A High Level of Blood Urea Nitrogen Is a Significant Predictor for In-hospital Mortality in Patients with Acute Myocardial Infarction

Yu Horiuchi, MD, Jiro Aoki, MD, Kengo Tanabe, MD, Koichi Nakao, MD, Yukio Ozaki, MD, Kazuo Kimura, MD, Junya Ako, MD, Satoshi Yasuda, MD, Teruo Noguchi, MD, Satoru Suwa, MD, Kazuteru Fujimoto, MD, Yasuharu Nakama, MD, Takashi Morita, MD, Wataru Shimizu, MD, Yoshihiko Saito, MD, Atsushi Hirohata, MD, Yasuhiro Morita, MD, Teruo Inoue, MD, Atsunori Okamura, MD, Masaaki Uematsu, MD, Kazuhito Hirata, MD, Yoshisato Shibata, MD, Michikazu Nakai, PhD, Kunihiro Nishimura, MD, Yoshihiro Miyamoto, MD and Masaharu Ishihara, MD on behalf of J-MINUET investigators

Summary
High levels of blood urea nitrogen (BUN) have been demonstrated to significantly predict poor prognosis in patients with acute decompensated heart failure. However, this relationship has not been fully investigated in patients with acute myocardial infarction (AMI). We investigated whether a high level of BUN is a significant predictor for in-hospital mortality and other clinical outcomes in patients with AMI. The Japanese registry of acute myocardial infarction diagnosed by Universal Definition (J-MINUET) is a prospective, observational, multicenter study conducted in 28 institutions, in which 3,283 consecutive AMI patients were enrolled. We excluded 98 patients in whom BUN levels were not recorded at admission and 190 patients who were undergoing hemodialysis. A total of 2,995 patients were retrospectively analyzed. BUN tertiles were 1.5-14.4 mg/dL (tertile 1), 14.5-19.4 mg/dL (tertile 2), and 19.5-240 mg/dL (tertile 3). Increasing tertiles of BUN were associated with stepwise increased risk of in-hospital mortality (2.5, 5.1, and 11%, respectively; \( P < 0.001 \)). These relationships were also observed after adjusting for reduced estimated glomerular filtration rate (estimated GFR < 60 mL/minute/1.73 m\(^2\)) or Killip classifications. In multivariable analysis, high levels of BUN significantly predicted in-hospital mortality, after adjusting for creatinine and other known predictors (BUN tertile 3 versus 1, adjusted odds ratio [OR]: 2.59, 95% confidence interval [95% CI]: 1.57-4.25, \( P < 0.001 \); BUN tertile 2 versus 1, adjusted OR: 1.60, 95% CI: 0.94-2.73, \( P = 0.081 \)). A high level of BUN could be a useful predictor of in-hospital mortality in AMI patients.

Key words: J-MINUET

Acute myocardial infarction (AMI) is the leading cause of death worldwide.1-12 Because considerable variability exists in the profiles of patients with AMI, risk stratification is crucial to provide an optimal level of care and the choice of interventional and medical treatments.2,3 Numerous risk stratification models have been developed for AMI patients. These models are composed of important prognostic factors, including age, sex, angina, risk factors for coronary artery disease, signs of heart failure, systolic blood pressure, heart rate, cardiac arrest during presentation, ST-segment change, cardiac enzymes, and serum creatinine.6-10 Creatinine is a marker of renal function, and the relationship between renal dysfunction and increased mortality is well established in AMI patients.5 Another creatinine-based estimation of renal function, estimated glomerular filtration ratio (GFR), has also been shown to be correlated with prognosis of AMI patients.1,13 Blood urea nitrogen (BUN) is an addi-

From the 1Mitsui Memorial Hospital, Tokyo, 2Saiseikai Kumamoto Hospital Cardiovascular Center, Kumamoto, 3Fujita Health University Hospital, Aichi, 4Yokohama City University Medical Center, Kanagawa, 5Kitasato University, Kanagawa, 6National Cerebral and Cardiovascular Center, Osaka, 7Juntendo University Shizuoka Hospital, Shizuoka, 8National Hospital Organization Kumamoto Medical Center, Kumamoto, 9Hiroshima City Hospital, Hiroshima, 10Osaka General Medical Center, Osaka, 11Nippon Medical School, Tokyo, 12Nara Medical University, Nara, 13The Sakakibara Heart Institute of Okayama, Okayama, 14Ogaki Municipal Hospital, Gifu, 15Dokkyo Medical University, Tochigi, 16Sakurabashi Watanabe Hospital, Osaka, 17Osaka National Hospital, Osaka, 18Okinawa Prefectural Chubu Hospital, Okinawa, 19Miyazaki Medical Association Hospital, Miyazaki and 20Hyogo College of Medicine, Hyogo, Japan.

