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Inflammation during acute coronary syndromes — Risk of cardiovascular events and bleeding

David Nanchen [a,*,1], Roland Klingenberg [b,1], Baris Gencer [c], Lorenz Räber [d], David Carballo [c], Arnold von Eckardstein [e], Stephan Windecker [d], Nicolas Rodondi [f,g], Thomas F. Lüscher [h], François Mach [c], Olivier Muller [i,1], Christian M. Matter [b,1]

[a] Department of Ambulatory Care and Community Medicine, University of Lausanne, Lausanne, Switzerland
[b] Department of Cardiology, University Heart Center, University Hospital Zurich and University of Zurich, Zurich, Switzerland
[c] Division of Cardiology, Faculty of Medicine, Geneva University Hospitals, Geneva, Switzerland
[d] Department of Cardiology, University Hospital Bern, Bern, Switzerland
[e] Institute of Clinical Chemistry, University Hospital Zurich and University of Zurich, Zurich, Switzerland
[f] Institute of Primary Health Care (BIHAM), University of Bern, Switzerland
[g] Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland
[h] Royal Brompton & Harefield Hospital Trust and Imperial College, London SW3 6NP, UK
[i] Service of Cardiology, Lausanne University Hospital, Lausanne, Switzerland

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ABSTRACT

Background: Many parameters can affect the level of inflammation during acute coronary syndromes (ACS). We aimed to assess the one-year risk of major adverse cardiovascular events (MACE) and bleeding associated with elevated hsCRP levels during ACS, taking into account the severity of myocardial infarction, the timing of blood sampling and established long-term prognostic factors.
Methods: We studied 1864 consecutive patients with ACS enrolled in a contemporary multicenter prospective cohort study in Switzerland. HsCRP levels were determined at hospital admission. One year after discharge MACE and bleeding events were assessed. Multivariable adjusted Cox proportional hazards were computed with age, sex, time from symptom onset to blood draw, body mass index, current smoking, hypertension, diabetes mellitus, pre-existing cardiovascular disease, history of inflammatory disease, LDL-cholesterol levels, type of ACS, left ventricular ejection fraction and GRACE 1.0 risk score.
Results: At one-year follow-up, 151 (8.1%) patients suffered MACE. Compared to patients with hsCRP below 2 mg/l, the risk of MACE was higher in patients with hsCRP levels between 2 and 5 mg/l, with a multivariate adjusted hazard ratio (HR) of 1.63 (95% confidence interval (CI) 0.93–2.84), in those with levels between 5 and 10 mg/l, with a HR of 2.80 (95% CI 1.58–4.96), and in those with levels above 10 mg/l, with a HR of 2.23 (95% CI 1.28–3.88). There was no difference in bleeding risk between the four groups.
Conclusions: Systemic inflammation in the acute phase of myocardial infarction is an independent predictor for cardiovascular events, but not for bleeding.

1. Introduction

For over 30 years, data have supported an association between inflammation and atherothrombosis [1–3]. High-sensitivity C-reactive protein (hsCRP) is an established marker of inflammation [4] associated with traditional cardiovascular risk factors [5,6]. Many studies have demonstrated the role of hsCRP to identify healthy adults or patients with stable coronary artery disease at risk for cardiovascular events [7,8]. However, studies that have examined the prognostic role of hsCRP in patients with acute coronary syndromes (ACS) are less conclusive, maybe because the interval between chest pain onset and blood draw partly explains the elevation of hsCRP concentrations [9,10]. Thus, the impact of hsCRP concentrations measured at the time of ACS regarding long-term recurrence of cardiovascular events or bleeding remains uncertain.

Use of anti-inflammatory agents after ACS may become a strategy to reduce the risk of recurrence among patients with persistently high concentrations of hsCRP after ACS. The inflammatory hypothesis of atherothrombosis was recently confirmed in the Canakinumab

* Corresponding author at: Department of Ambulatory Care and Community Medicine, University of Lausanne, Rue du Bugnon 44, CH-1011 Lausanne, Switzerland.
E-mail address: david.nanchen@chuv.ch (D. Nanchen).
[1] Contributed equally.

