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Predictive Value of C-Reactive Protein and Troponin T in Patients With Unstable Angina: A Comparative Analysis

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OBJECTIVES We evaluated C-reactive protein (CRP) and troponin T (TnT) for predicting six-month cardiac risk in patients with unstable angina.

BACKGROUND Troponin T is predictive of cardiac risk in patients with unstable angina. The clinical implications of elevated CRP in such patients remains controversial.

METHODS Baseline TnT and CRP values were determined in 447 patients with unstable angina enrolled in the placebo group of the Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment trial (CAPTURE) trial. All patients underwent a coronary intervention and were followed for a six month period in which 13 deaths and 47 myocardial infarctions were documented (MIs).

RESULTS Troponin T was >0.1 μg/liter in 30% and CRP was >10 mg/L in 41% of the patients. For the initial 72-h period (including coronary intervention), TnT (17.4% vs. 4.2%; $p < 0.001$) but not CRP (10.3% vs. 8%; $p = 0.41$) was predictive of mortality and MI. The TnT-positive patients displayed more frequent recurrent instability before the planned intervention (44.8% vs. 16.9%; $p < 0.001$), but in the CRP-positive patients, no such increase was observed (25.9% vs. 24.8%; $p = 0.92$). In contrast, for the six month follow-up period, CRP was predictive of cardiac risk (mortality, MI) (18.9% vs. 9.5%; $p = 0.003$). Using multivariate analysis, both CRP and TnT emerged as independent predictors of mortality and MI at six-month follow-up. Furthermore, the incidence of coronary restenosis during six-month follow-up was not related to TnT status (3% vs. 4.5%; $p = 0.49$); however, it was significantly related to CRP status (7% vs. 2.3%; $p = 0.03$).

CONCLUSIONS Troponin T, but not CRP, was predictive of cardiac risk during the initial 72-h period, whereas CRP was an independent predictor of both cardiac risk and repeated coronary revascularization (coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty) during six month follow-up. (J Am Coll Cardiol 2000;35: 1535–42) © 2000 by the American College of Cardiology

For patients with unstable coronary artery disease (i.e., unstable angina or non–Q wave myocardial infarction [MI]), the main pathophysiologic mechanisms, in the form of plaque rupture or erosion, are followed by exposure of thrombogenic contents, such as collagen, to the circulation (1,2). The resulting platelet activation and adhesion promote thrombus formation. Pathohistologic studies have disclosed focal cell necroses distal in the myocardium supplied by the culprit artery, which have been attributed to repetitive embolization from such friable thrombi (3,4). The resulting minor myocardial damage leads to troponin T (TnT) release in about one-third of such patients (5–13). Although enzyme activity of creatine kinase (CK) remains within the normal range, there is a five- to 10-fold higher incidence for mortality and MI during the 30-day follow-up period for such TnT-positive patients (5,6,13).

There is growing evidence that local and systemic inflammation plays a role in the initiation and progression of atherosclerosis (14,15); patients with unstable angina had higher plasma levels of C-reactive protein (CRP) than did patients with stable angina (16,17). Such inflammatory reactions may promote plaque fissuring or erosion and may be involved in the onset of an acute coronary syndrome. However, the clinical implications of elevated CRP levels for improved early risk stratification of such patients remain

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Abbreviations and Acronyms

CABG	=	coronary artery bypass graft surgery
CAPTURE	=	Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment trial
CI	=	confidence interval
CK	=	creatine kinase
CRP	=	C-reactive protein
FRISC	=	FRagmin during InStability in Coronary artery disease trial
MI	=	myocardial infarction
OR	=	odds ratio
PTCA	=	percutaneous transluminal coronary angioplasty
TnT	=	troponin T

controversial (14,18–22). To shed light on the clinical significance of elevated CRP levels, we performed a comparative analysis of the predictive values of both CRP and TnT for patients with unstable angina by using the data set of the Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment (CAPTURE) trial (23). The CAPTURE trial was designed to assess outcomes in patients with refractory unstable angina who were given either abciximab or placebo up to 24 h before scheduled percutaneous transluminal coronary angioplasty (PTCA).

