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# Association between temporal changes in C-reactive protein levels and prognosis in patients with previous myocardial infarction - A report from the CHART-2 Study

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ABSTRACT

*Background:* Several studies have reported that C-reactive protein (CRP), an inflammatory biomarker, predicts cardiovascular events independently of low-density lipoprotein cholesterol levels. However, no study examined whether temporal changes in CRP levels are associated with clinical events in patients with previous myocardial infarction (MI).

*Methods and results:* We examined 2184 consecutive patients with previous MI and CRP data at baseline in the Chronic Heart Failure Registry and Analysis in the Tohoku district-2 (CHART-2) Study. During the median 6.4 years follow-up, 592 all-cause, 245 cardiovascular, and 273 non-cardiovascular deaths occurred. Patients with CRP ≥ 2.0 mg/L at baseline had significantly increased incidence of all-cause (hazard ratio (HR) 1.68, $P < 0.001$) and non-cardiovascular death (HR 1.86, $P < 0.001$), compared with those with CRP < 2.0 mg/L. Temporal changes in CRP levels were associated with prognosis; among patients with CRP ≥ 2.0 mg/L at baseline, those with CRP ≥ 2.0 mg/L at 1-year had significantly increased incidence of all-cause (HR 2.12, $P < 0.001$), cardiovascular (HR 2.31, $P < 0.001$), and non-cardiovascular death (HR 2.29, $P < 0.001$). Among patients with CRP < 2.0 mg/L at baseline, those with CRP ≥ 2.0 mg/L at 1-year had significantly increased incidence of all-cause (HR 1.76, $P < 0.001$) and cardiovascular death (HR 2.10, $P = 0.001$). These results remained significant after adjusted with the inverse probability of treatment weighted models using propensity sore. Furthermore, as compared with patients with CRP < 2.0 mg/L at both baseline and 1-year, those with CRP ≥ 2.0 mg/L at both baseline and 1-year had increased incidence of all-cause, cardiovascular, and non-cardiovascular death.

*Conclusions:* These results provide the evidence that temporal increases in CRP levels are associated with increased clinical events in patients with previous MI.

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## 1. Introduction

C-reactive protein (CRP), an acute-phase plasma protein produced by the liver, increases in non-specific response to most forms of tissue injury, inflammation, infection and neoplastic disease, and thus is a biomarker for systemic inflammation and tissue damage [1]. Elevated serum levels of CRP have been reported in patients with ischemic heart disease and heart failure (HF) [1,2]. CRP has been considered as a predictive marker of atherosclerosis and future cardiovascular events in healthy population and patients with acute coronary syndrome (ACS), regardless of smoking history, total cholesterol level, and blood pressure (BP) [3–6]. Several studies have reported that increased CRP level is an independent predictor of incident HF in a community-based elderly population [7]. In addition, the Emerging Risk Factors Collaboration have reported that CRP level has continuous associations with the risk of not only cardiovascular disease but death from several cancers, and lung disease in an individual participant meta-analysis [8]. Based on these findings, several studies have reported that anti-inflammatory therapy with statin or canakinumab were associated with improved cardiovascular and non-cardiovascular events in

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patients with elevated high-sensitivity CRP (hsCRP) levels [9–11]. To date, a number of studies have investigated the association of elevated or achieved CRP levels with clinical events, but few have reported on the factors related to increased CRP levels. Furthermore, impacts of elevated CRP levels have been examined basically on the one-point evaluation of CRP, and thus few have reported on the temporal changes in CRP levels with regard to their prognostic impacts. Thus, the aim of this study was to assess the association between the temporal changes in CRP levels and clinical events in patients with previous myocardial infarction (MI).

## 2. Methods

### 2.1. The CHART-2 Study

Details of the Chronic Heart Failure Registry and Analysis in the Tohoku district-2 (CHART-2) Study have been previously described [12–14]. Briefly, the CHART-2 Study is a multicenter, prospective, observational cohort study in Japan, designed to identify the characteristics, mortality and prognostic risks of a total of 10,219 stable patients aged ≥20 years with HF (N = 4876) and those with asymptomatic precursors of HF (N = 5343), according to the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines [15]. All patients were enrolled between October 2006 and March 2010 with a written informed consent at outpatient clinics or just before discharge at the Tohoku University Hospital or 23 affiliated hospitals in the Tohoku District, Japan. HF was diagnosed by experienced cardiologists using the criteria of the Framingham Heart Study [16]. There were no exclusion criteria in the CHART-2 Study except for age < 20 years. The study protocol was approved by the local ethics committees at each hospital. Baseline and follow-up data, including medical history, laboratory and echocardiography data, and clinical outcomes, were collected at the time of baseline and have been recorded annually thereafter by clinical research coordinators. Follow-up by reviewing medical records, mail surveys, and telephone interviews were conducted by clinical research coordinators at least once a year.

### 2.2. Study design

The study flowchart is shown in eFig. 1. Among 10,219 patients in the CHART-2 Study, after excluding 7085 patients without previous MI, 940 without CRP data at baseline, and 10 without sufficient data, we finally enrolled 2184 consecutive patients. We initially compared the incidence of clinical events among 2 groups divided with a cutoff CRP 2.0 mg/L at baseline (eFig. 1). Then, after excluding patients without CRP data at 1-year, and those died within a year after enrollment, we compared the incidence of clinical events among each of the 2 groups stratified with a cutoff CRP 2.0 mg/L at baseline and at 1-year, respectively (eFig. 1).

### 2.3. Study outcome

The study outcomes were all-cause death and mode of death. For study patients, only the main mode of death was used. All clinical events were reviewed and assigned according to consensus of at least 2 independent physicians from the members of the Tohoku Heart Failure Association (Supplementary Appendix) after reviewing case reports, death certificates, and medical records provided by the investigators.

