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The Effect of Aspirin on C-Reactive Protein as a Marker of Risk in Unstable Angina

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OBJECTIVES This study was designed to assess the interaction between aspirin and C-reactive protein (CRP) release in unstable angina.

BACKGROUND C-reactive protein release in acute coronary syndromes may be a response to myocardial necrosis or may reflect the inflammatory process that drives atherogenesis. Aspirin has the potential to influence CRP release, either by its anti-inflammatory activity or by reducing myocardial necrosis. The clinical significance of this potential interaction has not previously been tested.

METHODS We conducted a prospective cohort study of 304 consecutive patients admitted with non-ST-elevation acute coronary syndromes. Serial blood samples were obtained for CRP and troponin I assay. End points were cardiac death and nonfatal myocardial infarction during follow-up for 12 months.

RESULTS A total of 174 patients (57%) were taking aspirin before admission. Patients taking aspirin had lower troponin I concentrations throughout the sampling period, only 45 (26.0%) having concentrations >0.1 mg/l compared with 48 (37.8%) patients not taking aspirin ($p = 0.03$). Maximum CRP concentrations were also lower in patients taking aspirin (8.16 mg/l [3.24 to 24.5]) than in patients not taking aspirin (11.3 mg/l [4.15 to 26.1]), although the difference was not significant. However, there was significant interaction ($p = 0.04$) between prior aspirin therapy and the predictive value of CRP concentrations for death and myocardial infarction at 12 months. Thus, odds ratios (95% confidence intervals) for events associated with an increase of 1 standard deviation in maximum CRP concentration were 2.64 (1.22–5.72) in patients not pretreated with aspirin compared with 0.98 (0.60–1.62) in patients pretreated with aspirin.

CONCLUSIONS The association between CRP and cardiac events in patients with unstable angina is influenced by pretreatment with aspirin. Modification of the acute-phase inflammatory responses to myocardial injury is the major mechanism of this interaction. (J Am Coll Cardiol 2001;37:1266–70) © 2001 by the American College of Cardiology

C-reactive protein (CRP) is an acute-phase reactant in myocardial infarction and unstable angina. It is an inflammatory marker, and peripheral blood concentrations are variably predictive of cardiac risk, probably because inflammation is related to the extent of myocardial necrosis (1–4). However, reports that CRP remains predictive of cardiac risk in troponin-negative individuals suggest that other mechanisms unrelated to myocardial necrosis may also be involved (2,3). One possibility is that CRP predicts prognosis because it is a marker of the chronic inflammatory state that drives atherogenesis and predisposes to plaque rupture (5–8). This mechanism provides a plausible explanation for the correlation between CRP concentrations and cardiac risk in apparently healthy individuals (9,10).

Ridker et al. (11) found that in apparently healthy subjects aspirin reduced event rates only for those with CRP levels in the highest quartile. This would be consistent with a direct anti-inflammatory effect, but at doses of aspirin used for secondary prevention the most important benefit is inhibition of platelet aggregation, which protects against ischemic injury by modifying the thrombotic response to plaque rupture (12–15). At these doses aspirin's anti-inflammatory activity is generally considered negligible.

Whatever the relative contributions of direct anti-inflammatory effects and indirect myocardial protective effects, aspirin has the potential to reduce CRP release and interfere with its predictive value for cardiac events. In order to examine this potential interaction, we have prospectively analyzed CRP concentrations in an unselected cohort of patients with non-ST-elevation acute coronary syndromes, approximately half of whom were taking aspirin, and logged cardiac events during the first 12 months.

METHODS

Patients. Consecutive patients with non-ST-elevation acute coronary syndromes were recruited if they fulfilled criteria for Braunwald class 3B unstable angina (16). Patients with serum creatine kinase ≥400 IU/l (upper limit of reference range: 200 IU/l) or CK-MB ≥4.0 μg/l without Q-wave development were diagnosed as non-Q-wave myo-

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Abbreviations and Acronyms
CRP = C-reactive protein
OR = odds ratio

cardial infarction. Electrocardiographic changes (ST depression, T-wave inversion) were not required for inclusion, but patients who developed Q-waves were excluded, as were patients with myocardial infarction in the previous 21 days. Other exclusion criteria included percutaneous coronary intervention in the previous six months and cardiac failure (New York Heart Association grade 3 or 4). The study protocol was approved by the East London and the City Health Authority Research Ethics Committee and all patients gave informed consent.

