**Different Apparent Prognostic Value of hsCRP in Type 2 Diabetic and Nondiabetic Patients with Acute Coronary Syndromes**

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**BACKGROUND:** C-reactive protein (CRP) is an established prognostic marker in acute coronary syndromes (ACS); however, no study has specifically addressed its prognostic role in type 2 diabetes with ACS. We evaluated the prognostic role of CRP separately in diabetic and nondiabetic patients with ACS.

**METHODS:** We enrolled 251 patients with unstable angina and measured serum concentrations of high sensitivity (hs)CRP. Ninety-seven patients underwent coronary angiography with evaluation of atherosclerotic disease severity and extent by Bogaty score. Assessed endpoint was the combined occurrence of myocardial infarction (MI) and death at 1 year.

**RESULTS:** No significant differences were found in hsCRP between patients with and without diabetes. By Cox regression, hsCRP was not associated with 1-year follow-up events in diabetic patients but was strongly associated with events in nondiabetic patients ($P = 0.0012$). Coronary angiography exhibited a higher extent index in patients with diabetes than in those without ($P = 0.04$). hsCRP concentrations were not associated with angiographic atherosclerotic burden. By Cox analysis, hsCRP and extent score were associated with events in patients who underwent coronary angiography ($P < 0.001$ and $P = 0.034$, respectively). In nondiabetic patients, hsCRP was the only predictor of events at 1-year follow-up ($P < 0.001$), whereas in diabetic patients, hsCRP was not associated with events and a weak association was observed for extent score ($P = 0.06$).

**CONCLUSIONS:** Our study suggests that different pathophysiological mechanisms may be responsible for MI and death in unstable angina patients with or without diabetes and that severity of coronary artery disease plays a major role in diabetes (and inflammation in the absence of diabetes).

Inflammation plays an important role in all stages of the atherosclerotic process, from the onset of initial lesions to plaque progression and complications (1). Prognostic studies have shown that C-reactive protein (CRP)4 is a strong predictor of cardiovascular events (2, 3). In particular, in acute coronary syndromes (ACS), high concentrations of CRP are a marker of recurrent cardiac events for up to 5 years (4–6).

Type 2 diabetes mellitus (DM) is a strong risk factor for coronary artery disease (CAD), which in turn is the leading cause of mortality and morbidity in diabetic patients (7). Although this increased risk has been attributed primarily to hyperglycemia, dyslipidemia, and a prothrombotic state, recent observations have focused attention on low-grade inflammation in the pathogenesis of type 2 DM and its complications (8).

Studies in nondiabetic patients (9) or subjects with impaired glucose tolerance or impaired fasting glucose (10) have confirmed that high concentrations of inflammatory markers predict the development of type 2 DM and are closely linked to insulin resistance. Although recent studies have shown that higher concentrations of high-sensitivity (hs)CRP are associated with an increased cardiovascular risk in type 2 DM patients without previous history of cardiovascular disease (11, 12), data on the prognostic value of hsCRP in type 2 DM with ACS are limited. Therefore, in this study, we sought to evaluate the prognostic role of CRP in patients with ACS with type 2 DM or without diabetes.

**Materials and Methods**

We enrolled 251 consecutive patients (80% male, mean age 65 years, range 44–75 years) who were admitted to the Coronary Care Unit of Catholic University of the Sacred Heart, Rome. All patients had Braunwald class IIIB unstable angina. We excluded all patients with type 1 DM or conditions likely to elicit an acute-phase response, including a myocardial infarction (MI) within the previous 3 weeks.

Ninety-seven patients underwent coronary angiography and were evaluated for atherosclerotic disease severity and extent using the Bogaty score (13). Briefly, we assessed disease severity by considering the

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4 Nonstandard abbreviations: CRP, C-reactive protein; ACS, acute coronary syndromes; DM, diabetes mellitus; CAD, coronary artery disease; hsCRP, high-sensitivity CRP; MI, myocardial infarction; OR, odds ratio.
number of diseased vessels, the number of vessels with stenosis >70% of lumen diameter, and the number of vessels with total occlusions to compute an extent score, which considers the proportion of abnormal coronary segments.