METHODS

Patients. The CAPTURE trial enrolled 1,265 patients with refractory unstable angina (61% men, 61 ± 10 years old) between May 1993 and December 1995. All CAPTURE patients had recurrent chest pain at rest associated with electrocardiographic (ECG) changes during treatment with intravenous heparin and glyceryl trinitrate for an average of 14 h. This entire group had coronary angiography before randomization, indicating significant coronary artery disease with a culprit lesion of ≥70% diameter stenosis suitable for angioplasty. The patients were randomly assigned to abciximab or placebo; treatment was initiated within 2 h of randomization. For all patients, coronary interventions were scheduled between 18 and 24 h after beginning study treatment (23).

The primary end points of our study were mortality, MI or the necessity for an urgent intervention (PTCA or coronary artery bypass graft surgery [CABG]) due to instability during the 30-day and six-month follow-up periods. Patients with MI during the index hospital stay were defined as having values of CK enzyme activity more than three times the upper limit of normal in at least two samples or an ECG with new significant Q waves in two or more contiguous leads. This strict definition was chosen to exclude any insignificant minor CK rise after PTCA. Patients with an MI after hospital discharge were defined as having values of CK enzyme activity more than two times the upper limit of normal or an ECG with new significant Q waves in two or more contiguous leads. The secondary end point was symptomatic coronary restenosis of the treated lesion with ≥70% diameter stenosis and the necessity for repeat revascularization during the six-month follow-up period.

Four time periods were considered for this study: 1) up to 24 h before PTCA; 2) up to 72 h after randomization (including coronary intervention); 3) 30-day follow-up period; and 4) 6-month follow-up period.

Analytic techniques. Determination of the cardiac markers in serum samples obtained at baseline (n = 1,096; mean 8.7 h [75% confidence interval 3.6 to 11.3] after the onset of symptoms) and before discharge (n = 918) was performed without knowledge of the patients' histories and allocated treatment. For quantification of TnT, a one-step enzyme immunoassay based on electrochemiluminescence technology (Elecsys 2010, Boehringer Mannheim, Germany) was used. The lower detection limit of this assay was 0.01 μg/liter, and the diagnostic threshold level was 0.10 μg/liter (24,25). C-reactive protein was measured by N Latex CRP Mono tests, performed on a Behring BN II Nephelometer (Behring Diagnostics) using polystyrene microbeads coated with monoclonal mouse antibodies (26). The intensity of scattered light due to formed aggregates was proportional to the CRP level present in the sample. The detection limit of the assay was 0.2 mg/liter. For clinical practice, a threshold level of 5.0 mg/liter is recommended.

Statistical methods. After blind assessment of CRP and TnT, the test results were merged with the CAPTURE data base. Continuous variables are expressed as the mean value ± SD, with analysis of subgroups by the Mann-Whitney *U* test (two-sided). Categoric variables were compared using the Fisher's exact test. Significance was set at $p < 0.05$.

To distinguish between patients with different degrees of cardiac risk, an exploratory data analysis was chosen. Patients were categorized according to the CRP concentration of quintiles of ~90 patients each. For each of the four time points, logistic regression analysis was performed, and patients in the first quintile (<2.8 mg/liter CRP) served as the control group (27,28). Receiver-operating characteristic curve analysis over the dynamic range of the CRP assay was used to identify the threshold level for CRP providing the highest predictive value for risk stratifying patients with unstable angina. Further, reverse stepwise logistic regression analysis, including the variables TnT >0.1 μg/liter, CRP >10 mg/liter, ECG findings and baseline characteristics, identified independent predictors of cardiac risk. All analyses were accomplished with SPSS 8.0.1 (SPSS Inc., Chicago, Illinois) or StatXact-3 (Cytel Software Corp., Cambridge, Massachusetts) software.

RESULTS

Because we have previously shown that patients with elevated TnT concentrations have outstanding benefit from additional treatment with abciximab (13), patients receiving abciximab had to be excluded from the main analysis. Furthermore, a subset of 100 patients of the 547 patients enrolled in the CAPTURE placebo group experienced MI within 14 days (6.5 ± 3.2 days) before enrollment. Because elevated TnT levels in these 100 patients do not necessarily reflect acute minor myocardial damage, data from this subset were also not included in the main analysis. Thus, the total number in our study was 447, with a total of 13 deaths and 47 MIs during six-month follow-up (total event rate 13.4%).

