Concomitant Impact of High-Sensitivity C-Reactive Protein and Renal Dysfunction in Patients with Acute Myocardial Infarction

Yong Un Kang, Min Jee Kim, Joon Seok Choi, Chang Seong Kim, Eun Hui Bae, Seong Kwon Ma, Young-Keun Ahn, Myung Ho Jeong, Young Jo Kim, Myeong Chan Cho, Chong Jin Kim, Soo Wan Kim, and Other Korea Acute Myocardial Infarction Registry Investigators

1Department of Internal Medicine, Chonnam National University Medical School, Gwangju; 2Cardiovascular Research Institute of Chonnam National University, Gwangju; 3Department of Internal Medicine, Yeungnam University, Daegu; 4Department of Internal Medicine, Chungbuk National University, Cheongju; 5Department of Internal Medicine, Kyunghee University, Seoul, Korea.

Received: January 15, 2013
Revised: March 16, 2013
Accepted: March 19, 2013
Corresponding author: Dr. Soo Wan Kim, Department of Internal Medicine, Chonnam National University Medical School, 42 Jebong-ro, Gwangju 501-757, Korea. Tel: 82-62-220-6271, Fax: 82-62-225-8578 E-mail: skimw@chonnam.ac.kr

Purpose: The present study aimed to investigate the impact of high-sensitivity C-reactive protein (hs-CRP) and renal dysfunction on clinical outcomes in acute myocardial infarction (AMI) patients. Materials and Methods: The study involved a retrospective cohort of 8332 patients admitted with AMI. The participants were divided into 4 groups according to the levels of estimated glomerular filtration rate (eGFR) and hs-CRP: group I, no renal dysfunction (eGFR ≥60 mL·min⁻¹·1.73 m⁻²) with low hs-CRP (≤2.0 mg/dL); group II, no renal dysfunction with high hs-CRP; group III, renal dysfunction with low hs-CRP; and group IV, renal dysfunction with high hs-CRP. We compared major adverse cardiac events (MACE) over a 1-year follow-up period. Results: The 4 groups demonstrated a graded association with increased MACE rates (group I, 8.8%; group II, 13.8%; group III, 18.6%; group IV, 30.1%; p<0.001). In a Cox proportional hazards model, mortality at 12 months increased in groups II, III, and IV compared with group I [hazard ratio (HR) 2.038, 95% confidence interval (CI) 1.450-2.863, p<0.001; HR 3.003, 95% CI 2.269-3.974, p<0.001; HR 5.087, 95% CI 3.755-6.891, p<0.001]. Conclusion: High hs-CRP, especially in association with renal dysfunction, is related to the occurrence of composite MACE, and indicates poor prognosis in AMI patients.

Key Words: C-reactive protein, glomerular filtration rate, myocardial infarction

INTRODUCTION

Chronic kidney disease (CKD) is strongly related to high risk for cardiovascular disease (CVD) and all-cause mortality. A recent meta-analysis demonstrated strong evidence that patients with CKD experience a 1.4- to 3.7-fold increased risk for CVD mortality compared with those without CKD. A reduced estimated glomerular filtration rate (eGFR) was also independently associated with the risk of death, cardiovascular events, and hospitalization in a large, community-based population. The unique pathophysiology of CKD leads to accelerated severe CVD.
CKD is primarily a state of accelerated atherosclerosis.\textsuperscript{4,5} Atherosclerosis in turn is a well-known inflammatory process associated with elevated levels of C-reactive protein (CRP).\textsuperscript{6} Thus, patients with CKD are known to demonstrate elevated CRP levels, which may be associated with high all-cause and cardiovascular mortality in CKD.\textsuperscript{7,9}

Among the available inflammatory biomarkers, high-sensitivity C-reactive protein (hs-CRP) is one of the most accessible for clinical practice. Several studies have demonstrated an association between elevated hs-CRP and cardiovascular events in healthy general populations.\textsuperscript{10} Recently, CKD and elevated hs-CRP were found to be additive associated with a higher risk of CVD and also to be independent predictors of cardiovascular events after acute coronary syndrome.\textsuperscript{11,12} Although strong evidence links high hs-CRP to poorer outcomes in patients with CKD, it is unclear whether the risk of CVD associated with decreased kidney function is at least partially mediated by inflammation, and whether the association between inflammation and CVD is influenced by the level of kidney function. Few studies have evaluated the relationship between hs-CRP and vascular events in patients with CKD.