All patients gave their informed consent, and the study was approved by the Ethics Committee of the Catholic University of Rome.

A blood sample was collected from each patient at admission, and the serum was divided and snap-frozen at −80 °C. We measured hsCRP concentrations using an ultrasensitive nephelometric method (Siemens Health Care Diagnostic BN100), with a lower detection limit of 0.2 mg/L, and cardiac troponin I concentrations using a Stratus system (Siemens Health Care Diagnostic BN), with a lower detection limit of 0.03 ng/L.

In all patients, we carefully documented the presence of risk factors, including type 2 DM, hypercholesterolemia, smoking, family history of CAD, age >65 years, and hypertension. Diagnosis of type 2 DM was according to current ADA criteria (14). Occurrence of MI and cardiac death was recorded in all patients for 1 year after discharge. MI was defined as detection of rise and fall of troponin with at least 1 value above the 99th percentile of the upper reference limit and at least 1 of the following: symptoms of ischemia, new ST-T changes or new left bundle branch block, or development of pathological Q waves in the electrocardiogram. Death was defined as cardiac death, including sudden, unexpected death.

Data distribution was assessed using Kolmogorov–Smirnov test. All continuous variables had a normal distribution except CRP. Thus, serum hsCRP concentrations were reported as median (interquartile range). We assessed differences between groups using unpaired 2-tailed t-test or Mann–Whitney test as appropriate and differences in dichotomous variables among groups using χ² test. hsCRP concentrations were divided by quintiles of the overall population in evaluating the incidence of events, risk odds ratios (ORs) were evaluated, and the same analysis was conducted separately for diabetic and nondiabetic patients. We performed survival analysis using Cox regression using quintiles of hsCRP, considering hypercholesterolemia and family history of CAD as other confounders for the whole population, and considering extent score and extent index for patients who underwent coronary angiography. A P value of <0.05 was considered significant. All statistical analyses were performed using SPSS 15 software.

Results

The clinical characteristics of the patients are presented in Table 1. Of the 251 patients, 53 (21%) had type 2 DM.

Death or MI was observed in 19 patients (6 cardiac death and 13 MI). There was no statistically significant difference in hsCRP concentrations between diabetic and nondiabetic patients (median hsCRP 4.2 mg/L, range 0.3–26, vs 5.2 mg/L, 0.4–30). The incidence of death or MI was 6% in nondiabetic patients and 13% in diabetic patients (P = 0.08).

Median hsCRP concentrations were 5 mg/L (range 0.3–30) in the whole population, 4.8 mg/L (0.3–6.3) in event-free patients, and 22.3 mg/L (8–30) in patients who suffered cardiac death or MI (P < 0.001). Ten of 19 hard endpoints (death or MI) were observed in nondiabetic patients (P = 0.08).

In nondiabetic patients, hsCRP concentrations were significantly higher among patients who died or had an MI than among patients without events at follow-up (24 mg/L, 3.5–25.8, vs 4.3 mg/L, 0.6–6, respectively; P < 0.001). Interestingly, among diabetic patients, no statistically significant difference in hsCRP concentrations was found between patients with or without hard endpoints (8 mg/L, 4.3–19, vs 3.9 mg/L, 0.3–4.8, respectively). In particular, although a significant difference was found comparing the event rates in the 5th quintile of hsCRP concentrations with the event rates in the other quintiles in nondiabetic patients (P < 0.001), no such difference in

Table 1. Clinical and laboratory characteristics of the study population.a

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetic patients</th>
<th>Diabetic patients</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>198</td>
<td>53</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>58 (9)</td>
<td>63 (7.3)</td>
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<tr>
<td>Male sex</td>
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<tr>
<td>Hypertension</td>
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<td>Median serum hsCRP, mg/L (IQR)b</td>
<td>5.2 (0.4–30)</td>
<td>4.2 (0.3–26)</td>
</tr>
</tbody>
</table>

a Data are % unless noted otherwise. All differences are nonsignificant (P > 0.05).
b IQR, interquartile range.
event rates was found among quintiles of hsCRP in diabetic patients (Fig. 1B).

