Independent prognostic value of C-reactive protein and troponin I in patients with unstable angina or non-Q-wave myocardial infarction

Robbert J. de Winter a,*, Radha Bholasingh a, Jeroen G. Lijmer c, Rudolph W. Koster a, Jozef P.M.C. Gorgels b, Yvonne Schouten b, Frans J. Hoek b, Gerard T. Sanders b

aDepartment of Cardiology, Room B2-125, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, Netherlands
bDepartment of Clinical Chemistry, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands
cDepartment of Clinical Epidemiology and Biostatistics, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Received 5 November 1998; accepted 15 January 1999

Abstract

Objectives: Elevated concentrations of C-reactive protein (CRP), a non-specific acute phase reactant, and troponin I (TnI), a cardiac-specific marker of myocardial damage, have been found to be associated with a higher risk for cardiac events in patients with an acute coronary syndrome. We evaluated CRP alone and in combination with TnI for predicting the incidence of major cardiac complications within 6 months in patients with unstable angina or non-Q-wave infaction (NQMI). Methods: CRP and TnI was measured on admission in patients with unstable angina or NQMI, but results were kept blinded. Patients were treated according to a conservative management strategy, and the incidence of major cardiac events within 6 months was assessed. Results: An abnormal CRP (>0.5 m g/l) and an abnormal TnI (>0.4 m g/l) were more frequent in patients that suffered a major cardiac event (CRP: 93 vs. 35%, P<0.0001; TnI: 73 vs. 26%, P<0.001). The incidence of major cardiac events was higher in patients with an abnormal CRP than in patients with a normal CRP, both when TnI was abnormal (42 vs. 4.5%, P<0.003) and when TnI was normal (11 vs. 0%, P=0.014). Mean event-free survival was excellent in patients with both a normal CRP and TnI, whereas survival was poorest in patients with both an abnormal CRP and TnI (121 ± 16 vs. 180 days, P<0.0001). Conclusions: An abnormal CRP on admission in patients with unstable angina or NQMI is associated with increased incidence of major cardiac events within 6 months, both in patients with normal and abnormal TnI. CRP and TnI have independent and additive prognostic value in this patient group, and the combination may be useful for early risk stratification. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Acute coronary syndromes; Prognosis; C-reactive protein; Troponin I

1. Introduction

Patients with an acute coronary syndrome, either severe unstable angina (UA) or non-Q-wave myocardial infarction (NQMI), have a high risk of suffering a subsequent cardiac events [1–3]. Several studies have shown that in about one third of these patients, an elevated troponin T [4–7] or troponin I (TnI) [8,9], can be found, and these elevations are an indicator of a poor prognosis. Other studies have shown that an increase in circulating concentrations of acute phase reactants such as C-reactive protein (CRP) and interleukin-6 (IL-6) are strong predictors of adverse outcome in patients with an acute coronary syndrome [10–12]. It has been demonstrated that an elevated CRP is not necessarily induced by ischemic injury, as normal CRP levels were measured after an episode of ischemia in patients with variant angina without atherosclerotic coronary artery disease [12]. Moreover, although myocardial necrosis can cause an acute phase reaction by itself, Liuzzo et al. reported an elevation of CRP in UA patients without an abnormal troponin T [10]. Finally, myocardial necrosis was an unlikely cause of a modest elevation of CRP in a large group of patients with stable angina in the ECAT

*Corresponding author. Tel.: +31-20-5669111; fax: +31-20-6962609. E-mail address: r.j.dewinter@amc.uva.nl (R.J. de Winter)

Time for primary review 33 days.
study, although no marker of necrosis was measured [13]. Thus, both CRP and troponin T or I are prognostic indicators in patients with unstable angina and NQMI, and may have independent and additive prognostic value.

The aim of this study was to assess the prognostic value of CRP and troponin I in patients with unstable angina or NQMI for the occurrence of major cardiac events within 6 months.

2. Methods

2.1. Patients

Consecutive patients presenting at the cardiac emergency room of the Academic Medical Center with typical chest pain of <8 h duration were eligible for the study. Patients were included if they had either diagnostic ST-segment depression or T-wave changes characteristic of myocardial ischemia. CK-MB was measured on admission, and at 5, 7 and 10 h after the onset of symptoms and, when CK-MB mass was abnormal, at frequent intervals thereafter. The diagnosis for AMI was established according to the WHO criteria [14], with a peak CK-MB above 14 μg/l (twice the upper limit of normal). Non-Q-wave AMI was considered present when peak CK-MB exceeded 14 μg/l and no new Q-waves developed on the electrocardiogram. Patients with a peak CK-MB above the upper limit of normal (7.0 μg/l), but below the predefined limit for AMI were classified as unstable angina, as were patients without CK-MB elevation.