This study was supported by the Intramural Research Fund, grant number 23-4-5, for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center.

Address for correspondence: Kengo Tanabe, MD, Division of Cardiology, Mitsui Memorial Hospital, Kanda-Izumi-cho 1, Chiyoda-ku, Tokyo 101-8643, Japan. E-mail: kengo-t@z5.so-net.ne.jp

Received for publication January 6, 2017. Revised and accepted May 12, 2017.

Released in advance online on J-STAGE February 20, 2018.

doi: 10.1536/ihj.17-009

All rights reserved by the International Heart Journal Association.
tional maker of renal function. In patients with acute decompensated heart failure (ADHF), a high BUN level is a risk factor for poor prognosis. Because BUN reflects both GFR and neurohormonal activations, it can serve as a stronger marker of mortality in ADHF patients compared with creatinine.14-17 In AMI patients, the relationship between BUN and poor clinical outcomes has not yet been fully elucidated. In a retrospective analysis of the Japanese registry of acute Myocardial Infarction diagnosed by Universal Definition (J-MINUET), we evaluated whether a high level of BUN is a significant predictor for inhospital mortality and other clinical outcomes in patients with AMI and whether it adds prognostic information to initial evaluation of AMI patients.

Methods

The study design and primary results of the J-MINUET study have been published previously.18 Briefly, J-MINUET was a prospective, observational, multicenter study conducted in 28 institutions, in which 3,283 consecutive AMI patients were enrolled between July 2012 and March 2014. These patients were followed up until discharge. AMI was diagnosed by the European Society of Cardiology (ESC)/ACC Foundation (ACCF)/American Heart Association (AHA)/World Heart Foundation Task Force for the Universal Definition of Myocardial Infarction.19 AMI was defined as detection of the rise and/or fall of cardiac biomarkers with at least 1 value above the 99th percentile of the upper reference limit, observed together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia, electrocardiography (ECG) changes indicative of new ischemia, development of pathological Q waves in the ECG, and imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities. Patients were evaluated at admission for baseline characteristics, which included age, sex, body weight, ST-elevated MI (STEMI), ventricular tachycardia/ventricular fibrillation (VT/VF) at admission, vital signs, Killip classification, concomitant disease, smoking history, previous medical history, laboratory data, and medication. STEMI was defined as the presence of new ST elevation at the J point in at least 2 contiguous leads ≥ 2 mm (0.2 mV) in men or ≥ 1.5 mm (0.15 mV) in women in leads V2-3 and/or ≥ 1 mm (0.1 mV) in other contiguous chest leads or the limb leads.20,21 New left bundle branch block was regarded as equivalent to ST elevation. The endpoints were in-hospital mortality and major cardiovascular events (MACE), which was defined as a composite of all-cause mortality, cardiac failure, VT/VF, and bleeding during hospitalization. Cardiac failure was defined as congestive heart failure and/or cardiogenic shock that required treatment. The J-MINUET study was conducted in accordance with the Declaration of Helsinki, and its protocol was approved by the ethics committees of each participating institution.

Continuous variables are described as mean ± standard deviation and categorical variables are described as percentages. Non-normally distributed data are expressed as medians and interquartile ranges. To compare characteristics across tertiles of BUN levels, we used one-way ANOVA tests for normally distributed continuous variables, Kruskal-Wallis tests for non-normally distributed continuous variables, and chi-square tests for categorical variables. We investigated the association between tertiles of BUN level and clinical outcomes, including in-hospital mortality and MACE. We also investigated the association between tertiles of BUN level and in-hospital mortality by stratifying normal or reduced estimated GFR (< 60 mL/minute/1.73 m²), or Killip classification 1 to 4. Probability values of < 0.05 were considered to be statistically significant. We performed multivariable logistic regression analysis to evaluate whether high BUN levels were a significant predictor for in-hospital mortality. Factors with a P value of < 0.05 by univariate analysis were included in regression models (Tertiles of BUN, age ≥ 65 years, male gender, STEMI, VT/VF at admission, Killip class 2-4, dyslipidemia, current smoking, history of stroke, creatinine, glucose, diuretics, anti-aldosterone, and insulin).