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Antiinflammatory Thrombosis Outcome Study (CANTOS) [11]. An anti-interleukin-1β antibody given to patients with a recent myocardial infarction and a high-sensitivity C-reactive protein (hsCRP) level of 2 mg/l or more led to a 15% reduction of cardiovascular events [12]. However, clinical decisions regarding initiation of preventive drugs after ACS are currently not based on in-hospital hsCRP levels. In the present study, we investigated the prognostic information of hsCRP levels measured in the acute phase of myocardial infarction.

2. Methods

2.1. Study population

The study population was part of the Special Program University Medicine-Acute Coronary Syndromes (SPUM-ACS) study, a prospective cohort study of consecutive patients hospitalized for ACS in Switzerland. The study was designed to identify new biomarkers pertinent to the pathobiology of ACS. Details regarding the methods of the SPUM-ACS study have been reported previously [13,14]. Briefly, all patients hospitalized for ACS in four university hospitals in Switzerland were invited to participate, except those with severe physical disability, inability to give consent due to dementia, and life expectancy of less than1 year for non-cardiac reasons. Inclusion criteria were age ≥ 18 years, a main diagnosis of ST-elevation myocardial infarction (STEMI) for patients presenting after pain onset, non-ST elevation myocardial infarction (NSTEMI), or unstable angina. Out of 2168 patients included from December 2009 to October 2012, 276 had missing values for hsCRP, and 28 patients were lost to follow-up at the one-year visit, leaving 1864 patients available for this analysis.

2.2. HsCRP measurement

HsCRP was determined at hospital admission for ACS in the first blood draw at the emergency department, or in blood drawn from the inguinal arterial sheath at coronary angiography prior to primary percutaneous coronary intervention. The interval between chest pain onset and blood draw was also recorded. Serum samples were centrifuged, aliquoted, stored at −80 °C and assayed for hsCRP in the Zurich Core Laboratory by the use of a latex enhanced immunoturbidimetric assay on a cobas c 501® autoanalyzer (Roche Diagnostics, Mannheim, Germany) with assay characteristics as reported by the manufacturer [15]. HsCRP concentrations were categorized in 4 groups, below 2.0 mg/l, 2.0 to 4.9 mg/l, 5.0 to 9.9 mg/l, and 10 mg/l or above, with below 2 mg/l as the referent group similar to previous studies [8].

2.3. Clinical outcomes

All-cause mortality and incidence of clinical events during the first year after hospital discharge were obtained by contacting patients by telephone at 30 days post-discharge, and again in a clinical face-to-face visit at 1 year post-ACS. Major adverse cardiovascular events (MACE) were defined as the occurrence of myocardial infarction, ischemic stroke, transient ischemic attack, or cerebrovascular or cardiovascular mortality. Clinically relevant bleeding events included all bleeding events that occurred during 1-year follow-up independently of severity. All endpoints used in this analysis were adjudicated by a panel of three certified cardiologists who served as independent experts blinded to hsCRP concentrations.

2.4. Covariables

Total cholesterol, HDL-cholesterol and triglyceride levels were processed locally using standardized dosage methods. LDL-cholesterol was calculated using the Friedewald formula. Medications that were taken prior to hospitalization or prescribed at discharge were collected by trained study nurses. Pre-existing cardiovascular disease was defined as a previous diagnosis of coronary heart disease, ischemic cerebrovascular disease or peripheral artery disease. Family history was based on patient reports of a coronary event in a first-degree relative younger than 55 years old for men, or younger than 60 years old for women. Education status was dichotomized as having graduated from high school or university or having a lower-level education. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or use of blood pressure lowering drugs. Smoking status was categorized into current, former and never-smokers. Diabetes was either self-reported or diagnosed by the use of anti-hyperglycemic medication, or a hemoglobin A1c of 6.5% or greater at admission. The Global Registry of Acute Coronary Events (GRACE 1.0) risk score was used to calculate 6-month predictions of mortality, and comprised age, heart rate, systolic blood pressure, initial serum creatinine, history of congestive heart failure, history of myocardial infarction, elevated cardiac markers (conventional troponins as per local laboratories), ST-segment depression and in-hospital revascularization [16].