TnT. For 30% of the patients (n = 134), TnT was above the diagnostic threshold level of 0.1 μg/liter. Baseline characteristics, according to the TnT status, are depicted in Table 1, with no significant differences between the groups. Figure 1A shows the clinical outcomes of patients during the first 72 h after randomization according to TnT status. Notwithstanding identical treatment regimens, cardiac risk (mortality, MI) was higher in TnT-positive patients during both the first 24 h before PTCA (6.6% vs. 0.7%; $p < 0.001$) and, especially, within first 72 h including the coronary intervention (17.4% vs. 4.2%; $p < 0.001$). This absolute difference in cardiac risk (Δ13.2%) increased only slightly during the 30-day follow-up period (Δ14.7%; 19.6% vs. 4.9%; $p < 0.001$); this absolute difference was sustained during the six-month follow-up period (Δ14.5%; 23.9% vs. 9.4%; $p < 0.001$).

Within the first 24 h before the planned coronary intervention, 44.8% of the TnT-positive patients had at least one episode of recurrent angina pectoris (mean 2.1 episodes). In contrast, symptoms recurred at least once for only 16.9% of TnT-negative patients ($p < 0.001$; mean 1.2 episodes; $p = 0.004$). Premature coronary revascularization before scheduled PTCA was necessary for 6.7% of the TnT-positive patients as compared with only 0.6% of the TnT-negative patients ($p = 0.002$). Further, for TnT-positive patients, the rate of urgent coronary reinterventions (PTCA, CABG) remained higher during the 30-day follow-up period (11.2% vs. 3.8%; $p = 0.006$), whereas repeat nonurgent coronary revascularization (PTCA, CABG) did not significantly differ between TnT-positive and TnT-negative patients (3.0% vs. 4.5%; $p = 0.49$).

CRP. INTERACTION BETWEEN CRP LEVEL AND CARDIAC RISK. Patients were stratified into quintiles according to their measured CRP levels: CRP-1) <2.8 mg/liter (n = 83); CRP-2) 2.9 to 5.3 mg/liter (n = 85); CRP-3) 5.4 to 9.0 mg/liter (n = 94); CRP-4) 10.0 to 22.6 mg/liter (n = 98); and CRP-5) >22.6 mg/liter (n = 87). The CRP concentration did not correlate with measured TnT levels ($r^2 = 0.12$). A significantly higher mean level of TnT was documented for the fifth CRP quintile only ($p < 0.01$). Likewise, the proportion of patients with a positive TnT test result (>0.1 μg/liter) was significantly higher only for the highest CRP quintile ($p < 0.01$).

Table 1. Baseline Characteristics According to Troponin T Status

	TnT-Positive Patients (n = 134)	TnT-Negative Patients (n = 313)
Male gender	66.7%	73.7%
Age (yrs)	62.7 ± 10.5	60.9 ± 10.2
History of		
Angina >4 weeks	53.8%	57.3%
MI 14 to 30 days	2.2%	3.3%
MI >30 days	15.6%	22.7%
PTCA	15.1%	18.6%
CABG	3.8%	3.3%
Risk factors		
Diabetes	11.3%	9.7%
Hypertension	36%	37.1%
Current smokers	40.8%	41.8%
Medication before enrollment		
Aspirin	97.3%	98.3%
IV heparin	97.8%	99.5%
IV nitrates	98.4%	100%
Beta-blockers	62.9%	63.2%
Calcium antagonists	51.1%	57.9%
Medication after enrollment		
Aspirin	97.3%	97.5%
Ticlopidine	2.7%	2.2%
IV heparin	97.3%	97.8%
IV nitrates	97.8%	98.3%
Beta-blockers	64%	60.7%
Calcium antagonists	50%	58.4%

Data are presented as percentage of patients or mean value ± SD.
CABG = coronary artery bypass graft surgery; IV = intravenous; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; TnT = troponin T.

For the first 24- and 72-h periods, mortality and the incidence of MI, respectively, for the second to fifth quintile were not increased as compared with the first quintile (Fig. 2). However, patients in the forth and fifth quintiles (CRP >10.0 mg/liter) had significantly higher event rates at 30-day and six-month follow-up, as compared with patients in the first quintile. For the end point mortality at six-month follow-up, in each of the first three quintiles, one patient died, whereas in the fourth and fifth quintiles, four and six patients, respectively, died. Receiver operating characteristic curve analysis confirmed a threshold level of 10 mg/liter of CRP for maximized predictive value.

