

Concentrations of C-Reactive Protein and B-Type Natriuretic Peptide 30 Days after Acute Coronary Syndromes Independently Predict Hospitalization for Heart Failure and Cardiovascular Death

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BACKGROUND: Heart failure (HF) is an important cause of morbidity in patients with acute coronary syndromes (ACS). C-reactive protein (CRP) has been implicated in experimental models as exacerbating myocardial injury, but data regarding the clinical relationship of high-sensitivity CRP (hsCRP) and B-type natriuretic peptide (BNP) concentrations with the risk of HF after ACS are few.

METHODS: PROVE IT–TIMI 22 randomized 4162 patients who had been stabilized after ACS to either intensive or moderate statin therapy. hsCRP and BNP were measured 30 days after randomization. Hospitalizations for HF and cardiovascular death occurring after day 30 were assessed for a mean follow-up of 24 months.

RESULTS: Patients who developed HF had higher concentrations of hsCRP (3.7 mg/L vs 1.9 mg/L, $P < 0.001$) and BNP (59 ng/L vs 22 ng/L, $P < 0.0001$). HF increased in a stepwise manner with hsCRP quartile [adjusted hazard ratio (HR_{adj}) for Q4 vs Q1, 2.5; $P = 0.01$] and BNP quartile (HR_{adj} for Q4 vs Q1, 5.8; $P < 0.001$), with similar results obtained for HF and cardiovascular death. In a multivariable analysis, higher concentrations of hsCRP and BNP were both independently associated with HF [HR_{adj}, 1.9 for hsCRP >2.0 mg/L ($P = 0.01$) and 4.2 for BNP >80 ng/L ($P < 0.001$)]. Patients with increases in both markers were at the greatest risk of HF, compared with patients without an increased marker concentration (HR_{adj}, 8.3; $P = 0.01$). The benefit of intensive statin therapy in reducing HF

was consistent among all patients, regardless of hsCRP or BNP concentration.

CONCLUSIONS: Both hsCRP and BNP measured 30 days after ACS are independently associated with the risk of HF and cardiovascular death, with the greatest risk occurring when both markers are increased.

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Current treatment strategies for patients admitted with acute coronary syndrome (ACS)⁴ focus primarily on preventing recurrent ischemia or infarction, whereas therapy targeted specifically to prevent heart failure (HF) has generally been a secondary objective. Nonetheless, the development of HF after ACS carries an especially poor overall prognosis (1, 2). Both the identification of patients at high risk for developing HF after ACS and determining whether specific therapy can modify that risk are therefore of clinical importance. The use of cardiac biomarkers, especially B-type natriuretic peptide (BNP) (3, 4), has greatly improved the ability to identify patients who are at high risk of death or HF after ACS. In particular, those patients with persistently high markers of hemodynamic stress several weeks after ACS are at highest risk (4, 5).

When measured immediately after the onset of ischemic symptoms, C-reactive protein (CRP), a marker of inflammation, has also been associated with poor cardiovascular outcomes (6, 7). Because of the acute-phase response, however, the concentration of high-sensitivity CRP (hsCRP) varies widely in the days after

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⁴ Nonstandard abbreviations: ACS, acute coronary syndrome; HF, heart failure; BNP, B-type natriuretic peptide; CRP, C-reactive protein; hsCRP, high-sensitivity CRP; PROVE IT, Pravastatin or Atorvastatin Evaluation and Infection Trial; TIMI, Thrombolysis in Myocardial Infarction; Po₂, oxygen pressure; HR, hazard ratio; HR_{adj}, adjusted HR; Q4, quartile 4.

ACS, and the association can be confounded by the extent of necrosis (8) and the timing of the measurement (6). The association of CRP with subsequent risk of death or myocardial infarction has been well documented in the convalescent phase after ACS, when hsCRP concentrations have returned to baseline (9). In contrast, the relationship between convalescent concentrations of hsCRP (alone and in combination with natriuretic peptides) and the risk of HF has not been well described. The present analysis focuses on the relationship between hsCRP concentration after the index ACS event and the subsequent risk of HF, and on whether intensive statin therapy modifies this relationship.

Materials and Methods

The Pravastatin or Atorvastatin Evaluation and Infection Trial (PROVE IT)—Thrombolysis in Myocardial Infarction (TIMI) 22 trial enrolled 4162 patients hospitalized for an ACS—either acute myocardial infarction (with or without electrocardiographic evidence of ST-segment elevation) or high-risk unstable angina—in the preceding 10 days. Patients had to be in stable condition and have a total cholesterol concentration within the first 24 h after the onset of the index event of <240 mg/dL (6.21 mmol/L) or <200 mg/dL (5.18 mmol/L) if they were on prior lipid-lowering therapy. Full inclusion and exclusion criteria have previously been reported (10, 11).

