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The impact of hs C-reactive protein and other inflammatory biomarkers on long-term cardiovascular mortality in patients with acute coronary syndromes

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Abstract

We evaluated whether high circulating levels of serum amyloid A (SAA), fibrinogen, interleukin-6 (IL-6) or leukocytes count (LC), can provide any additional predictive value over that provided by hs C-reactive protein (hs-CRP) for the incidence of 5-year cardiovascular mortality, in 458 and 476 consecutive patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndromes (NSTE-ACS), respectively.

By 5 years the incidence of cardiovascular mortality was 37.3% and 35.5% in patients with STEMI and NSTE-ACS, respectively. Each of the study inflammatory biomarkers conferred independent to clinical risk predictors (and to cardiac troponin I) long-term prognostic information (all $p < 0.05$), but only LC provided additional predictive value over that provided by hs-CRP, in either cohort ($p < 0.05$). By multivariate Cox regression analysis, hs-CRP ($p < 0.001$ for both cohorts) and LC ($p = 0.009$ and $p < 0.001$ for STEMI and NSTE-ACS, respectively) were the only inflammatory biomarkers independently associated with the incidence of 5-year cardiovascular mortality.

According to the present results high circulating levels of LC but not of SAA, fibrinogen or IL-6 can provide additional long-term predictive value over that provided by hs-CRP in patients with acute coronary syndromes.

Keywords: Acute coronary syndromes; Inflammatory biomarkers; Risk stratification; Prognosis

1. Introduction

Inflammation has a key role in the pathogenesis and outcome of acute coronary syndromes [1]. Previous studies have constantly shown that high circulating levels of C-reactive protein (CRP) confer an increased risk of long-term cardiovascular mortality in patients with either ST-segment elevation myocardial infarction (STEMI) [2–6], or non-ST-segment elevation acute coronary syndromes (NSTE-ACS) [6–11]. Moreover, high circulating levels of other inflammatory biomarkers including, serum amyloid A (SAA) [12,13], fibrinogen [10,14], interleukin-6 (IL-6) [15] and leukocytes count (LC) [16–19], have been connected with adverse prognosis during the long-term, in these settings. However, whether these inflammatory biomarkers can provide any additional long-term predictive value over that provided by hs-CRP, in patients with acute coronary syndromes, has not been thoroughly evaluated.

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2. Patients and methods

2.1. Study patients

The Biomarkers of Inflammation and Outcome in Acute Coronary Syndromes (BIAS) study was a prospectively designed observational study to investigate whether high circulating levels of SAA, fibrinogen, IL-6 or LC can provide any additional predictive value over that provided by hs-CRP for the incidence of 5-year cardiovascular mortality, in patients with either STEMI, or NSTE-ACS.

Consecutive eligible patients with either STEMI, or NSTE-ACS who were admitted at our institute from September 1998 through December 2000 were recruited. Patients with STEMI were required to have: (1) continuous chest pain upon presentation, refractory to nitrates, and lasting $\geq$30 min; (2) ST-segment elevation of $\geq$0.2 mV in $\geq$2 contiguous precordial leads, or $\geq$0.1 mV in $\geq$2 contiguous limb leads, or new (or presumably new) left bundle branch block on admission electrocardiogram; (3) presentation in the first 12 h from index pain. Due to the fact that primary percutaneous coronary angioplasty was not the standard of care at the time the study was started, patients who receive this type of reperfusion were not included. Patients with NSTE-ACS were required to have angina like chest pain at rest in the last 24 h lasting $\geq$5 min, with associated ST-segment depression of $\geq$0.1 mV in $\geq$2 contiguous leads upon presentation. Patient with (1) angina of secondary etiology, (2) myocardial infarction, revascularization procedure or surgery, (3) active infection, or chronic inflammatory diseases, (4) significant hepatic or renal dysfunction, and (5) malignancy, were not included.