STRATIFICATION ACCORDING TO CRP STATUS. In respect to the aforementioned findings, the patient sample was dichotomized according to this calculated threshold level. We identified 185 patients (47%) with CRP >10 mg/liter (CRP-positive) and 262 patients with CRP <10 mg/liter (CRP-negative). As Table 2 shows, there are no significant

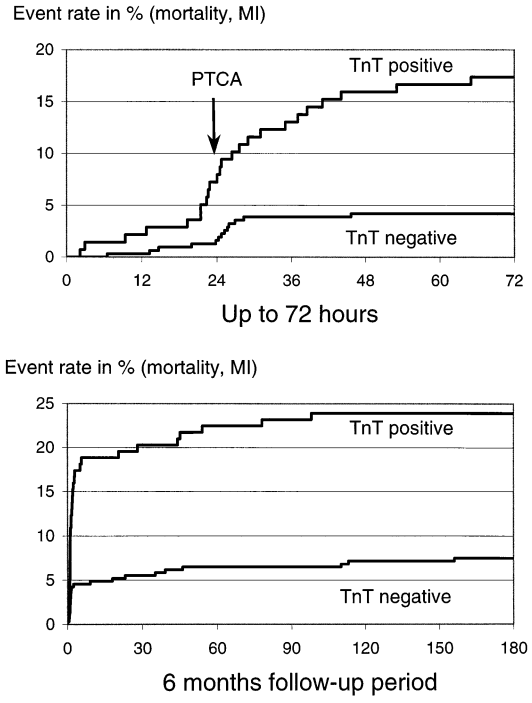

Figure 1. Event rates (mortality and MI) according to the patients' TnT status during first 72 h (**top panel**) and after six months of follow-up (**bottom panel**).

differences in the baseline characteristics between the two groups.

For CRP-negative patients, events (mortality and MI) during the first 72 h were not significantly different from those in patients with elevated CRP levels, neither during 24 h before the procedure (2.7% vs. 2.2%; p = 1.00) nor after 72 h (including the coronary intervention) (10.3% vs. 8%; p = 0.41) (Fig. 3). During the six-month follow-up period, however, the event rate curves for CRP-positive and CRP-negative patients continually diverged. There were significant differences both after 30 days (14.1% vs. 7.6%; p = 0.03) and especially at six months (18.9% vs. 9.5%; p = 0.003). This elevated risk in CRP-positive patients was related to both a higher incidence of MI (13.5% vs. 8.4%; p = 0.16) for this subgroup and a significantly higher mortality rate (5.4% vs. 1.1%; p = 0.005).

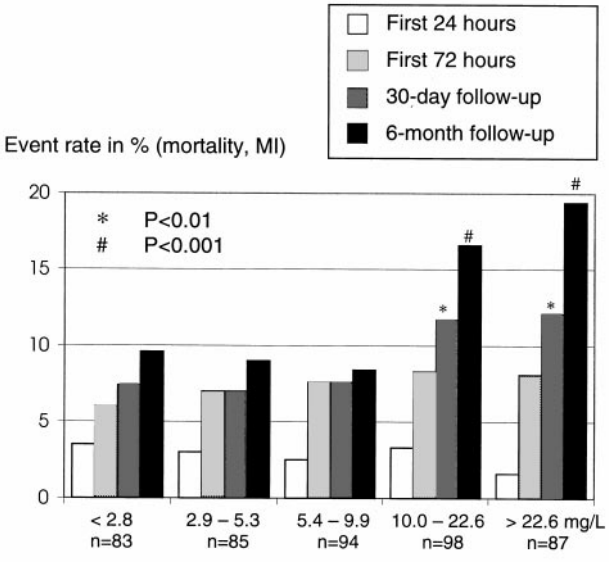

Figure 2. Event rates observed for the CRP quintiles according to the four investigated periods after randomization.