The present study was undertaken to evaluate the impact of hs-CRP and renal dysfunction on clinical outcomes in patients with acute myocardial infarction (AMI).

**MATERIALS AND METHODS**

**Korea Acute Myocardial Infarction Registry**

The study subjects were enrolled from the Korea Acute Myocardial Infarction Registry (KAMIR). The KAMIR is a Korean prospective, open, observational, multi-center online registry and aimed to investigate the risk factors of mortality in patients with myocardial infarction (MI) since November 2005. The 52 hospitals with primary percutaneous coronary intervention (PCI) facilities entered and enrolled patients who agreed with participation in this registry. Data were collected by a well-trained study coordinator on the basis of a standardized case report form and protocol. The study protocol was approved by the ethics committee at each participating institution.

**Study design and patient population**

We assessed a retrospective cohort of 13901 consecutive patients who were admitted to the hospital between November 2005 and July 2008 and diagnosed as AMI. The following patients were excluded sequentially: patients who were not available for estimation of glomerular filtration rate; patients lacking information on levels of hs-CRP; patients with hs-CRP greater than 10 mg/dL and with active infections, tumors, or inflammatory disease; and patients who could not be followed over 1 year or whose data were uncertain. A final population of 8332 patients were analyzed in this study.

The patients were categorized into 4 groups on the basis of the presence of renal dysfunction (eGFR $\leq$60 mL·min$^{-1}$·1.73 m$^{-2}$) and hs-CRP greater than 2.0 mg/dL. This hs-CRP value was selected as the cut-off point because it was previously used to predict adverse outcomes in several trials.\textsuperscript{13,14} Levels of hs-CRP were measured at the admission time of each patient and analyzed by immunoturbidimetric analysis (Tina-quant hs-CRP latex assay, Roche/Hitachi, Cobas, Mannheim, Germany). Group I (n=5166) had no renal dysfunction (eGFR $\geq$60 mL·min$^{-1}$·1.73 m$^{-2}$) and low hs-CRP ($\leq$2.0 mg/dL); group II (n=1065), no renal dysfunction and high hs-CRP ($>$2.0 mg/dL); group III (n=1489), renal dysfunction (eGFR $<$60 mL·min$^{-1}$·1.73 m$^{-2}$) and low hs-CRP; group IV (n=612), renal dysfunction and high hs-CRP.

**Assessment of renal function**

Renal function was assessed based on eGFR. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR in mL·min$^{-1}$·1.73 m$^{-2}$.\textsuperscript{15}

**Definitions**

Renal dysfunction was defined by eGFR ($<$60 mL·min$^{-1}$·1.73 m$^{-2}$).\textsuperscript{16} AMI was determined by positive cardiac biomarkers (creatine kinase-MB, troponin-I, or troponin-T) or 12-lead electrocardiography. ST-segment elevation myocardial infarction (STEMI) definition was the presence of new ST-segment elevation of more than 1 mm (0.1 mV) in continuous leads or new left bundle-branch block on electrocardiography. Non ST-segment elevation myocardial infarction (NSTEMI) was defined as those who were not classified as STEMI and the presence of positive biomarkers. Left ventricular ejection fraction (LVEF) was assessed by 2-dimensional echocardiography. In-hospital outcome was death over the course of hospital treatment. The primary endpoints were major adverse cardiac events (MACE) including cardiogenic death, MI, and need for emergency or elective repeat PCI or coronary artery bypass graft (CABG) over a 1-y follow-up period.

**Data collection**

Baseline variables included age, gender, body mass index
of the 4 groups on survival over the 12-month follow-up period. Analyses were adjusted for age, Killip class 4, gender, hypertension, DM, hyperlipidemia, previous CAD, smoking, PCI, medication (aspirin, beta-blocker, ACEi or ARB, and statin), and angiographic findings (left anterior descending artery, Thrombolysis in Myocardial Infarction (TIMI) flow 0-1 before PCI, and complex left main disease) in a 1-year follow-up period. A p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed with the SPSS (Version 17.0, SPSS Inc., Chicago, IL, USA).

**RESULTS**

**Baseline characteristics**

A total of 8332 patients (age, 62±13 years; male, 71.2%) were included in the present study (STEMI, 60.5%; NSTEMI, 39.5%). The patients in groups I and II were younger than those in groups III and IV and demonstrated a higher proportion of males; lower rates of previous hypertension, DM, and CAD; lower frequency of Killip class 4 MI; and higher prevalence of STEMI. Groups I and II had higher BMI, rates of positive smoking history, and systolic blood pressure at admission (Table 1).

