The High-Sensitivity C-Reactive Protein Level One Month After Bare-Metal Coronary Stenting May Predict Late Adverse Events

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The significance of the high-sensitivity C-reactive protein (hs-CRP) level in percutaneous coronary interventions (PCIs) is unclear. Troponin-T and hs-CRP levels were measured before PCI, after stenting, and 8 h, 24 h, and 30 days after the procedure in 68 consecutive patients who received bare-metal stents. The study endpoints were death, nonfatal myocardial infarction, and the need for revascularization. The mean follow-up time after PCI was 16.6 months. Patients who experienced an event had higher hs-CRP levels 24 h (P=.05) and 30 days (P<.02) after stenting. The area under the receiver operating characteristic (ROC) curve at 30 days had the highest sensitivity (ie, 80%) and specificity (ie, 72%) for predicting an event. The 12-month event-free survival rate (Kaplan-Meier) was greater when the hs-CRP level at 30 days was ≤2.5 mg/L than when it was above this value (P=.04). Consequently, measuring the hs-CRP level 30 days after stenting may be useful for predicting late events.

Key words: *Coronary angioplasty. Coronary stent. C-reactive protein.*

La PCR-as al mes de implantar un *stent* coronario metálico puede ser predictora de eventos adversos tardíos

La proteína C reactiva de alta sensibilidad (PCR-as) tiene un valor incierto en el intervencionismo coronario percutáneo (ICP). En 68 pacientes consecutivos tratados con *stents* metálicos, se determinaron PCR-as y troponina T pre-ICP, post-*stent*, a las 8 h, a las 24 h y a los 30 días. Los objetivos finales fueron muerte, infarto de miocardio y nueva revascularización. El seguimiento medio post-ICP fue 16,6 meses. Los pacientes con eventos tuvieron PCR-as más alta a las 24 h (p = 0,05) y a los 30 días (p < 0,02). El área bajo la curva ROC de 30 días fue la más sensible (80%) y específica (72%) para predecir eventos. La supervivencia libre de eventos a los 12 meses fue superior cuando la PCR-as a los 30 días era ≤ 2,5 mg/l que cuando estuvo más elevada (p = 0,04). Por lo tanto, determinar PCR-as 30 días tras el ICP puede ser útil para predecir eventos tardíos.

Palabras clave: *Angioplastia coronaria.* Stent *coronario. Proteína C reactiva.*

INTRODUCTION

The prognostic value of high-sensitivity C-reactive protein (hs-CRP) has been extensively studied in ischemic heart disease.[1] However, the significance of this marker in percutaneous coronary interventions (PCIs) may differ, because mechanical damage to the vessel wall can, in itself, induce a systemic inflammatory response.[2] In addition, the differences between samples obtained at baseline and those taken following the procedure have not been well-established.

The aim of this study is to assess hs-CRP values in serial samples from a prospective group of patients who underwent implantation of a bare-metal coronary stent.

METHODS

From May 2002 to January 2003, 68 consecutive patients, 12 (18%) with stable angina and 56 with non-ST-elevation acute coronary syndrome (NSTEACS), were included in an open, prospective study on hs-CRP values

TABLE 1. Clinical Characteristics of the Patient Population Receiving Bare-Metal Stents According to Baseline Values of High-Sensitivity C-Reactive Protein

	Total	hs-CRP ≤2.5 mg/L	hs-CRP >2.5 mg/L	P
Patients	68 (100)	26 (38)	42 (62)	
Age, mean (SD), y	61 (10)	59.5 (11)	62.3 (10)	.26
Males	53 (78)	20 (77)	33 (79)	.87
Hypertension	36 (53)	14 (54)	22 (52)	.90
Diabetes	23 (34)	13 (50)	10 (24)	.02
Hyperlipidemia	34 (50)	13 (50)	11 (50)	1.00
Smoking	26 (38)	10 (39)	16 (38)	.98
Obesity	17 (25)	7 (27)	10 (25)	.77
Stable angina	12 (18)	4 (15)	8 (19)	.90
NSTEACS with normal TnT	45 (66)	18 (69)	17 (64)	.90
NSTEACS with high TnT (non-Q AMI)	11 (16)	4 (15)	7 (17)	.90
Ejection fraction, mean (SD)	61 (4)	62 (3)	61 (5)	.60
Vessels treated per patient, mean (SD)	2.0 (1.1)	2.2 (1.1)	1.9 (1.0)	.17
Stents per patient, mean (SD)	2.3 (1.3)	2.5 (1.2)	2.2 (1.2)	.37