To avoid multicollinearity, we excluded the following variables: body weight, systolic blood pressure, diastolic blood pressure, heart rate, and hemoglobin. Missing values were imputed by using the multivariable normal model, using the chained equations approach.22 Multiple imputation is used to replace each missing value with two or more acceptable values, representing a distribution of possibilities of covariates. Multiple imputation method is a more sophisticated imputation method than case-wise deletion method, which analyzes the cases with complete information, or single imputation method.23 We used backward stepwise elimination to exclude non-significant variables to perform a multivariable logistic regression analysis. The criteria for inclusion and exclusion of variables were 0.05 and 0.20, respectively. All statistical analysis was performed using STATA version 13 (College Station, Texas, USA).

Results

We excluded 98 patients in whom BUN levels were not recorded at admission, and a further 190 patients who were undergoing hemodialysis. A total of 2,995 patients were retrospectively analyzed to investigate the relationship among BUN level and clinical outcomes. The flowchart of patients who met exclusion or inclusion criteria is shown in Figure 1. The median age of patients was 69 (60, 78) years, 75.6% were men, 28.7% had diabetes mellitus, and 69.3% had STEMI. We performed immediate coronary angiography in 94.0% and percutaneous coronary intervention (PCI) in 86.2% of patients. Multivessel disease was observed in 43.3% of patients. The maximum level of creatinine kinase was 1473 (536, 3231) IU/L and the median length of hospitalization was 14 (9, 21) days. In-hospital mortality was 6.3%. Baseline characteristics according to BUN tertiles are shown in Table I. The BUN tertiles were 1.5 to 14.4 mg/dL (tertile 1), 14.5 to 19.4 mg/dL (tertile 2), and 19.5 to 240 mg/dL (tertile 3). Increasing BUN levels were associated with clinical features, including older age, a higher percentage of men, lower body weight, and a lower percentage of STEMI. Increasing BUN levels were also associated with physical findings, such as lower systolic and diastolic blood pres-
sure, higher heart rate, and more severe Killip classification. Concomitant diseases and previous histories were more frequently observed in patients with higher BUN levels. With regard to laboratory data, lower hemoglobin, higher creatinine, lower estimated GFR, higher glucose, higher hemoglobin A1c, lower serum sodium, higher serum potassium, and a higher percentage of positive troponin were more frequently associated with higher BUN levels.

Higher BUN levels were associated with a stepwise increase in worse outcomes. In-hospital mortality of the BUN tertiles was 2.5%, 5.1%, and 11%, respectively ($P < 0.001$; Table II). Patients with higher BUN levels were more likely to experience MACE (10%, 16%, and 29%, $P < 0.001$). Cardiac failure was more frequently observed in patients with higher BUN levels (7.5%, 14%, and 24%, $P < 0.001$), although these relationships were not observed for VT/VF and bleeding (Table II). The scatter diagram that plots BUN versus creatinine is shown in Figure 2, where patients with in-hospital death are plotted in red. BUN was moderately correlated with creatinine ($r = 0.634, P < 0.001$). The relationship between BUN level and in-hospital mortality was statistically significant among patients with reduced estimated GFR (7.8%, 10%, and 14%, $P = 0.031$). Among patients with estimated GFR $\geq 60$ mL/minute/1.73 m$^2$, these relationships were also observed, but they did not reach statistical significance (1.7%, 2.1%, and 3.7%, $P = 0.149$; Figure 3). Stratification of patients by Killip classification showed that higher BUN levels were associated with higher rates of in-hospital mortality (Killip class 1; 1.1%, 1.6%, and 2.7%, $P = 0.063$; Killip class 2; 2.6%, 4.8%, and 15%, $P = 0.004$; Killip class 3; 0%, 14%, and 18%, $P = 0.085$; Killip class 4; 23%, 32%, and 44%, $P = 0.011$; Figure 4).