Data Collection

CLINICAL DATA. Baseline characteristics including demographic, clinical and biochemical data as well as details of the presenting ECG were collected prospectively and stored electronically. Medication being taken before admission was documented and all subjects were asked directly regarding use of aspirin.

BLOOD SAMPLING AND BIOCHEMICAL ANALYSIS. In addition to samples taken for routine laboratory analysis according to hospital protocols, samples were also taken on admission (before antithrombotic therapy) and at 12, 24 and 48 h after admission for CRP and troponin I assays. After separation, serum samples were stored at −80°C for analysis in batches. The troponin I concentrations were measured using a one-step sandwich immunoassay with magnetic separation (Bayer Immuno 1 Analyzer: Bayer PLC, Newbury, United Kingdom). The minimum detection limit was 0.1 μg/l. The coefficient of variation was 3.2% at 2.5 μg/l and 10% at 0.3 μg/l (manufacturer's datasheet). As recommended by the manufacturers, the cutoff point used was 0.1 μg/l. C-reactive protein was measured by nephelometry (N Latex CRP Mono, Dade-Behring, Marburg, Germany). The lower detection limit was 0.042 mg/l and the coefficient of variation was 1.5% at 0.3 mg/l, and 1.8% at a concentration of 3 mg/l; the test had been modified to lower the limit of detection.

FOLLOW-UP. Patients were followed up for 12 months. Deaths from cardiac causes and nonfatal myocardial infarction were documented. For patients in whom information about nonfatal ischemic events was not already available from outpatient follow-up or readmission to the coronary care unit, postal questionnaires were used to obtain the information, backed up by telephone inquiry for nonresponders. In this way, 12-month follow-up data were obtained in 95.1% of the study group.

STATISTICAL ANALYSIS. C-reactive protein results are presented as median and interquartile range. Differences in CRP levels by group were tested using the Mann-Whitney *U* test. Troponin-I was analyzed using a cut point of 0.1 μg/l. Associations with events were assessed using logistic regression models. C-reactive protein was log-transformed before being entered in the model. Results are presented as odds ratios (ORs) and 95% confidence intervals. For CRP the OR represents the increased risk associated with an increase of 1 standard deviation in maximum blood level, equivalent to a fourfold increase in the untransformed level. An interaction term was fitted in the model to test whether the CRP association was modified by aspirin use. Stepwise logistic regression models were fitted and stratified by aspirin use to determine independent predictors of death and myocardial infarction within each group.

Table 1. Patient Characteristics: Data Are Numbers (%), Except for Age and Cholesterol, Which Are Years and mmol/l (Standard Deviation), Respectively

Variable	Entire Cohort (n = 304)	12-Month Follow-Up		
		No Event* (n = 261)	Event* (n = 28)	p Value
Age	60.5 (11.2)	60.0 (11.1)	67.5 (11.3)	0.001
Male	227 (74.7)	192 (73.9)	23 (82.1)	0.34
Diabetic	67 (22.0)	53 (20.3)	11 (39.3)	0.03
Hypertensive	135 (44.4)	116 (44.4)	14 (50.0)	0.58
Smoker	97 (31.9)	85 (32.6)	6 (21.4)	0.23
Cholesterol	5.80 (1.17)	5.62 (1.12)	6.11 (1.22)	0.05
Prior aspirin†	174 (57)	152 (58.5)	17 (60.7)	0.82
Troponin I >0.1 μg/l‡	93 (30.9)	68 (26.4)	19 (67.9)	<0.0001

*Events are death from cardiac causes or nonfatal myocardial infarction. †Patients on regular treatment with aspirin before presentation. ‡Patients with one or more serum troponin concentrations >0.01 μg/l.