AMI indicates acute myocardial infarction; hs-CRP, high-sensitivity C-reactive protein; NSTEACS, non-ST-elevation acute coronary syndrome; TnT, troponin T. Values are expressed as n (%) or mean (standard deviation).

in PCIs. All patients had received at least 1 bare-metal coronary stent. The main aim of the study was to predict major adverse coronary events (MACEs) at 1 year, defined as death, acute myocardial infarction (AMI), and the need for a new coronary revascularization procedure. Patients with transmural AMI and ST segment elevation, prior coronary revascularization, drug-eluting stents, abciximab, or eptifibatide administration (because of the anti-inflammatory action of these drugs), patients with infectious, neoplastic, or systemic diseases with associated inflammation that could be confused with the inflammatory status of ischemic heart disease, and patients who developed MACE before completion of serial sample collection. Post-PCI AMI was established on troponin T (TnT) elevation ≥2.5 times the normal values. All patients agreed to participate in the study. Follow-up was conducted by personal interviews or by contacting family members or physicians outside the hospital.

Bare-metal stent implantation was performed by standard techniques, generally with a radial access. The outcome was considered satisfactory when there were no immediate complications and residual stent stenosis was <20%. Following PCI, all patients received clopidogrel for at least 1 month, as well as aspirin, beta-blockers, and statins indefinitely. Any other medication was prescribed at the discretion of the attending physician.

Serial blood samples for hs-CRP analysis were taken immediately before PCI, after stent implantation, at 8 and 24 h, and at 30 days. Serum was obtained by centrifugation and stored at –20°C until analysis. Quantitative determination of hs-CRP was done by the N latex CRP mono assay with a Behring NB II nephelometer (Dade Behring, Marburg, Germany). TnT determination was performed with Troponin T STAT reagent (Roche Diagnostics).

Statistical Analysis

Categorical variables are expressed as percentage and quantitative variables as the mean (standard deviation [SD]) or median (interquartile range), depending on whether or not they followed a normal distribution. hs-CRP values at each sampling time point were compared with the Mann-Whitney U test. Categorical values were compared with Pearson's χ^2 test. The sensitivity and specificity of hs-CRP samples taken at the different time points was determined by receiver operating characteristic (ROC) curves, calculating the area under the curve for each time point. Using the sample that showed greatest sensitivity and specificity, a table was designed with the coordinates of the curve, and the cut-off point for hs-CRP that marked the highest sensitivity and specificity was determined. Multivariate analysis could not be performed because of the limited sample size. Event-free survival was analyzed with the Kaplan-Meier method and the curves were compared with the log-rank test. A P value less than .05 was considered significant. All analyses were performed with SPSS 14.0 (SPSS, Inc., Chicago, Illinois, USA).

RESULTS

The study included a total of 68 patients. Two patients were excluded because of TnT elevation more than 2.5-fold the normal limits (0.60 and 0.74 µg/mL) in the first 24 h. There were no exclusions between 24 h and 30 days. The clinical characteristics of the study population are summarized in Table 1. Mean age of the women was higher than that of the men (67 [9] vs 58 [10] years; P=.01). Median follow-up was 16.6 (range, 15.3-19.4) months. Patients who experienced a MACE and those that did not showed no significant differences at baseline.