Multivariable logistic regression analysis showed that higher BUN levels were associated with increased in-hospital mortality (BUN tertile 3 versus 1, adjusted odds ratio [OR]: 2.59, 95% confidence interval [95% CI]: 1.57-4.25, $P < 0.001$; BUN tertile 2 versus 1, adjusted OR: 1.60, 95% CI: 0.94-2.73, $P = 0.081$; Table III). Similar relationships between BUN and in-hospital mortality were observed when reduced estimated GFR ($< 60$ mL/minute/1.73 m$^2$) was added to the multivariable analysis (BUN tertile 3 versus 1, adjusted OR: 1.82, 95% CI: 1.07-3.09, $P = 0.028$; BUN tertile 2 versus 1, adjusted OR: 1.34, 95% CI: 0.78-2.32, $P = 0.287$).

**Discussion**

Our study revealed that a high level of BUN was associated with an increase of in-hospital mortality and MACE in AMI patients and was a significant predictor for in-hospital mortality, independent of serum creatinine, estimated GFR, and other known predictors.

Patients with AMI have a wide spectrum of clinical characteristics, which leads to a great variability in cardiovascular outcomes.2-5) To provide an optimal level of treatment for such patients with complex profiles, numerous risk stratification models have been developed. The Thrombolysis in Myocardial Infarction (TIMI) and Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (PURSUIT) risk scores are risk stratification models for patients with unstable angina/non-STEMI.7,8,24) The Global Registry of Acute Coronary Events (GRACE) risk score is a risk stratification model for ACS patients with or without ST segment elevation.6,20) These models comprise several important predictors for worse cardiovascular outcomes in AMI patients: age, sex, angina, risk factors for coronary artery disease, signs of heart failure, systolic blood pressure, heart rate, cardiac arrest during presentation, ST-segment change, cardiac enzymes, and serum creatinine.6-10,24)

Creatinine is traditionally used as a marker of renal function, and reduced renal function is a known predictor for worse outcomes in ACS patients.8 Estimated GFR, which is calculated by serum creatinine, is another marker...
of renal function. Reduced estimated GFR has also been reported to be a predictor for poor prognosis in ACS patients. 

However, renal function estimated by serum creatinine levels may not perfectly reflect actual GFR. Serum creatinine levels are influenced by several factors, such as age, sex, muscle mass, and diet. Although estimated GFR improves the assessment of renal function, overestimation and underestimation still exist among patients with a wide range of serum creatinine levels.

BUN is another marker of renal function, and its concentration is determined by the balance of excretion and reabsorption in the kidneys. Reabsorption of BUN is

| Table 1. Baseline Characteristics |
|----------------------------------|
|                       | Tertile 1 (1.5 to 14.4 mg/dL) | Tertile 2 (14.5 to 19.4 mg/dL) | Tertile 3 (19.5 to 240 mg/dL) | P value | Number of missing |
| Age (years)             | 63 (54, 72)                  | 69 (61, 77)                  | 75 (66, 82)                  | <0.001  | 0                |
| Age ≥ 65 years (%)      | 462 (46.3%)                  | 649 (64.2%)                  | 778 (79.0%)                  | <0.001  | 0                |
| Male gender (%)         | 221 (22.1%)                  | 235 (23.2%)                  | 275 (27.9%)                  | 0.006   | 0                |
| Body weight (kg)        | 65.2 ± 13.6                  | 63.3 ± 13.1                  | 59.4 ± 12.8                  | <0.001  | 49 (1.7%)        |
| STEMI (%)               | 718 (71.9%)                  | 701 (69.3%)                  | 656 (66.6%)                  | 0.039   | 0                |
| VT/VF at admission (%)  | 45 (4.5%)                    | 63 (6.3%)                    | 56 (5.7%)                    | 0.218   | 4 (0.1%)         |

Vital signs

- Systolic blood pressure (mmHg): 144.3 ± 31.5 vs 139.3 ± 32.4 vs 134.7 ± 34.2
- Diastolic blood pressure (mmHg): 84.7 ± 21.1 vs 81.3 ± 20.9 vs 75.8 ± 21.4
- Heart rate (bpm): 78.1 ± 18.2 vs 77.6 ± 20.5 vs 80.3 ± 22.9

