The prognostic value of pre-procedural plasma C-reactive protein in patients undergoing elective coronary angioplasty

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Aims The acute phase reactant C-reactive protein is an important prognostic risk factor in patients with both stable and unstable coronary artery disease. The potential prognostic implications of an abnormal pre-procedural C-reactive protein concentration in patients undergoing elective coronary angioplasty may be relevant for subsequent treatment.

Methods and Results Pre-procedural plasma levels of C-reactive protein were measured in 501 patients with stable coronary artery disease undergoing elective coronary angioplasty. The incidence of death or myocardial infarction during a 2-year follow-up was 10.6% (24/227) in patients with an increased C-reactive protein level (>3 mg/l) and 2.9% (8/274) in patients with a normal C-reactive protein level (RR 3.9, 95% CI 1.7–8.9). Survival without death, myocardial infarction, urgent revascularization or hospital admission for unstable angina was significantly lower in patients with an increased C-reactive protein vs patients with a normal C-reactive protein (log-rank 14.62, P<0.0001). Logistic regression analysis identified an increased C-reactive protein level as a strong independent predictor of event-free survival (RR 2.54, 95% CI: 1.44–4.47, P=0.001).

Conclusion Pre-procedural C-reactive protein levels are increased in 45% of patients undergoing elective coronary angioplasty. An increased C-reactive protein level is a powerful independent prognostic indicator for subsequent cardiac events, suggesting that late clinical outcome is markedly influenced by pre-procedural systemic activation of inflammation.

Key Words: Inflammation, coronary angioplasty, prognosis, angina pectoris.

Introduction

Activation of inflammation plays an important role in the onset and progression of atherosclerosis and is associated with the occurrence of coronary thrombosis and the acute coronary syndromes[1-3]. C-reactive protein is an easily measurable acute phase reactant synthesized by hepatocytes in response to pro-inflammatory cytokines, predominantly interleukin-6[4,5]. An elevated C-reactive protein has been identified as a strong predictor of prognosis in healthy individuals[6,7], in patients with stable angina[8-11] and unstable angina[12-17] and in patients after an acute myocardial infarction[18,19]. C-reactive protein may also become elevated as a consequence of myocardial damage[20]. The pathophysiological explanation of this association between C-reactive protein and the incidence of cardiovascular adverse events is currently the subject of intense study. Baseline levels of C-reactive protein may represent a molecular marker for the extent of atherosclerosis[21], or may represent unstable and possibly vulnerable plaques[22,23]. Elevated C-reactive protein may be causally related to the occurrence of adverse coronary events through its ability to bind complement[24,25]. In addition,
it has recently been shown in vitro that C-reactive protein itself induces adhesion molecule expression on human endothelial cells in the presence of serum\cite{26}, and elevated C-reactive protein is associated with endothelial dysfunction\cite{27}. In patients undergoing coronary angioplasty, it has been shown that elevated C-reactive protein was associated with early complications and late clinical restenosis\cite{28-30}. However, other studies failed to confirm the association between restenosis and pre-procedural C-reactive protein levels\cite{31}. Increased C-reactive protein may become an important factor in pre-procedural risk stratification. As an independent marker for the rapid progression of atherosclerosis or the presence of an increased risk of subsequent adverse clinical outcome, increased C-reactive protein may identify high-risk patients as candidates for high dose lipid lowering therapy and treatment with ACE inhibition\cite{32}. The aim of this study was to assess the long term prognostic value of pre-procedural C-reactive protein and compare it with other known risk factors in a large group of consecutive patients undergoing elective coronary angioplasty.

**Methods**

**Participants**

Consecutive patients undergoing elective percutaneous transluminal coronary angioplasty at the catheterization laboratory of the Academic Medical Center at the University of Amsterdam were eligible. Patients undergoing direct percutaneous coronary intervention for ST-elevation acute myocardial infarction, or urgent percutaneous intervention for unstable angina Braunwald class II and III were excluded. Patients referred for a single-vessel procedure as well as for a multivessel procedure were included. In case of multilesion percutaneous intervention, the lesion was treated was classified according to the first lesion attempted (usually the most complex lesion or culprit lesion). Procedures were performed using standard angioplasty techniques using the femoral access route and 6 French guiding catheters.