Figure 1. Box-Whisker chart showing results of serial hs-CRP determinations in PCI with bare-metal stent placement, stratified according to clinical diagnosis. AMI indicates acute myocardial infarction; PCI, percutaneous coronary intervention; hs-CRP, high-sensitivity C-reactive protein; TnT, troponin T.
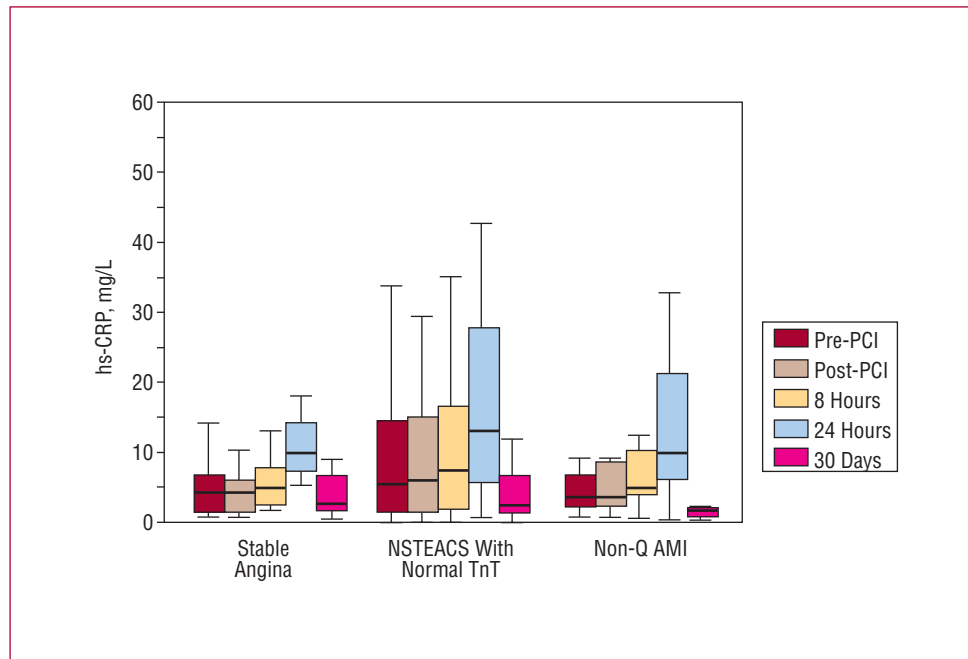
The Box-Whisker chart shows that hs-CRP values always rise following PCIs, reach maximum values at 24 h, and return to normal or near-normal values at 30 days (Figure 1).

The following MACEs were recorded: 3 deaths due to cardiac causes (2 sudden deaths and 1 cardiogenic shock) and 7 percutaneous revascularizations, all for in-stent restenosis. The 3 patients who died were men and were older than the survivors (72 [5] and 60.4 [10] years; P=.06). Mean time before the development of events was 129 (107) days. High-sensitivity CRP values in patients who developed a MACE versus those who did not showed no significant differences in samples taken before the PCI, after the PCI, or at 8 h, but were more elevated at 24 h (23.30 [range, 9.90-42.00] vs 10.75 [range, 6.04-19.1]; P=.05) and at 30 days (7.15 [range, 2.54-9.20] vs 2.25 [range, 1.30-5.00]; P<.02) (Table 2). The increase at 24 h relative to baseline showed no significant differences (Δ=2.9 and Δ=2.5; P=.45).

The various ROC curves for samples taken before 24 h showed no significant differences for predicting MACEs. In contrast, the areas under the curve for 24 h (0.72 [0.55-0.89]; P=.017) and 30 days (0.77 [0.62-0.92]; P=.003) were both similarly significant for predicting events. The cut-off value that provided the highest sensitivity (80%) and specificity (72%) in the 30-day curve was 2.5 mg/L. An hs-CRP value >2.5 mg/L at 30 days was associated with a 6.15-fold increase in the risk of experiencing a MACE. Event-free survival (Kaplan-Meier) at 12 months was significantly lower when hs-CRP was >2.5 mg/L than when it was ≤2.5 mg/L (76.5% vs 94.1%; P=.04).

TABLE 2. Bivariate Analysis of Serial High-Sensitivity C-Reactive Protein Determinations in a Population of Patients Receiving Bare-Metal Stents, Stratified According to the Development of Adverse Events After a 12-Month Follow-up

	Without MACE* (n=58)	With MACE (n=10)	P
Pre-PCI	4.18 (1.47-9.63)	7.97 (2.40-28.5)	.13
Post-PCI	4.34 (1.61-10.10)	8.88 (2.70-22.70)	.10
At 8 h	5.11 (2.20-11.80)	11.82 (4.30-25.00)	.14
At 24 h	10.75 (6.04-19.1)	23.30 (9.90-42.00)	.05
At 30 days	2.25 (1.30-5.00)	7.15 (2.54-9.20)	.02

AMI indicates acute myocardial infarction; hs-CRP, high-sensitivity C-reactive protein; MACE, major adverse cardiac event; NSTEACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; TnT, troponin T.
*MACE only refers to the combination of death and restenosis; there were no cases of AMI during the follow-up.
Values are expressed as the median (interquartile range). Comparative analysis between groups was done with the Kruskal Wallis test.