Patients with ST-elevations on the admission-electrocardiogram that were candidates for reperfusion therapy (either primary PTCA or thrombolytic therapy) were excluded. Patients were also excluded when the evolution of the electrocardiogram showed the development of new left bundle branch block or new Q-waves. Other exclusion criteria were a known or suspected infectious or inflammatory condition and a scheduled revascularization procedure. The protocol was approved by the institutions Medical Ethics Committee and all patients gave informed consent. The investigation conforms with the principles outlined in the Declaration of Helsinki.

2.2. Assays

CRP and TnI were measured from samples drawn on admission, and results were kept blinded from the physicians treating the patients. Blood samples were drawn in vacuum tubes containing lithium heparin, centrifuged, and remaining plasma stored at −70°C for later measurements. Patients were treated with aspirin, heparin i.v., nitrates i.v., β-blockers etc. according to a conservative management strategy as outlined in the TIMI IIb trial [15].

CRP was measured with a nephelometric assay (Behring Diagnostics, Marburg, Germany). The detection limit was 0.2 mg/l, linearity was from 0.2–230 mg/l, and the coefficient of variation (CV) was <3% at a concentration of 2 mg/l. The 95th percentile in 120 healthy donors in our institution was established at 5.0 mg/l.

TnI was measured with the fluorometric enzyme immunoassay on the Stratus II (Dade, Miami, FL, USA). The lower detection limit was 0.35 μg/l, linearity was from 0.35 to 50 μg/l, CV. was 11.7% in the concentration range of 1.4 μg/l. The upper limit of normal as previously established [8] and according to the manufacturer was 0.4 μg/l.

CK-MB was measured with the Immuno-1 (Bayer, Leverkusen, Germany). The upper limit of normal was 7.0 μg/l. CV. at 5.0 μg/l was 2.5%.

2.3. Follow-up

A 6-month follow-up was assessed by telephone interview, either with the patient, the cardiologist or general practitioner caring for the patient, or the patient’s relatives. Primary outcome was defined as cardiac death, recurrent non-fatal AMI or recurrent hospital admission for severe unstable angina (defined as recurrent unstable angina at rest with diagnostic ST-segment depression or T-wave changes characteristic of myocardial ischemia). Secondary outcome was defined as (the need for) percutaneous transluminal coronary angioplasty or coronary bypass grafting. Patients underwent revascularization only when they did not respond to optimal medical therapy. Physicians caring for the patients during follow-up who were responsible for scheduled revascularization procedures, were unaware of the CRP or TnI results.

2.4. Statistical analysis

CRP and TnI were treated as a dichotomous variable (either elevated or normal) with cut-off value for CRP: 5.0 mg/l and for TnI: 0.4 μg/l. Two-by-two contingency tables for the primary outcome were constructed for CRP>5.0 mg/l, TnI>0.4 μg/l or both elevated. The prognostic value of CRP and TnI was assessed in a multivariate logistic regression model with the primary outcome as the dependent variable. Models with age, gender, history of hypertension, diabetes mellitus, previous myocardial infarction and ‘aspirin use’ in combination with either an abnormal CRP, an abnormal TnI or both were compared with a log likelihood test. [16,17] To assess event-free survival, Kaplan–Meier curves were constructed both for the primary outcome and for all outcome including revascularizations, and differences in mean survival were compared using the log-rank test. Calculations were done with a statistical software package (SPSS 6.01 for windows, SPSS, USA). All statistical comparisons were two-tailed, and a P value of <0.05 was considered statistically significant.
Table 1
Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>No event</th>
<th>n (%)</th>
<th>Death/AMI/UAP</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>135</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>88 (65)</td>
<td>9 (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>62±14</td>
<td>72±13*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20 (15)</td>
<td>2 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (30)</td>
<td>5 (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>46 (34)</td>
<td>6 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prev AMI</td>
<td>36 (27)</td>
<td>7 (47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prev PTCA/CABG</td>
<td>40 (30)</td>
<td>5 (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>42 (31)</td>
<td>9 (60)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP&gt;5.0 mg/l</td>
<td>47 (35)</td>
<td>14 (93)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TnI&gt;0.4 mg/l</td>
<td>35 (26)</td>
<td>11 (73)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Differences between groups were compared with the χ² statistic or Fishers exact test where appropriate, differences in means were compared with the t-test. Age and aspirin use were different between the two groups. Both variables were included in the multiple logistic regression analysis, as were diabetes mellitus, hypertension and previous AMI as known prognostic indicators. AMI = acute myocardial infarction. Rec. UAP = admission due to recurrent unstable angina pectoris. CRP = C-reactive protein. TnI = troponin I.

b Categories for which P<0.05.

c Categories for which P<0.001.