STUDY PROTOCOL

The protocol specified that patients were to receive standard medical and interventional treatment for ACS. Eligible patients were randomly assigned in a 1:1 ratio to receive 40 mg of pravastatin or 80 mg of atorvastatin daily in a double-blind, double-dummy fashion. Patients were seen for follow-up at 30 days, at 4 months, and every 4 months thereafter until their final visit. Plasma samples were obtained at baseline and 30 days after randomization. Plasma samples were collected in EDTA-containing plastic tubes, frozen at the study site at -20°C or lower for no longer than 8 weeks, and then shipped on dry ice to the TIMI Biomarker Core Laboratory (Boston, MA), where the samples were stored below -70°C . Samples were stored for a maximum of 5 years before testing for BNP. Plasma was analyzed with validated assays for hsCRP (Denka Seiken) and BNP (ADVIA Centaur BNP; Siemens Medical Diagnostics). The manufacturer's claimed concentration interval for the hsCRP assay was 0.05–10 mg/L with a limit of detection of 0.03 mg/L and imprecision (CV) values of 5.1%, 3.3%, 6.1%, 2.2%, and 2.5% at hsCRP concentrations of 0.17, 0.41, 0.37, 1.16, and 1.88 mg/L, respectively (12).

The ADVIA Centaur assay has reported CV values of 3.4%, 2.9%, and 2.4% at BNP concentrations of 48, 461, and 1768 ng/L (13). We evaluated biomarkers as quartiles and based the prespecified cutpoints of 2 mg/L for hsCRP (14) and 80 ng/L for BNP (4) on our previous studies.

ENDPOINTS

The primary efficacy outcomes for this analysis were the time from day 30 after randomization until the first occurrence of hospitalization for congestive HF and until the composite of hospitalization for HF or cardiovascular death. Cardiovascular death was adjudicated by a blinded clinical-event committee. Hospitalization for HF was categorized by the investigator as a hospitalization for new or worsening HF with evidence of pulmonary congestion on a chest radiograph and fulfillment of 2 of the following 6 criteria: rales in the midlung that do not clear with coughing; a left ventricular ejection fraction <40%; a mean pulmonary capillary wedge pressure ≥ 18 mmHg and a cardiac index ≥ 2.2 L/min \cdot m²; use of diuretics to treat pulmonary congestion in patients not previously taking diuretics or an increase in dose in patients taking diuretics chronically; need for intubation for hypoxia; or an oxygen saturation <90% or an oxygen pressure (P_{O_2}) <60 mmHg. Myocardial infarction was defined as the presence of symptoms suggestive of ischemia or infarction, with either electrocardiographic evidence (new Q waves in 2 or more leads) or cardiac-marker evidence of infarction (10, 11).

STATISTICAL ANALYSIS

All analyses are based on the intention-to-treat principle. Kaplan–Meier estimates for the rate of HF and cardiovascular death are presented at 2 years. Estimates of hazard ratio (HR) and associated 95% CI values were obtained with the use of the Cox proportional hazards model. The relationship between the individual biomarkers and clinical outcomes was evaluated in an adjusted Cox model that included the following variables: age, sex, diabetes mellitus, hypertension, body mass index, creatinine clearance, history of HF, treatment with atorvastatin, and percutaneous intervention during the index period. Cox models that included both hsCRP and BNP were adjusted for age, sex, creatinine clearance, and body mass index. Continuous variables were compared with the Wilcoxon rank sum test. All statistical analyses were performed with Stata/SE, version 9.1 (StataCorp).

Results

Thirty-day samples were available for hsCRP in 3807 patients and for BNP in 3251 patients. The median

hsCRP concentration was 1.9 mg/L (interquartile range, 0.92–4.2 mg/L), with 1857 patients (48.8%) having a concentration >2.0 mg/L. The median BNP concentration was 23 ng/L (interquartile range, 11–48 ng/L), with 402 patients (12.4%) having a concentration >80 ng/L. Table 1 categorizes the patients according to high hsCRP and BNP concentrations. Thirty-day hsCRP and BNP concentrations were weakly but significantly correlated ($r = 0.249$; $P < 0.001$).