DISCUSSION

A recent study involving sample collection in the coronary sinus has shown that the mechanical compression produced by balloon inflation and stent deployment causes CRP release from the atheroma plaque.[3] For this reason, the significance of CRP elevation following PCI is still controversial. In addition, it has been hypothesized that elevated baseline CRP is associated with a higher incidence of MACEs,[4] but not of restenosis.[5,6] In the present study, the absence of significant differences in hs-CRP levels of patients with stable angina or NSTEACS at baseline and in relation to risk factors, should be
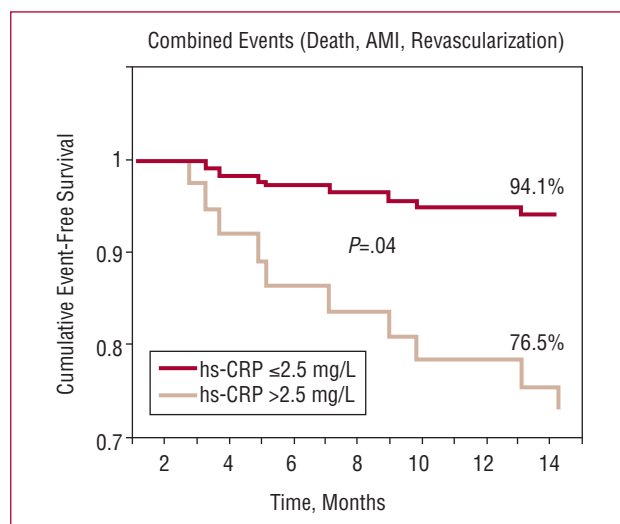
Figure 2. Estimated cumulative event-free survival (Kaplan-Meier) at 12 months, according to high-sensitivity C-reactive protein concentration (hs-CRP) >2.5 mg/L or not at 30 days following bare-metal stent implantation.
AMI indicates acute myocardial infarction

interpreted with caution, since the study population was limited. Consistent with these findings, Ridker et al[7] reported that more than 30% of patients with severe unstable angina show no hs-CRP elevation, and Heeschen et al[8] indicated that the risk of restenosis is independent of prior TnT values. The influence of risk factors on CRP levels has always been considered weak and for some authors, even controversial.[9]

The present study, in keeping with previous efforts, shows that CRP elevation at 24 h following bare-metal stent placement may indicate a greater risk of experiencing a MACE at long term.[10] The main interest of the study, however, lies in the fact that at 30 days following PCI hs-CRP is sufficiently sensitive and specific to predict late MACEs. Patients with hs-CRP levels >2.5 mg/L at 30 days had a 6-fold higher risk of experiencing a MACE at 1 year, particularly stent restenosis. These findings indicate that not only the peak inflammation in the first 24-48 h, but also persistence of a maintained inflammatory state has prognostic value following implantation of a bare-metal stent. Hahn et al[11] also found CRP determination at 1 month to be useful in 87 patients followed up for 3 years after PCI, and Kinjo et al[12] similarly observed that when PCR concentrations remain persistently elevated at 25 days following AMI, long-term mortality is higher. Nonetheless, this data should be confirmed in studies performed with larger patient series.

The most important limitation of this study is the small population included, a fact that did not allow multivariate analysis to establish the independent character of the relationship between hs-CRP and late MACE. Another limitation is not having determined the time at which hs-CRP levels first peaked, which may have been after 24 h. This would have allowed better assessment of the increase occurring after a PCI.

In conclusion, in patients receiving a conventional stent, hs-CRP values >2.5 mg/L at 30 days following the procedure seem to be associated with a greater incidence of late MACEs, particularly in-stent restenosis.

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