2.5. Statistical analysis

We categorized patients according to hsCRP concentrations at hospital admission, and reported clinical characteristics in each four groups. ANOVA and chi-square tests were used for group comparisons. In sensitivity analyses, we used alternative categories for hsCRP, such as low hsCRP levels (<2 mg/l), moderate hsCRP (2 to 4.9 mg/l) or elevated hsCRP levels (5 mg/l or above), or equal to or greater than the study median value of 2.8 mg/l. We applied a log transformation for continuous measurement of hsCRP because of right-skewed distribution. We assessed the associations between eligibility for inflammation reduction and outcomes using age and sex-adjusted and multivariable Cox proportional hazard models. For the multivariate models, potential confounders were determined by biological plausibility. In the first model, we adjusted for age, sex, time from symptoms to blood draw ≥ 12 h, body mass index, current smoking, hypertension, diabetes mellitus, pre-existing cardiovascular disease, history of inflammatory disease, baseline LDL-cholesterol levels, and type of ACS STEMI vs others. In the second model, we further adjusted for left ventricular ejection fraction (LVEF) below 40%. In the final model, we further adjusted for results of the 6-months' GRACE 1.0 risk score. Subgroup analyses were conducted in men and women separately, smokers and former or non-smokers, patients with or without diabetes, type of ACS and across strata of age, BMI, GRACE score, Killip class, time from symptoms to blood draw (<6 h, 6–12 h and >12 h), or LVEF (at <30%, 30–45% and >45%). The significance of the multiplicative interaction term between hsCRP as a continuous variable and subgroups in the age and sex-adjusted model was reported.

To account for the inflammatory phase of ACS, we conducted sensitivity analyses excluding events that occurred within the first 30 days of follow-up and computed unadjusted Kaplan-Meier curves. All hypothesis tests were two-sided and the significance level was set at 5%. Statistical analyses were performed using STATA 14® (STATA Corp, College Station, TX, USA).

2.6. Ethics statement

The Medical Ethics Committee of each center (Lausanne, Geneva, Bern and Zurich) approved the study and all participants gave written informed consent to participate in the study.

3. Results

Overall, 1132 (60.7%) patients had hsCRP values of 2.0 mg/l or higher at the time of hospitalization for an ACS. Clinical characteristics of patients with an ACS with respect to hsCRP categories are reported in Table 1. Compared to patients with low levels of inflammation (<2 mg/l), patients with hsCRP levels above 2 mg/l were older, more frequently men, current smokers or diabetic, presented more frequently with NSTEMI, had higher numbers of coronary lesions treated during PCI, and higher GRACE risk scores for 6-month mortality. Comparisons of clinical management during hospitalization for ACS and after discharge are reported in Table 2. Acute revascularization with percutaneous coronary intervention and cardiac rehabilitation were performed less frequently among patients with hsCRP levels of 5 mg/l or higher as compared to patients with hsCRP values below 2 mg/l. One-year after discharge, high-dose statins were less frequently used among patients with high levels of inflammation during the acute phase of the ACS compared to patients with low levels of inflammation.

During the year following hospitalization for an ACS, 80 (4.3%) died, 67 (3.6%) patients had suffered a fatal or non-fatal myocardial infarction, 35 (1.9%) had experienced a fatal or non-fatal stroke or transient ischemic attack, and 151 (8.1%) had had a bleeding event. Unadjusted rates of cardiovascular events but not bleeding were increased among patients with hsCRP levels of 5 mg/l or above as compared to patients with hsCRP levels below 2 mg/l (Appendix Fig. 1). In a fully adjusted multivariable model, patients with hsCRP levels >2 to <5 mg/l, 5 to <10 mg/l, and 10 mg/l or above had an increased risk of MACE with multivariate adjusted hazard ratios (HR) of 1.63 (95% confidence interval (CI) 0.93–2.84), 2.80 (95% CI 1.58–4.96), and 2.23 (95% CI 1.28–3.88), respectively as compared to patients with hsCRP values below 2 mg/l (Table 3). There were no differences in bleeding risk between the four groups.