CARDIAC BIOMARKERS AND THE RISK OF HF

Patients who developed HF during follow-up had higher 30-day hsCRP and BNP concentrations than patients without any subsequent hospitalization for HF [median, 3.7 mg/L vs 1.9 mg/L for hsCRP ($P < 0.001$) and 59 ng/L vs 22 ng/L ($P < 0.001$) for BNP]. More patients who developed HF had hsCRP concentrations >2.0 mg/L (70.5% vs 48.0%, $P < 0.001$) or BNP concentrations >80 ng/L (41.8% vs 11.2%, $P < 0.001$).

The adjusted risks of HF and of HF or cardiovascular death increased with quartile in a stepwise manner for both hsCRP and BNP (Fig. 1). These results were unchanged after excluding any episode of HF or cardiovascular death that occurred after a recurrent myocardial infarction [adjusted HR (HR_{adj}) for HF in hsCRP quartile 4 (Q4) vs hsCRP Q1, 2.4 (95% CI, 1.2–4.9; $P = 0.014$); HR_{adj} for HF in BNP Q4 vs BNP Q1, 6.5 (95% CI, 2.5–17.1; $P < 0.001$)] or when the left ventricular ejection fraction ($n = 1833$) was incorporated into the multivariable model [HR_{adj} for HF in hsCRP Q4 vs hsCRP Q1, 3.9 (95% CI, 1.3–11.4; $P = 0.01$); HR_{adj} for HF in BNP Q4 vs BNP Q1, 5.2 (95% CI, 1.5–17.9; $P = 0.01$)].

The association of hsCRP and BNP with cardiovascular outcomes was also consistent among patients without clinical signs of HF [i.e., excluding patients without a history of HF or an episode of HF after randomization but before day 30 ($n = 140$)] for HF [HR_{adj} for hsCRP Q4 vs hsCRP Q1, 3.2 (95% CI, 1.1–10.4; $P = 0.04$); HR_{adj} for BNP Q4 vs BNP Q1, 16.4 (95% CI, 2.1–125.4; $P < 0.001$)] and for HF or cardiovascular death [HR_{adj} for hsCRP Q4 vs hsCRP Q1, 3.1 (95% CI, 1.3–7.3; $P = 0.011$); HR_{adj} for BNP Q4 vs BNP Q1, 8.0 (95% CI, 2.4–27.1; $P < 0.001$)].

Patients with a high concentration of hsCRP (>2 mg/L) or BNP (>80 ng/L) were at increased risk of hospitalization for HF compared with patients without an increased concentration (Fig. 2). Patients at the greatest risk of HF were those with increased concentrations of both BNP and hsCRP. Patients with an increased concentration of either hsCRP or BNP were at a similar and moderate risk of hospitalization for HF or cardiovascular death, compared with patients without an increased concentration ($P = 0.04$; Fig. 3).

Table 1. Categorization of patients by cutpoint concentrations for hsCRP (2 mg/L) and BNP (80 ng/L).

		BNP		Totals
		≤80 ng/L	>80 ng/L	
hsCRP	≤2 mg/L	1524 (47.0%)	157 (4.8%)	1681 (51.8%)
	>2 mg/L	1319 (40.6%)	244 (7.5%)	1563 (48.2%)
Totals		2843 (87.6%)	401 (12.4%)	3244