Table 2. Baseline Characteristics According to C-Reactive Protein Status

	CRP-Negative Patients (n = 185)	CRP-Positive Patients (n = 262)
Male gender	73.9%	69%
Age (years)	59.8 ± 10.8	63.1 ± 10.3
History of		
Angina >4 weeks	58.8%	53.8%
MI 14 to 30 days	3.5%	2.4%
MI >30 days	19.5%	21%
PTCA	19.1%	15.9%
CABG	3.5%	3.4%
Risk factors		
Diabetes	12.1%	8.6%
Hypertension	39.3%	34.5%
Current smokers	40.9%	42.1%
Medication before enrollment		
Aspirin	98.1%	97.9%
IV heparin	99.2%	98.6%
IV nitrates	98.8%	99.7%
Beta-blockers	65%	61.4%
Calcium antagonists	56%	55.2%
Medication after enrollment		
Aspirin	97.7%	97.2%
Ticlopidine	2.3%	2.4%
IV heparin	97.7%	97.6%
IV nitrates	98.1%	98.3%
Beta-blockers	61.9%	61.7%
Calcium antagonists	54.9%	56.2%

Data are presented as percentage of patients or mean value ± SD.
CRP = C-reactive protein; other abbreviations as in Table 1.

Within the first 24 h before the planned coronary intervention, 25.9% of the CRP-positive patients had at least one episode of recurrent angina pectoris (mean 1.5 episodes). Symptoms recurred at least once in 24.8% of the CRP-negative patients (p = 0.92; mean 1.7 episodes; p = 0.74). Likewise, the rate of urgent coronary reinterventions (PTCA, CABG) was not elevated in CRP-positive patients both before planned PTCA (3.1% vs. 1.6%; p = 0.61) and during the first 72 h including the coronary intervention (5.9% vs. 3.1%; p = 0.46). A trend toward a higher rate of urgent interventions was observed in the CRP-positive group only at 30-day follow-up (9.2% vs. 3.8%; p = 0.08). Further, repeat nonurgent coronary interventions (PTCA,

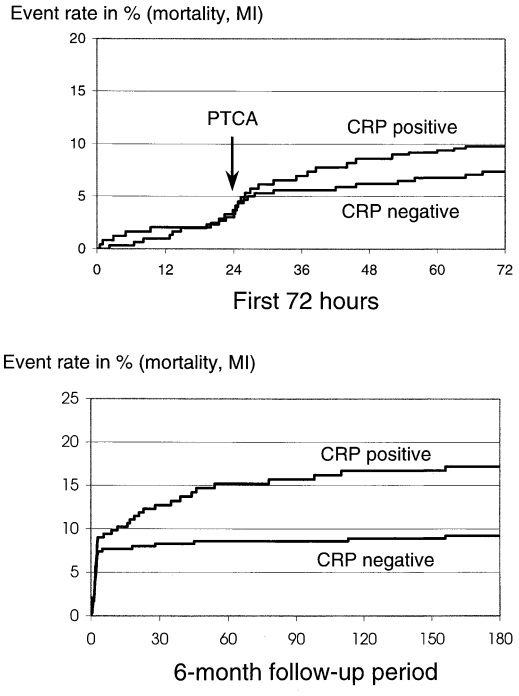

Figure 3. Event rates (mortality and MI) according to the patients' CRP status during first 72 h (**top panel**) and after six months of follow-up (**bottom panel**).

CABG) during the six month follow-up period were significantly more frequent in CRP-positive patients (7% vs. 2.3%; p = 0.03).

PREDICTIVE VALUE OF CRP LEVEL AT DISCHARGE. A second blood sample drawn before discharge (7.2 ± 4.5 days after randomization) was available for 402 (90%) of the 447 patients included in this study. Baseline CRP levels of 17.1 ± 25.6 mg/liter increased until hospital discharge to a mean value of 26.1 ± 32.9 mg/liter (p < 0.001). The CRP level was above the threshold level of 10.0 mg/liter for 265 patients (66%). For these CRP-positive patients, the incidence of mortality and MI did not differ from that in patients with CRP concentrations below this threshold level. This was observed at 30 days (7.2% vs. 7.3%; p = 1.00) and also at six months (11.7% vs. 9.5%; p = 0.61). There were also no significant differences of recurrent instability requiring an urgent coronary intervention between CRP-positive and CRP-negative patients during the 30-day follow-up period (4.9% vs. 6.6%; p = 0.44).