### 2.4. Statistical analysis

All continuous variables are described as mean (standard deviation) or median (interquartile range). All categorical variables are described as frequency (percentage). To compare 2 groups, Welch's *t*-test or Wilcoxon rank sum test for continuous variables and Pearson's chi-squared test for categorical variables were used. Multiple logistic regression analysis was used to determine the related factors of CRP levels ≥ 2.0 mg/L at baseline, and those of CRP levels < 2.0 mg/L at baseline and CRP levels ≥ 2.0 mg/L at 1-year, and those of CRP levels ≥ 2.0 mg/L at both baseline and at 1-year. To examine the relationship between CRP levels at baseline and all time-to-event outcomes, and the relationship between 1-year transition of CRP level and all time-to-event outcomes after 1-year, Kaplan-Meier analysis, log-rank tests, and Cox proportional hazard models were used. To adjust for confounding effects and differences in the patient background between the 2 groups, the propensity score (PS) matching method and the inverse probability of treatment weighted (IPTW) using PS were used [17]. A PS was estimated by logistic regression model with 26 baseline variables, including age, sex, body mass index (BMI), systolic BP, smoking, hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, atrial fibrillation (AF), stroke, HF admission, cancer, anemia, chronic kidney disease (CKD), low-density lipoprotein cholesterol (LDL-C), brain natriuretic peptide (BNP), angiotensin converting enzyme inhibitor (ACE—I) or angiotensin II receptor blocker (ARB), β-blocker, diuretic, aldosterone antagonist, antiplatelet, statin, nitrate, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). The caliper for the PS-matching was set to be 1% of the standard deviation of PS. To assess discrimination in logistic regression to estimate PS, the area under the receiver operating characteristic (ROC) curve (AUC) and the Hosmer-Lemeshow goodness of fit test were evaluated; AUC 0.648, P = 0.703, for patients with CRP < 2.0 mg/L vs. ≥2.0 mg/L at baseline among the all patients, AUC 0.675, P = 0.902, for patients with CRP < 2.0 mg/L vs. ≥2.0 mg/L at 1-year among those with CRP < 2.0 mg/L at baseline, and AUC 0.696, P = 0.554, for patients with CRP < 2.0 mg/L vs. ≥2.0 mg/L at 1-year among those with CRP ≥ 2.0 mg/L at baseline. Cox proportional hazard models were used to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs). In addition, in order to directly compare the 4 groups stratified with a cutoff CRP levels ≥ 2.0 mg/L at baseline and 1-year, we used the multiple Cox proportional hazard models. The covariates that may have potentially influenced outcomes in these analyses included the following items; age, sex, BMI, systolic BP, diastolic BP, heart rate, New York Heart Association (NYHA) class III/IV, smoking, hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, AF, stroke, HF admission, cancer, anemia, CKD, hemoglobin A1c (HbA1c), BNP, LDL-C, left ventricular ejection fraction (LVEF), left ventricular dimension at end-diastole (LVDd), left atrial diameter (LAD), ACE-I/ARB, β-blocker, Ca channel blocker, diuretics, aldosterone antagonists, antiplatelet, statin, nitrate, PCI, and CABG. Anemia was defined as hemoglobin <12 g/dL in female and <13 g/dL in male, following the World Health Organization definition [18]. CKD was diagnosed when estimated glomerular filtration rate (eGFR) was <60 ml/min/1.73 $m^2$, which was calculated using the formula for Japanese individuals [19]. Statistical computing software, R version 3.4.3, was used for all statistical analysis [20]. P < 0.05 was considered to be statistically significant.

## 3. Results

### 3.1. Patient characteristics

In this cohort, mean age was 68.8 years and male patients accounted for 81.2%. Baseline characteristics of the overall and PS-matched cohorts divided by a cutoff CRP 2.0 mg/L at baseline are shown in eTable 1. There were significant differences in several variables in the total cohort, but not in the PS-matched cohort. Patients with CRP ≥ 2.0 mg/L at baseline, as compared with those with CRP < 2.0 mg/L, had higher age, higher heart rate, more enlarged LAD, higher levels of HbA1c and BNP, lower diastolic BP, more decreased LVEF and eGFR, lower levels of hemoglobin, and higher prevalence of NYHA class III/IV, smoking and HF admission history, and were more frequently treated with diuretic and less frequently with antiplatelet and statin. Prevalences of male sex, hypertension, diabetes, dyslipidemia, AF, stroke and cancer were comparable among the two groups. In addition, prescription rates of ACE-I/ARB, β-blocker, Ca channel blocker, aldosterone antagonist, and nitrate, and the prevalence of previous PCI and CABG did not differ among the 2 groups (eTable 1). Baseline characteristics were comparable between the 2 groups in general, with minimal standardized difference scores in all variables in the PS-matched cohort (eTable 1). Tables 1A, 1B show the baseline characteristics of patients in the 4 groups according to cutoff CRP 2.0 mg/L at baseline and 1-year. Among the patients with CRP < 2.0 mg/L at baseline, those with CRP ≥ 2.0 mg/L at 1-year, as compared with those with CRP < 2.0 mg/L at 1-year, were older and had higher levels of LDL-C and BNP, lower eGFR, higher prevalence of AF and higher prescription rates of diuretics (Table 1A). Meanwhile, among the patients with CRP ≥ 2.0 mg/L at baseline, those with CRP ≥ 2.0 mg/L at 1-year, as compared with those with CRP < 2.0 mg/L, had higher age, systolic BP and heart rate, higher levels of LDL-C and BNP, lower eGFR, higher prevalences of hypertension, hyperuricemia, AF, HF admission and cancer, a higher prescription rate of Ca channel blocker, and a lower prescription rate of statin (Table 1B). In the PS-matched cohort, baseline characteristics were comparable between the 2 groups in general (Tables 1A, 1B).

### 3.2. Factors related to CRP levels

eTable 2A shows the factors associated with CRP levels ≥ 2.0 mg/L at baseline. BMI, heart rate, smoking, anemia, BNP and diuretics were positively associated with an increase in CRP at baseline, while β-blocker and statin negatively (eTable 2A). eTables 2B, 2C show the factors associated with emersion and or sustainment of CRP elevation. Diastolic BP, AF, anemia, LDL-C, diuretics and antiplatelet were positively associated with an emersion of CRP elevation from baseline to 1-year (from CRP < 2.0 mg/L to ≥2.0 mg/L), while LAD negatively (eTable 2B). On the other hand, age, heart rate, smoking, hyperuricemia, HF admission, cancer, and Ca channel blocker were positively