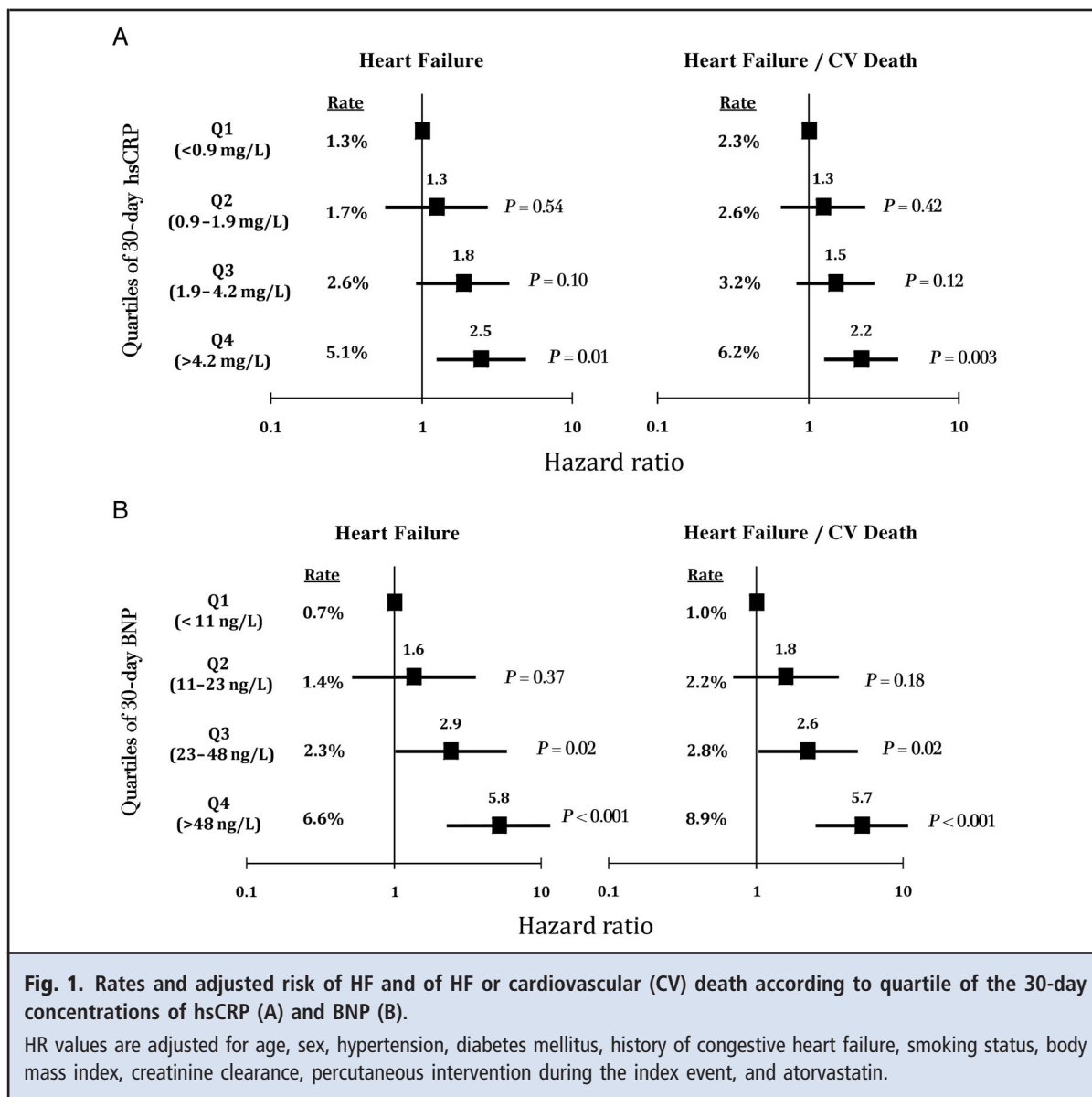
When hsCRP and BNP were included together in a full multivariable model with baseline clinical features, both a hsCRP concentration >2 mg/L and a BNP concentration >80 ng/L were independently associated with HF [HR_{adj} , 1.9 (95% CI, 1.2–3.0; $P = 0.01$) for hsCRP and 4.2 (95% CI, 2.6–6.7; $P < 0.001$) for BNP] and with cardiovascular death or HF [HR_{adj} , 1.7 (95% CI, 1.1–2.5; $P = 0.009$) for hsCRP and 3.5 (95% CI, 2.2–5.2; $P < 0.001$) for BNP].

EFFECT OF INTENSIVE STATIN THERAPY ACCORDING TO hsCRP OR BNP CONCENTRATION

Compared with pravastatin, treatment with atorvastatin produced lower hsCRP concentrations at 30 days (1.7 mg/L vs 2.3 mg/L, $P < 0.001$) but not lower BNP concentrations (23 ng/L vs 23 ng/L, $P = 0.8$). The effect of intensive statin therapy (i.e., atorvastatin) was consistent among all patients, regardless of the 30-day concentration of BNP or hsCRP. Specifically, intensive statin therapy had no greater benefit in reducing the risk of HF among patients with high hsCRP concentrations compared with those with typical concentrations [HR, 0.68 (95% CI, 0.43–1.1; $P = 0.098$) in patients with higher hsCRP concentrations vs 0.81 (95% CI, 0.39–1.6; $P = 0.55$) in patients with low hsCRP concentrations (P -interaction = nonsignificant)] or in patients with higher BNP concentrations compared with those with typical concentrations [HR, 0.73 (95% CI, 0.40–1.4; $P = 0.318$) in patients with high BNP concentrations vs 0.54 (95% CI, 0.31–0.94; $P = 0.03$) in patients with typical BNP concentrations (P -interaction = nonsignificant)] (Fig. 4). Similar results were seen with the outcome of cardiovascular death or HF.