3. Results

A total of 150 patients were included in the study, 115 patients with unstable angina and 35 patients with non-Q-wave AMI. The patients’ characteristics are summarized in Table 1, comparing patients that reached a primary endpoint with the other patients. Follow-up at six month was 100% complete. There were 15 major cardiac events (10%) and 28 revascularizations (19%), listed in Table 2. One patient died from lung cancer 30 days after admission and this patient was censored at day 30. CRP values ranged from 0.0 to 76.1 mg/l (median 3.35; 25th and 75th percentiles 1.4 and 8.85 mg/l, respectively). An abnormal CRP (>5.0 mg/l) was present in 61 patients (41%), median CRP for the 15 patients with a major cardiac event was 12.5 mg/l (range 3.0-57.1 mg/l), compared to 3.0 mg/l (range 0-76.1 mg/l) for the 135 patients without a major cardiac event. TnI values ranged from 0.0 to 41.4 μg/l (median 0.0 μg/l; 25th and 75th percentiles 0.0 and 0.83 μg/l, respectively). An abnormal TnI (>0.4 μg/l) was present in 44 patients (29%), median TnI for the 15 patients with a major cardiac event was 2.4 μg/l (range 0.0 to 13.4 μg/l) compared to 0.0 μg/l (range 0.0 to 41.3 μg/l) for the 135 patients without a major cardiac event.

Patients with a major cardiac event were older, and more frequently had an elevated CRP or TnI. In addition, patients with a primary event were more often already on aspirin. The incidence of a major cardiac event was significantly higher among patients with CRP>5.0 mg/l than in other patients (23 (13±36%) vs. 1.1 (0±6%), P=0.00001), and this was evident both in patients with an elevated TnI (42 (22±63%) vs. 4.5 (0±23%), P=0.003) and in patients without an elevated TnI (0 vs. 11 (3±25%), P=0.014) (Fig. 1). The multivariate logistic regression model with age, gender, history of infarction, hypertension, aspirin use and diabetes significantly improved when either an abnormal CRP or an abnormal TnI or both were included in the model (Δ2 log LR for CRP and TnI: 11.915 and 10.060 respectively, P<0.001), demonstrating the additive prognostic value of both markers. A multivariate model including both markers showed improved performance in comparison with models with a single marker (P<0.001), demonstrating their independent predictive value.

Table 2
Events during 6 months follow-up in 150 patients with unstable angina or NQMI

<table>
<thead>
<tr>
<th>Events</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>8</td>
</tr>
<tr>
<td>Recurrent AMI</td>
<td>3</td>
</tr>
<tr>
<td>Rec. UAP</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
</tr>
<tr>
<td>Revascularizations</td>
<td></td>
</tr>
<tr>
<td>PTCA</td>
<td>20</td>
</tr>
<tr>
<td>CABG</td>
<td>8</td>
</tr>
</tbody>
</table>

* One patient died of lung cancer at day 30 of follow-up. AMI = acute myocardial infarction; Rec. UAP = recurrent admission due to unstable angina pectoris; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass grafting.

4. Discussion

The present study confirms earlier studies, showing that both CRP, a non-specific acute phase reactant, and TnI, a cardiac specific marker of myocardial damage, are elevated
early in a substantial number of patients with unstable angina and non-Q-wave AMI. It shows that CRP and TnI are independent prognostic indicators of adverse outcome. The incidence of a major cardiac event was 23% in patients with an abnormal CRP vs. 1.1% in patients with a normal CRP. Moreover, in patients without a TnI elevation, a CRP > 5.0 mg/l carried a significantly higher risk for a major cardiac event within 6 months (11 vs. 0%). Patients with both CRP and TnI elevated had the highest incidence of cardiac death, recurrent AMI or admission for recurrent unstable angina within 6 months, and had a poor mean event free survival. The difference in the incidence of events is apparent within the first two weeks, but the survival curves continue to diverge during the subsequent 6-month follow-up (Fig. 2). In contrast, patients with both a normal CRP and TnI have an excellent prognosis. In this patient group there were no cardiac deaths, recurrent AMIs or recurrent admissions for unstable angina during the 6 months follow-up.