**Table 1A**
Clinical characteristics of patients with previous MI by changes in CRP levels (baseline CRP < 2.0 mg/L).

| | Total cohort | | | PS-matched cohort | | | |
|---|---|---|---|---|---|---|---|
| | CRP < 2.0 mg/L (baseline) | | P value | CRP < 2.0 mg/L (baseline) | | P value | Standardized difference |
| | CRP < 2.0 mg/L (1-year) (N = 660) | CRP ≥ 2.0 mg/L (1-year) (N = 210) | | CRP < 2.0 mg/L (1-year) (N = 155) | CRP ≥ 2.0 mg/L (1-year) (N = 155) | | |
| Age, mean (SD), y | 67.7 (11.4) | 70.1 (10.7) | 0.005 | 68.9 (10.2) | 68.9 (11.2) | 0.954 | −0.007 |
| Male sex, no. (%) | 529 (80.2) | 169 (80.5) | 0.997 | 124 (80.0) | 128 (82.6) | 0.662 | 0.066 |
| BMI, mean (SD), kg/m$^2$ | 24.0 (3.2) | 24.3 (3.3) | 0.196 | 24.6 (3.0) | 24.3 (3.3) | 0.458 | −0.084 |
| Systolic BP, mean (SD), mmHg | 127.9 (18.1) | 130.6 (19.4) | 0.076 | 129.0 (18.6) | 129.2 (18.3) | 0.924 | 0.011 |
| Diastolic BP, mean (SD), mmHg | 73.9 (11.0) | 74.7 (11.8) | 0.414 | 74.5 (12.0) | 74.3 (11.1) | 0.841 | −0.023 |
| Heart rate, mean (SD), /min | 69.5 (12.8) | 69.9 (12.6) | 0.707 | 69.2 (13.7) | 69.9 (12.7) | 0.655 | 0.051 |
| NYHA class III/IV, no. (%) | 25 (3.8) | 10 (4.8) | 0.652 | 6 (3.9) | 6 (3.9) | 1.000 | 0.001 |
| Smoking, no. (%) | 334 (53.8) | 108 (55.1) | 0.810 | 82 (52.9) | 88 (56.8) | 0.568 | 0.078 |
| Medical history | | | | | | | |
| Hypertension, no. (%) | 605 (91.8) | 198 (94.3) | 0.302 | 146 (94.2) | 145 (93.5) | >0.99 | −0.027 |
| Diabetes mellitus, no. (%) | 293 (44.4) | 97 (46.2) | 0.707 | 71 (45.8) | 73 (47.1) | 0.909 | 0.026 |
| Dyslipidemia, no. (%) | 611 (92.6) | 200 (95.2) | 0.238 | 151 (97.4) | 148 (95.5) | 0.541 | −0.105 |
| Hyperuricemia, no. (%) | 301 (45.6) | 112 (53.3) | 0.061 | 76 (49.0) | 83 (53.5) | 0.495 | 0.090 |
| Atrial fibrillation, no. (%) | 95 (14.4) | 50 (23.8) | 0.002 | 32 (20.6) | 32 (20.6) | 1.000 | 0.000 |
| Stroke, no. (%) | 124 (18.8) | 51 (24.3) | 0.103 | 32 (20.6) | 32 (20.6) | 1.000 | 0.000 |
| HF admission, no. (%) | 127 (19.2) | 53 (25.2) | 0.077 | 34 (21.9) | 39 (25.2) | 0.593 | 0.076 |
| Cancer, no. (%) | 94 (14.2) | 29 (13.8) | 0.966 | 16 (10.3) | 19 (12.3) | 0.720 | 0.061 |
| Echocardiography data | | | | | | | |
| LVEF, mean (SD), % | 57.6 (13.4) | 55.5 (13.9) | 0.067 | 56.5 (12.9) | 55.3 (14.3) | 0.424 | −0.093 |
| LVDd, mean (SD), mm | 52.1 (7.4) | 53.0 (8.6) | 0.191 | 53.2 (7.6) | 52.9 (9.0) | 0.767 | −0.034 |
| LAD, mean (SD), mm | 39.6 (6.4) | 40.1 (7.3) | 0.380 | 40.8 (6.9) | 39.3 (6.9) | 0.063 | −0.217 |
| Laboratory data | | | | | | | |
| Hemoglobin, mean (SD), g/dL | 13.6 (1.8) | 13.4 (1.9) | 0.159 | 13.6 (1.7) | 13.5 (1.8) | 0.468 | −0.082 |
| eGFR, mean (SD), mL/min/1.73m$^2$ | 63.7 (18.7) | 59.6 (19.3) | 0.008 | 63.7 (20.1) | 60.5 (18.3) | 0.146 | −0.166 |
| HbA1c, mean (SD), % | 6.3 (0.9) | 6.3 (0.8) | 0.518 | 6.3 (0.8) | 6.3 (0.8) | 0.761 | 0.036 |
| LDL-C, mean (SD), mg/dL | 99.3 (27.6) | 105.7 (30.4) | 0.007 | 103.6 (29.1) | 104.0 (28.1) | 0.900 | 0.014 |
| BNP, median (IQR), pg/mL | 53.7 (25.0, 126.7) | 69.2 (29.6, 186.0) | 0.016 | 60.9 (26.4, 128.1) | 58.8 (27.7, 147.0) | 0.770 | 0.022 |
| Medical treatment | | | | | | | |
| ACE-I/ARB, no. (%) | 514 (77.9) | 154 (73.3) | 0.206 | 123 (79.4) | 116 (74.8) | 0.418 | −0.108 |
| β-Blocker, no. (%) | 338 (51.2) | 121 (57.6) | 0.123 | 91 (58.7) | 89 (57.4) | 0.908 | −0.026 |
| Ca channel blocker, no. (%) | 270 (40.9) | 98 (46.7) | 0.164 | 65 (41.9) | 69 (44.5) | 0.731 | 0.052 |
| Diuretic, no. (%) | 139 (21.1) | 70 (33.3) | <0.001 | 49 (31.6) | 49 (31.6) | 1.000 | 0.000 |
| Aldosterone antagonist, no. (%) | 77 (11.7) | 25 (11.9) | >0.99 | 15 (9.7) | 21 (13.5) | 0.376 | 0.121 |
| Antiplatelet, no. (%) | 610 (92.4) | 200 (95.2) | 0.213 | 150 (96.8) | 148 (95.5) | 0.770 | −0.067 |
| Statin, no. (%) | 472 (71.5) | 147 (70.0) | 0.738 | 117 (75.5) | 113 (72.9) | 0.697 | −0.059 |
| Nitrates, no. (%) | 272 (41.2) | 95 (45.2) | 0.343 | 67 (43.2) | 73 (47.1) | 0.568 | 0.078 |
| PCI, no. (%) | 509 (77.1) | 168 (77.2) | 0.436 | 123 (79.4) | 120 (77.4) | 0.783 | −0.047 |
| CABG, no. (%) | 89 (13.5) | 30 (14.3) | 0.864 | 17 (11.0) | 21 (13.5) | 0.604 | 0.079 |

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HF, heart failure; IQR, interquartile range; LAD, left atrial diameter; LDL-C, low-density lipoprotein cholesterol; LVDd, left ventricular dimension diastolic; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PS, propensity score; SD, standard deviation.

associated with sustained elevation of CRP (from CRP ≥ 2.0 mg/L to ≥2.0 mg/L), while aldosterone antagonist and statin negatively (eTable 2C).

### 3.3. Prognostic impact of CRP levels at baseline in post-MI patients

During the median 6.4 years follow-up (12,726 person-years), 592 all-cause deaths, 245 cardiovascular deaths, and 273 non-cardiovascular deaths occurred. Patients with CRP ≥ 2.0 mg/L at baseline had significantly increased incidence of all-cause death, cardiovascular death, and non-cardiovascular death, compared with those with CRP < 2.0 mg/L (Fig. 1, eFig. 2). Analyses with PS matching and IPTW with PS showed that patients with CRP ≥ 2.0 mg/L at baseline had significantly increased risks of all-cause death (HR 1.25, 95%CI 1.01–1.54, P = 0.039, and HR 1.14, 95%CI 1.00–1.30, P = 0.046, respectively) and non-cardiovascular death (HR 1.44, 95%CI 1.06–1.95, P = 0.019, and HR 1.44, 95%CI 1.019–1.75, P < 0.001, respectively), but not those of cardiovascular death, HF death, sudden death, or cancer death after adjustment of clinical backgrounds (eFig. 2).