Discussion

Among patients hospitalized for ACS, the subsequent development of HF portends a poor prognosis (1, 2). In this analysis, we found that serum concentrations of hsCRP assessed 1 month after an ACS are independently associated with the risk of future HF and identify

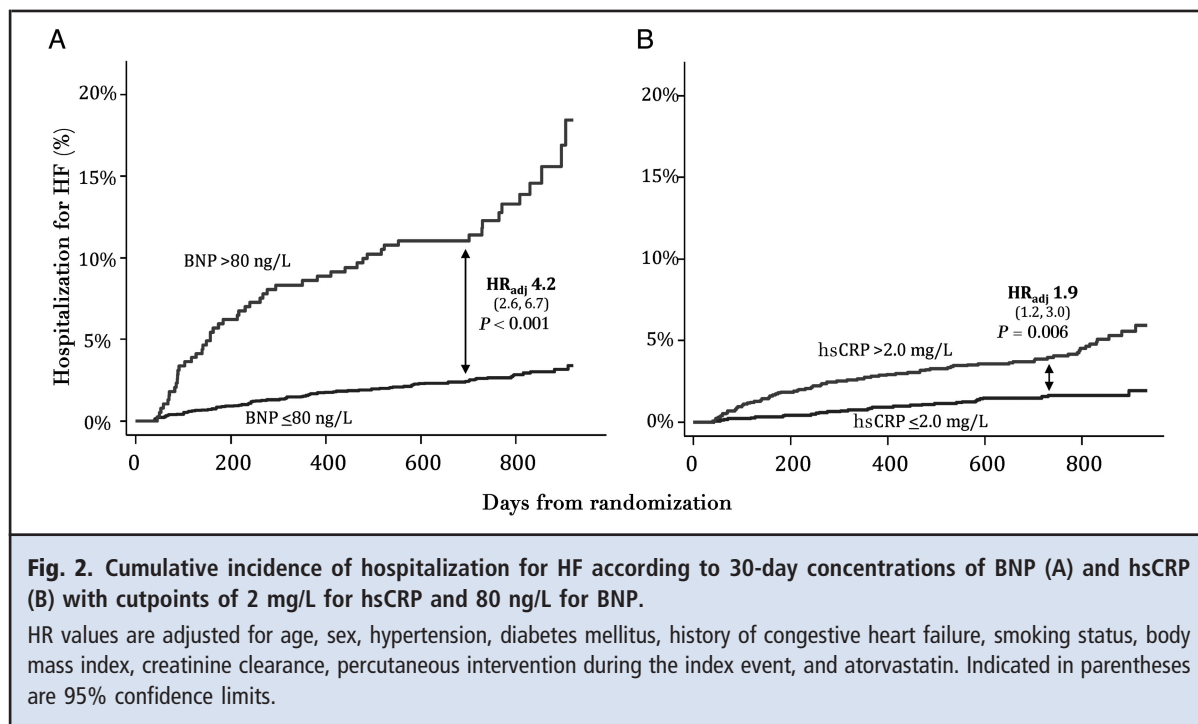


a substantial proportion of the population who are at increased risk of HF despite having a low BNP concentration. Notably, patients with both evidence of persistent inflammation and hemodynamic stress are at the highest risk for future HF (9). The relative benefit of intensive statin therapy compared with moderate therapy in reducing hospitalization for HF was consistent among all patients, regardless of the 30-day biomarker concentrations.

INFLAMMATION IN HF

An association between increased concentrations of inflammatory markers and chronic HF was first reported more than 50 years ago (15). Further research

suggested that inflammation is central to the pathobiology of HF, with inflammatory cytokines playing a direct role in worsening HF through the induction of myocyte apoptosis, ventricular dilation, and endothelial dysfunction (16). For example, CRP, which can be identified in myocardial tissue after an acute myocardial infarction, has been shown to colocalize with and activate complement, thereby potentially exacerbating tissue damage (17). These observations have stimulated interest in the potential role of inflammatory biomarkers for assessing prognosis and guiding therapy in patients at risk for or with established HF. In studies of patients with documented HF, the concentrations of hsCRP (18–20) and other inflammatory markers, such



as interleukin-6 and tumor necrosis factor receptor (21–23), have been correlated with worse outcomes. The association between CRP and the development of HF in patients after an ACS, however, has not been as well described. Moreover, prior studies of CRP have had limited opportunity to evaluate this inflammatory marker in conjunction with a biomarker of hemodynamic stress.