Stratified analyses performed for the risk of MACE associated with one unit increase in log hsCRP showed no effect modification in men or women, current smokers, patients with diabetes, type of ACS and across strata of age, time from symptoms to blood draw, BMI, GRACE score, Killip class or LVEF (Fig. 1). On the basis of whether the concentration of hsCRP was less than, equal to or greater than the median value of 2.8 mg/l, or on the basis of three categories of hsCRP, the association was similar for MACE in the age and sex-model as well as in the fully-adjusted multivariable models (Appendix Fig. 2). Using quartiles to stratify hsCRP levels yielded similar results (Appendix Fig. 2). In a

Table 1
Characteristics of patients with an acute coronary syndrome (ACS) and categorized by hsCRP values ($n = 1864$).

	hsCRP < 2.0 mg/l	hsCRP ≥2.0 and <5.0 mg/l	hsCRP ≥5.0 and <10.0 mg/l	hsCRP ≥10.0 mg/l	*p*-Value
Number	732	482	261	389	
Percentage	39.3	25.7	14.0	20.9	
hsCRP, mg/l	0.9 (0.5)	3.2 (0.9)	7.0 (1.4)	39.9 (39.7)	<**0.001**
Symptoms to blood draw ≥12 h ($n = 1821$)	271 (37.5)	246 (52.7)	141 (55.7)	268 (70.7)	<**0.001**
Demographics					
Age, years	62.8 (12.0)	63.1 (12.5)	63.8 (12.3)	66.9 (12.2)	<**0.001**
Female	131 (17.9)	118 (24.5)	63 (24.1)	87 (22.4)	**0.024**
Higher education[a] ($n = 1514$)	149 (24.5)	92 (23.2)	40 (19.0)	72 (24.2)	0.42
Smoking status ($n = 1833$)					
Never	267 (37.0)	139 (29.4)	66 (25.6)	104 (27.4)	<**0.001**
Former	209 (28.9)	123 (26.0)	78 (30.2)	127 (33.4)	
Current	246 (34.1)	211 (44.6)	114 (44.2)	149 (39.2)	
Elevated alcohol use[b] ($n = 1542$)	73 (11.8)	66 (16.5)	30 (13.7)	43 (14.0)	0.21
Comorbidities					
Hypertension[c]	335 (45.8)	197 (40.9)	103 (39.5)	131 (33.7)	**0.001**
Diabetes mellitus[d]	109 (14.9)	83 (17.2)	56 (21.5)	90 (23.1)	**0.003**
Pre-existing CVD[e]	193 (26.4)	105 (21.8)	78 (29.9)	121 (31.1)	**0.011**
Inflammatory disease	23 (3.1)	23 (4.8)	11 (4.2)	29 (7.5)	**0.013**
Objective measures					
Total cholesterol, mmol/l ($n = 1755$)	5.0 (1.2)	5.1 (1.2)	5.0 (1.4)	4.6 (1.1)	<**0.001**
LDL-cholesterol, mmol/l ($n = 1755$)	3.2 (1.1)	3.3 (1.1)	3.2 (1.2)	2.8 (1.0)	<**0.001**
HDL-cholesterol, mmol/l ($n = 1795$)	1.2 (0.3)	1.2 (0.4)	1.1 (0.4)	1.1 (0.3)	<**0.001**
Triglycerides, mmol/l ($n = 1806$)	1.3 (1.1)	1.3 (1.0)	1.6 (1.9)	1.3 (1.1)	**0.003**
Body mass index, kg/m[b] ($n = 1841$)	26.4 (3.8)	27.5 (4.4)	27.6 (4.5)	27.7 (4.6)	<**0.001**
eGFR, ml/min ($n = 1857$)	92.6 (24.1)	92.0 (28.3)	90.2 (29.0)	84.6 (31.0)	<**0.001**
Medication at admission					
Aspirin	229 (31.3)	136 (28.2)	88 (33.7)	15§ (38.8)	**0.008**
Statins	242 (33.1)	127 (26.3)	72 (27.6)	136 (35.0)	**0.014**
Anti-hypertensive drugs[f]	330 (45.1)	235 (48.8)	129 (49.4)	222 (57.1)	**0.002**
Immunosuppressive drugs	11 (1.5)	10 (2.1)	5 (1.9)	19 (4.9)	**0.004**
Type of ACS					
STEMI	427 (58.3)	243 (50.4)	128 (49.2)	176 (45.2)	<**0.001**
NSTEMI	265 (36.2)	216 (44.8)	123 (47.3)	206 (53.0)	<**0.001**
Unstable angina	40 (5.5)	22 (4.6)	9 (3.5)	7 (1.8)	**0.029**
Severity of ACS					
Killip class III or above	21 (2.9)	12 (2.5)	14 (5.4)	30 (7.7)	<**0.001**
LVEF < 40% ($n = 1648$)	65 (10.1)	57 (13.2)	31 (13.4)	68 (20.1)	<**0.001**
GRACE 1.0 score for 6-months mortality, points ($n = 1709$)[g]	131 (24)	133 (25)	134 (25)	142 (26)	<**0.001**
Severity of coronary lesions					
Two or more treated coronary lesions ($n = 1743$)	224 (32.2)	160 (35.1)	97 (39.9)	144 (41.4)	**0.014**
ACC/AHA classification grade B2 or C any lesion ($n = 1452$)	239 (42.0)	149 (39.2)	92 (44.2)	141 (47.8)	0.15

