Early risk stratification in patients with chest pain

Bholasingh, R.

Citation for published version (APA):
Chapter 8

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
Radha Bholasingh
Jeroen G. Lijmer
Rudolph W. Koster
Jozef P. M. C. Gorgels
Yvonne Schouten
Frans J. Hoek
Gerard T. Sanders

*Cardiovascular Research* 1999, 42: 240-5
ABSTRACT

Objectives
Elevated concentrations of C-reactive protein, a non-specific acute phase reactant, and troponin I, 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 C-reactive protein alone and in combination with troponin I for predicting the incidence of major cardiac complications within six months in patients with unstable angina or non-Q-wave myocardial infarction.

Methods
C-reactive protein and troponin I was measured on admission in patients with unstable angina or non-Q-wave myocardial infarction, but results were kept blinded. Patients were treated according to a conservative management strategy, and the incidence of major cardiac events within six months was assessed.

Results
An abnormal C-reactive protein (>5 mg/l) and an abnormal troponin I (>0.4 μg/l) were more frequent in patients that suffered a major cardiac event (C-reactive protein: 93% vs 35%, p<0.0001; troponin I: 73% vs 26%, p<0.001). The incidence of major cardiac events was higher in patients with an abnormal C-reactive protein than in patients with a normal C-reactive protein, both when troponin I was abnormal (42% vs 4.5%, p=0.003) and when troponin I was normal (11% vs 0%, p=0.014). Mean event-free survival was excellent in patients with both a normal C-reactive protein and troponin I, whereas survival was poorest in patients with both an abnormal C-reactive protein and troponin I (121 ±16 versus 180 days, p<0.0001).

Conclusions
An abnormal C-reactive protein on admission in patients with unstable angina or non-Q-wave myocardial infarction is associated with increased incidence of major cardiac events within six months, both in patients with normal and abnormal troponin I. C-reactive protein and troponin I have independent and additive prognostic value in this patient group, and the combination may be useful for early risk stratification.
INTRODUCTION

Patients with an acute coronary syndrome, either severe unstable angina (UA) or non-Q-wave myocardial infarction, have a high risk of suffering a subsequent cardiac events(177-179). Several studies have shown that in about one third of these patients, an elevated troponin T(114;117;138;180) or troponin I(139;181), 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 and interleukin-6 are strong predictors of adverse outcome in patients with an acute coronary syndrome(124;182;183). It has been demonstrated that an elevated C-reactive protein is not necessarily induced by ischemic injury, as normal C-reactive protein levels were measured after an episode of ischemia in patients with variant angina without atherosclerotic coronary artery disease(183). Moreover, although myocardial necrosis can cause an acute phase reaction by itself, Liuzzo and colleagues reported an elevation of C-reactive protein in UA patients without an abnormal troponin T(124). Finally, myocardial necrosis was an unlikely cause of a modest elevation of C-reactive protein in a large group of patients with stable angina in the ECAT study, although no marker of necrosis was measured(184). Thus, both C-reactive protein and troponin T or I are prognostic indicators in patients with unstable angina and non-Q-wave myocardial infarction, and may have independent and additive prognostic value.

The aim of this study was to assess the prognostic value of C-reactive protein and troponin I in patients with unstable angina or non-Q-wave myocardial infarction for the occurrence of major cardiac events within six months.

METHODS

Patients

Consecutive patients presenting at the cardiac emergency room of the Academic Medical Center with typical chest pain of less than 8 hours 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 hours after the onset of symptoms and, when CK-MBmass was abnormal, at frequent intervals thereafter. The diagnosis for acute myocardial infarction was established according to the WHO criteria(87), with a peak CK-MB above 14 μg/l (twice the upper limit
of normal). Non-Q-wave myocardial infarction 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 acute myocardial infarction 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 percutaneous transluminal coronary angioplasty 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.

Assays
C-reactive protein and troponin I 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(185).

C-reactive protein 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 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.

Troponin I was measured with the fluorometric enzyme immunoassay on the Stratus II (Dade, Miami, Florida USA). The lower detection limit was 0.35 µg/l, linearity was from 0.35-50 µg/l, the coefficient of variation was 11.7% in the concentration range of 1.4 µg/l. The upper limit of normal as previously established(139) 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, the coefficient of variation at 5.0 µg/l was 2.5%.
Follow-up
Six months 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 MI 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 C-reactive protein or troponin I results.

Statistical analysis
C-reactive protein and troponin I were treated as a dichotomous variable (either elevated or normal) with cut-off value for C-reactive protein: 5.0 mg/l and for troponin I: 0.4 μg/l. Two-by-two contingency tables for the primary outcome were constructed for C-reactive protein > 5.0 mg/l, troponin I > 0.4 μg/l or both elevated. The prognostic value of C-reactive protein and troponin I 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 C-reactive protein, an abnormal troponin I or both were compared with a log likelihood test(186;187). 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 6.0 for windows, SPSS Inc, USA). All statistical comparisons were two-tailed, and a p-value of less than 0.05 was considered statistically significant.