### 3.4. Temporal changes in CRP levels and outcomes

Among patients with CRP < 2.0 mg/L at baseline, those with CRP ≥ 2.0 mg/L at 1-year had significantly increased incidence of all-cause death (HR 1.76, 95%CI 1.31–2.36, P < 0.001) and cardiovascular death (HR 2.10, 95%CI 1.33–3.30, P = 0.001), but not that of non-cardiovascular death, as compared with those with CRP < 2.0 mg/L at 1-year (Figs. 2A, 3A). These results remained unchanged after adjustment with clinical backgrounds in the IPTW models using PS (Fig. 3A). In contrast, among patients with CRP ≥ 2.0 mg/L at baseline, those with CRP ≥ 2.0 mg/L at 1-year had significantly increased incidence of not only all-cause death (HR 2.12, 95%CI 1.60–2.80, P < 0.001) and cardiovascular death (HR 2.31, 95%CI 1.48–3.61, P < 0.001), but also that of non-cardiovascular death, HF death, sudden death, and cancer death, as compared with those with CRP < 2.0 mg/L at 1-year (Figs. 2B, 3B). After adjustment with clinical backgrounds in the IPTW models using PS, patients with CRP ≥ 2.0 mg/L at both baseline and 1-year had still significantly higher incidences of all-cause, cardiovascular, non-cardiovascular, HF, and sudden deaths, as compared with those with CRP ≥ 2.0 mg/L at baseline and CRP < 2.0 mg/L at 1-year (Fig. 3B). Direct comparison of the 4 groups stratified with a cutoff CRP ≥ 2.0 mg/L at

**Table 1B**
Clinical characteristics of patients with previous MI by changes in CRP levels (baseline CRP ≥ 2.0 mg/L).

| | Total cohort | | | PS-matched cohort | | | |
|---|---|---|---|---|---|---|---|
| | CRP ≥ 2.0 mg/L (baseline) | | P value | CRP ≥ 2.0 mg/L (baseline) | | P value | Standardized difference |
| | CRP < 2.0 mg/L (1-year) (N = 379) | CRP ≥ 2.0 mg/L (1-year) (N = 401) | | CRP < 2.0 mg/L (1-year) (N = 222) | CRP ≥ 2.0 mg/L (1-year) (N = 222) | | |
| Age, mean (SD), y | 66.6 (11.3) | 70.6 (9.9) | <0.001 | 68.1 (10.0) | 68.2 (10.1) | 0.959 | 0.005 |
| Male sex, no. (%) | 309 (81.5) | 332 (82.8) | 0.714 | 181 (81.5) | 185 (83.3) | 0.708 | 0.047 |
| BMI, mean (SD), kg/m$^2$ | 24.3 (3.2) | 24.1 (3.5) | 0.381 | 24.2 (3.2) | 24.3 (3.6) | 0.664 | 0.041 |
| Systolic BP, mean (SD), mmHg | 125.2 (18.9) | 130.6 (19.2) | <0.001 | 126.7 (18.7) | 126.4 (17.4) | 0.867 | −0.016 |
| Diastolic BP, mean (SD), mmHg | 72.6 (11.2) | 73.7 (11.8) | 0.189 | 73.1 (11.5) | 73.5 (11.1) | 0.694 | 0.037 |
| Heart rate, mean (SD), /min | 70.5 (13.5) | 72.6 (13.6) | 0.039 | 70.0 (13.3) | 72.5 (13.2) | 0.053 | 0.185 |
| NYHA class III/IV, no. (%) | 18 (4.8) | 22 (5.5) | 0.755 | 14 (6.3) | 9 (4.1) | 0.392 | −0.102 |
| Smoking, no. (%) | 211 (58.8) | 245 (64.5) | 0.129 | 139 (62.6) | 133 (59.9) | 0.626 | −0.056 |
| Medical history | | | | | | | |
| Hypertension, no. (%) | 340 (89.7) | 382 (95.3) | 0.005 | 205 (92.3) | 208 (93.7) | 0.710 | 0.053 |
| Diabetes mellitus, no. (%) | 173 (45.6) | 196 (48.9) | 0.406 | 110 (49.5) | 109 (49.1) | >0.99 | −0.009 |
| Dyslipidemia, no. (%) | 353 (93.1) | 371 (92.5) | 0.844 | 208 (93.7) | 212 (95.5) | 0.530 | 0.080 |
| Hyperuricemia, no. (%) | 171 (45.1) | 227 (56.6) | 0.002 | 116 (52.3) | 129 (58.1) | 0.252 | 0.118 |
| Atrial fibrillation, no. (%) | 59 (15.6) | 86 (21.4) | 0.044 | 38 (17.1) | 34 (15.3) | 0.700 | −0.049 |
| Stroke, no. (%) | 66 (17.4) | 85 (21.2) | 0.213 | 43 (19.4) | 43 (19.4) | 1.000 | 0.000 |
| HF admission, no. (%) | 79 (20.8) | 128 (31.9) | 0.001 | 63 (28.4) | 57 (25.7) | 0.593 | −0.061 |
| Cancer, no. (%) | 34 (9.0) | 70 (17.5) | 0.001 | 27 (12.2) | 21 (9.5) | 0.445 | −0.087 |
| Echocardiography data | | | | | | | |
| LVEF, mean (SD), % | 56.5 (13.4) | 54.6 (14.0) | 0.066 | 56.1 (14.2) | 53.7 (14.6) | 0.079 | −0.171 |
| LVDd, mean (SD), mm | 52.3 (8.1) | 53.0 (8.3) | 0.259 | 52.8 (8.8) | 53.3 (8.2) | 0.538 | 0.060 |
| LAD, mean (SD), mm | 39.9 (6.7) | 40.6 (7.4) | 0.168 | 40.6 (6.9) | 40.0 (7.3) | 0.406 | −0.082 |
| Laboratory data | | | | | | | |
| Hemoglobin, mean (SD), g/dL | 13.1 (1.7) | 13.0 (1.8) | 0.263 | 13.0 (1.8) | 13.2 (1.8) | 0.467 | 0.069 |
| eGFR, mean (SD), mL/min/1.73m$^2$ | 62.7 (20.3) | 56.1 (21.1) | <0.001 | 60.2 (20.8) | 59.1 (20.4) | 0.563 | −0.055 |
| HbA1c, mean (SD), % | 6.3 (1.0) | 6.5 (1.1) | 0.077 | 6.4 (1.0) | 6.5 (1.2) | 0.329 | 0.099 |
| LDL-C, mean (SD), mg/dL | 99.7 (29.5) | 104.1 (29.2) | 0.040 | 100.0 (28.9) | 100.8 (29.1) | 0.763 | 0.029 |
| BNP, median (IQR), pg/mL | 72.7 (36.8, 174.6) | 98.3 (40.8, 222.0) | 0.039 | 72.5 (38.0, 169.0) | 78.0 (37.7, 201.8) | 0.512 | 0.018 |
| Medical treatment | | | | | | | |
| ACE-I/ARB, no. (%) | 306 (80.7) | 308 (76.8) | 0.210 | 171 (77.0) | 176 (79.3) | 0.646 | 0.055 |
| β-Blocker, no. (%) | 177 (46.7) | 195 (48.6) | 0.641 | 114 (51.4) | 117 (52.7) | 0.849 | 0.027 |
| Ca channel blocker, no. (%) | 140 (36.9) | 191 (47.6) | 0.003 | 88 (39.6) | 95 (42.8) | 0.563 | 0.064 |
| Diuretic, no. (%) | 103 (27.2) | 132 (32.9) | 0.095 | 74 (33.3) | 68 (30.6) | 0.611 | −0.058 |
| Aldosterone antagonist, no. (%) | 46 (12.1) | 47 (11.7) | 0.945 | 29 (13.1) | 25 (11.3) | 0.663 | −0.055 |
| Antiplatelet, no. (%) | 349 (92.1) | 360 (89.8) | 0.319 | 201 (90.5) | 204 (91.9) | 0.738 | 0.048 |
| Statin, no. (%) | 272 (71.8) | 230 (57.4) | <0.001 | 151 (68.0) | 153 (68.9) | 0.919 | 0.019 |
| Nitrates, no. (%) | 163 (43.0) | 169 (42.1) | 0.864 | 101 (45.5) | 93 (41.9) | 0.503 | −0.073 |
| PCI, no. (%) | 308 (81.3) | 314 (78.3) | 0.347 | 174 (78.4) | 171 (77.0) | 0.820 | −0.032 |
| CABG, no. (%) | 49 (12.9) | 60 (15.0) | 0.474 | 37 (16.7) | 33 (14.9) | 0.696 | −0.049 |