**Biochemical parameters, LVEF, and hospital treatment on admission**

eGFR levels did not differ between groups I and II, and the

| Table 1. Baseline Characteristics |
|----------------------------------|
| **Baseline variables** | Group I (n=5166) | Group II (n=1065) | Group III (n=1489) | Group IV (n=612) | p value |
| Age (yrs) | 60.0±12.2 | 62.3±12.6 | 70.8±11.0 | 72.0±11.0 | <0.001 |
| Male (%) | 3931 (76.1) | 801 (75.2) | 863 (58.0) | 339 (55.4) | <0.001 |
| Body mass index (kg/m²) | 24.2±3.1 | 23.9±3.4 | 23.7±3.2 | 23.1±3.5 | <0.001 |
| Risk factor (%) | | | | |
| Hypertension | 2174 (42.2) | 486 (45.9) | 973 (65.6) | 416 (68.2) | <0.001 |
| Diabetes mellitus | 1167 (22.6) | 281 (26.4) | 579 (39.0) | 266 (43.5) | <0.001 |
| Smoking | 2549 (49.6) | 540 (50.8) | 404 (27.4) | 161 (26.5) | <0.001 |
| Hyperlipidemia | 521 (10.1) | 88 (8.3) | 152 (10.2) | 54 (8.9) | 0.231 |
| Previous CAD | 696 (13.5) | 118 (11.1) | 343 (23.1) | 138 (22.7) | <0.001 |
| At admission | | | | |
| SBP (mm Hg) | 132±27 | 126±26 | 127±33 | 124±35 | <0.001 |
| DBP (mm Hg) | 80±16 | 78±16 | 76±19 | 74±20 | <0.001 |
| Killip class 4 (%) | 101 (2.0) | 56 (5.3) | 112 (7.7) | 67 (11.2) | <0.001 |
| Diagnosis (%) | | | | |
| STEMI | 3188 (61.7) | 670 (62.9) | 861 (57.8) | 319 (52.1) | <0.001 |
| NSTEMI | 1978 (38.3) | 395 (37.1) | 628 (42.2) | 293 (47.9) | <0.001 |

CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment myocardial infarction.
Impact of hs-CRP and Renal Dysfunction in AMI

Yonsei Med J  http://www.eymj.org  Volume 55  Number 1  January 2014

135

hs-CRP (Table 3).

In-hospital and out-of-hospital outcomes among the 4 groups

A graded association was observed between each group, the risk of in-hospital death and the incidence of MACE during follow-up (Table 4).

Multivariate analysis of 1-year MACEs after AMI

MACEs at 12 months increased in groups II, III, and IV compared with group I [hazard ratio (HR) 1.478, 95% confidence interval (CI) 1.187-1.840, \( p < 0.001 \); HR 1.513, 95% CI 1.234-1.855, \( p < 0.001 \); HR 2.638, 95% CI 2.051-3.392, \( p < 0.001 \)] (Table 5). Other predictors of 1-year MACEs were older age (HR 1.011, 95% CI 1.004-1.019, \( p = 0.001 \)), previous CAD (HR 1.314, 95% CI 1.080-1.598, \( p = 0.006 \)), DM (HR 1.314, 95% CI 1.117-1.546, \( p = 0.001 \)), Killip class 4 MI (HR 2.355, 95% CI 1.774-3.128, \( p < 0.001 \)), TIMI flow 0-1 before PCI (HR 1.298, 95% CI 1.113-1.514, \( p = 0.001 \)), and complex left main disease (HR 3.058, 95% CI 2.177-4.296, \( p < 0.001 \)). However, the use of beta blocker (HR 0.780, 95% CI 0.653-0.932, \( p = 0.006 \)), ACEi or ARB (HR 0.691, eGFR of group IV was lower than that of group III. Creatine kinase-MB and high-density lipoprotein cholesterol did not differ among groups I, II, and III, and were lower in group IV. TC, LDL-C, and LVEF did not differ between groups II and III and were lowest in group IV and highest in group I. hs-CRP levels did not differ between groups I and III, while the hs-CRP level of group IV was higher than that of group II. N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels increased stepwise from groups II to IV compared with group I. The use of aspirin, beta blocker, ACEi or ARB, and statins was lower with decreasing eGFR and increasing hs-CRP. However, CCB was used more in group III and IV (Table 2).