RESULTS
A total of 150 patients were included in the study, 115 patients with unstable angina and 35 patients with non-Q-wave myocardial infarction. 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. C-reactive protein 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 C-reactive protein (> 5.0 mg/l) was present in 61 patients (41%), median C-reactive protein for the 15 patients with a major cardiac event was 12.5 mg/l (range 3.0 to 57.1 mg/l), compared to 3.0 mg/l (range 0 to 76.1 mg/l) for the 135 patients without a major cardiac event. Troponin I 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 troponin I (>0.4 µg/l) was present in 44 patients (29%), median troponin I 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 C-reactive protein or troponin I. 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 C-reactive protein > 5.0 mg/l than in other patients (23% (13-36%) versus 1.1% (0-6%), p=0.00001), and this was evident both in patients with an elevated troponin I (42% (22-63%) versus 4.5% (0-23%), p=0.003) and in patients without an elevated troponin I (0% versus 11% (3-25%), p=0.014) (figure 1). The multivariate logistic regression model with age, gender, history of infarction, hypertension, aspirin use and diabetes significantly improved when either an abnormal C-reactive protein or an abnormal troponin I or both were included in the model (-2 log LR for C-reactive protein and troponin I: 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 3 shows the event rate and mean event free survival for patients having both C-reactive protein and troponin I elevated, either C-reactive protein or troponin I elevated or no C-reactive protein or troponin I elevation. Primary outcome was significantly more frequent in patients having both C-reactive protein/troponin I elevated (10/24) than patient having either (5/58) or none elevated (0/68) (both versus either: p<0.0001; both versus none: p<0.0001; either versus none: p=0.015). Kaplan-Meier survival analysis showed that mean event-free survival for the primary outcome was significantly lower in patients having both C-reactive
protein/troponin I elevated versus patients with either C-reactive protein/troponin I elevated or no elevations (figure 2A, p<0.0001 and p=0.0226 respectively). Incidence of the combined endpoint cardiac death, non-fatal MI, recurrent severe unstable angina and the need for revascularizations was no longer statistically significantly different (table 3). However, mean event-free survival was still significantly different between both C-reactive protein and troponin I elevated versus no elevations and between either elevated versus no elevations (table 3, figure 2B; p=0.0015).

DISCUSSION

The present study confirms earlier studies, showing that both C-reactive protein, a non-specific acute phase reactant, and troponin I, a cardiac specific marker of myocardial damage, are elevated early in a substantial number of patients with unstable angina and non-Q-wave MI. It shows that C-reactive protein and troponin I are independent prognostic indicators of adverse outcome. The incidence of a major cardiac event was 23% in patients with an abnormal C-reactive protein versus 1.1% in patients with a normal C-reactive protein. Moreover, in patients without a troponin I elevation, a C-reactive protein > 5.0 mg/l carried a significantly higher risk for a major cardiac event within six months (11% versus 0%). Patients with both C-reactive protein and troponin I elevated had the highest incidence of cardiac death, recurrent acute myocardial infarction 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 C-reactive protein and troponin I have excellent prognosis. In this patient group there were no cardiac deaths, recurrent acute myocardial infarctions or recurrent admissions for unstable angina during the six 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 value of an abnormal C-reactive protein and a positive rapid troponin T test for the prediction of 14-day mortality in patients with acute coronary syndromes(13). Although the patient group differed due to different enrollment and timing of bloodsamples, the troponin measured was I instead of T, and the follow-up period was different, the results of our study are consistent with the findings of the TIMI 11A substudy.
In a substudy of the FRISC study, Toss et al.(127) could not demonstrate a worse outcome in patients with unstable angina with increased C-reactive protein but no troponin T elevation. This may have been caused by the large proportion of 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.(124) demonstrated that C-reactive protein 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 C-reactive protein(183). Therefore, it is likely that C-reactive protein elevations are due to activation of inflammation. It has been shown that other pro-inflammatory cytokines such as interleukin-6, interleukin-8 and TNF-α are elevated on admission in patients with acute coronary syndromes(182;188;189), and that these elevations may be associated with worse outcome(182). We have previously shown that IL-6 has equivalent discriminatory capacity as the pro-coagulant factor fibrinopeptide A to distinguish between patients with stable coronary artery disease from patients with unstable coronary artery disease(154).