CRP, BNP, AND THE RISK OF INCIDENT HF

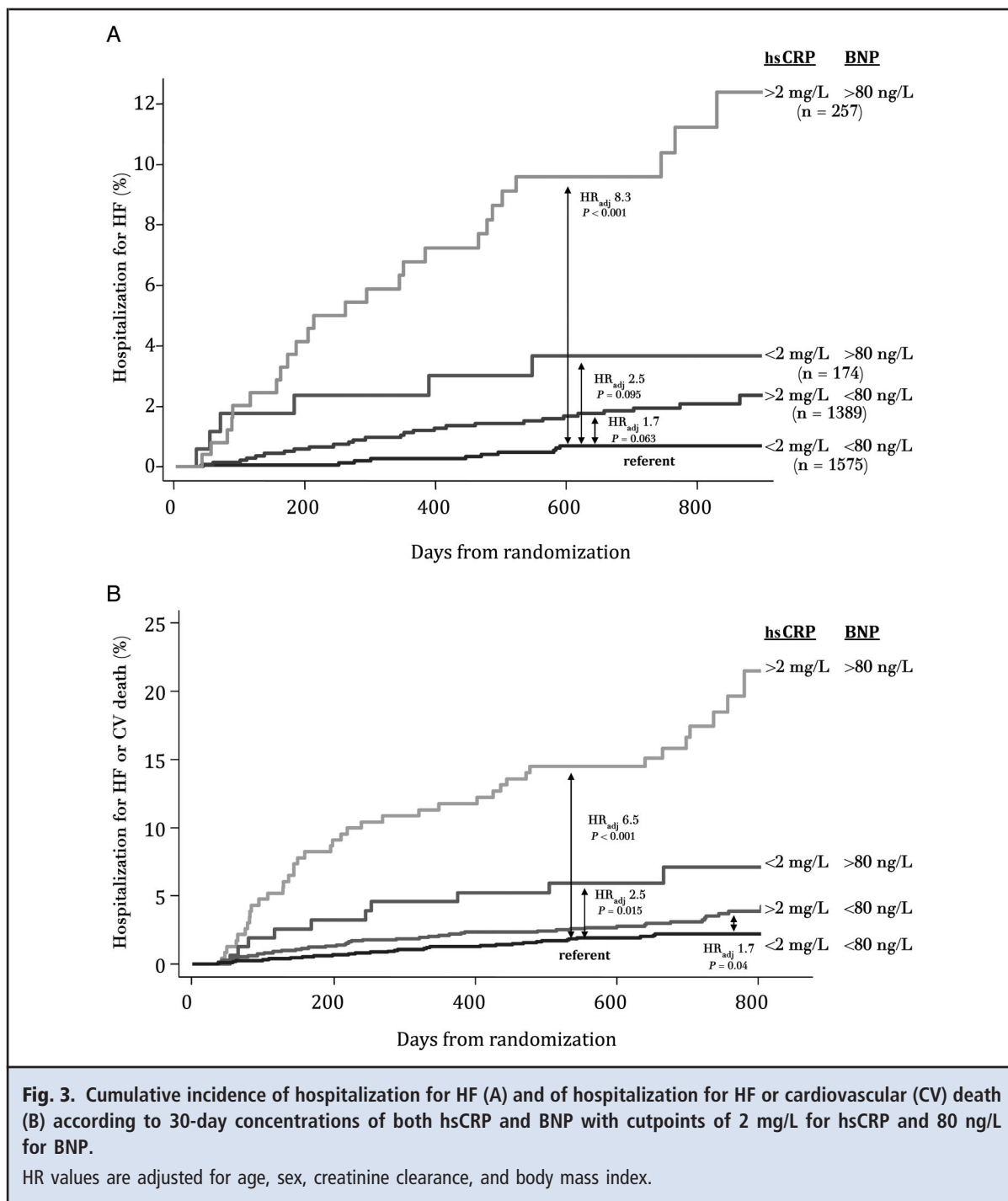
In a large population supporting a robust adjustment for BNP as well as potentially important clinical confounders, we have demonstrated that the hsCRP concentration at 30 days after an ACS is associated with the risk of subsequent HF, even after adjusting for baseline risk factors, after adjusting for BNP concentration, and after excluding patients with a history of HF. Our finding that this heightened risk was not explained entirely by the risk of recurrent ischemia and infarction points to the need to identify other pathophysiological targets for preventing HF in this population.