Killip classification

- Class 1 (%): 835 (83.9%) vs 793 (79.1%) vs 634 (64.5%)
- Class 2 (%): 77 (7.7%) vs 83 (8.3%) vs 115 (11.7%)
- Class 3 (%): 23 (2.3%) vs 35 (3.5%) vs 99 (10.1%)
- Class 4 (%): 60 (6.0%) vs 91 (9.1%) vs 135 (13.7%)

Concomitant disease

- Hypertension (%): 609 (61.4%) vs 622 (62.1%) vs 738 (75.5%)
- Diabetes (%) 226 (23.1%) vs 266 (26.7%) vs 352 (36.4%)
- Dyslipidemia (%) 513 (51.9%) vs 545 (54.4%) vs 478 (49.2%)
- Current smoking (%) 461 (47.7%) vs 316 (32.2%) vs 249 (26.1%)

Previous history

- Previous MI (%) 79 (8.0%) vs 116 (11.5%) vs 154 (15.7%)
- Previous PCI (%) 109 (11.4%) vs 144 (14.9%) vs 173 (18.3%)
- Previous CABG (%) 7 (0.7%) vs 19 (2.0%) vs 48 (5.0%)
- Stroke (%) 66 (7.0%) vs 79 (8.2%) vs 119 (12.7%)

Laboratory data

- Hemoglobin (mg/dL): 14.5 (13.3, 15.6) vs 14.1 (12.8, 15.2) vs 12.6 (11, 14.1)
- Creatinine (mg/dL): 0.72 (0.61, 0.85) vs 0.85 (0.70, 1.02) vs 1.14 (0.86, 1.75)
- estimated GFR (mL/minute/1.73 m²): 80.6 (68.7, 94.1) vs 65.9 (53.6, 79.4) vs 45.0 (28.2, 62.1)
- estimated GFR < 60mL/minute/1.73 m² (%) 129 (12.9%) vs 389 (38.5%) vs 714 (72.5%)
- Glucose (mg/dL): 143 (118, 190) vs 152 (123, 197) vs 158 (123, 224)
- Hemoglobin A1c (%) 5.8 (5.4, 6.5) vs 5.9 (5.5, 6.6) vs 6.0 (5.6, 6.7)
- Serum sodium (mEq/L): 140 (137, 141) vs 140 (138, 141) vs 139 (137, 141)
- Serum potassium (mEq/L): 3.9 (3.7, 4.2) vs 3.9 (3.6, 4.2) vs 4.2 (3.9, 4.7)
- Positive troponin at admission (%) 72 (73.0%) vs 686 (67.9%) vs 773 (78.6%)
- Maximum creatinine kinase (U/L): 1508 (531-3274) vs 1461 (552-3232) vs 1487 (534-3172)

Medication at admission

- Antiplatelet (%) 175 (17.5%) vs 225 (22.3%) vs 371 (37.7%)
- Anticoagulant (%) 14 (1.4%) vs 14 (1.4%) vs 39 (4.0%) 0.001 0
- ACE-inhibitor (%) 54 (5.4%) vs 55 (5.4%) vs 72 (73%) 0.126 0
- Angiotensin receptor blocker (%) 185 (18.5%) vs 228 (22.3%) vs 361 (36.7%)
- Calcium channel blocker (%) 259 (25.9%) vs 328 (32.4%) vs 429 (43.6%)
- Beta-blocker (%) 87 (8.7%) vs 116 (11.5%) vs 194 (19.7%)
- Diuretics (%) 33 (3.3%) vs 47 (4.7%) vs 165 (16.8%)
- Nitric oxide (%) 38 (3.8%) vs 60 (5.9%) vs 91 (9.2%)
- Nicorandil (%) 30 (3.0%) vs 39 (3.9%) vs 59 (6.0%)
- Anti-aldosterone (%) 10 (1.0%) vs 10 (1.0%) vs 21 (2.1%)
- Statins (%) 189 (19.0%) vs 234 (23.5%) vs 270 (27.8%)
- Insulin (%) 30 (3.0%) vs 30 (3.0%) vs 79 (8.0%)
- Proton pump inhibitor (%) 100 (10.1%) vs 131 (13.1%) vs 222 (22.9%)

STEMI indicates ST-elevated myocardial infarction; VT, ventricular tachycardia; VF, ventricular fibrillation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; and ACE, angiotensin converting enzyme.
In the heartJ
March 2018
BUN PREDICTS MORTALITY IN AMI PATIENTS