Coronary angiographic findings

The number of involved vessels, complex left main lesions, and type C lesion was higher with decreasing eGFR and increasing hs-CRP levels. By contrast, the prevalence of single vessel disease was higher with increasing eGFR and decreasing hs-CRP. The use of thrombolysis and PCI was lower with decreasing eGFR and increasing hs-CRP, but CABG was higher with decreasing eGFR and increasing hs-CRP (Table 3).

Table 2. Biochemical Parameters, LVEF, and Hospital Treatment at Admission among the 4 Groups

| Group | Biochemical Parameters | Group | Biochemical Parameters | Group | Biochemical Parameters | Group | Biochemical Parameters | p value |
|-------|------------------------|-------|------------------------|-------|------------------------|-------|------------------------|---------|
| I (n=5166) | GFR (mL·min⁻¹·1.73 m²⁻¹) 85±15 | II (n=1065) | Creatinine (mg/dL) 0.9±0.2 | III (n=1489) | CK-MB (U/L) 151±291 | IV (n=612) | GFR (mL·min⁻¹·1.73 m²⁻¹) 84±14 | <0.001 |
|       | Glomerular filtration rate; CK, creatine kinase; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; hs-CRP, high sensitive C-reactive protein; NT-proBNP, N-terminal pro B type natriuretic peptide; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker. |       | Glomerular filtration rate; CK, creatine kinase; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; hs-CRP, high sensitive C-reactive protein; NT-proBNP, N-terminal pro B type natriuretic peptide; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker. |       | Glomerular filtration rate; CK, creatine kinase; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; hs-CRP, high sensitive C-reactive protein; NT-proBNP, N-terminal pro B type natriuretic peptide; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker. |       | Glomerular filtration rate; CK, creatine kinase; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; hs-CRP, high sensitive C-reactive protein; NT-proBNP, N-terminal pro B type natriuretic peptide; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker. |       | Glomerular filtration rate; CK, creatine kinase; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; hs-CRP, high sensitive C-reactive protein; NT-proBNP, N-terminal pro B type natriuretic peptide; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker. | <0.001 |


Yong Un Kang, et al.

**Table 3. Baseline Coronary Angiographic Findings**

| Variable                        | Group I (n=5166) | Group II (n=1065) | Group III (n=1489) | Group IV (n=612) | p value |
|---------------------------------|-----------------|------------------|-------------------|-----------------|---------|
| Coronary angiography (%)        | 5041 (97.9)     | 1022 (96.4)      | 1362 (91.7)       | 515 (84.6)      | <0.001  |
| Infarct-related artery (%)      |                 |                  |                   |                 |         |
| Left anterior descending artery | 2339 (48.7)     | 492 (50.0)       | 560 (42.6)        | 215 (43.3)      | <0.001  |
| Left circumflex artery          | 854 (17.8)      | 157 (16.0)       | 197 (15.0)        | 74 (14.9)       | 0.041   |
| Right coronary artery           | 1537 (32.0)     | 314 (31.9)       | 522 (39.7)        | 188 (37.9)      | <0.001  |
| Left main stem                  | 68 (1.4)        | 21 (2.1)         | 37 (2.8)          | 19 (3.8)        | <0.001  |
| Involved vessel number (%)      |                 |                  |                   |                 |         |
| 1 vessel                        | 2327 (48.5)     | 403 (40.9)       | 425 (32.2)        | 131 (26.1)      | <0.001  |
| 2 vessels                       | 1438 (30.0)     | 294 (29.8)       | 406 (30.8)        | 147 (29.3)      | 0.922   |
| 3 vessels                       | 910 (19.0)      | 256 (26.0)       | 434 (32.9)        | 197 (39.2)      | <0.001  |
| Left main, isolated             | 18 (0.4)        | 3 (0.3)          | 9 (0.7)           | 2 (0.4)         | 0.439   |
| Left main, complex              | 104 (2.2)       | 29 (2.9)         | 46 (3.5)          | 25 (5.0)        | <0.001  |
| ACC/AHA classification (%)      |                 |                  |                   |                 |         |
| A                               | 227 (5.0)       | 28 (3.0)         | 50 (4.2)          | 19 (4.1)        | 0.043   |
| B1                              | 851 (18.9)      | 176 (19.0)       | 200 (16.7)        | 71 (15.3)       | 0.090   |
| B2                              | 1353 (30.1)     | 270 (29.1)       | 279 (23.2)        | 121 (26.0)      | <0.001  |
| C                               | 2067 (46.0)     | 453 (48.9)       | 672 (56.0)        | 254 (54.6)      | <0.001  |
| TIMI flow (%)                   |                 |                  |                   |                 |         |
| TIMI 0                          | 1949 (42.0)     | 459 (48.5)       | 554 (44.2)        | 188 (39.4)      | <0.001  |
| TIMI 1                          | 458 (9.9)       | 111 (11.7)       | 138 (11.0)        | 52 (10.9)       | 0.285   |
| TIMI 2                          | 727 (15.7)      | 138 (14.6)       | 211 (16.8)        | 105 (22.0)      | 0.002   |
| TIMI 3                          | 1502 (32.4)     | 238 (25.2)       | 350 (37.9)        | 132 (27.7)      | <0.001  |