In Cox regression analysis of the whole population, diabetes status was not found to predict the end-points, and no correlation was observed between diabetes status and hsCRP \( (r = -0.002) \). By Cox regression analysis, hsCRP was strongly and independently associated with the risk of the combined end-points in nondiabetic patients \( (OR 1.9, 95\% CI 1.3–2.8, P = 0.0012 \) for death and MI at 1-year follow-up), but not in diabetic patients.

In analysis of the angiography data, diabetic patients exhibited a higher extent index than nondiabetic patients \( [mean (SD) 0.94 (0.1) vs 0.70 (0.04); P = 0.04] \) and a trend for a more severe disease \( [4.10 (0.6) vs 2.90 (0.2); P = 0.08] \). However, hsCRP serum concentrations were not correlated with angiographic measures of atherosclerotic burden.

In patients who underwent coronary angiography, Cox analysis revealed that hsCRP and extent score were associated with the risk of death and MI in the whole population \( (OR 1.046, 95\% CI 1.027–1.06, P < 0.001) \), and \( OR 1.1, 95\% CI 1.007–1.2, P = 0.034 \), respectively. In nondiabetic patients, hsCRP was the only significant predictor of events at 1-year follow-up \( (OR 1.050, 95\% CI 1.029–1.071, P < 0.001) \), whereas in diabetic patients, hsCRP was not associated with events at 1-year follow up and a weak association was observed for extent score \( (OR 1.34, 95\% CI 0.98–1.84, P = 0.06) \).

**Discussion**

Our data confirm that in patients with unstable angina, higher hsCRP serum concentrations are strong and independent predictors of short-term and midterm death and MI. Moreover, our study suggests that hsCRP may have different prognostic value in diabetic and nondiabetic patients with unstable angina.

This finding is novel and apparently at odds with the finding that the prognostic value of hsCRP is independent from diabetic status and that diabetes is a proinflammatory condition. Several studies have found that diabetes does not significantly affect the prognostic value of hsCRP in population studies but such data in patients with ACS are lacking \( (15, 16) \).

Because diabetes is associated with higher risk, the additional risk carried by hsCRP may not become apparent unless the inflammatory component related to the disease is very prominent. Our study also provides a possible explanation for the apparent paradox that unstable angina patients with diabetes had a greater coronary atherosclerotic burden \( (17) \). Thus it is possible that in diabetic patients with ACS the extent and severity of disease are more important than inflammation in determining the outcome, or that mechanisms not directly related with inflammation are more important in destabilization of atherosclerotic plaques. Evidence of higher platelet reactivity in diabetic patients on antiplatelet treatment might also help to explain our findings \( (18, 19) \). Our data are not at odds with the important inflammatory component of diabetes and its proatherosclerotic role. In fact, inflammation associated with diabetes is likely to play a key role in the early initiation and aggressive progression of atherosclerosis, whereas it might play a less relevant role in the mechanisms responsible for the shift from stable disease to ACS.

Among the limitations of our study, in addition to the relatively small number of patients enrolled, is the

**Fig. 1.** (A), Rate of death and MI in unstable angina patients at 1 year according to hsCRP quintiles in the whole population \( (5th\ quintile vs the others, \*P < 0.001) \).

(B) Rate of death and MI in unstable angina patients at 1 year according to hsCRP quintiles in nondiabetic and diabetic patients. In nondiabetic patients there was a significant difference in event rates between the 5th quintile and the others \( (^\*P < 0.001) \); conversely, in diabetic patients there was no difference in event rates among quintiles of hsCRP \( (^\not P < 0.001) \).
short follow-up, which does not allow evaluation of the long-term prognostic role of hsCRP in type 2 DM.

In conclusion, our study suggests that different pathophysiological mechanisms may be responsible for development of ACS in diabetic and nondiabetic patients and that these mechanisms may differently affect the short-term to midterm outcome.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

References