All patients received aspirin orally in a dose of 100–325 mg upon presentation and it was continued as a daily dose indefinitely. Heparin was given in a bolus dose of 5000 units upon admission in all patients, followed by intravenous infusion titrated to a therapeutic activated partial thromboplastin time. Heparin was continued in uncomplicated cases for 48 h followed by subcutaneous administration of enoxaparin. Streptokinase or tissue plasminogen activator was the thrombolytic agent used in patients with ST-segment elevation myocardial infarction. Clopidogrel was not routinely administered at the time the study was running. Further medical therapy including β-blockers, nitrates, Ca channels antagonists, angiotensin converting enzyme inhibitors, glycoprotein IIb/IIIa inhibitors and statins, was left at the discretion of the attending physician.

The study complies with the Declaration of Helsinki, the ethics committee of the hospital has approved the research protocol and informed consent has been obtained from all participants.

2.2. Clinical follow-up and study endpoint

In-hospital and post-discharge follow-up data were prospectively collected on pre-designed case report forms. Before discharge, all patients were advised for smoking cessation, body weight reduction, regular exercise and lipids monitoring. After discharge, patients were followed-up at 30 days and subsequently every 6 months for a whole period of 5 years, on an outpatient basis or by telephone interview. Cardiovascular mortality at 5 years was the pre-specified study endpoint. Cardiovascular death was considered, as sudden unexplained death, death due to fatal myocardial infarction, death after re-hospitalization because of heart failure or possible acute myocardial ischemia and death related to stroke or peripheral artery disease. The diagnosis of cardiovascular death was verified by review of death certificates, discharge medical reports, hospitals records, or contact with the attending physicians.

2.3. Collection of blood samples and biochemical assays

Upon presentation, venous blood samples were obtained before administration of drugs. LC was measured upon patients' presentation. Coded serum samples were stored at $-80\,^{\circ}$C until biomarkers assays. hs-CRP and fibrinogen were measured by a highly sensitive nephelometric method (BNII Dade Behring Inc., Germany) with a lower limit of detection at 0.2 mg/l and 0.1 g/l, respectively. Cardiac troponin I and SAA were determined by an enzyme based immunoassay (Abbot Diagnostics, IL), with a threshold level for the diagnosis of myocardial infarction $\geq$0.4 ng/ml and with a lower limit of detection for SAA at 0.08 mg/dl. IL-6 was assayed by a high sensitive quantitative sandwich enzyme immunoassay (Quantikine HS, R&D Systems Inc., Minneapolis) with a lower limit of detection at 0.01 pg/ml.

3. Statistical analysis

Normally distributed continuous variables are expressed as mean $\pm$ S.D. Non-normally distributed study biomarkers are expressed as median with 25th and 75th percentiles and natural logarithm transformation was used for correlation or regression analysis. Normal distribution was evaluated with Kolmogorov–Smirnov test. Continuous variables were compared using unpaired *t*-test or Mann–Whitney *U*-test as appropriate. Dichotomous variables are presented as numbers and percentages. Associations between dichotomous variables were tested by χ^2 or Fisher's exact test as appropriate. Bivariate correlations were evaluated by Spearman's ρ. Unadjusted and adjusted predictive effect of each inflammatory biomarker was evaluated with univariate and multivariate Cox regression models, in order to evaluate whether these biomarkers can provide any additional long-term predictive value over that provided by hs-CRP. A multivariate Cox regression model, for each cohort, was constructed, in which all the study inflammatory biomarkers were included, to detect those inflammatory biomarkers that independently associated with the incidence of 5-year cardiovascular mortality. Patients who died because of non-cardiovascular

causes were censored at the time of death. All tests were two-tailed and a $p < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS statistical software (release 11.0, SPSS Inc., Chicago, IL).

4. Results

4.1. Baseline characteristics

During the recruiting period 458 and 476 patients with STEMI and NSTE-ACS were respectively included in the study. Baseline characteristics and interrelations between the study inflammatory biomarkers for both cohorts are presented in Tables 1 and 2, respectively. Patients with NSTE-ACS were older and had more adverse risk profile than those with STEMI (Table 1). All inflammatory biomarkers were significantly interrelated in both cohorts. hs-CRP, SAA, fibrinogen and IL-6 were strongly interrelated but they were weakly correlated with LC (Table 2).