MULTIVARIATE ANALYSIS OF PREDICTIVE VALUES. Stepwise backward regression analysis was used to identify variables of independent predictive value for six-month outcome (mortality and MI). Only TnT (p < 0.001), CRP (p = 0.01), age >65 years (p = 0.02) and a history of MI were independent predictors of an adverse clinical outcome (Table 3). The inclusion of CK, MB fraction >5 μg/liter and ECG findings such as ST segment depression and T wave inversion or cardiac risk factors did not improve the fit of the statistical model. When both clinical and ECG findings were forced into the model first, the insertion of both TnT and CRP significantly reduced the deviance of the regression model. The likelihood ratio statistic was 5.31 after inclusion of clinical findings (p = 0.023) and 18.38 after inclusion of both CRP and TnT (p < 0.001). After inclusion of TnT and CRP, however, clinical and ECG findings did not provide significant predictive value anymore, and consequently were dropped from the model.

Patients with elevation of both TnT and CRP had the highest incidence of mortality (5.3%), as measured at six-month follow-up. For the TnT-negative group, the determination of CRP identified a subgroup of patients with increased mortality (2.1%). No deaths were documented during the six-month follow-up period in those patients with all negative tests for both TnT and CRP (n = 202) (Fig. 4).

EFFICACY OF TREATMENT WITH ABCIXIMAB ACCORDING TO THE CRP STATUS. For this analysis, we examined data from both the placebo (n = 447) and abciximab (n = 433) groups of the CAPTURE trial participants. Regression analysis, including a term of interaction, indicated no significant correlation between CRP level and benefit of treatment with abciximab. The treatment benefit was consistent throughout all concentration levels for any chosen threshold level and for all four time periods. At 30-day follow-up, no significant differences were observed between benefit of treatment with abciximab in patients with CRP levels >10 mg/liter (odds ratio [OR] 0.52, 95% confidence interval [CI] 0.21 to 0.92; p = 0.011) and patients with CRP levels <10 mg/liter (OR 0.56, 95% CI 0.18 to 0.97; p = 0.008). At six-month follow-up, the benefit of abciximab was not statistically significant for either group of patients; for the samples with CRP levels >10 mg/liter, the OR was 0.72 (95% CI 0.34 to 1.32; p = 0.21) and for

Table 3. Results of Multivariate Analysis

Variable	OR	95% CI	p Value
Gender	0.91	0.65–1.49	0.59
Age >65 yrs	1.79	1.12–4.26	0.02
Diabetes mellitus	1.15	0.84–1.46	0.64
Hypercholesterolemia	0.89	0.71–1.16	0.65
Hypertension	0.99	0.85–1.06	0.99
History of angina	0.94	0.67–1.52	0.74
History of MI	0.89	0.72–1.25	0.66
History of PTCA	0.73	0.58–1.13	0.53
History of CABG	1.16	0.91–1.24	0.65
ST segment depression	1.21	0.86–1.98	0.21
T wave inversion	0.84	0.65–1.05	0.14
TnT >0.1 μg/liter	2.64	1.64–15.27	<0.001
CRP >10.0 mg/liter	1.97	1.21–3.59	0.01
CK-MB >5.0 μg/liter	1.34	0.86–2.69	0.34

CI = confidence interval; CK-MB = creatine kinase, MB fraction; CRP = C-reactive protein; OR = odds ratio; other abbreviations as in Table 1.

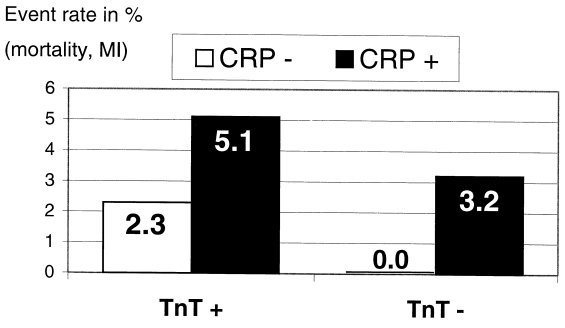

Figure 4. Predictive value for the end point of mortality during the 6-month follow-up period according to both TnT and CRP status. **Open bar** = CRP-negative patients; **solid bars** = CRP-positive patients.

patients with normal CRP values, the OR was 0.67 (95% CI 0.46 to 1.06; p = 0.13).