RESULTS

Discharge diagnosis and outcome. Patient characteristics are summarized in Table 1. The discharge diagnosis was non-Q-wave myocardial infarction in 92 patients (30%) and unstable angina in 212 (70%). Thirty-day follow-up was obtained in 303 patients (99.7%), of whom one died and 14 had nonfatal myocardial infarction. Twelve-month follow-up was obtained in 289 patients (95.1%), of whom seven died and 21 had nonfatal myocardial infarction. All deaths were attributable to cardiac causes. Event rates in those who were and were not receiving aspirin therapy prior to presentation were not significantly different.

Aspirin, troponin I and CRP concentrations (Table 2, Fig. 1). C-reactive protein collection was complete, but aspirin data were unavailable in one case and troponin data in a further three cases. Of the 304 patients, 174 (57%) were taking aspirin before admission and 129 were not. Patients taking aspirin had lower troponin I concentrations throughout the sampling period, only 45 (26.0%) having maximum concentrations >0.1 μg/l compared with 48 (37.8%) patients not taking aspirin (p = 0.03). Patients taking aspirin also tended to have lower CRP concentrations than patients not taking aspirin, although the differences were not signif-

Table 2. Troponin I (μg/l) and C-reactive protein (CRP) (mg/l) Concentrations According to Prior Aspirin Use: Data for Troponin I Are Number (%) of Patients With Serum Concentration >0.1 μg/l, and for CRP Are Medians (Interquartile Range)

Sample Time (h)	Serum Marker	No Aspirin (n = 129)	Prior Aspirin (n = 174)	p Value
0	Troponin I	32 (25.6)	29 (18.0)	0.12
	CRP	4.57 (2.36–9.59)	4.25 (1.58–9.56)	0.40
12	Troponin I	42 (36.5)	39 (25.3)	0.05
	CRP	4.72 (2.13–11.8)	5.33 (2.05–10.9)	0.31
24	Troponin I	41 (35.0)	39 (25.8)	0.10
	CRP	7.69 (3.75–15.9)	5.96 (2.48–16.5)	0.36
48	Troponin I	30 (29.7)	30 (24.8)	0.41
	CRP	9.99 (2.47–25.9)	7.38 (3.31–25.6)	0.62
Maximum	Troponin I	48 (37.8)	45 (26.0)	0.03
	CRP	11.3 (4.15–26.1)	8.16 (3.24–24.5)	0.22

icant. Significant correlation was confirmed between CRP and troponin I concentrations (Fig. 1).

CRP and cardiac events (Tables 3 and 4). Table 3 shows that at all sampling times, CRP concentrations were higher in patients who experienced cardiac events than in patients who did not. However, differences only became significant after 24 h and were particularly marked in patients not taking aspirin before admission. Conversely, in patients taking aspirin, differences never reached statistical significance. For an increase of 1 standard deviation in maximum CRP concentrations, ORs (95% confidence intervals) for events at 30 days and 12 months were 1.09 (0.52 to 2.31) and 0.98 (0.60 to 1.62) respectively, rising to 2.65 (1.10 to 6.40) and 2.64 (1.22 to 5.72) in patients not taking aspirin before admission (Table 4). Thus, in patients taking aspirin, the ORs showed marked attenuation with lower limits of confidence well below unity. Significant interaction ($p = 0.04$) was confirmed between prior aspirin therapy and the predictive value of CRP concentrations for cardiac events during the first 12 months. In a multivariate analysis that included age, gender and troponin measurements, CRP was not retained as an independent predictor of events, either for the entire cohort or the subgroup not taking aspirin.

DISCUSSION

This prospective study of non-ST-elevation acute coronary syndromes has shown significant association between CRP concentrations and future cardiac events, particularly in patients not pretreated with aspirin. The association was attenuated, however, by pretreatment with aspirin, which reduced myocardial injury and acute-phase inflammatory responses.