4.2. Study endpoint

Five-year mortality data were obtained for all patients and the study endpoint was reached by 171 (37.3%) and 169 (35.5%) patients with STEMI and NSTE-ACS, respectively. Cardiovascular mortality rates at 1, 2, 3, 4, and 5 years were 22.9%, 29.1%, 32.7%, 34.7%, and 37.3%, respectively, in patients with STEMI and 15.1%, 22.7%, 27.5%, 30.1%, and 35.5%, respectively, in patients with NSTE-ACS (Fig. 1).

Unadjusted and adjusted predictive effect of circulating levels of each of the study inflammatory biomarkers, for either cohort, is presented in Table 3. Circulating levels of each inflammatory biomarker were significantly associated with an increased unadjusted risk of cardiovascular death at 5 years and it was true and after adjustment for the other significant clinical risk predictors and cardiac troponin I. However, only circulating levels of LC were significantly associated with an increased risk for the primary endpoint after adjustment for the other significant clinical risk predictors, cardiac troponin I and hs-CRP (Table 3).

The multivariate Cox regression models, in which all five inflammatory biomarkers were introduced simultaneously in the models, are presented in Tables 4 and 5. Although circulat-

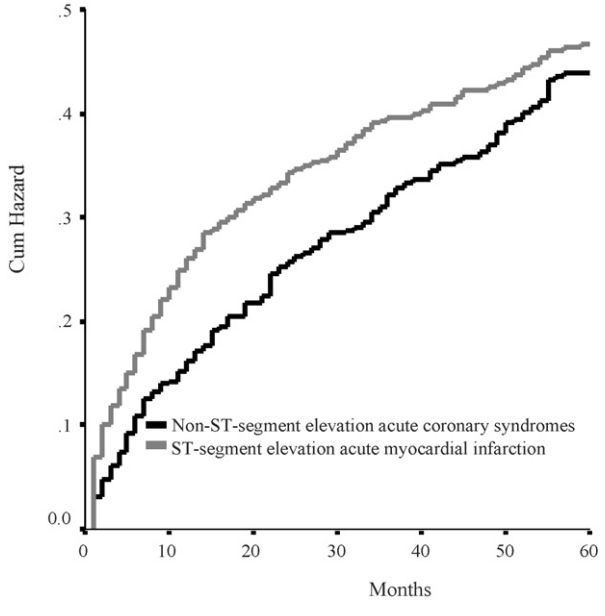

Fig. 1. Cumulative hazard curves for the incidence of 5-year cardiovascular death in patients with either ST-segment elevation myocardial infarction, or non-ST-segment elevation acute coronary syndromes.

Table 1
Baseline characteristics of the study population

	STEMI ($n = 458$)	NSTE-ACS ($n = 476$)
Age (years), mean ± S.D.	60.1 ± 11.5	70.2 ± 7.9
Male gender (%)	77.3	65.8
Cardiovascular risk factors (%)		
Hypertension	49.6	64.3
Current smoking	65.9	45.4
Diabetes mellitus	27.1	34.2
Hypercholesterolemia	63.3	68.3
Family history of coronary artery disease	38	39.5
Medical history (%)		
History of myocardial infarction	13.1	29.2
History of heart failure	6.3	13.7
History of cerebrovascular or peripheral artery disease	8.3	11.1
History of coronary angioplasty	13.3	15.8
History of coronary bypass grafting	10	15.1
Anterior STEMI or new (or presumably new) LBBB (%)	52.4	–
Killip classes II–IV (%)	12	18.3
From onset of symptoms to treatment in hours, mean ± S.D.	4.3 ± 1.9	8.7 ± 4.5
Treatment with intravenous thrombolysis (%)	69.4	–
Cardiac troponin I, median (25th; 75th percentile) (ng/ml)	25 (14.4; 41)	11 (6.3; 21.4)
hs C-reactive protein, median (25th; 75th percentile) (mg/l)	4.7 (3.2; 10)	5.4 (3.6; 12.4)
Serum amyloid A, median (25th; 75th percentile) (mg/dl)	1.5 (0.4; 7.3)	1.7 (0.5; 9.3)
Fibrinogen, median (25th; 75th percentile) (g/l)	6.1 (4.8; 7.2)	6.6 (5.1; 7.8)
Interleukin-6, median (25th; 75th percentile) (pg/ml)	4.8 (3.5; 7.6)	6.1 (4.1; 11.2)
Leukocytes count, median (25th; 75th percentile) ($\times 10^9\ l^{-1}$)	9 (5.9; 11.6)	9.7 (6.4; 12.6)

STEMI, ST-segment elevation myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; S.D., standard deviation; LBBB, left bundle brunch block.