ACC/AHA, American College of Cardiology/American Heart Association; TIMI, Thrombolysis in Myocardial Infarction.

**Table 4. In-Hospital and Out-of-Hospital Outcomes among the 4 Groups**

| Outcomes                           | Group I (n=5166) | Group II (n=1065) | Group III (n=1489) | Group IV (n=612) | p value |
|------------------------------------|-----------------|------------------|-------------------|-----------------|---------|
| In-hospital outcomes (%)           |                 |                  |                   |                 |         |
| In-hospital death                  | 127 (2.5)       | 74 (6.9)         | 220 (14.8)        | 162 (26.5)      | <0.001  |
| Out-hospital outcomes (%)          |                 |                  |                   |                 |         |
| 1 month MACEs                      | 157 (3.0)       | 79 (7.4)         | 177 (11.9)        | 118 (19.3)      | <0.001  |
| Cardiac death                      | 79 (1.5)        | 53 (5.0)         | 146 (9.8)         | 107 (17.5)      | <0.001  |
| Non-cardiac death                  | 12 (0.2)        | 7 (0.7)          | 14 (0.9)          | 15 (2.5)        | <0.001  |
| Myocardial infarction              | 23 (0.4)        | 4 (0.4)          | 10 (0.7)          | 4 (0.7)         | 0.608   |
| Repeat-PCI                         | 45 (0.9)        | 14 (1.3)         | 17 (1.1)          | 6 (1.0)         | 0.522   |
| CABG                               | 10 (0.2)        | 8 (0.8)          | 4 (0.3)           | 1 (0.2)         | 0.016   |
| 12 month MACEs                     | 454 (8.8)       | 147 (13.8)       | 277 (18.6)        | 184 (30.1)      | <0.001  |
| Cardiac death                      | 100 (1.9)       | 59 (5.5)         | 185 (12.4)        | 136 (22.2)      | <0.001  |
| Non-cardiac death                  | 27 (0.5)        | 15 (1.4)         | 35 (2.4)          | 27 (4.4)        | <0.001  |
| Myocardial infarction              | 38 (0.7)        | 8 (0.8)          | 17 (1.1)          | 9 (1.5)         | 0.148   |
| Repeat-PCI                         | 301 (5.8)       | 70 (6.6)         | 68 (4.6)          | 37 (6.0)        | 0.262   |
| CABG                               | 15 (0.3)        | 10 (0.9)         | 7 (0.5)           | 2 (0.3)         | 0.025   |

MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

95% CI 0.572-0.835, p<0.001, and statin (HR 0.676, 95% CI 0.574-0.797, p<0.001) was associated with reduced risk of MACEs.

**Cox regression analysis for mortality during follow-up**

Mortality at 12 months increased in groups II, III, and IV compared with group I (HR 2.038, 95% CI 1.450-2.863, p<0.001; HR 3.003, 95% CI 2.269-3.974, p<0.001; HR 5.087, 95% CI 3.755-6.891, p<0.001) (Table 6, Fig. 1).

The most common cause of death in patients with CKD is
Furthermore, recent studies clearly provided an independent, and inversely graded association between decreasing levels of renal function and increasing risk of death, and cardiovascular events as eGFR fell below 60 mL·min⁻¹·1.73²⁴.

The high prevalence of CVD in CKD patients suggests the importance of traditional (hypertension, DM, smoking, and hyperlipidemia) as well as non-traditional [CRP, fibrinogen, interleukin-6, factor VIIc, lipoprotein(a) and hemoglobin] CKD risk factors in the pathogenesis of CVD.⁷,¹⁷

The present study compared clinical outcomes and investigated the association between CKD and hs-CRP in patients with AMI.