Patients routinely received 5000 IU of unfractionated heparin, activated clotting times were not routinely measured. Prior to the procedure, patients were treated with aspirin 100–300 mg. Some patients were treated with oral anticoagulants because of side effects of, or intolerance to, aspirin (9%). After the procedure, patients received aspirin at least 100 mg daily and ticlopidine 250 mg b.i.d. or clopidogrel 75 mg daily for 4 weeks after stent placement. Provisional stent implantation was performed in cases with suboptimal result after balloon angioplasty or after major dissection. Elective stenting was used in patients with chronic total occlusions, restenotic lesions, ostial lesions or severe vein graft disease. Only a few patients (<2%) received treatment with a glycoprotein IIb/IIIa inhibitor. The institutional committee on human research approved the protocol.

**Procedures**

Blood was collected in 10 ml heparin coated tubes through the arterial sheath at the start of the procedure and centrifuged without delay. Cells were discarded and plasma was stored at \(-20 \text{°C}\) until further analysis. C-reactive protein was measured with a nephelometric assay (Dade Behring Diagnostics, Marburg, Germany). Calibrators were supplied by the manufacturer. The detection limit was 0.2 mg l\(^{-1}\), linearity was from 0.2–230 mg l\(^{-1}\), and the coefficient of variation was <3% at a concentration of 2 mg l\(^{-1}\). For the present analysis, we used a cut-off value of 3.0 mg l\(^{-1}\) (i.e., 90th percentile of the normal distribution) as reported previously\cite{15,33,34}.

Follow-up was obtained through written questionnaires sent to the patients, review of hospital records, chart review and telephone contact with the patient, with the referring cardiologists, the patient’s general practitioner or the patient’s relatives. Patients with residual or recurrent anginal symptoms requiring repeat revascularization procedures were all referred to our hospital, and data regarding these procedures were collected. Major adverse cardiac events were defined as: death from all causes, myocardial infarction with documented elevation of cardiac markers or the development of new Q-waves on the electrocardiogram, hospital admission for unstable angina (Braunwald class IIb or IIIb) or urgent revascularization (either coronary angioplasty or cardiac bypass surgery as soon as possible for unstable angina Braunwald class IIb or IIIb). Elective coronary angioplasty or cardiac bypass surgery for restenosis without CK-MB elevation were not included in major adverse cardiac events, but were classified as non-urgent revascularization.

**Analysis**

Continuous baseline variables with normal distribution are expressed as mean ± SD and compared by t-test. Categorical baseline variables were compared by Fisher exact test or chi-square statistic where appropriate. Kaplan-Meier survival analysis and life tables were constructed and mean event-free survival between patients with an abnormal or normal C-reactive protein was compared with the log-rank test. Multiple logistic regression analysis was performed to establish the independent predictive value of pre-procedural C-reactive protein in addition to other traditional prognostic risk factors (control of confounding). The statistical analysis was performed using the Statistical Package for Social Sciences software (SPSS 10.01 for Windows, SPSS inc., Chicago, Illinois). A P-value <0.05 was considered statistically significant.

**Results**

A total of 501 patients undergoing elective percutaneous coronary intervention between March 1997 and January
1999 were included in the study. Clinical variables, angiographic findings and procedural variables are summarized in Table 1. An abnormal pre-procedural C-reactive protein (>3 mg . l\(^{-1}\)) was present in 227 of 501 patients (45%). Patients with an abnormal C-reactive protein were significantly older, were more often smokers and more often had Braunwald class I, whereas patients with a normal C-reactive protein were more often hypercholesterolaemic and were more often on statin therapy. All other clinical and procedural variables were equally distributed between the two groups.

Median time of follow-up was 425 days, (range 1–1112). Follow-up was complete for all patients. There were no peri-procedural deaths and there were no patients with (subacute) vessel closure requiring emergency repeat angioplasty or emergency bypass surgery within the first 24 h. The incidence of major adverse cardiac events during follow-up is summarized in Table 2. All deaths were cardiac deaths. The incidence of death or myocardial infarction was significantly higher in the patients with a normal pre-procedural C-reactive protein, but this difference did not reach statistical significance. The Kaplan–Meier survival analysis demonstrated a significant difference in event-free survival at 2 years in patients with an abnormal pre-procedural C-reactive protein compared to patients with a normal pre-procedural C-reactive protein (log-rank 14.62, \(P=0.0001\), Fig. 1).

The univariate analysis for C-reactive protein and other known risk factors and the results of the multivariate logistic regression analysis are shown in Table 3. Logistic regression analysis identified C-reactive protein as a significant independent predictor for future adverse cardiac events. Furthermore, the relative risk of C-reactive protein showed little change when the other potential predictors were entered into the model (absence of confounding) (RR 2.54, 95% CI: 1.44–4.47, \(P=0.001\)). Once C-reactive protein was entered into the model, other risk factors no longer contributed significantly to the predictive model.