Table 2
Bivariate Spearman's correlations between the study inflammatory biomarkers

	Serum amyloid A	Fibrinogen	Interleukin-6	Leukocyte count
STEMI				
hs C-reactive protein	0.73; <0.001	0.37; <0.001	0.79; <0.001	0.17; <0.001
Serum amyloid A	–	0.42; 0.01	0.51; 0.004	0.15; <0.001
Fibrinogen	–	–	0.46; <0.001	0.13; <0.001
NSTE-ACS				
hs C-reactive protein	0.79; <0.001	0.51; <0.001	0.85; <0.001	0.23; <0.001
Serum amyloid A	–	0.39; <0.001	0.44; <0.001	0.19; <0.001
Fibrinogen	–	–	0.41; <0.001	0.22; <0.001

Values of all inflammatory biomarkers were logarithmically transformed. Values in each cell represent Spearman's ρ and p. STEMI, ST-segment elevation myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndromes.

Table 3
Unadjusted and adjusted predictive value of the study inflammatory biomarkers for the incidence of 5-year cardiovascular death in both cohorts

	Unadjusted		Adjusted for clinical variables and cTnI		Adjusted for clinical variables, cTnI and hs-CRP	
	H.R. (95% CI)	p	H.R. (95% CI)	p	H.R. (95% CI)	p
hs C-reactive protein						
STEMI	2.9 (1.8–3.5)	<0.001	2.5 (1.8–3.2)	<0.001	–	
NSTE-ACS	2.9 (2.1–3.8)	<0.001	2.6 (1.8–3.1)	<0.001	–	
Serum amyloid A						
STEMI	1.9 (1.1–3.9)	0.002	1.4 (1.1–2.3)	0.01	1.1 (0.7–1.2)	0.4
NSTE-ACS	1.8 (1.6–2.1)	<0.001	1.5 (1.2–2.3)	0.004	1.1 (0.9–1.3)	0.3
Fibrinogen						
STEMI	2.3 (1.4–4.1)	<0.001	1.6 (1.2–3.8)	0.004	1.2 (0.6–2.4)	0.6
NSTE-ACS	1.7 (1.3–3.5)	<0.001	1.5 (1.2–3.2)	<0.001	1.2 (0.7–1.9)	0.5
Interleukin-6						
STEMI	2.1 (1.3–4.5)	0.001	1.7 (1.4–2.9)	0.008	1.1 (0.9–1.3)	0.2
NSTE-ACS	1.9 (1.5–2.7)	<0.001	1.6 (1.3–2.4)	0.008	0.9 (0.7–1.2)	0.4
Leukocytes count						
STEMI	3.2 (2–4.2)	<0.001	2.2 (1.5–3.1)	<0.001	1.9 (1.4–3.1)	0.004
NSTE-ACS	3.4 (2.2–6.6)	<0.001	2.6 (1.8–4.3)	<0.001	2.2 (1.5–2.9)	<0.001

Values of all inflammatory biomarkers and cardiac troponin I were logarithmically transformed. cTnI, cardiac troponin I; hs-CRP, hs C-reactive protein; H.R., hazard ratio; CI, confidence interval; STEMI, ST-segment elevation myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndromes.

ing levels of all five inflammatory biomarkers were significant univariate predictors of the study endpoint, only circulating levels of hs-CRP and LC were independently associated with the study endpoint in patients with STEMI (Table 4) or NSTE-ACS (Table 5).