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HF, heart failure; IQR, interquartile range; LAD, left atrial diameter; LDL-C, low-density lipoprotein cholesterol; LVDd, left ventricular dimension diastolic; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PS, propensity score; SD, standard deviation.

baseline and 1-year showed that CRP ≥ 2.0 mg/L at both baseline and 1-year was associated with increased incidence of all-cause, cardiovascular, non-cardiovascular, and HF deaths, while CRP < 2.0 mg/L at baseline but ≥2.0 mg/L at 1-year with increased incidence of all-cause and cardiovascular death, but not with non-cardiovascular death or HF death (eFig. 3).

## 4. Discussion

The present study provides the first evidence that temporal increases in CRP levels are associated with increased clinical events in patients with previous MI. The results clearly demonstrate that elevated CRP levels were associated with worse outcomes, particularly when it persisted. Importantly, however, even among the patients with increased CRP levels at baseline, those who had decreased CRP levels at 1-year had better prognosis, while those with increased CRP levels at 1-year had worse prognosis among those with low CRP levels at baseline. These results indicate that sustained or worsening inflammation as evidenced by increased CRP are significantly associated with clinical events in patients with previous MI.

### *4.1. Association of persistent inflammation and cardiovascular events*

To date, only a few prospective large-scale cohort studies have examined the relationship between CRP levels and cardiovascular events in cardiovascular patients. Yoshinaga et al. examined 12,211 cardiovascular patients aged ≥ 18 years who were hospitalized to an emergency department by ambulance and found that elevated hsCRP level was a significant risk of in-hospital mortality [21]. Shiba et al. reported that, as compared with high CRP level at baseline, increase in CRP at late-phase (8 to 12 months after stenting) was more powerful predictor of late cardiovascular events in 1234 patients after drug eluting stents (DES) implantation, indicating the role of later inflammation in patients with DES implantation [22]. However, although these studies underlined the importance of assessment of inflammation in cardiovascular patients, few studies have examined the significance of serial assessments of inflammation in those patients. In the present study, using the annual database of CHART-2 Study [12–14], we were able to examine the prognostic impact of inflammation (as defined as serum CRP ≥ 2.0 mg/L) in patients with previous MI. The results showed that patients with CRP ≥ 2.0 mg/L at baseline have significantly higher risk of all-cause and non-cardiovascular deaths, and particularly when

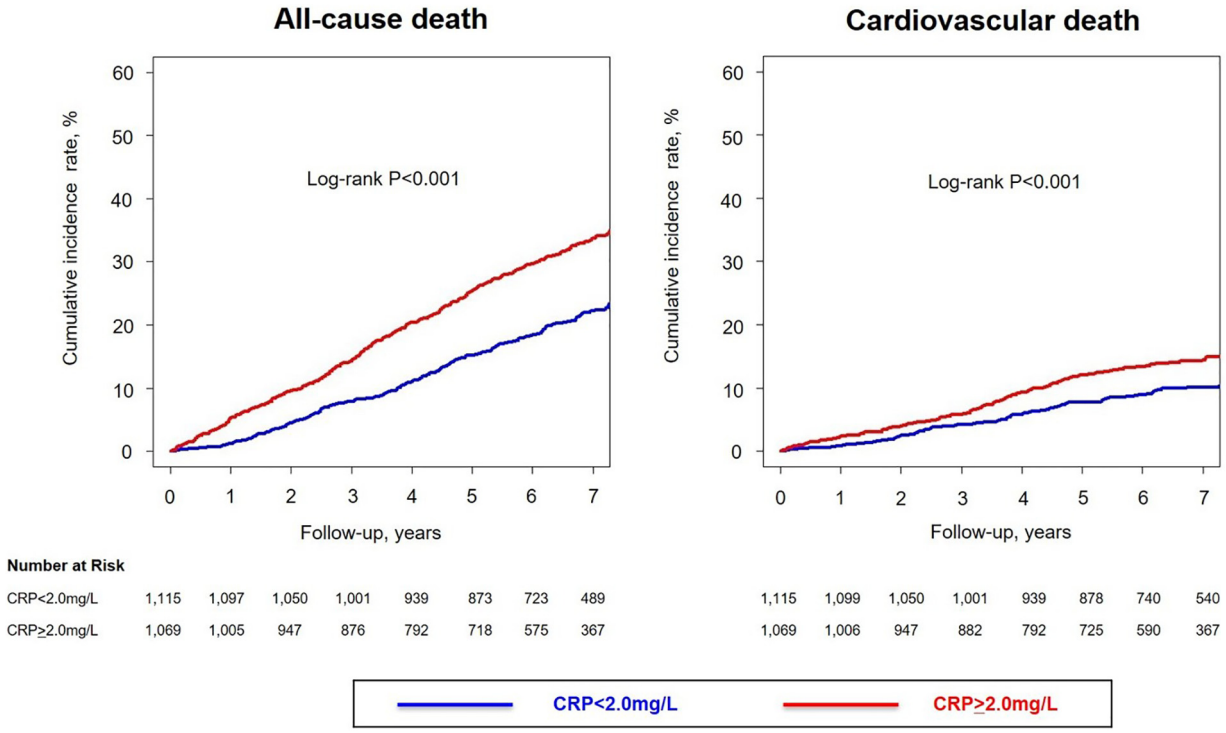



**Fig. 1.** Incidence curves for all-cause and cardiovascular death by CRP levels at baseline. Abbreviations: CRP, C-reactive protein.

inflammation (CRP ≥ 2.0 mg/L) persisted at 1-year, they have increased incidence of cardiovascular, all-cause, and non-cardiovascular deaths, thereafter. These results indicate that inflammation, particularly persistent one, is associated with increased mortality. Furthermore, the present study also showed that even among the patients with low CRP levels at baseline, those who had CRP ≥ 2.0 mg/L at 1-year had increased risk of all-cause and cardiovascular death. These lines of evidence underline the prognostic impact of persistent inflammation and importance of repeated evaluation of inflammation in patients with previous MI.