Data are given as number (percentage) or mean (standard deviation).
Abbreviations: hsCRP, high-sensitivity C-reactive protein; CVD, cardiovascular disease; CHD, coronary heart disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; GRACE, global registry of acute coronary events; TIMI, thrombolysis in myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction.
[a] Defined as a high school or university graduation or higher.
[b] Defined as >14 units alcohol/week.
[c] Defined as a systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or use of blood pressure lowering drugs.
[d] Based on patient self-reporting, use of anti-hyperglycemic medication/insulin or hemoglobin A1c of ≥6.5%.
[e] Defined as coronary heart disease, ischemic cerebrovascular disease or peripheral artery disease.
[f] Include angiotensin converting enzyme inhibitors, or angiotensin II receptor blockers, or beta-blockers, or calcium-channel blockers, or diuretics.
[g] Include age, heart rate, systolic blood pressure, initial serum creatinine, history of congestive heart failure, history of myocardial infarction, elevated cardiac markers (conventional troponins as per local laboratories), ST-segment depression and in-hospital revascularization.

further sensitivity analysis, after excluding events that occurred within the first 30 days of follow-up, unadjusted 1-year rates of MACE remained higher in patients with high levels of inflammation compared to those with low levels (Appendix Fig. 3).

4. Discussion

In this multicenter observational study, we found that patients with ACS and increased hsCRP levels at admission conferred an increased risk of MACE within one year after discharge compared with patients with ACS and low hsCRP concentrations. These findings were independent of the ACS severity or the time interval between symptom onset and blood draw. This increased risk was similar across strata of age, sex, smoking status, BMI, diabetes status, type of ACS, GRACE 1.0 score, Killip class, or LVEF. There was no association between hsCRP concentrations and the risk of bleeding after ACS.

Our results are in line with the hypothesis that atherothrombosis is an inflammation-driven process, as has already been described in numerous studies of patients without pre-existing cardiovascular disease [17,18] or with stable coronary artery disease [7,19]. In addition, our study provides new prognostic information for hsCRP concentrations measured in ACS patients at hospital admission. First, our results have strong external validity based on our study population derived from non-selected patients presenting with an ACS at either of the four centers; this is in contrast to other studies that were mainly designed as randomized controlled trials [20,21] or were monocentric [22,23]. Second, many studies examining the role of hsCRP among patients with pre-existing cardiovascular disease have focused on patients undergoing elective percutaneous coronary intervention or with stable coronary artery disease [24–31].

Third, the prognostic role of hsCRP was mainly examined for in-hospital outcomes [32] or all-cause mortality [22,33,34], with very few data on cardiovascular event recurrence or risk of bleeding [23,29,35].

Table 2
Comparison of clinical management of patients after an acute coronary syndrome and categorized by hsCRP values ($n = 1864$).