Our results revealed that the prevalence of hypertension, DM, and previous CAD were higher with decreasing eGFR and increasing hs-CRP levels. The prevalence of smoking was highest in group II and lower with decreasing eGFR and increasing hs-CRP in the other groups. These findings are consistent with the results of previous studies.¹,¹⁴

As eGFR decreased and hs-CRP increased, the frequency of high Killip class 4 and NT-proBNP levels were increased and LVEF decreased at admission. Based on the finding that increased NT-proBNP in patients with decreased eGFR was correlated with severity of heart failure, left ventricle dysfunction, volume overload, and ischemic heart disease, it was assumed that clinically severe manifestations such as cardiogenic shock and pulmonary edema are developed in patients with more decreased eGFR.¹⁸ Conversely, BMI and LDL-C level were significantly lower with decreasing eGFR and increasing hs-CRP. Therefore, the age-related decline in eGFR and lower prevalence of hyperlipidemia may indicate increased malnutrition and inflammation in patients with severely decreased kidney function.¹⁹

Table 5. Multivariate Analysis of 1-Year MACEs after AMI

| Analyses                                | Hazard ratio (95% confidence interval) | p value  |
|-----------------------------------------|----------------------------------------|----------|
|                                         | Group I                                 | Group II | Group III | Group IV |          |
| Unadjusted                              | 1.662 (1.362-2.028)                     | 2.372 (2.017-2.790) | 4.462 (3.661-5.438) | <0.001   |
| 1) Adjusted for age, sex                | 1.603 (1.313-1.958)                     | 2.000 (1.683-2.376) | 3.704 (3.009-4.558) | <0.001   |
| 2) Model 1 plus comorbidity*            | 1.614 (1.320-1.974)                     | 1.912 (1.601-2.283) | 3.528 (2.851-4.366) | <0.001   |
| 3) Model 2 plus killip class 4          | 1.545 (1.261-1.894)                     | 1.776 (1.482-2.128) | 3.137 (2.521-3.902) | <0.001   |
| 4) Model 3 plus PCI                     | 1.544 (1.251-1.893)                     | 1.750 (1.459-2.099) | 2.991 (2.400-3.729) | <0.001   |
| 5) Model 4 plus medication¹             | 1.511 (1.230-1.856)                     | 1.638 (1.363-1.969) | 2.801 (2.242-3.500) | <0.001   |
| 6) Model 5 plus angiographic findings²  | 1.478 (1.187-1.840)                     | 1.513 (1.234-1.855) | 2.638 (2.051-3.392) | <0.001   |

MACE, major adverse cardiac events; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction. *Hypertension, diabetes mellitus, hyperlipidemia, previous coronary artery disease, smoking.

Table 6. Multiple Cox Proportional Hazards Regression Analysis for Mortality Over 1-Year Follow-Up

| Categories                                | Hazard ratio (95% CI) | p value  |
|-------------------------------------------|-----------------------|----------|
| Group I                                   | 1                     |          |
| Group II                                  | 2.038 (1.450-2.863)   | <0.001   |
| Group III                                 | 3.003 (2.269-3.974)   | <0.001   |
| Group IV                                  | 5.097 (3.755-6.891)   | <0.001   |

CI, confidence interval; TIMI, Thrombolysis in Myocardial Infarction; PCI, percutaneous coronary intervention. Adjusted for factors included in age, sex, hypertension, diabetes mellitus, hyperlipidemia, previous coronary artery disease, smoking, killip class 4, percutaneous coronary intervention, aspirin, beta blocker, angiotensin converting enzyme inhibitor or angiotensin receptor blocker, statin, left anterior descending artery, TIMI flow 0-1 before PCI, and complex left main disease.

Table 5.

![Fig. 1. Cox regression survival curve in patients with acute myocardial infarction over a 1-year follow-up according to each group.](image-url)
In the present study, the prevalence of in-hospital death and short- and long-term MACE was higher in patients with renal dysfunction compared to those without renal dysfunction. Furthermore, mortality at 12 months increased in renal dysfunction patients compared with non-renal dysfunction patients (HR 2.991, 95% CI 2.454-3.645, \(p<0.001\); data not shown).