PREDICTIVE VALUE OF CRP FOR THE ENTIRE STUDY GROUP. Because no interaction was observed between CRP values and benefit of treatment with abciximab, the predictive value of CRP was also investigated for the entire CAPTURE study population, including all 1,081 patients with an available baseline serum sample. A total of 23 deaths and 89 acute MIs were documented, resulting in a total event rate of 10.4% at six month follow-up. For the first 72 h, as already seen for the substudy group, CRP-positive patients (n = 516) did not have a higher event rate, as compared with CRP-negative patients (n = 565), neither during the 24 h before the procedure (1.7% vs. 1.2%; p = 0.72) nor after 72 h (including the coronary intervention) (6.4% vs. 5.1%; p = 0.56). During the six-month follow-up period, however, event rates were significantly higher for CRP-positive patients both at 30 days (8.1% vs. 5.3%; p = 0.04) and at six months (14.9% vs. 6.2%; p < 0.001). This elevated risk for patients with CRP levels >10 mg/liter was driven by both a higher incidence for MI (OR 1.92, p = 0.04) for this subgroup and, in particular, a significantly higher mortality (OR 3.62, p < 0.001).

DISCUSSION

Consistent with previous studies (5–13), our results show that patients with refractory unstable angina and minor myocardial damage, evidenced by elevated TnT, are at highest cardiac risk. Such risk was particularly marked during the first 72 h after randomization and primarily associated with evidence of MI after the percutaneous coronary intervention. In contrast, CRP did not serve as a significant predictor for such immediate risk. During the first 72 h after randomization, including the coronary intervention, cardiac risk in CRP-positive patients did not differ significantly from that in CRP-negative patients. However, for the six-month follow-up period, this study confirms a strong and independent prognostic value for this inflammatory marker. Elevation of CRP in patients with refractory unstable angina differentiated TnT-negative patients with increased cardiac risk.

TnT. Cardiac TnT is a strong predictor for elevated cardiac risk within the first days after the onset of symptoms. In the CAPTURE trial, in addition to the allocated treatment (abciximab vs. placebo), all patients were identically treated with aspirin, intravenous heparin and nitrates before their scheduled coronary interventions (Table 1) (23). Despite such maximized treatment, there were significantly more cardiac complications occurring in patients with a positive TnT test, both during the first 24 h before the coronary intervention (6.6% vs. 0.7%; p < 0.001) and, in particular, in association with PTCA (17.4% vs. 4.2%; p < 0.001). Likewise, recurrence of symptoms (45% vs. 17%; p < 0.001) and, consequently, recurrent instability with the necessity for a premature coronary intervention before the scheduled intervention were more frequent in the TnT-positive group than in the TnT-negative group (6.7% vs. 0.7%; p < 0.001).

Such high risk patients should be given the highest priority for transfer to a tertiary care center or to a catheterization laboratory. However, these striking differences, despite aspirin and intravenous heparin therapy, emphasize the necessity for a new and more effective therapeutic strategy for such high risk patients. Increasing evidence suggests that TnT elevation in patients with unstable angina must be understood as a surrogate marker for friable thrombus formation and complex lesion characteristics (29,30). Accordingly, more potent platelet blockade appears to be a reasonable approach. The glycoprotein IIb/IIIa antagonist abciximab was particularly effective in the treatment of TnT-positive patients in the CAPTURE trial, with an 82% reduction of primary end points (mortality and MI) during the first 72 h after randomization (OR 0.18, p < 0.001) (13). In contrast, TnT-negative patients were less symptomatic and at lower cardiac risk before and in association with the coronary intervention. There were no significant benefits of treatment with abciximab documented during the first 72-h period (OR 1.07, p = 0.37). After this 72 h after randomization, there were no significant differences in cardiac risk between TnT-positive and TnT-negative patients (6.5% vs. 5.2%; p = 0.47)—a finding that was independent of treatment. Troponin T, a marker of acute risk in patients with unstable angina, identifies those patients with the greatest benefit from abciximab.