Discussion

This prospective study in a large group of patients undergoing elective coronary angioplasty for stable coronary artery disease demonstrates that pre-procedural C-reactive protein is an important independent prognostic indicator. Patients with single and
multivessel disease, bifurcated lesions, graft disease, etc. (all-comers) were included; only patients with an acute coronary syndrome were not included. Our data show that C-reactive protein predicts prognosis independently of, and in addition to, other traditional prognostic factors. Moreover, logistic regression analysis showed that other traditional risk factors such as age, gender, diabetes mellitus, did not substantially alter the prognostic value of C-reactive protein. The use of statins at the time of percutaneous coronary intervention was associated with event-free survival in the univariate analysis, and statin therapy was more prevalent in the patients with a normal pre-procedural C-reactive protein. In the multivariate analysis, however, once C-reactive protein

Table 2  Clinical events by pre-procedural CRP status

<table>
<thead>
<tr>
<th>Patients</th>
<th>CRP &gt;3 mg . l⁻¹</th>
<th>CRP ≤3 mg . l⁻¹</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical events</td>
<td>n=227 (%)</td>
<td>n=274 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>11 (4·8%)</td>
<td>4 (1·5%)</td>
<td>3·44 (1·08–10·95)</td>
<td>0·025</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13 (5·7%)</td>
<td>4 (1·5%)</td>
<td>4·10 (1·32–12·76)</td>
<td>0·012</td>
</tr>
<tr>
<td>Urgent revascularization</td>
<td>11 (4·8%)</td>
<td>5 (1·8%)</td>
<td>2·74 (0·94–8·01)</td>
<td>0·073</td>
</tr>
<tr>
<td>Recurrent unstable angina</td>
<td>11 (4·8%)</td>
<td>10 (3·6%)</td>
<td>1·34 (0·56–3·23)</td>
<td>0·51</td>
</tr>
<tr>
<td>Non-urgent PTCA</td>
<td>23 (10·1%)</td>
<td>36 (13·1%)</td>
<td>0·75 (0·43–1·30)</td>
<td>0·33</td>
</tr>
<tr>
<td>Non-urgent CABG</td>
<td>8 (2·9%)</td>
<td>7 (3·1%)</td>
<td>1·06 (0·38–2·96)</td>
<td>1·00</td>
</tr>
<tr>
<td>Composite end-points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>46 (20·3%)</td>
<td>23 (8·4%)</td>
<td>2·77 (1·62–4·74)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Death or MI</td>
<td>24 (10·6%)</td>
<td>8 (2·9%)</td>
<td>3·93 (1·73–8·93)</td>
<td>0·001</td>
</tr>
</tbody>
</table>

Incidence of major adverse cardiac events (death, myocardial infarction, urgent revascularization for unstable angina or rehospitalizations for unstable angina) and non-urgent revascularizations after a median follow-up of 425 days in 501 consecutive patients with stable angina pectoris undergoing elective coronary angioplasty. The rate of events was compared between patients with an abnormal pre-procedural C-reactive protein (defined as >3 mg . l⁻¹) and patients with a normal pre-procedural C-reactive protein (≤3 mg . l⁻¹).

MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty; CABG=coronary artery bypass grafting; CRP=C-reactive protein; RR=relative risk; CI=confidence interval.

Figure 1  The Kaplan–Meier survival curves for the 227 patients with abnormal pre-procedural C-reactive protein and the 274 patients with normal pre-procedural C-reactive protein during a follow-up of 2 years. Major adverse cardiac events were prospectively defined as either the occurrence of death, myocardial infarction, urgent revascularization for unstable angina or rehospitalization for unstable angina. The event curves separate early and continue to separate during a median follow-up of 425 days. Pre-procedural C-reactive protein was identified as an important predictor for the occurrence of future adverse cardiac events (log rank 14·62, P<0·0001).
was included in the model, statin use did not alter the prognostic value of pre-procedural C-reactive protein levels. Hence, the prognostic value of pre-procedural C-reactive protein in the present study cannot be explained by differences in statin use.