### *4.2. Factors related to elevation of CRP levels*

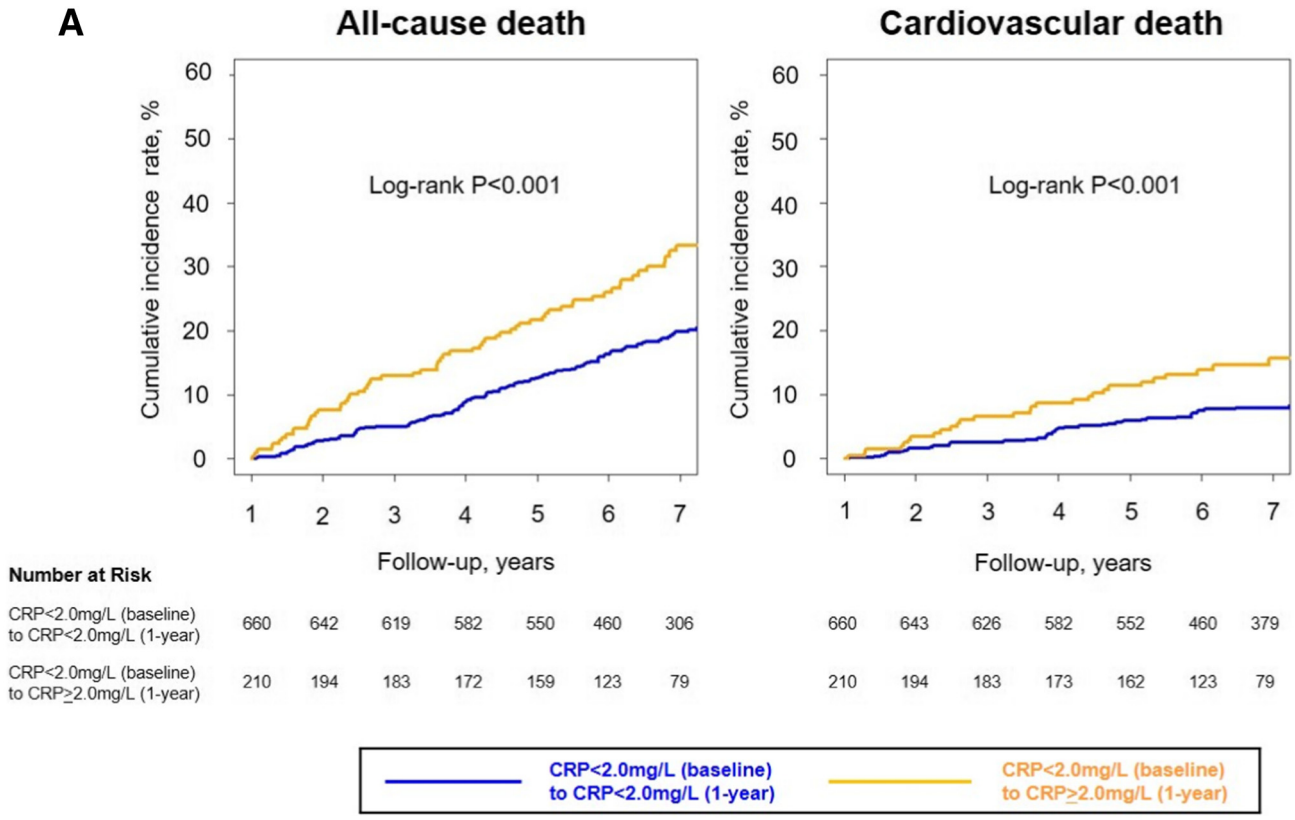
In the present study, we examined the factors related to inflammation at baseline and 1-year. The results showed that BMI, heart rate, smoking, anemia, BNP, and diuretic use were positively associated with inflammation (defined as CRP ≥ 2.0 mg/L at baseline), while β-blocker and statin use was negatively associated. Qintar et al. examined the prevalence and predictors of elevated hsCRP in post-MI patients and found that patients with elevated hsCRP at 30 days were characterized by higher age, female sex, obesity, diabetes, hypertension, higher LDL-C levels on admission, smoking history, and financial difficulties, and furthermore, baseline hsCRP ≥ 2 mg/L was significantly associated with elevated hsCRP at follow-up [23]. Although the factors related to elevated CRP in the present study were different from those found by Qintar et al. [23], the only common factor was smoking history, indicating an importance of smoking cessation in the management of post-MI patients. We also noted that patients with persistent elevation of CRP levels had higher incidence of non-cardiovascular death as compared with those without CRP elevation, which was mostly attributable to increased deaths due to cancer and infection. It has been shown that chronic inflammation predisposes individuals to various types of cancer and that underlying infections and inflammatory responses are linked to 15–20% of cancer deaths worldwide [24]. Although cause-effect relationships were unclear between persistent elevation of CRP levels and cardiovascular or non-cardiovascular events in the present study, chronic inflammation could be a significant risk of both cardiovascular and non-cardiovascular deaths. Indeed, in the JUPITER trial [9] and PROVE IT-TIMI 22 study [10], statin therapy has been shown to reduce cardiovascular events in both healthy population and ACS patients with hsCRP ≥ 2.0 mg/L, respectively, regardless of LDL-C levels. Statin use in patients with cancer has also been reported to be associated with reduced cancer-related mortality [25,26]. Furthermore, in the CANTOS study, anti-inflammatory therapy with canakinumab, an antibody to IL-1β, significantly reduced cancer mortality and the incidence of cardiovascular events in patients with previous MI and hsCRP ≥ 2.0 mg/L. [11] In the present study, patients with persistent elevation of CRP level were less frequently treated with statins as compared with other 3 groups. Taken together, these findings suggest that anti-inflammatory therapy, such as statin or canakinumab use, have beneficial prognostic impacts in patients with persistent elevation of CRP and history of MI, regardless of LDL-C levels.