	hsCRP < 2.0 mg/l	hsCRP ≥2.0 and <5.0 mg/l	hsCRP ≥ 5.0 and <10.0 mg/l	hsCRP ≥ 10.0 mg/l	*p*-Value
Acute revascularization ($n = 1855$)					
PCI	671 (91.9)	435 (90.8)	228 (87.7)	325 (84.2)	<**0.001**
CABG	17 (2.3)	17 (3.5)	11 (4.2)	19 (4.9)	0.12
Lipid lowering drugs at discharge ($n = 1836$)					
Statins	716 (98.8)	473 (98.5)	251 (98.8)	362 (96.0)	**0.008**
High-dose statins[a]	518 (71.4)	348 (72.5)	185 (72.8)	244 (64.7)	**0.047**
Secondary prevention					
Cardiac rehabilitation ($n = 1837$)	493 (68.0)	328 (68.2)	157 (61.6)	223 (59.3)	**0.009**
P2Y12 inhibitors ($n = 1556$)[b]	617 (98.4)	411 (99.5)	213 (99.1)	294 (97.7)	0.17
Lipid lowering drugs one year after hospital discharge ($n = 1728$)					
Statins	667 (95.3)	433 (93.5)	212 (90.2)	305 (92.4)	**0.036**
High-dose statins[a]	431 (61.6)	277 (59.8)	134 (57.0)	164 (49.7)	**0.003**
Lipid values one year after hospital discharge ($n = 879$)					
LDL-cholesterol, mmol/l	2.2 (0.8)	2.3 (0.9)	2.2 (0.7)	2.3 (0.9)	0.19
LDL equal or below 1.8 mmol/l	129 (35.9)	83 (33.6)	46 (39.0)	50 (32.3)	0.64

Data are given as number (percentage), except for LDL-cholesterol given in mean (standard deviation).
Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LDL, low-density lipoprotein.
[a] High-dose statins included atorvastatin 40–80 mg or rosuvastatin 20–40 mg.
[b] Prescription of clopidogrel, prasugrel or ticagrelor in addition to aspirin after PCI with stent.

In our study, the large sample size, the comprehensive characterization of ACS patients included and the 1-year follow-up performed to assess clinical outcomes enabled us to provide prognostic information associated with hsCRP measured at hospital admission for an ACS, with and without adjustment for major prognostic factors such as the GRACE risk score and LVEF.

Previous reports have measured hsCRP at least 30 days after ACS to assess residual inflammation [21,36] or have examined pre-discharge hsCRP concentrations [37]. In ACS patients, hsCRP concentrations increase beginning 6 h after the onset of ischemia and peaking at approximately 48 h [9,38,39]. In our study, the median hsCRP level was greater in NSTEMI/UA patients compared with STEMI patients (3.4 vs 2.4 mg/l), which is in contrast to previous reports [38,39]. The elevated level of hsCRP in NSTEMI patients in our study is likely attributable to the longer time interval from symptom onset to blood draw (NSTEMI/UA: 13 h and 30 min vs. STEMI: 3 h and 35 min). Another explanation is that hsCRP elevation rather reflects the inflammatory response to the amount of ischemic and reperfusion myocardial injury than the inflammation elicited from plaque rupture/erosion at the culprit lesion [40]. Thus, intermittent occlusion with ensuing reperfusion myocardial injury may account for the observed high hsCRP levels in NSTEMI patients. We speculate that in our study, most STEMI patients with an acutely occluded epicardial coronary artery had blood draws before reperfusion therapy occurred. Thereby, sampling in these patients likely preceded the peak in hsCRP concentrations occurring after myocardial or reperfusion injury. These differences may have differentially affected hsCRP levels in patients with STEMI or NSTEMI. However, we could not find any effect modification when examining STEMI vs. NSTEMI patients, or those who had a longer time interval between symptoms and angioplasty, with regard to one-year clinical outcomes.

Recent data have demonstrated the beneficial effects of antibody-based interleukin-1β inhibition on cardiovascular outcome in high-risk patients after ACS [12]. Novel anti-inflammatory drugs are anticipated to further reduce the risk of recurrent events in patients with ACS in whom low levels of LDL-cholesterol have already been achieved using lipid-lowering therapies [41]. Prescription strategies for these drugs will need to specifically target adults most likely to benefit from inflammation reduction, such as patients with persistent elevation of hsCRP after ACS, and those with the largest potential of hsCRP reduction under treatment [11]. The benefit of systematically identifying patients with high levels of inflammation at the time of hospitalization for ACS in order to reduce subsequent cardiovascular events still needs to be demonstrated. Nevertheless, we found that elevated hsCRP concentrations are frequent at the time of ACS with a prevalence of 60% for hsCRP levels of 2 mg/l or higher. We further reported that hsCRP screening at the time of an ACS was able to identify patients at higher risk of cardiovascular recurrence, in addition to the severity of the ACS or quality of care. We also found no effect modification based on time interval between chest pain onset