Patients with concentrations of both hsCRP and BNP greater than the commonly used cutpoints (2 mg/L for hsCRP and 80 ng/L for BNP) (9, 24) are at the greatest risk of hospitalization for HF (>8-fold increased risk compared with patients without increased hsCRP and BNP concentrations). Thus, these 2 biomarkers, one reflecting inflammation and the other ventricular stress, yield complementary information regarding future risk. Moreover, even among patients

with low BNP concentrations (<80 ng/L), an increased hsCRP concentration is associated with an increased risk of adverse cardiovascular outcomes. Patients with a BNP concentration <80 ng/L but a hsCRP concentration >2.0 mg/dL accounted for 40.6% of the entire study cohort; thus, CRP identifies a sizeable high-risk subgroup within a patient population that would otherwise be deemed at low risk for HF or cardiovascular death. Therefore, both biomarkers may be useful in selecting patients for targeted investigation of the next generation of treatments for preventing HF after an ACS.

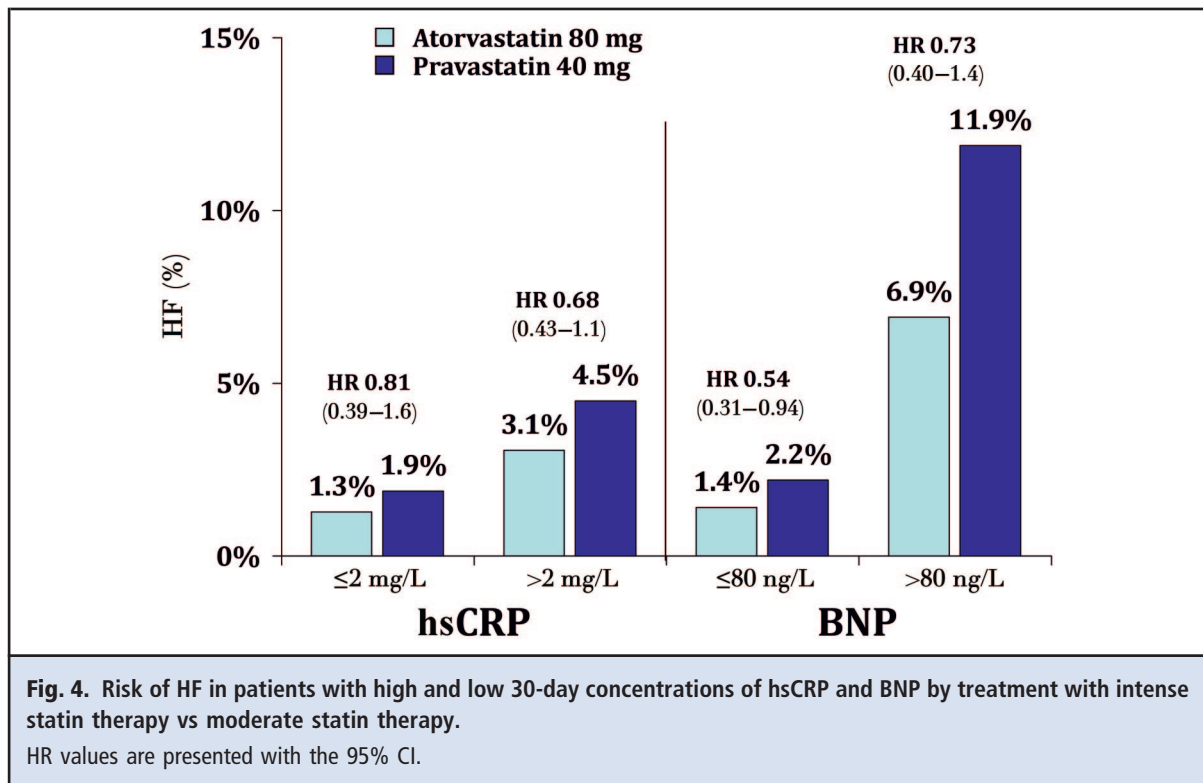
TIMING OF MEASUREMENT

The timing of measurement in our study was important, and these data add to information from previous investigations. hsCRP concentrations rise immediately after the onset of an ACS but do not peak until 48–72 h later; CRP then returns to a stable concentration over the subsequent weeks. The timing of hsCRP measurement after an ACS appears to be important for evaluating its association with subsequent cardiovascular outcomes, because the increase in hsCRP concentration after an ACS likely represents both the underlying chronic inflammation that preceded the event and the acute-phase reaction to the necrosis of the ischemic event (6, 25, 26). The early phase of the CRP response after an ACS is most likely due to the patient's underlying inflammatory state, and this state appears to be more closely associated with an increased risk of HF