### *4.3. Study limitations*

Several limitations should be mentioned for the present study. First, about 40% of the patients had no CRP data at baseline or 1-year, and were thus excluded from present study. Although most baseline characteristics were comparable between the patients with and those without CRP data (eTable 3), possible selection bias cannot be completely ruled out. Second, since the CHART-2 Study is a prospective observational study in Japan, cautions are needed when generalizing the present findings to other populations in different countries. Third, in the present study, we did not take into consideration the severity or duration of MI, or drug strategies at the time of enrollment. Fourth, since no information on drug adherence was available in the present study, differences in drug adherence among the patient groups might have affected the present results. Finally, the present study employed CRP, but not hsCRP, as an inflammation marker. However, CRP is more widely used in daily practice than hsCRP.

## 5. Conclusion

These results provide the first evidence that temporal increases in CRP levels are associated with increased clinical events in patients



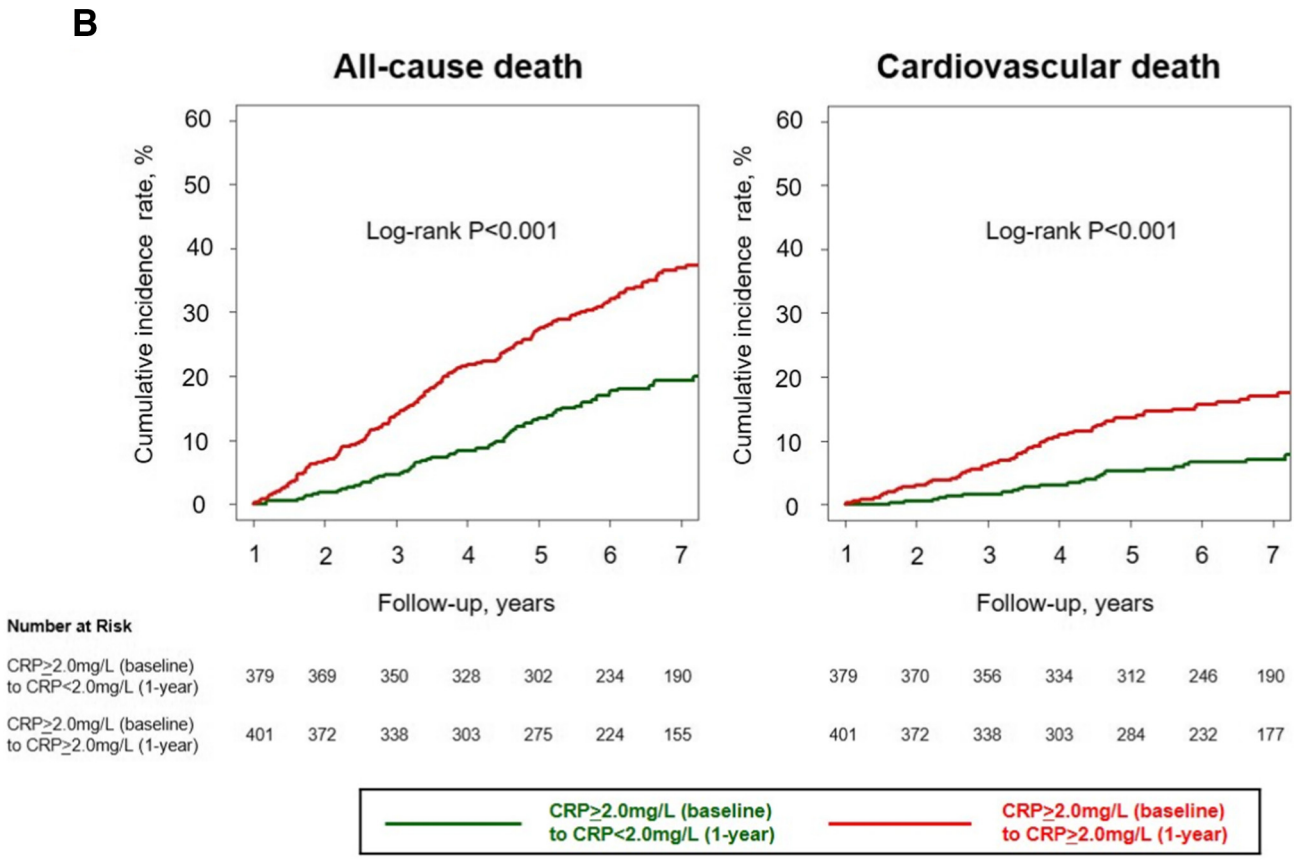




**Fig. 2.** Incidence curves for all-cause and cardiovascular deaths in patients with MI by CRP levels at baseline and 1-year. (A) Patients with low levels of CRP at baseline, (B) patients with high levels of CRP at baseline. Abbreviations: CRP, C-reactive protein; MI, myocardial infarction.