Table II. In-hospital Clinical Outcomes

|                        | Tertile 1 | Tertile 2 | Tertile 3 | P     |
|------------------------|-----------|-----------|-----------|-------|
| In-hospital mortality  | 25 (2.5%) | 52 (5.1%) | 112 (11%) | <0.001|
| MACE                   | 104 (10%) | 165 (16%) | 287 (29%) | <0.001|
| Cardiac failure        | 74 (7.5%) | 140 (14%) | 231 (24%) | <0.001|
| VT/VF                  | 30 (3.0%) | 36 (3.6%) | 47 (4.8%) | 0.103 |
| Bleeding               | 24 (2.4%) | 15 (1.5%) | 36 (3.7%) | 0.008 |

MACE indicates major adverse cardiovascular events; VT, ventricular tachycardia; and VF, ventricular fibrillation.

Figure 2. Scatter diagram that plots BUN versus creatinine. The patients with in-hospital death are plotted in red. BUN was moderately correlated with creatinine ($r = 0.634, P < 0.001$).

closely linked to water reabsorption at the distal nephron under the influence of antidiuretic hormone, which is affected by angiotensin II. Norepinephrine may also be increased in patients with high BUN levels. In addition to reduced GFR, high BUN levels are related to activation of the renin-angiotensin-aldosterone and sympathetic nerve systems, which may be caused by renal hypoperfusion from hypovolemia, renovascular disease, and reduced cardiac output. Therefore, BUN could serve as an encompassing marker by reflecting impaired cardiorenal function and neurohormonal activation. Among ADHF patients, a high BUN level has been demonstrated to be a stronger marker of mortality than creatinine. These relationships have also been demonstrated in patients with ACS. Kirtane, et al. reported that BUN is an independent predictor for poor clinical outcomes in ACS patients with normal or mildly reduced renal function. High BUN levels were associated with increased mortality, independent of serum creatinine and estimated GFR. However, in this study, patients with serum creatinine > 1.6 mg/dL or estimated GFR < 40 mL/minute were excluded, and all patients were treated with oral IIb/IIIa inhibitors. These results could not be extrapolated to patients with severely impaired renal function or treated with other antiplatelet regimens. Saygitow, et al. also reported that an increased BUN level is a more significant risk factor for ACS patients than is an increase of creatinine, although these findings were results from a single-center study and estimated GFR was not evaluated. Smith, et al. demonstrated that increased BUN levels is a significant predictor of mortality in AMI patients, while the study includes only elderly patients (age ≥ 65 years). In real-world settings of AMI patients, the relationships between BUN and clinical outcomes have not been fully elucidated.

In the present study, we investigated AMI patients who enrolled in a prospective, observational, multicenter registry. Younger patients (age < 65 years) and patients with severely impaired renal function were not excluded. These patients were treated with standard treatment, including PCI and medical therapy. Therefore, these patients reflect a more representative AMI population than do prior studies. Increased BUN levels were associated with lower blood pressure, higher heart rate, and more severe Killip classification. These unfavorable hemodynamic conditions may lead to activation of the renin-angiotensin-aldosterone and sympathetic nerve systems, and can cause reabsorption of BUN at distal nephron. In addition, increasing ter-
in-hospital mortality and MACE. With regard to components of MACE, patients with higher BUN levels more frequently had cardiac failure. High BUN levels at admission, which indicate impaired cardiorenal functions and unfavorable neurohormonal activation, could be prognostic for cardiac failure during hospitalization. Furthermore, in multivariable analysis, a high level of BUN was demonstrated to be a significant predictor for in-hospital mortality, after adjusting for creatinine, estimated GFR, and other known predictors. Although a high level of creatinine was significantly associated with in-hospital mortality in univariate analysis, it was not a significant predictor for in-hospital mortality after adjusting for the other covariates including BUN. These results suggest that a high level of BUN could be a useful predictor for inhospital mortality in AMI patients, and adds important prognostic information for the initial evaluation of AMI patients.