Aspirin and myocardial injury. The minimal myocardial injury that may occur in non-ST-elevation coronary syndromes is now recognized as a major predictor of cardiac events and results in the release of troponins into the circulation (17–19). Troponin release is almost certainly the

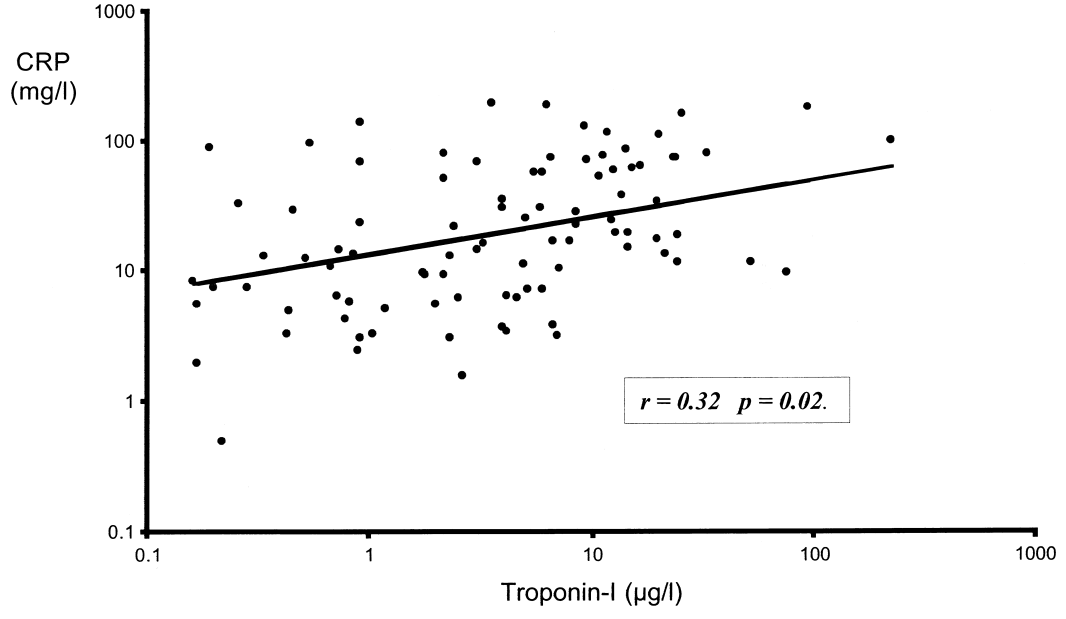

Figure 1. Correlation between peak C-reactive protein (CRP) (mg/l) and troponin I (μg/l) concentrations. Both CRP and troponin concentrations are plotted on a log scale. Only patients with elevated (>0.1 μg/l) troponin I levels are represented.

Table 3. C-Reactive Protein Concentrations (mg/l) as a Univariate Predictor of Death or Nonfatal Myocardial Infarction at 30 Days and 12 Months According to Prior Aspirin Treatment: Data Are Median Values (Interquartile Range)

Sample Time	Cohort	30-Day Follow-Up			12-Month Follow-Up		
		No Event (n = 288)	Event (n = 15)	p Value	No Event (n = 261)	Event (n = 28)	p Value
0	All patients	4.34 (1.83–9.59)	6.54 (4.08–9.26)	0.16	4.25 (1.73–9.59)	5.37 (2.91–10.1)	0.38
	No aspirin	4.35 (2.17–10.5)	6.54 (4.52–8.59)	0.31	4.24 (1.95–10.6)	5.96 (4.12–8.71)	0.23
	Prior aspirin	4.25 (1.58–9.39)	7.09 (3.29–13.1)	0.38	4.36 (1.58–9.11)	3.99 (1.23–13.4)	0.91
12	All patients	4.86 (2.09–11.8)	7.68 (2.88–10.4)	0.52	4.86 (2.02–11.8)	7.41 (2.4–11.7)	0.81
	No aspirin	4.42 (2.11–12.1)	7.9 (6.22–10.05)	0.51	4.37 (1.85–13.4)	7.90 (5.03–10.40)	0.41
	Prior aspirin	5.34 (2.05–10.9)	4.05 (1.45–27.4)	0.84	5.34 (2.05–10.6)	3.89 (1.45–13.10)	0.73
24	All patients	6.36 (2.8–15.2)	20.2 (7.12–34.2)	0.02	6.15 (2.8–14.2)	15.7 (4.0–30.0)	0.06
	No aspirin	7.02 (3.38–14.4)	21.7 (10.3–34.2)	0.02	6.76 (2.93–13.60)	24.25 (10.30–34.20)	0.007
	Prior aspirin	5.96 (2.48–15.4)	12.4 (4.0–42.4)	0.37	5.96 (2.62–15.10)	5.16 (2.11–27.65)	0.84
48	All patients	8.5 (3.04–24.95)	40.4 (7.03–89.4)	0.01	8.3 (2.72–24.25)	39.3 (6.36–56.8)	0.004
	No aspirin	9.66 (2.44–24.7)	56.8 (30.4–98.2)	0.02	9.36 (2.41–24.6)	47.9 (18.09–77.5)	0.009
	Prior aspirin	7.34 (3.31–25.2)	23.4 (7.03–50.4)	0.17	7.38 (3.31–19.7)	23.4 (6.36–50.4)	0.13
Maximum	All patients	9.31 (3.43–24.6)	23.4 (7.03–56.8)	0.08	9.3 (3.44–23.7)	17.6 (4.24–56.65)	0.15
	No aspirin	10.4 (3.83–24.6)	32.3 (11–77.5)	0.03	10.9 (3.71–24.6)	34.2 (10.3–63.9)	0.01
	Prior aspirin	8.52 (3.31–23.8)	7.03 (2.09–50.4)	0.95	8.54 (3.43–19.7)	6.36 (2.4–46.1)	0.78