Previous studies have shown that hs-CRP elevation is associated with CVD in the healthy general population.\(^{21,22}\) Recently, CKD and high hs-CRP were found to be additively associated with a higher risk of CVD and found to be independent predictors of cardiovascular events after acute coronary syndrome.\(^{11,12}\) Furthermore, CRP was independently associated with all-cause and cardiovascular mortality in dialysis patients.\(^{23}\) The rationales that inflammatory biomarkers can selectively predict cardiovascular event risk in patients with renal dysfunction are unclear. But, several studies in literature proposes that renal dysfunction may result from and directly cause a chronic inflammatory state.\(^{24}\)

The pathophysiologic changes associated with renal dysfunction, such as endothelial dysfunction and increased hemodynamic stress, may produce more vulnerable development and rupture of coronary artery plaques in the setting of increased chronic inflammation.\(^{25,26}\) We found that eGFR as determined by the CKD-EPI equation was correlated negatively with hs-CRP (\(r=-0.64, p<0.001\); data not shown). LDL-C levels, LVEF, percentage of PCI and thrombolysis, and use of beta blocker, ACEi or ARB, and statin were lower in group IV compared with the other groups. The number of involved vessels and complex left main lesions in coronary angiographic findings were higher with more decreased eGFR and increased hs-CRP. These factors may affect the grave prognosis in group IV.

Additionally, the prevalence of in-hospital death and short- and long-term MACE was consistently higher with decreasing eGFR and increasing hs-CRP. Furthermore, Cox proportional hazards model indicated that, mortality at 12 months was increased in groups II, III, and IV compared with group I (HR 2.038, 95% CI 1.450-2.863, \(p<0.001\); HR 3.003, 95% CI 2.269-3.974, \(p<0.001\); HR 2.038, 95% CI 1.450-2.863, \(p<0.001\)) and significantly differ between groups II and III (HR 1.525, 95% CI 1.099-2.117, \(p=0.012\); data not shown). Also, mortality in group IV was higher than that in group III (HR 1.735, 95% CI 1.342-2.242, \(p<0.001\); data not shown). These findings suggested that high hs-CRP levels provided prognostic information in AMI patients with or without renal dysfunction. Concomitant high hs-CRP and renal dysfunction were a highly independent predictor of mortality.

The present study has several limitations. First, Increased hs-CRP levels after AMI can not differentiate the component related to baseline inflammation from that related to myocardial necrosis. Because the extent of myocardial necrosis is a known prognostic factor after AMI, this potentially confounds the association between hs-CRP and renal dysfunction. The second limitation is that patients with acute kidney injury might have been included, because assessment of kidney function was based on a single serum creatinine value obtained at the time of presentation to the hospital. Third, we could not assess the different predictive value of elevated inflammatory biomarkers between pre-dialysis and dialysis patients by the lack of data regarding renal replacement therapy. Forth, regarding the laboratory determination, specifically hs-CRP, these determinations were done in each hospital. Therefore, there can be an inter-laboratory variability. However, we emphasize that these potential limitations should be consistently attenuated by the very large sample size of our study.

In conclusion, the present findings confirmed that high hs-CRP levels were prognostic indicators in AMI patients independent of renal dysfunction, and highlighted concomitant high hs-CRP and renal dysfunction as a predictor of short- and long-term MACE. Therefore, randomized trials are needed to determine whether individuals with kidney dysfunction and elevated levels of these inflammatory biomarker may selectively benefit through preventative strategies to reduce inflammation, and consequently CVD.\(^{27}\)

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2011-0009743), and by the National Research Foundation of Korea (NRF) grant (MRC for Gene Regulation, 2011-0030132) funded by the Korea government (MSIP).

Korea Acute Myocardial infarction Registry (KAMIR) Investigators are; Myung Ho Jeong, MD, Young Keun Ahn, MD, Sung Chull Chae, MD, Jong Hyun Kim, MD, Seung Ho Hur, MD, Young Jo Kim, MD, In Whan Seong, MD, Dong Hoon Choi, MD, Jei Keon Chae, MD, Taek Jong Hong, MD, Jae Young Rhew, MD, Doo Il Kim, MD, In Ho Chae, MD, Jung Han Yoon, MD, Bon Kwon Koo,
MD, Byung Ok Kim, MD, Myoung Yong Lee, MD, Kee Sik Kim, MD, Jin Yong Hwang, MD, Myeong Chan Cho, MD, Seok Kyu Oh, MD, MD, Nae Hee Lee, MD, Kyoungho Jeong, MD, Seung Jea Tahk, MD, Jang Ho Bae, MD, Seung Woon Rha, MD, Keum Soo Park, MD, Chong Jin Kim, MD, Kyoo Rok Han, MD, Tae Hoon Ahn, MD, Moo Hyun Kim, MD, Ki Bae Seung, MD, Wook Sung Chung, MD, Ju Young Yang, MD, Chong Yun Rhim, MD, Hyeon Cheol Gwon, MD, Seong Wook Park, MD, Young Youp Koh, MD, Seung Jae Joo, MD, Soo Joong Kim, MD, Dong Kyu Jin, MD, Jin Man Cho, MD, Byung Ok Kim, MD, Sang-Wook Kim, MD, Jeong Kyung Kim, MD, Tae Ik Kim, MD, Deug Young Nah, MD, Si Hoon Park, MD, Sang Hyun Lee, MD, Seung Uk Lee, MD, Hang-Jae Chung, MD, Jang Hyun Cho, MD, Seung Won Jin, MD, Yang Soo Jang, MD, Jeong Gwan Cho, MD, and Seung Jung Park, MD.