Whether C-reactive protein elevations are causal to the initiation of an episode of unstable coronary artery disease is unknown. It has been shown that C-reactive protein stimulates production of tissue factor by mononuclear cells, the main initiator of blood coagulation(190). In addition, it has been suggested that C-reactive protein together with phospholipase A2 may cause complement activation and promote phagocytosis of damaged cells by activated neutrophils(191). 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 within the vessel wall(192). Therefore, it is conceivable that an elevated C-reactive protein 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 relatively few events. Separate analysis of the patients with unstable angina or non-Q-wave myocardial infarction 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 C-reactive protein or troponin I elevations are striking. Together with another report(13), 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 C-reactive protein and troponin I in patients with unstable angina or non-Q-wave myocardial infarction, for long term adverse outcome. Incidence of events was high and mean event-free survival was low in patients with combined elevation of C-reactive protein and troponin I, whereas prognosis is excellent for patients without elevations of C-reactive protein and troponin I. 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 C-reactive protein and troponin I could be studied in a prospective study.

![Graph](image)

**Figure 1**
Incidence of major cardiac complications by normal or abnormal CRP concentration in all patients and in 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 Chi-square test or Fisher exact test.
Figure 2

A. Kaplan-Meier survival curves for 150 patients with unstable angina or non-Q-wave infarction during a follow up of 6 months. Patient groups were defined as having both an abnormal CRP (> 5.0 mg/l) and an abnormal Tnl (> 0.4 µg/l), either an abnormal CRP or Tnl, or both CRP and Tnl normal. Major cardiac events were defined as cardiac death, recurrent non-fatal acute myocardial infarction or recurrent admission for severe unstable angina. Differences in
survival were compared with the log rank test (table 3). Mean event free survival for the primary outcome was significantly lower in patients having both CRP/TnI elevated versus patients with either CRP/TnI elevated or no elevations (p<0.0001 and p=0.0226 respectively).

B. Kaplan-Meier survival curves for 150 patients with unstable angina or non-Q-wave infarction during a follow-up of 6 months. Event free survival was assessed for all outcome including (the need for) revascularization, i.e. either PTCA or CABG. Differences in survival were compared with the log rank test (table 3). Mean event free survival was significantly different between patients with both CRP and TnI elevated versus no elevations and between either elevated versus no elevations (p=0.0015). There was no significant difference between patients with either CRP/TnI elevated versus no CRP/TnI elevations (p=0.379).

CABG, coronary artery bypass grafting; CRP, C-reactive protein; PTCA, percutaneous transluminal coronary angioplasty; TnI, troponin I.

**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>No event n (%)</th>
<th>Death/AMI/UAP n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>135</td>
<td>15</td>
</tr>
<tr>
<td>Age</td>
<td>62 ± 14</td>
<td>72 ±13*</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>20 (15%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (30%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>46 (34%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Prev AMI</td>
<td>36 (27%)</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>Prev PTCA/CABG</td>
<td>40 (30%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>42 (31%)</td>
<td>9 (60%)*</td>
</tr>
<tr>
<td>CRP &gt;5.0 mg/l</td>
<td>47 (35%)</td>
<td>14 (93%)*</td>
</tr>
<tr>
<td>TnI &gt;0.4 μg/l</td>
<td>35 (26%)</td>
<td>11 (73%)*</td>
</tr>
</tbody>
</table>

Differences between groups were compared with the Chi-square 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; CABG=coronary artery bypass grafting; CRP= C-reactive protein; PTCA=percutaneous transluminal coronary angioplasty; Rec. UAP= admission due to recurrent unstable angina pectoris; TnI= troponin I.

*categories for which p<0.05; † categories for which p < 0.001.
**Table 2. Events during 6 months follow up in 150 patients with unstable angina or non-Q-wave AMI**

<table>
<thead>
<tr>
<th>Events</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Recurrent AMI</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Rec. UAP</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

**Revascularizations**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<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; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; Rec. UAP, recurrent admission due to unstable angina pectoris.

**Table 3. Number of events and event free survival in patients with no CRP or Tnl elevations, either CRP or Tnl elevated or both CRP and Tnl elevated**

<table>
<thead>
<tr>
<th></th>
<th>No elevations</th>
<th>Either CRP/Tnl</th>
<th>Both CRP/Tnl</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>68</td>
<td>58</td>
<td>24</td>
</tr>
<tr>
<td>Death/AMI/UAP</td>
<td>0</td>
<td>5†</td>
<td>10*</td>
</tr>
<tr>
<td>Event free Survival (days)</td>
<td>180</td>
<td>169±5†</td>
<td>121±16*</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*</td>
</tr>
</tbody>
</table>

Differences in proportions between groups were compared with the Chi-square statistic. Mean event free survival was calculated with Kaplan-Meier survival analysis and differences were compared with the Logrank test.

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CRP, C-reactive protein; PTCA, percutaneous transluminal coronary angioplasty; UAP, recurrent admission due to unstable angina pectoris; Tnl, troponin I.

† significant difference between group with both CRP/Tnl versus group with no elevations

§ significant difference between group with both CRP/Tnl versus group with either CRP or Tnl

†† significant difference between group with either CRP or Tnl versus group with no elevations

120