5. Discussion

The BIAS study examining the predictive value of five inflammatory biomarkers in patients with either STEMI or NSTE-ACS, has shown that elevated circulating levels of hs-CRP, SAA, fibrinogen, IL-6, or LC upon admission, can each confer incremental, and independent to clinical risk predictors (and to cardiac troponin I), prognostic information for the incidence of cardiovascular death at 5 years. However, only LC, but not SAA, fibrinogen or IL-6 can provide additional predictive value over that provided by hs-CRP. Furthermore when all five inflammatory biomarkers were introduced in the same multivariate model hs-CRP and LC were the only inflammatory biomarkers, which conferred independent predictive value over that provided by the other well established clinical risk predictors (and to cardiac troponin I) for the incidence of cardiovascular death at 5 years.

In agreement with the present findings, many other investigators have found that high circulating CRP (or hs-CRP) levels can significantly and independently predict the occurrence of the hard endpoint of cardiovascular related death in follow ups through to 4 years, in patients with either STEMI [2–6], or NSTE-ACS [6–11]. Similarly, the present results are in agreement with some recent reports that support a strong relation between elevated LC and long-term cardiovascular related death in these settings [16–19]. Concerning to the predictive value of the other study inflammatory biomarkers, the findings of the BIAS study confirm the results of the few previous studies that demonstrated a positive association of high circulating levels of SAA [12,13], fibrinogen [10,14], or IL-6 [15] with the incidence of short or midterm cardiovascular related death in these settings.

Table 4
Univariate and multivariate predictors of 5-year cardiovascular death in patients with STEMI

	Univariate Cox regression		Multivariate Cox regression	
	H.R. (95% CI)	*p*	H.R. (95% CI)	*p*
Age (per 10 years)	2 (1.7–2.3)	<0.001	1.3 (1.1–1.5)	0.007
Male gender	0.7 (0.5–0.9)	0.03	1 (0.7–1.5)	1
Hypertension	1.4 (1.1–1.8)	0.04	1.2 (0.9–1.7)	0.3
Current smoking	0.5 (0.4–0.7)	<0.001	0.9 (0.7–1.3)	0.6
Diabetes mellitus	3.4 (2.5–4.7)	<0.001	1.6 (1.1–2.2)	0.01
History of myocardial infarction	5.2 (3.7–7.2)	<0.001	2.1 (1.4–3)	<0.001
History of heart failure	6.3 (4.1–9.7)	<0.001	1.7 (1.1–2.9)	0.03
History of cerebrovascular or peripheral artery disease	2.2 (1.4–3.4)	0.001	1.6 (1–2.7)	0.04
History of coronary angioplasty	1.4 (1–2.1)	0.07	1 (0.6–1.5)	0.9
History of coronary bypass grafting	1.7 (1.1–2.7)	0.01	0.8 (0.5–1.3)	0.4
Anterior STEMI or new (or presumably new) LBBB	2.7 (1.9–3.7)	<0.001	1.5 (1.1–2.2)	0.02
Killip classes II–IV	6.1 (4.4–8.6)	<0.001	2.2 (1.5–3.3)	<0.001
From onset of symptoms to treatment in hours	4.2 (2.9–6.3)	<0.001	1.9 (1.4–4.7)	<0.001
Administration of intravenous thrombolysis	0.3 (0.2–0.5)	<0.001	0.7 (0.5–0.9)	0.02
Cardiac troponin I	2.7 (2.2–3.6)	<0.001	1.8 (1.4–2.2)	<0.001
hs C-reactive protein	2.9 (1.8–3.5)	<0.001	2.1 (1.6–2.7)	<0.001
Serum amyloid A	1.9 (1.1–3.9)	0.002	1.1 (0.5–1.5)	0.7
Fibrinogen	2.3 (1.4–4.1)	<0.001	0.9 (0.6–1.4)	0.9
Interleukin-6	2.1 (1.3–4.5)	0.001	1.1 (0.5–1.2)	0.7
Leukocytes count	3.2 (2–4.2)	<0.001	1.6 (1.1–2.3)	0.009

Values of all inflammatory biomarkers and cardiac troponin I were logarithmically transformed. STEMI, ST-segment elevation myocardial infarction; H.R., hazard ratio; CI, confidence interval.