**Prior studies**

Our study confirms and extends the findings from a small study by Buffon *et al.*[28] in which increased pre-procedural C-reactive protein was identified as an important independent predictor for early adverse events and late clinical restenosis during a 1-year follow-up in 52 stable angina and 59 unstable angina patients with single vessel disease. In that study, abnormal C-reactive protein was present in 29% of the patients with stable angina compared to 45% of our patients. Among 52 patients with stable angina, two early events occurred, while incidence of clinical restenosis was 40% (30% in patients with normal C-reactive protein compared to 67% in patients with abnormal C-reactive protein). Interestingly these authors also reported a significantly higher incidence of clinical restenosis presenting as rest angina in patients with abnormal pre-procedural C-reactive protein compared to patients with normal pre-procedural C-reactive protein (40.7% vs 1.9%), whereas no difference was observed in the incidence of clinical restenosis presenting as stable angina (CCS class I–II).

In another study by Versaci *et al.*[30], which comprised 62 patients with Braunwald class IIIB unstable angina undergoing coronary angioplasty and stent placement, abnormal pre-procedural C-reactive protein was associated with a 60% incidence of adverse cardiac events during a 1-year follow-up compared to 3% in patients with a normal pre-procedural C-reactive protein. However, in an atherectomy and restenosis study, which included 75 patients, Zhou *et al.* could not demonstrate a relationship between pre-procedural C-reactive protein measurements and the occurrence of angiographic restenosis[31]. In our study, the incidence of the composite end-point of death, myocardial infarction, urgent revascularization, or rehospitalizations for unstable angina was higher in the patients with increased pre-procedural C-reactive protein, but other manifestations of restenosis such as restenosis-associated stable angina were not correlated with pre-procedural C-reactive protein. The high proportion of patients with abnormal C-reactive protein in our study (45%) was surprising. Elevated C-reactive protein has been associated with the extent and activity of atherosclerotic disease. Moreover, it has been shown that activation of coagulation may subsequently remain elevated for several months in patients with stabilized angina. The most likely explanation for the high proportion of patients with abnormal pre-procedural C-reactive protein in the present study is both the presence of extensive coronary artery disease, or persistent elevation of markers of systemic

### Table 3 Logistic regression analysis of predictive value of pre-procedural C-reactive protein on major adverse cardiac events

<table>
<thead>
<tr>
<th>Univariate relative risk (95% CI)</th>
<th>P-value</th>
<th>Multivariate relative risk* (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>0.78 (0.45–1.36)</td>
<td>0.38</td>
<td>0.88 (0.48–1.61)</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>0.78 (0.45–1.36)</td>
<td>0.38</td>
<td>0.88 (0.48–1.61)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>1.40 (0.83–2.36)</td>
<td>0.21</td>
<td>1.14 (0.65–2.00)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>1.73 (0.86–3.45)</td>
<td>0.12</td>
<td>1.63 (0.77–3.43)</td>
</tr>
<tr>
<td><strong>Family history of CAD</strong></td>
<td>0.84 (0.50–1.42)</td>
<td>0.51</td>
<td>0.84 (0.50–1.42)</td>
</tr>
<tr>
<td><strong>Statin therapy</strong></td>
<td>0.59 (0.34–1.00)</td>
<td>0.052</td>
<td>0.60 (0.34–1.06)</td>
</tr>
<tr>
<td><strong>Cigarette smoking</strong></td>
<td>0.06 (0.02–1.08)</td>
<td>0.84</td>
<td>0.03 (0.01–0.85)</td>
</tr>
<tr>
<td><strong>Braunwald class I</strong></td>
<td>1.50 (0.77–2.91)</td>
<td>0.23</td>
<td>1.24 (0.60–2.55)</td>
</tr>
<tr>
<td><strong>Coronary artery treated LAD</strong></td>
<td>0.99 (0.60–1.67)</td>
<td>0.99</td>
<td>0.99 (0.60–1.67)</td>
</tr>
<tr>
<td><strong>ACC/AHA lesion class B2-C†</strong></td>
<td>1.30 (0.72–2.27)</td>
<td>0.41</td>
<td>1.43 (0.71–2.65)</td>
</tr>
<tr>
<td><strong>First/restenotic lesion</strong></td>
<td>0.85 (0.40–1.83)</td>
<td>0.68</td>
<td>0.85 (0.40–1.83)</td>
</tr>
<tr>
<td><strong>Use of stents</strong></td>
<td>0.97 (0.57–1.66)</td>
<td>1.0</td>
<td>0.97 (0.57–1.66)</td>
</tr>
<tr>
<td><strong>%DS pre PTCA</strong></td>
<td>0.99 (0.98–1.01)</td>
<td>0.40</td>
<td>0.99 (0.98–1.01)</td>
</tr>
<tr>
<td><strong>Lesion length (mm)</strong></td>
<td>1.01 (0.97–1.05)</td>
<td>0.69</td>
<td>1.01 (0.97–1.05)</td>
</tr>
<tr>
<td><strong>%DS post PTCA</strong></td>
<td>1.00 (0.99–1.01)</td>
<td>0.93</td>
<td>1.00 (0.99–1.01)</td>
</tr>
<tr>
<td><strong>CRP &gt;3.0 mg·1−1</strong></td>
<td>2.77 (1.62–4.74)</td>
<td>$&lt;0.0001$</td>
<td>2.54 (1.44–4.47)</td>
</tr>
</tbody>
</table>

Major adverse cardiac events were defined as death, myocardial infarction, urgent revascularization for unstable angina or rehospitalizations for unstable angina during a median follow-up of 425 days.