C-reactive protein. There have been several recent studies regarding elevated levels of CRP in patients with unstable angina (16,17–19). They found that CRP in patients with unstable angina was predictive of adverse clinical outcomes. Because the present study embraced a large high risk patient group, we expected CRP to be a significant predictor of increased cardiac risk. However, in our work, the predictive value of CRP was not correlated with increased cardiac risk during the first 72 h; rather, it was associated with a higher incidence of cardiac events during the six-month follow-up

period. Event rate curves according to the CRP status diverged only slightly during the immediate phase of the coronary syndrome, with no significant differences at 72 h (10.3% vs. 8%; p = 0.41). However, the curves diverged during the six month follow-up period, resulting in highly significant differences (18.9% vs. 9.5%; p = 0.003). Because no interaction between treatment with abciximab and CRP level was documented, we were able to confirm these findings by investigating the predictive value of CRP for the entire study population (n = 1,091), which cannot be done for TnT due to the significant interaction between abciximab and TnT level.

Thus, CRP levels might be of less predictive value for the acute risk of patients with unstable angina than has been suggested from previous experiences in, however, limited patient groups. The larger FRagmin during InStability in Coronary artery disease (FRISC) trial documented no differences in cardiac risk (mortality and MI) for their patient groups categorized in tertiales according to the patients' CRP level (20). This finding was consistent for both the first hospital period and the six-month follow-up period. The CRP tertiales differed only slightly in the respective measures of the end point mortality at six-month follow-up. However, it should be noted that for the subgroup analysis of the FRISC trial, those patients treated with low molecular weight heparin for five weeks and those patients receiving placebo were included, possibly biasing the analyses. Further, the total event rate in FRISC was markedly low as compared with that of the CAPTURE trials. In the Thrombolysis in Myocardial Infarction (TIMI) 11A substudy of patients with unstable angina or non–Q wave MI, elevated CRP levels at presentation (threshold level 15.5 mg/liter) were associated with increased 14-day mortality (19). This was observed even in patients with a negative TnT rapid test. These findings are fully consistent with our CAPTURE results. Our analysis shows that despite the negative TnT test result, the group of patients with elevated CRP levels had particularly high mortality, both at 30 days and six months (5.4% vs. 1.1%; p = 0.002). All CRP-positive patients died of cardiac causes, mainly MI.

Discharge CRP values were not predictive of either the composite end point of mortality/MI or the end point of restenosis at six-month follow-up. This might be due to the fact that all patients underwent a coronary intervention, and CRP levels consequently increased from baseline to hospital discharge.

Therapeutic consequences for high risk patients. In contrast to the findings with TnT (13), the efficacy of treatment with abciximab in the CAPTURE trial did not differ between patients stratified according to CRP status. Studies with platelet glycoprotein IIb/IIIa receptor blockers have unequivocally shown that after the unstable phase of the acute coronary syndrome, cardiac events continue to occur for both the treatment and placebo groups at comparable frequencies (23,31–33). In such studies, there was no incremental benefit of glycoprotein IIb/IIIa receptor blockade in preventing later events. Because CRP values did not predict the instability of patients during the first days after the onset of symptoms, it was not unexpected that CRP was not predictive of the efficacy of treatment with abciximab.

However, the observed event rate after stabilization of the patients for the period between four-day and six-month follow-up is of clinical significance. In the CAPTURE trial, event rates during first 72-h period were 4.2% for the abciximab group and 8.3% for the placebo group (p = 0.003). Between day four and six-month follow-up, however, the event rate was ~5% and was independent of randomized treatment. In this study, CRP was identified as a marker of increased risk after this first 72-h period. All patients with positive CRP baseline values, regardless of treatment group, were at increased risk during the follow-up period (8.7% event rate for the placebo group and 8.3% for the abciximab group), whereas patients with normal CRP values were at low risk (1.5% for the placebo group and 2.6% for the abciximab group). Further, the incidence of symptomatic coronary restenosis during the six-month follow-up period was not related to the patients' TnT status (3% vs. 4.5%; p = 0.49), but was significantly correlated to the patients' CRP status (7% vs. 2.3%; p = 0.03).

These findings support the hypothesis that local or systemic inflammation plays an important role in the progression of atherosclerosis. The absolute difference in cardiac risk of ~7% between CRP-positive and CRP-negative patients may be useful in clinical practice to guide more aggressive and uncompromising medical treatment. We speculate that these patients, in particular, would benefit from treatment with cholesterol-synthesizing enzymes inhibitors (34).

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