Table 3
Risk of recurrent cardiovascular disease or bleeding in patients after acute coronary syndromes and categorized by hsCRP values ($n = 1864$).

	hsCRP < 2.0 mg/l	hsCRP ≥ 2.0 and <5.0 mg/l	hsCRP ≥ 5.0 and <10.0 mg/l	hsCRP ≥ 10.0 mg/l
Major adverse cardiovascular events				
Number of events/patients	36/732	33/482	30/261	52/389
Incidence rate, per 100 person-years	5.2	7.4	12.9	15.9
Age sex adjusted HR (95% CI)	1.00 (ref)	1.39 (0.86; 2.23)	2.35 (1.45; 3.81)	2.45 (1.60; 3.76)
Model 1-adjusted HR (95% CI)[a] ($n = 1695$)	1.00 (ref)	1.49 (0.90; 2.45)	2.22 (1.31; 3.75)	2.27 (1.40; 3.66)
Model 2-adjusted HR (95% CI)[b] ($n = 1500$)	1.00 (ref)	1.59 (0.94; 2.70)	2.40 (1.38; 4.18)	1.96 (1.15; 3.35)
Model 3-adjusted HR (95% CI)[c] ($n = 1436$)	1.00 (ref)	1.63 (0.93; 2.84)	2.80 (1.58; 4.96)	2.23 (1.28; 3.88)
Bleeding				
Number of events/patients	50/732	50/482	18/261	33/389
Incidence rate, per 100 person-years	6.6	4.2	2.3	3.2
Age sex adjusted HR (95% CI)	1.00 (ref)	1.48 (1.00; 2.19)	0.99 (0.58; 1.70)	1.13 (0.72; 1.75)
Model 1-adjusted HR (95% CI)[a] ($n = 1695$)	1.00 (ref)	1.43 (0.95; 2.16)	0.91 (0.51; 1.64)	1.10 (0.68; 1.77)
Model 2-adjusted HR (95% CI)[b] ($n = 1500$)	1.00 (ref)	1.50 (0.98; 2.29)	0.72 (0.37; 1.41)	0.95 (0.56; 1.60)
Model 3-adjusted HR (95% CI)[c] ($n = 1436$)	1.00 (ref)	1.46 (0.94; 2.27)	0.70 (0.35; 1.41)	0.95 (0.55; 1.62)

Abbreviations: HR, hazard ratio; CI, confidence interval; GRACE, global registry of acute coronary events; LDL, low-density lipoprotein; STEMI, ST-segment elevation myocardial infarction.
[a] Adjusted for age, sex, time from symptoms to blood draw ≥ 12 h, body mass index, current smoking, hypertension, diabetes mellitus, pre-existing cardiovascular disease, history of inflammatory disease, baseline LDL-cholesterol levels, and type of ACS STEMI vs others.
[b] Model 1 additionally adjusted for left ventricular ejection fraction below 40%.
[c] Model 2 additionally adjusted for 6-month GRACE 1.0 risk score results.

