.015 \)) and a lower prevalence of smoking (26.7 versus 57.3% \( P=0.005 \)) were noted.

There were no differences regarding in-hospital treatment, for example, use of intravenous nitroglycerin, oral aspirin, or intravenous heparin, or in the use of coronary angiography and revascularization procedures up to 90 days between patients with CRP levels at admission above or below 1.5 mg/dL (Table 1).

**Correlation With In-Hospital and 90-Day Events**

**Univariate Analysis**

Univariate markers of worse in-hospital evolution were the presence of ST-segment depression on admission ECG, detection of silent ischemia, and high-risk presentation (NHLBI class) (Table 2). There was no significant association between CRP level on admission or the LVWM score and the rate of in-hospital events. Median values and 25% to 75% interquartile ranges of CRP were 0.75 (0.3 to 0.6) and 0.4 (0.2 to 0.9), respectively (\( P=\text{NS} \), Wilcoxon rank sum test). The occurrence of refractory angina, myocardial infarction, or death at 90-day follow-up was related to CRP level at

![Figure 1. Changes in serum CRP levels from admission through discharge. Different patterns were observed: persistent elevation in 48.5% of all patients, increasing values in 10.0%, decreasing values in 12.5%, and persistently normal values in 29.0%, respectively.](image)

### TABLE 1. Baseline Characteristics (Derivation and Validation Sets)

<table>
<thead>
<tr>
<th></th>
<th>Derivation Set</th>
<th>Validation Set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRP &lt;1.5 mg/dL</td>
<td>CRP &gt;1.5 mg/dL</td>
</tr>
<tr>
<td>Age &gt;65 y</td>
<td>(n=75) n (%)</td>
<td>(n=30) n (%)</td>
</tr>
<tr>
<td>Male</td>
<td>39 (52.0)</td>
<td>23 (76.7)</td>
</tr>
<tr>
<td>Prior acute myocardial infarction</td>
<td>20 (26.6)</td>
<td>12 (46.0)</td>
</tr>
<tr>
<td>Progressive angina</td>
<td>38 (50.7)</td>
<td>14 (56.7)</td>
</tr>
<tr>
<td>Recent-onset angina</td>
<td>34 (45.3)</td>
<td>14 (46.7)</td>
</tr>
<tr>
<td>Pain lasting &gt;20 min</td>
<td>50 (66.7)</td>
<td>20 (66.7)</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>13 (17.3)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (18.7)</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>43 (57.3)</td>
<td>8 (26.7)*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50 (66.7)</td>
<td>27 (90.0)†‡</td>
</tr>
<tr>
<td>Known lipid disorders</td>
<td>37 (49.3)</td>
<td>15 (50.0)</td>
</tr>
<tr>
<td>Prior aspirin treatment</td>
<td>45 (60.0)</td>
<td>22 (73.3)</td>
</tr>
<tr>
<td>Heart failure at entry</td>
<td>6 (8.0)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>High-risk NHLBI class at entry</td>
<td>37 (49.3)</td>
<td>20 (66.7)</td>
</tr>
<tr>
<td>ST-segment depression at entry</td>
<td>25 (33.3)</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>T-wave changes at entry</td>
<td>32 (42.7)</td>
<td>15 (50.0)</td>
</tr>
<tr>
<td>Silent ischemia</td>
<td>11 (16.9)</td>
<td>13 (32.5)‡‡</td>
</tr>
<tr>
<td>LVWM score &gt;1.5</td>
<td>5 (6.6)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>In-hospital treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>75 (100.0)</td>
<td>30 (100.0)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>75 (100.0)</td>
<td>30 (100.0)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>70 (93.3)</td>
<td>29 (96.7)</td>
</tr>
<tr>
<td>IV heparin</td>
<td>41 (54.7)</td>
<td>20 (66.7)</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>25 (33.3)</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>14 (18.7)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>90-Day death/acute myocardial infarction/refractory angina</td>
<td>10 (15.4)</td>
<td>23 (76.7)§</td>
</tr>
</tbody>
</table>

\*\( P=0.005 \), †\( P=0.015 \), ‡\( P<0.01 \), §\( P<0.001 \).
admission (34.7 versus 73.3%, OR 5.18, 95% CI 2.02 to 13.2, \( P < 0.001 \)) and discharge (15.1% versus 78.8%, OR 20.89, 95% CI 6.8 to 64.2, \( P < 0.001 \)) (Table 3). Kaplan-Meier survival curves of patients with CRP at discharge above and below 1.5 mg/dL are shown in Figure 2. The 90-day prognosis was also related to the high-risk category of the NHLBI classification and the presence of silent ischemia in the Holter recording (Table 2).