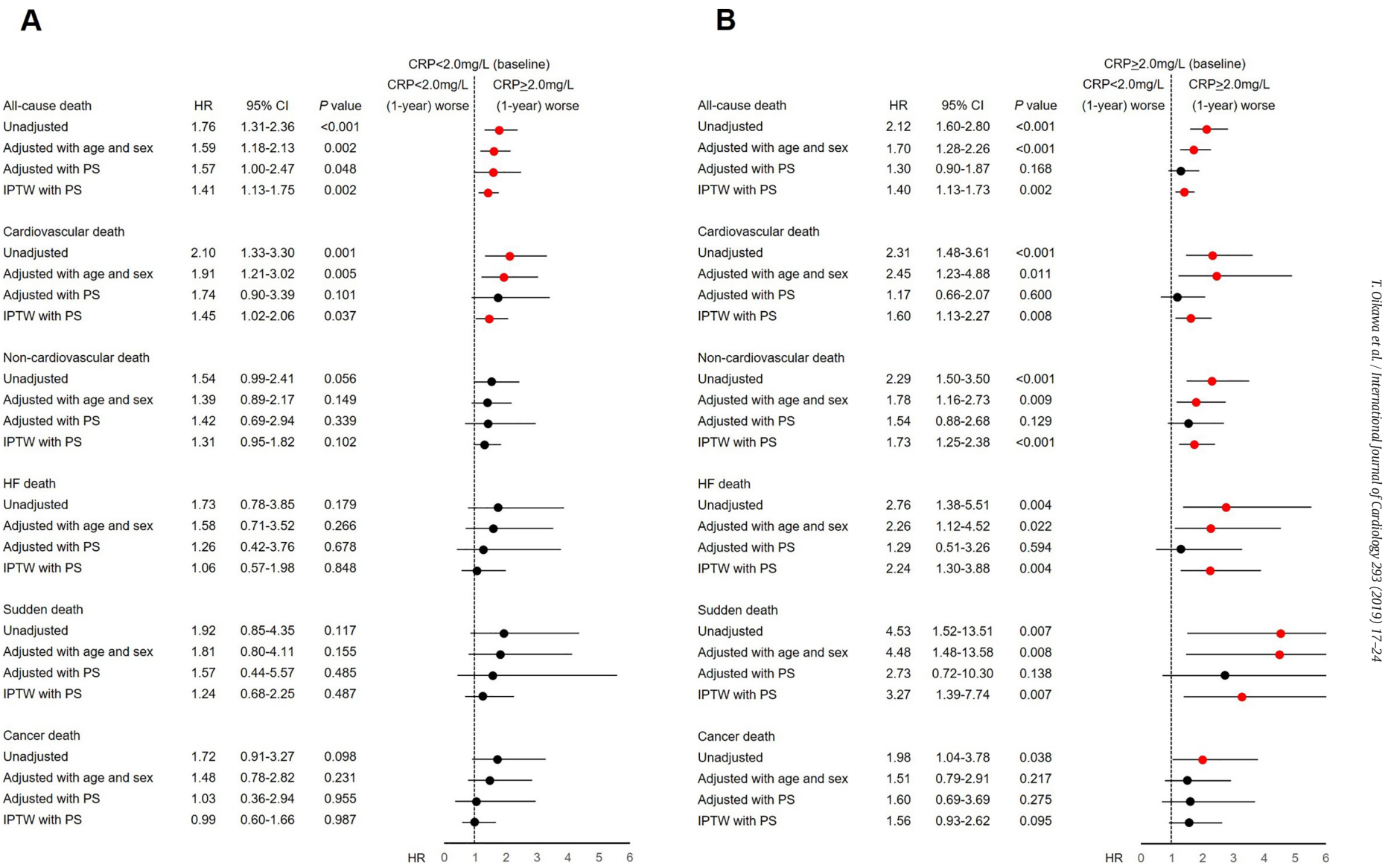



**Fig. 3.** Cox proportional hazard models for prognostic impact of temporal changes in inflammation. (A) Among patients with CRP < 2.0 mg/L at baseline (CRP < 2.0 mg/L at 1-year (reference) vs. CRP ≥ 2.0 mg/L at 1-year), (B) among patients with CRP ≥ 2.0 mg/L at baseline (CRP < 2.0 mg/L at 1-year (reference) vs. CRP ≥ 2.0 mg/L at 1-year). Abbreviations: CI, confidence interval; CRP, C-reactive protein; HF, heart failure; HR, hazard ratios; IPTW, inverse probability of treatment weighted; PS, propensity score.

with previous MI, suggesting the pathogenetic roles of chronic inflammation in the pathogenesis of cardiovascular diseases.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.07.022.

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## Declaration of Competing Interest

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## References

[1] M.B. Pepys, G.M. Hirschfield, C-reactive protein: a critical update, J. Clin. Invest. 111 (2003) 1805–1812.
[2] M. Pye, A.P. Rae, S.M. Cobbe, Study of serum C-reactive protein concentration in cardiac failure, Br. Heart J. 63 (1990) 228–230.
[3] P.M. Ridker, M. Cushman, M.J. Stampfer, R.P. Tracy, C.H. Hennekens, Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men, N. Engl. J. Med. 336 (1997) 973–979.
[4] P.M. Ridker, C.H. Hennekens, J.E. Buring, N. Rifai, C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women, N. Engl. J. Med. 342 (2000) 836–843.
[5] J. Danesh, J.G. Wheeler, G.M. Hirschfield, et al., C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease, N. Engl. J. Med. 350 (2004) 1387–1397.
[6] B. Lindahl, H. Toss, A. Siegbahn, P. Venge, L. Wallentin, Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease, N. Engl. J. Med. 343 (2000) 1139–1147.
[7] J.S. Gottdiener, A.M. Arnold, G.P. Aurigemma, et al., Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study, J. Am. Coll. Cardiol. 35 (2000) 1628–1637.
[8] The Emerging Risk Factors Collaboration, C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis, Lancet 375 (2010) 132–140.
[9] P.M. Ridker, E. Danielson, F.A. Fonseca, et al., Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein, N. Engl. J. Med. 359 (2008) 2195–2207.
[10] P.M. Ridker, C.P. Cannon, D. Morrow, et al., C-reactive protein levels and outcomes after statin therapy, N. Engl. J. Med. 352 (2005) 20–28.
[11] P.M. Ridker, B.M. Everett, T. Thuren, et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease, N. Engl. J. Med. 377 (2017) 1119–1131.
[12] N. Shiba, K. Nochioka, M. Miura, H. Kohno, Shimokawa H; CHART-2 Investigators. Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan -first report from the CHART-2 study, Circ. J. 75 (2011) 823–833.
[13] K. Tsuji, Y. Sakata, K. Nochioka, et al., Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 study, Eur. J. Heart Fail. 19 (2017) 1258–1269.
[14] T. Oikawa, Y. Sakata, K. Nochioka, et al., Prognostic impact of statin intensity in heart failure patients with ischemic heart disease: a report from the CHART-2 study, J. Am. Heart Assoc. 7 (2018), e007524.
[15] C.W. Yancy, M. Jessup, B. Bozkurt, et al., 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, J. Am. Coll. Cardiol. 62 (2013) e147–e239.
[16] P.A. McKee, W.P. Castelli, P.M. McNamara, W.B. Kannel, Natural history of congestive heart failure: the Framingham Study, N. Engl. J. Med. 285 (1971) 1441–1446.
[17] P.C. Austin, An introduction to propensity score methods for reducing the effects of confounding in observational studies, Multivariate Behav. Res. 46 (2011) 399–424.
[18] World Health Organization, Nutritional anaemias: report of a WHO scientific group, WHO Tech. Rep. Ser. 405 (1968) 3–37.
[19] P.E. Stevens, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline, Ann. Intern. Med. 158 (2013) 825–830.
[20] R. Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2017http://www.R-project.org/, Accessed date: 30 December 2017.
[21] R. Yoshinaga, Y. Doi, K. Ayukawa, S. Ishikawa, High-sensitivity C reactive protein as a predictor of inhospital mortality in patients with cardiovascular disease at an emergency department: a retrospective cohort study, BMJ Open 7 (2017), e015112.
[22] M. Shiba, H. Itaya, R. Iijima, M. Nakamura, Influence of late vascular inflammation on long-term outcomes among patients undergoing implantation of drug eluting stents: role of C-reactive protein, J. Am. Heart Assoc. 5 (2016), e003354.
[23] M. Qintar, P.P. Sharma, Y. Pokharel, et al., Prevalence and predictors of elevated high-sensitivity C-reactive protein in post-myocardial infarction patients: insights from the VIRGO and TRIUMPH registries, Clin. Cardiol. 40 (2017) 1205–1211.
[24] A. Mantovani, P. Allavena, A. Sica, F. Balkwill, Cancer-related inflammation, Nature. 454 (2008) 436–444.
[25] S.F. Nielsen, B.G. Nordestgaard, S.E. Bojesen, Statin use and reduced cancer-related mortality, N. Engl. J. Med. 367 (2012) 1792–1802.
[26] A. Wang, A.K. Aragaki, J.Y. Tang, et al., Statin use and all-cancer survival: prospective results from the Women's Health Initiative, Br. J. Cancer 115 (2016) 129–135.