(6, 7, 25). Biasucci et al. first reported that discharge hsCRP concentrations in blood drawn 12 days after admission were more strongly associated with subsequent outcomes than hsCRP concentrations measured at the time of admission for an ACS (25). In the OPUS-TIMI 16 trial, for example, hsCRP measurements ob-

tained within 48 h of the onset of ischemic symptoms were independently associated with death and HF. In contrast, there was no relationship between cardiovascular outcomes and hsCRP measurements in samples drawn more than 48 h after symptom onset, likely because a substantial acute-phase response to myocar-



dial necrosis confounded the relationship with the underlying inflammatory process (6, 8). In this study, samples for hsCRP analysis were collected 30 days after the index event, by which time the initial necrosis and reactive inflammatory process had resolved. Concentrations of hsCRP had returned to a stable concentration that reflected the patient's chronic inflammatory state. Our findings, therefore, reflect the ability to assess the risk for new HF in the stable patient recovering after an ACS. Our observations are supported by the findings from the PEACE trial, which included patients with stable coronary artery disease and found that even small increases in the hsCRP concentration were associated with an increased risk of HF (24).

EFFECT OF INTENSIVE STATIN THERAPY

Patients assigned to treatment with an 80-mg atorvastatin dosage achieved lower hsCRP concentrations and were more likely to have hsCRP concentrations <2 mg/L; however, the benefit of intensive statin therapy appeared to be consistent regardless of the 30-day hsCRP concentration. A growing body of evidence suggests that statin therapy, especially intensive statin therapy, may reduce the risk of HF among patients with ACS (27) and stable coronary artery disease (28). As we have previously shown in the PROVE IT–TIMI 22 trial, treatment with high-dose statin therapy reduced the rate of hospitaliza-

tion for HF among all patients. Although treatment with atorvastatin was not associated with a significant reduction in HF among patients with either a low or increased hsCRP concentration, the magnitude of the benefit in reducing HF (an HR of 0.68 in patients with increased hsCRP concentrations and 0.81 in patients with low concentrations) is consistent with the overall PROVE IT–TIMI 22 trial results (27) and with other trials of patients with ACS or documented coronary artery disease that compared intensive and moderate statin therapy (29, 30).

In contrast to our prior report (27), in this analysis we concentrated on the convalescent concentration of hsCRP and found that hsCRP was complementary in assessing the risk of new HF. The findings of the CORONA (31) and GISSI-HF (32) studies, which did not detect any benefit of rosuvastatin vs placebo in patients with HF, suggest that further risk stratification, perhaps with these or other biomarkers, may be of use for identifying the patients who are at greatest risk and could potentially benefit from targeted therapy.

LIMITATIONS

Our analysis was conducted post hoc and therefore is exploratory in nature; however, the consistency of the results after stratification and multivariable modeling support our findings and conclusions. Our study was not designed to elucidate differences in the underlying

pathophysiology, such as atherothrombosis, ventricular dysfunction, myocardial remodeling, or endothelial function, which might contribute to the higher risk of HF associated with CRP. Moreover, this study was of patients with a recent ACS, and thus the relationship between biomarkers and HF and the potential for modifying this risk with specific therapy should not be generalized to include other populations.

Community-based studies of this biomarker strategy will be valuable for confirming the application of our findings to patients without a confirmed ACS and to “real-world” patients not selected for participation in a clinical trial. Because BNP recovery may diminish with prolonged storage, it is possible that our results underestimate the strength of the relationship between BNP and outcome. Nevertheless, the handling of samples in this study was consistent with that in our previous studies that have established the prognostic value of BNP in this setting after ACS.

Conclusions

Higher concentrations of hsCRP and BNP in patients who are recovering from a recent ACS are associated with an increased risk for hospitalization for HF and for cardiovascular death. Addition of the inflammatory biomarker hsCRP to BNP, a well-recognized marker of ventricular stress, helps to identify patients at increased risk. Further studies of intensive and targeted therapy aimed specifically at these patients at highest risk are warranted.

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