Although, a direct effect of CRP [20] on the progression of atherosclerotic artery disease has been proposed, the etiology of the superior predictive value of hs-CRP and LC over that provided by the other study inflammatory biomarkers could be only speculative. In the present study circulating levels of hs-CRP, SAA, fibrinogen, and IL-6 were strongly interrelated but all they were weakly correlated with LC. These results suggest that elevated circulating levels of hs-CRP, SAA, fibrinogen, and IL-6 may, to a certain extent, reflect a similar aspect of inflammatory response that is different to that involved in the elevation of LC. Actually, IL-6 is one of the main triggers of CRP and fibrinogen release [21], and high circulating levels of hs-CRP, SAA, fibrinogen, or IL-6 levels have been connected with a generalized coronary artery tree destabilization in the setting of acute coronary syndromes [22–24]. Moreover, it seems possible that the better biological profile of CRP than that of SAA, fibrinogen, and IL-6 may, at least partially, explain the superior predictive value of the former [25]. In particular, the long half-life of circulating CRP, the consumption of circulating fibrinogen during

Table 5
Univariate and multivariate predictors of 5-year cardiovascular death in patients with NSTE-ACS

	Univariate Cox regression		Multivariate Cox regression	
	H.R. (95% CI)	*p*	H.R. (95% CI)	*p*
Age (per 10 years)	2.9 (2.3–3.7)	<0.001	1.6 (1.3–2.1)	<0.001
Male gender	0.6 (0.5–0.8)	0.002	0.8 (0.6–1.1)	0.2
Hypertension	1.6 (1.1–2.2)	0.006	1.1 (0.8–1.2)	0.3
Current smoking	0.6 (0.4–0.8)	<0.001	1 (0.7–1.4)	0.9
Diabetes mellitus	3.9 (2.9–5.3)	<0.001	2.3 (1.7–3.2)	<0.001
History of myocardial infarction	4.1 (2.4–6.4)	<0.001	1.8 (1.3–2.5)	0.001
History of heart failure	5.7 (4.1–7.8)	<0.001	2 (1.3–3)	0.002
History of cerebrovascular or peripheral artery disease	3.3 (2.3–4.7)	<0.001	1.5 (1.1–2.3)	0.04
History of coronary angioplasty	2.4 (1.7–3.3)	<0.001	1.1 (0.7–1.6)	0.7
History of coronary bypass grafting	1.5 (1.1–2.2)	0.04	0.9 (0.6–1.4)	0.8
Killip classes II–IV	6.3 (4.6–8.5)	<0.001	1.7 (1.1–2.6)	0.01
Cardiac troponin I	3.6 (1.8–4.7)	<0.001	1.9 (1.2–2.6)	<0.001
hs C-reactive protein	2.9 (2.1–3.8)	<0.001	2.4 (1.5–3.1)	<0.001
Serum amyloid A	1.8 (1.6–2.1)	<0.001	1.1 (0.5–1.3)	0.8
Fibrinogen	1.7 (1.3–3.5)	<0.001	0.8 (0.4–1.5)	0.7
Interleukin-6	1.9 (1.5–2.7)	<0.001	0.9 (0.4–1.2)	0.8
Leukocytes count	3.4 (2.2–6.6)	<0.001	2 (1.4–2.7)	<0.001

Values of all inflammatory biomarkers were logarithmically transformed. NSTE-ACS, non-ST-segment elevation acute coronary syndromes; H.R., hazard ratio; CI, confidence interval.

the acute phase of acute coronary syndromes and the short half-life of circulating IL-6 may have a role [25].

In conclusion, the results of the BIAS study suggest that high circulating levels of LC but not of SAA, fibrinogen, or IL-6 can provide additional predictive value, over that provided by hs-CRP, for the incidence of long-term cardiovascular death, in patients with either STEMI, or NSTE-ACS. Simultaneous assessment of hs-CRP and LC can confer enhanced early risk stratification beyond well established clinical, electrocardiographic or biochemical risk predictors.

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