**Multivariate Analysis**

Independent markers of in-hospital events were the finding of silent ischemia (hazard ratio [HR] 1.69, 95% CI 1.01 to 2.89, \( P = 0.041 \)) and the presence of ST-segment depression on baseline ECG (HR 1.62, 95% CI 0.96 to 2.74, \( P = 0.07 \)).

CRP level at hospital discharge showed the strongest independent association with the combined end point of refractory angina, myocardial infarction, or death at 90 days (HR 3.16, 95% CI 2.0 to 5.2, \( P < 0.001 \), Table 4).

**Incremental Value of CRP**

The area of the ROC curve of the prognostic model increased from 0.68 ± 0.06 to 0.79 ± 0.05 (\( P = 0.047 \)) when CRP values were added to the model including clinical, ECG, Holter, and 2D echocardiographic variables. When repeated in reverse order, the addition of the clinical model to the CRP data did not significantly improve the ROC area (0.84 ± 0.05 and 0.83 ± 0.05, \( P = \text{NS} \)).

**Validation Set**

Table 1 describes the baseline characteristics of the derivation and validation sets. Median and 25th to 75th percentile baseline CRP values were similar in both sets (0.60, 0.30 to 0.90 versus 0.50, 0.20 to 0.90, \( P = \text{NS} \)). In the ROC curve of the validation set, a CRP value of 1.5 mg/dL at discharge was also associated with the best likelihood ratio of major events at 90 days.

Although there was no statistically significant association, a trend was noted between CRP levels >1.5 mg/dL on admission and in-hospital prognosis (refractory angina, acute myocardial infarction, or death 50% versus 21%, \( P = 0.12 \)). A CRP value >1.5 mg/dL at admission was significantly associated with a worse 90-day outcome (100% versus 44.6%, \( P = 0.01 \)).

A strong relation was observed between CRP >1.5 mg/dL at discharge and 90-day outcome (95.2% versus 8.3%, \( P = 0.001 \)), similar to that shown in the derivation set. In the...
validation set, CRP at discharge remained the strongest independent prognostic marker of 90-day outcome (HR 3.3, 95% CI 2.0 to 7.69, \( P < 0.001 \)).

**Incremental Value of CRP**

The addition of CRP data to the non-CRP model significantly increased the area of the ROC curve from 0.78±0.06 to 0.97±0.02 (\( P = 0.0097 \)). Conversely, no significant differences in the ROC areas were observed when the non-CRP model was added to the CRP values.

The overall predictive performance of the multivariate model elaborated with the CRP value at discharge was also confirmed (area of ROC curves for the derivation and validation sets 0.79±0.05 and 0.97±0.02, respectively; \( P = 0.0007 \)).

**Discussion**

Our data indicate that patients with unstable angina who have serum CRP levels >1.5 mg/dL have a significantly worse outcome. Another important finding of this study is that CRP adds independent prognostic information to that provided by the clinical, ECG, Holter, and 2D-echocardiographic variables. We also demonstrate that compared with CRP at admission, CRP at discharge has the strongest association with 90-day evolution in a multivariate model.