Our study confirms and extends the findings of one recent report from the TIMI 11A substudy investigators, which demonstrated independent and combined prognostic

![Graph showing incidence of major cardiac complications by normal or abnormal CRP concentration in all patients and those with a normal and abnormal TnI concentration. Primary outcome was defined as cardiac death, non-fatal acute myocardial infarction or admission for recurrent unstable angina. Statistical comparison was made by χ² test of Fisher exact test.](image)

**Table 3**

<table>
<thead>
<tr>
<th></th>
<th>No elevations</th>
<th>Either CRP/TnI</th>
<th>Both CRP/TnI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>68</td>
<td>58</td>
<td>24</td>
</tr>
<tr>
<td>Death/AMI/UAP</td>
<td>0</td>
<td>4b</td>
<td>10⁻²ᵃ</td>
</tr>
<tr>
<td>Event-free survival (days)</td>
<td>180</td>
<td>169±5b</td>
<td>121±16⁻ᵃ</td>
</tr>
<tr>
<td>All events</td>
<td>18</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Event-free survival (days)</td>
<td>138±9</td>
<td>152±8</td>
<td>107±16⁻ᵃ</td>
</tr>
</tbody>
</table>

* Differences in proportions between groups were compared with the χ² statistic. Mean event-free survival was calculated with Kaplan-Meier survival analysis and differences were compared with the Log rank test. AMI = acute myocardial infarction; Rec. UAP = recurrent admission due to unstable angina pectoris; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass grafting; CRP = C-reactive protein; TnI = troponin I.

ᵇ Significant difference between group with either CRP or TnI vs. group with no elevations.

ᵇ Significant difference between group with both CRP/TnI vs. group with no elevations.

ᵇ Significant difference between group with both CRP/TnI vs. group with either CRP or TnI.
patients with an elevated troponin T in the FRISC study which used a cut-off value $\geq 1 \mu g/l$. In contrast, Liuzzo et al. [10] demonstrated that CRP elevation in patients with unstable angina, without evidence of myocardial damage as assessed with troponin T, is associated with poor outcome. In addition, in another paper, Liuzzo et al. showed that severe myocardial ischemia in patients with variant angina without atherosclerotic coronary artery disease does not by itself induce an increase in plasma CRP [12]. Therefore, it is likely that CRP elevations are due to activation of inflammation. It has been shown that other pro-inflammatory cytokines such as interleukin-6, interleukin-8 and TNF-\(\alpha\) are elevated on admission in patients with acute coronary syndromes [11,20,21], and that these elevations may be associated with a worse outcome [11]. We have previously shown that IL-6 has equivalent discriminatory capacity to the pro-coagulant factor fibrinopeptide A to distinguish between patients with stable and unstable coronary artery disease [22].

Whether CRP elevations are causal to the initiation of an episode of unstable coronary artery disease is unknown. It has been shown that CRP stimulates production of tissue factor by mononuclear cells, the main initiator of blood coagulation [23]. In addition, it has been suggested that CRP together with phospholipase A2 may cause complement activation and promote phagocytosis of damaged cells by activated neutrophils [24]. Unstable atherosclerotic plaques have an increased number of macrophages that seem to be most abundant in the vulnerable shoulder region of the fibrous cap overlying the core of atheroma [25]. Therefore, it is conceivable that an elevated CRP signifies ongoing activation of inflammation that characterizes unstable coronary artery disease and indeed may be one of the causal factors of instability.

Limitations of the study are the relatively small number of patients and the relatively few events. Separate analysis of the patients with unstable angina or non-Q-wave AMI gave comparable results, but in order to increase study population size the two patient groups were considered together. However, even in this relatively small patient group, differences between patients with and without CRP or TnI elevations are striking. Together with another report [18], our findings suggest the possibility for risk stratification with the combination of these two markers.

In conclusion, our study demonstrates the independent prognostic value of CRP and TnI in patients with unstable angina or NQMI, for long term adverse outcome. Incidence of events was high and mean event-free survival was low in patients with combined elevation of CRP and TnI, whereas prognosis is excellent for patients without elevations of CRP and TnI. These findings suggest that the effects of a comprehensive treatment, e.g. with IIb/IIIa antagonists, of patients with both markers elevated or early discharge of patients with both a normal CRP and TnI could be studied in a prospective study.
Acknowledgements

We are thankful to the physicians and nursing staff of the Cardiac Emergency Room and the Coronary Care Unit of the Academic Medical Center for their efforts in completing this study. Special thanks is due to Mariandl vt Hof for all the work involved in completing the follow-up.

References