consequence of significant intraluminal thrombosis, with ischemic injury resulting either from transient coronary occlusion or from thrombotic embolization into the distal arterial bed (20). Although the finding that troponin release is reduced in patients taking aspirin has not previously been reported, it is a predictable result of antiplatelet activity modifying the thrombotic response to plaque rupture and reducing ischemic injury. In this respect it is analagous to previous studies of acute coronary syndromes in which pretreatment with aspirin has been associated with less severe modes of presentation (14,15).

Risk assessment. Our study confirmed the highly significant association between troponin positivity and cardiac risk in non-ST-elevation coronary syndromes, patients with concentrations >0.1 μg/l comprising 67.9% of the group with ischemic events in the first 12 months. C-reactive protein showed a weaker association, similar to that reported by other investigators (1–4). The association between CRP and cardiac risk is consistent with current understanding of the inflammatory process acting as a driver of the atherosclerotic process, and in some (4,21) but not all studies (22), CRP has been reported to predict death from cardiac causes independent of troponin status. In this study an independent association was not demonstrated and the univariate association only became significant 24 h after presentation, suggesting that acute-phase inflammatory responses to myocardial injury were a more important mechanism in our patients. The correlation between CRP and troponin I concentrations lends some weight to this suggestion.

Table 4. Odds Ratios for Association of Maximum C-Reactive Protein (CRP) Concentrations With 30-Day and 12-Month Event-Free Survival According to Prior Aspirin Treatment

	Odds Ratio (95% Confidence Interval)	p Value for Interaction
30-day follow-up		
No aspirin	2.65 (1.10–6.40)	0.13
Prior aspirin	1.09 (0.52–2.31)	
12-month follow-up		
No aspirin	2.64 (1.22–5.72)	0.04
Prior aspirin	0.98 (0.60–1.62)	

Odds ratios for a 1 standard deviation increase in maximum CRP are from a logistic regression model with an interaction term to test if the association between CRP and event rates differs according to prior aspirin treatment.

Aspirin, CRP and risk. An important, and hitherto unreported, observation in the present study was the interaction between prior aspirin therapy and the predictive value of CRP concentrations for cardiac events during the first 12 months. In patients not pretreated with aspirin each standard deviation increase in CRP more than doubled the odds of ischemic events at 30 days and 12 months. In patients pretreated with aspirin, however, CRP provided no useful information about cardiac risk. C-reactive protein concentrations tended to be lower in these patients, suggesting that the protection aspirin provided against ischemic myocardial injury, reflected in reduced troponin release, attenuated acute-phase inflammatory responses to the point that associations between CRP and ischemic events were lost.

Conclusion. The association between CRP and cardiac events in patients with non-ST-elevation coronary syndromes is influenced by pretreatment with aspirin. The mechanism of this interaction is not clear, although the effect of aspirin on troponin release suggests that modification of the acute-phase inflammatory responses to myocardial injury may have a role. Regardless of the mechanism, this study of non-ST-elevation coronary syndromes has shown that CRP is a significant predictor of cardiac events only in patients not pretreated with aspirin.

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