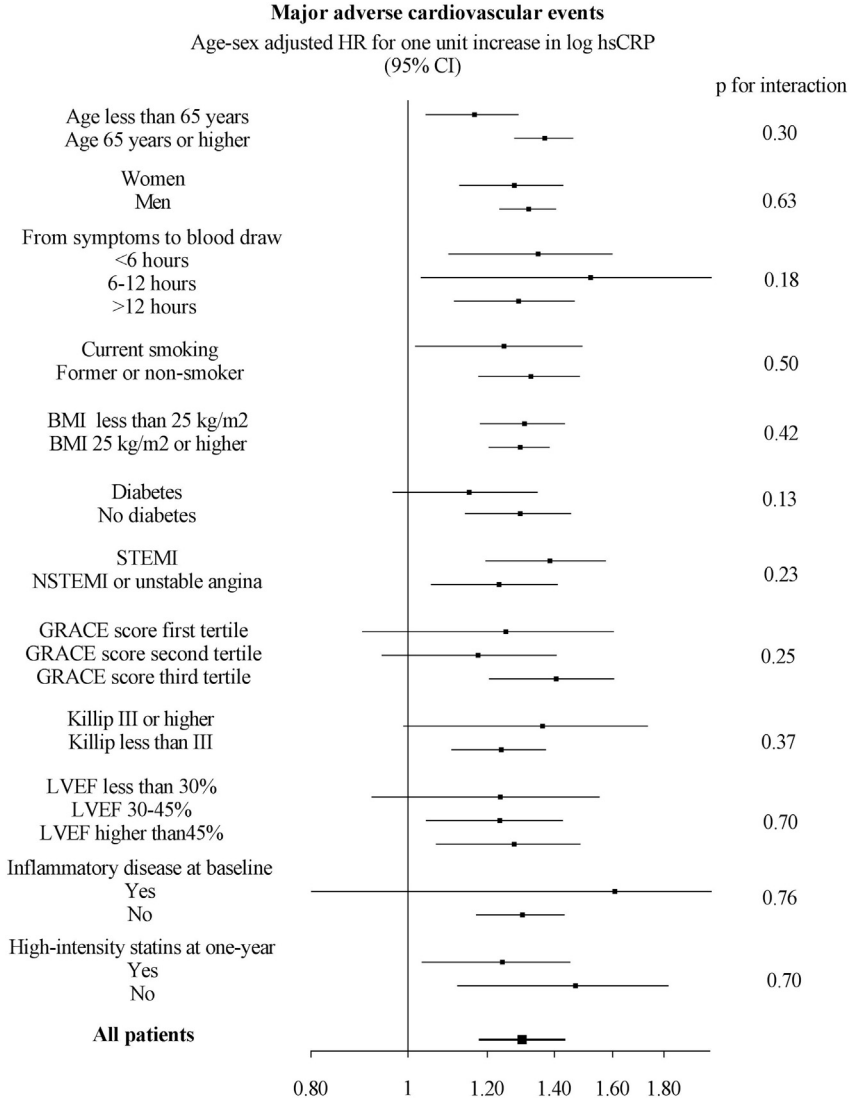

Fig. 1. Age and sex-adjusted hazard ratio (HR) for one unit of increase in log hsCRP for major adverse cardiovascular events, according to age, sex, time from symptoms to blood draw, smoking status, BMI, diabetes mellitus, ACS diagnosis, GRACE 1.0 score, Killip class, LVEF, baseline inflammatory disease, and use of high-intensity statins at one-year. Abbreviations: hsCRP, high-sensitivity C-reactive protein; BMI, body mass index; GRACE, global registry of acute coronary events; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction.

and blood draw in the catheterization lab, supporting the notion that early admission hsCRP cannot differentiate between pre-existing chronic inflammation and the peracute burst of inflammation induced by the ACS. Thus, it appears appealing to investigate the effects of anti-inflammatory strategies in the acute phase of myocardial infarction on outcome [10].

Our study has limitations. Despite the fact that we adjusted our estimate to major prognostic variables after ACS, including results of the GRACE risk score, residual confounding is possible. Nevertheless, we found an increased risk of MACE associated with elevated hsCRP levels after excluding events within the first 30 days after ACS. The consistency of these results indicates that hsCRP measured at the time of ACS is a valuable long-term marker of cardiovascular events. We were not able to obtain repeated measurements of hsCRP at a distance of the qualifying myocardial infarction to assess the prognostic information provided by changes in hsCRP concentrations shortly after an ACS. As the acute inflammatory mechanisms generated by plaque rupture may overestimate the residual inflammation [9], many of our patients with ACS and elevated hsCRP values may in fact have a low chronic inflammatory status. This misclassification may have underestimated the cardiovascular risk of patients with elevated hsCRP in the early phase of an ACS. Thus, patients with elevated hsCRP concentrations at the time of an ACS may be at even higher risk of cardiovascular events than what we found in our study if their level of inflammation remains persistently high after ACS.

5. Conclusions

Patients with elevated hsCRP concentrations at the time of their hospital admission for an ACS are at higher risk of cardiovascular event recurrence after discharge compared to patients with low systemic inflammation (hsCRP < 2 mg/l). Patients with a high level of inflammation in the acute phase of an ACS need to be identified to provide appropriate secondary prevention after discharge, and new anti-inflammatory approaches will need to be tested in the early phase of myocardial infarction.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.03.049.

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