**TABLE 4. Predictors of Events at 90-Day Follow-Up: Multivariate Cox Proportional Hazard Analysis (Derivation Set)**

<table>
<thead>
<tr>
<th>Myocardial Infarction/Death/Refractory Angina</th>
<th>( \chi^2 )</th>
<th>df</th>
<th>HR</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP &gt;1.5 at discharge</td>
<td>32.15</td>
<td>1</td>
<td>3.16</td>
<td>2.0–5.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Silent ischemia</td>
<td>4.92</td>
<td>1</td>
<td>1.39</td>
<td>1.02–2.84</td>
<td>0.026</td>
</tr>
<tr>
<td>CRP &gt;1.5 on admission</td>
<td>13.6</td>
<td>1</td>
<td>1.9</td>
<td>1.2–8.3</td>
<td>0.002</td>
</tr>
<tr>
<td>LVWM score &gt;1.5</td>
<td>0.93</td>
<td>1</td>
<td>…</td>
<td>…</td>
<td>0.10</td>
</tr>
<tr>
<td>ST depression on admission</td>
<td>0.69</td>
<td>1</td>
<td>…</td>
<td>…</td>
<td>0.55</td>
</tr>
<tr>
<td>High-risk NHLBI class at entry</td>
<td>0.50</td>
<td>1</td>
<td>…</td>
<td>…</td>
<td>0.70</td>
</tr>
<tr>
<td>Age &gt;65 y</td>
<td>0.61</td>
<td>1</td>
<td>…</td>
<td>…</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Several prior studies have reported elevated CRP values in patients with unstable coronary artery disease.\(^{14,15}\) However, variations in CRP levels during in-hospital treatment were not previously analyzed in detail. According to our data, 2 distinctive patterns have a different prognostic message can be described: a benign pattern, consisting of either persistently normal or decreasing values from admission through discharge, and an adverse pattern, represented by those patients with persistently elevated or increasing values from admission to discharge. These variations in CRP levels cannot be explained by different in-hospital treatment because the use of anti-ischemic and antithrombotic medications was similar in patients with CRP levels above and below 1.5 mg/dL. Persistently elevated or “crescendo” patterns may represent either an ongoing inflammatory process or, in some cases, the presence of subtle myocardial necrosis. All our patients had normal serial CK-MB values; however, the latter possibility may not be excluded because of the lack of troponin measurements.

Although all CRP determinations were significantly associated with 90-day outcome, those performed at discharge showed a better relation with prognosis. Our data indicate that the persistence of elevated CRP despite intense hospital treatment and waning of symptoms could be a strong marker of persistent plaque instability and increased subsequent risk.

There are no good gold standards for risk stratification of unstable angina after the completion of in-hospital treatment.\(^{18–20}\) Although the exploration of coronary reserve is routinely used for this purpose, we must remember that the presence of an unstable plaque without an underlying fixed component capable of significantly reducing coronary reserve may also explain the development of ischemic complications after discharge in many cases.\(^{19,20}\) These data emphasize the importance of methods that demonstrate the presence of persistently active plaques in patients who are clinically stable.

A problem of circular reasoning may arise when findings are used both as prognostic and diagnostic criteria. This is a well-known limitation of the prognostic information provided by stress tests. In contrast, this limitation is absent in the present study, because the treatment of all patients was pursued without any knowledge regarding CRP values.

**Comparison With Other Studies of Unstable Angina**

Liuzzo and coworkers\(^{14}\) found a higher incidence of ischemic episodes in patients with elevated CRP; however, in contrast to the results of our study, theirs did not demonstrate a relation with other clinically important end points such as myocardial infarction or death. Another difference from the previous observation by Liuzzo and coworkers is that the present study did not show a relation between CRP on admission and in-hospital outcome. Morrow and colleagues,\(^{21}\) using a cutoff point of 1.5 mg/dL, observed that an elevated CRP level at admission was associated with a higher mortality rate at 14 days, but they did not include data about the relation of CRP with in-hospital prognosis. Haverkate and colleagues\(^{22}\) reached similar conclusions. Conversely, in the study by Montalescot and coworkers,\(^{23}\) CRP level at entry...
was not associated with 14-day outcome. These differences can be attributed to the use of different cutoff points and inclusion criteria, but they also may be explained by the smaller sample size of all these studies.

**Study Limitations**

A limitation of this study is the lack of troponin determinations. Morrow and coworkers reported that the probability of a positive troponin T assay increased with rising concentrations of CRP, and in their study, the combination of troponin T and CRP was found to have additive prognostic value. In addition, as previously discussed, the role of myocardial necrosis in CRP elevation cannot be fully analyzed without troponin T measurements.

**Conclusions**

Elevation of CRP is common in unstable angina and probably indicates the presence of evolving inflammation at the coronary plaque or myocardial necrosis. In patients who have overcome the acute phase and are clinically stabilized, the finding of elevated CRP levels at hospital discharge suggests persistent instability of the disrupted plaque and is strongly related to the occurrence of subsequent ischemic complications. Conversely, a low CRP level after in-hospital treatment could be an indicator of quiescence of the injured plaque. This information may be very useful for the selection of patients who are potential candidates for more aggressive therapy.

**Acknowledgments**

We thank the medical residents, nurses, and laboratory staff of the coronary care unit of the Hospital Italiano for their collaborations in this trial and Dr Marcus Flather for his careful revision of the manuscript.

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