*Multivariate analysis was performed forcing traditional prognostic risk factors as variables in the model together with pre-procedural C-reactive protein (control of confounding).

†Modified scheme from American College of Cardiology/American Heart Association Task Force classification.

CAD = coronary artery disease; LAD = left anterior descending; %DS = percent diameter stenosis; CRP = C-reactive protein; PTCA = percutaneous transluminal coronary angioplasty; CI = confidence interval.
inflammatory activity such as C-reactive protein in patients with ‘stabilized’ coronary artery disease.

**Implications for revascularization**

In another recent study by Anderson et al., C-reactive protein predicted mortality independent of traditional risk factors in patients with angiographically defined coronary artery disease. This suggests that C-reactive protein is a potent independent marker for atherosclerosis progression. Although our patients may perhaps represent just another subgroup with angiographically documented coronary artery disease, information concerning the prospected progression of disease may be important for subsequent treatment decisions. Patients undergoing bypass surgery for multivessel coronary artery disease may be less vulnerable to the consequences of native coronary atherosclerosis progression than patients undergoing initial percutaneous intervention. Prior studies have shown an increased incidence of adverse events in patients with diabetes mellitus who underwent percutaneous coronary intervention as opposed to cardiac bypass surgery (Referred to by R. Kuntz as the ‘diabetes–PTCA dilemma’). It is therefore important to extend the event horizon beyond the typical 6 months in which restenosis may occur to a period of 2 or even 5 years. Indeed, in our analysis, elevated C-reactive protein was a more important predictor of adverse cardiac events than the presence of diabetes mellitus. However, abnormal C-reactive protein prior to bypass surgery has been shown to be associated with poor outcome.

**Implications for medical therapy**

Ridker et al. have shown that increased C-reactive protein is independent but adds prognostic value to standard lipid screening. These authors proposed using C-reactive protein measurements for the identification of candidates for lipid lowering therapy in the general population, an unorthodox point of view. Using C-reactive protein measurements for screening in specific subgroups of patients, such as our study group, may be an alternative. These patients may benefit from intensive treatment with statins, as there are indications that these drugs have antiinflamatory properties, and maximal benefit may be derived from high-dose statin use (MIRACL study, AHA scientific sessions, New Orleans 2000). Moreover, ACE inhibition may improve the prognosis in high risk patients.

**Study limitations**

Although risk factors were recorded prospectively, the dose of statin use was not systematically recorded. In a substantial proportion of patients on statin therapy, pre-procedural C-reactive protein was abnormal. However, abnormal pre-procedural C-reactive protein was the only significant, independent predictor of prognosis, even after including statin use into the model. Whether more aggressive treatment with higher doses of statins could normalize C-reactive protein in these patients cannot be answered with our data. Moreover, in patients with documented coronary artery disease such as those included in the present study, statin therapy nowadays would be given more frequently. In addition, stents were used in only 34% of patients, whereas routine angioplasty procedures in the past 2 years are accompanied by stent placement in 65% to 85% of cases. Additionally, the number of procedures performed with the concomitant use of glycoprotein IIb/IIIa inhibitors is currently higher compared to the number of procedures in our study population. However, the incidence of peri-procedural complications was low and was not different between the patients with and without increased C-reactive protein.

Our study shows that pre-procedural plasma levels of C-reactive protein provide a powerful predictor of adverse cardiac events, independent of traditional prognostic risk factors. These findings show that late clinical outcome is markedly influenced by pre-procedural systemic activation of inflammation. The measurement of C-reactive protein as a marker for prospected progression of coronary atherosclerotic disease may be part of the assessment of a pre-procedural risk profile that may identify candidates for intensive medical therapy.

We are very grateful to the nursing staff of the catheterization laboratory of the Academic Medical Center of the University of Amsterdam and to all the cardiologists from referring centers and general practitioners who kindly assisted in completing the follow-up data collected in this study.

**References**

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