REFERENCES

1. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension 2003;42:1050-65.
2. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol 2006;17:2034-47.
3. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-305.
4. McCullough PA. Why is chronic kidney disease the “spoiler” for cardiovascular outcomes? J Am Coll Cardiol 2003;41:725-8.
5. Arici M, Walls J. End-stage renal disease, atherosclerosis, and cardiovascular mortality: is C-reactive protein the missing link? Kidney Int 2001;59:407-14.
6. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115-26.
7. Muntner P, Hamm LL, Kusek JW, Chen J, Whelton PK, He J. The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. Ann Intern Med 2004;140: 9-17.
8. Menon V, Greene T, Wang X, Pereira AA, Marcovina SM, Beck GJ, et al. C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. Kidney Int 2005;68:766-72.
9. Caravaca F, Martin MV, Barroso S, Ruiz B, Hernández-Gallego R. Do inflammatory markers add predictive information of death beyond that provided by age and comorbidity in chronic renal failure patients? Nephrol Dial Transplant 2006;21:1575-81.
10. Goel K, Lemmon RJ, Tilbury RT, Squires RW, Thomas RJ. Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community. Circulation 2011;123:2344-52.
11. Mielniczuk LM, Pfeffer MA, Lewis EF, Blazing MA, de Lemos JA, Shui A, et al. Estimated glomerular filtration rate, inflammation, and cardiovascular events after an acute coronary syndrome. Am Heart J 2008;155:725-31.
12. Mielniczuk LM, Pfeffer MA, Lewis EF, Blazing MA, de Lemos JA, Mohanavelu S, et al. Acute decline in renal function, inflammation, and cardiovascular risk after an acute coronary syndrome. Clin J Am Soc Nephrol 2009;4:1811-7.
13. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359:2195-207.
14. Yang EY, Nambi V, Tang Z, Virani SS, Boerwinkle E, Hoogeveen RC, et al. Clinical implications of JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) in a U.S. population insights from the ARIC (Atherosclerosis Risk in Communities) study. J Am Coll Cardiol 2009;54: 2388-95.
15. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
16. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 Suppl 1):S1-266.
17. Shlipak MG, Fried LF, Cushman M, Manolio TA, Peterson D, Stehman-Breen C, et al. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. JAMA 2005;293:1737-43.
18. DeFilippi C, van Kimmenade RR, Pinto YM. Amino-terminal pro-B-type natriuretic peptide testing in renal disease. Am J Cardiol 2008;101:82-8.
19. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. Am J Kidney Dis 2003;42:864-81.
20. Bae EH, Lim SY, Cho KH, Choi JS, Kim CS, Park JW, et al. GFR and cardiovascular outcomes after acute myocardial infarction: results from the Korea Acute Myocardial Infarction Registry. Am J Kidney Dis 2012;59:795-802.
21. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557-65.
22. Daresh J, Wheeler JG, Hirschfield GM, Esa S, Eiriksdottir G, Rumlsey A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 2004;350:1387-97.
23. Punichi V, Rizza GM, Paoletti S, Bigazzi R, Aloisi M, Barsotti G, et al. Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies. Results from the RISCADIV study. Nephrol Dial Transplant 2008;23:2337-43.
24. Klahr S, Norrissey JI. The role of vasoactive compounds, growth factors and cytokines in the progression of renal disease. Kidney Int Suppl 2000;75:S7-14.
25. Libby P. Inflammation in atherosclerosis. Nature 2002;420:868-74.
26. Rajavashisth TB, Liao JK, Galis ZS, Tripathi S, Laufs U, Tripathi J, et al. Inflammatory cytokines and oxidized low density lipoproteins increase endothelial cell expression of membrane type 1-ma-
trix metalloproteinase. J Biol Chem 1999;274:11924-9.
27. Ridker PM, MacFadyen J, Cressman M, Glynn RJ. Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. J Am Coll Cardiol 2010;55:1266-73.