In the analysis, current smoking was associated with better prognosis even after the adjustment for possible confounding factors. In AMI patients, several studies have reported that the outcomes of smokers were the same or better than those of nonsmokers. These findings were reported as “smoker’s paradox.” Smokers were younger than nonsmokers. In addition, smokers were usually less likely to have diabetes mellitus and hypertension than nonsmokers. These differences in baseline characteristics can be the causes of the paradox. In the present study, smokers were younger than nonsmokers. Smokers were less likely to be associated with hypertension, chronic kidney disease, previous MI, previous PCI, previous CABG, and multivessel disease than nonsmokers (data not shown). These cofounders might not be fully adjusted in multivariable analysis.

The present study has several limitations. First, this analysis was a retrospective study and it is possible that unidentified cofounders were not fully adjusted and influenced the result. Several known risk factors, such as symptoms and ECG changes, were not recorded in the registry. Possible cofounders, such as liver enzymes, were not recorded. Second, several risk scores (GRACE, TIMI, and PURSUIT risk score) have been utilized for the stratification of ACS patients. Because symptoms and ECG changes were not recorded in the reg-
BUN PREDICTS MORTALITY IN AMI PATIENTS

Table III. Multivariable Analysis of Predictors for In-hospital Mortality

| Variables                  | OR      | 95% CI          | P value | Adjusted OR | 95% CI          | P value |
|----------------------------|---------|-----------------|---------|-------------|-----------------|---------|
| Blood urea nitrogen        |         |                 |         |             |                 |         |
| Tertile 2 to 1             | 2.11    | 1.30-3.43       | 0.003   | 1.60        | 0.94-2.73       | 0.081   |
| Tertile 3 to 1             | 5.00    | 3.21-7.78       | < 0.001 | 2.59        | 1.57-4.25       | < 0.001 |
| Age ≥ 65 years             | 2.82    | 1.93-4.12       | < 0.001 | 2.06        | 1.32-3.22       | 0.001   |
| Male gender                | 0.58    | 0.43-0.79       | 0.001   |             |                 |         |
| STEMI                      | 1.45    | 1.03-2.05       | 0.034   | 1.51        | 1.02-2.22       | 0.037   |
| VT/VF at admission         | 7.05    | 4.81-10.33      | < 0.001 | 3.37        | 2.14-5.33       | < 0.001 |
| Killip class 2-4           | 14.6    | 10.2-21.0       | < 0.001 | 8.08        | 5.46-11.94      | < 0.001 |
| Dyslipidemia               | 0.45    | 0.34-0.64       | < 0.001 | 0.54        | 0.38-0.78       | 0.001   |
| Current smoking            | 0.50    | 0.34-0.74       | 0.001   | 0.54        | 0.35-0.83       | 0.005   |
| Stroke                     | 2.05    | 1.38-3.05       | < 0.001 |             |                 |         |
| Creatinine (per mg/dL)     | 1.15    | 1.08-1.22       | < 0.001 |             |                 |         |
| Glucose (per mg/dL)        | 1.01    | 1.01-1.01       | < 0.001 | 1.00        | 1.00-1.00       | < 0.001 |
| Diuretics                  | 1.70    | 1.09-2.67       | 0.021   |             |                 |         |
| Anti-aldosterone           | 3.71    | 1.69-8.16       | 0.001   | 2.99        | 1.18-7.55       | 0.021   |
| Insulin                    | 2.02    | 1.17-3.47       | 0.011   |             |                 |         |

CI indicates confidence interval; OR, odds ratio; STEMI, ST-elevated myocardial infarction; VT, ventricular tachycardia; and VF, ventricular fibrillation.

Acknowledgments

The authors thank all the enrolled patients, participating cardiologists, medical, and other staff who have contributed to this study. The J-MINUET investigators are listed in Appendix 1.

Disclosure

Conflicts of interest: Kengo Tanabe has received remuneration from Abbott Vascular, Terumo, Kaneka, Zeon, Sanofi, Daiichi-Sankyo, and Tanabe-Mitsubishi. Yoshihiko Saito has received honoraria from Otsuka Pharmaceutical Co., Ltd, Takeda Pharmaceutical Co., Ltd, Mitsubishi Tanabe Pharma Corporation, Daiichi Sankyo Co., Ltd, and Novartis Pharma. K.K., has received research funding from Grants-in-Aid for Scientific Research (B), Challenging Exploratory Research (FY 2015) and Health, Labor and Welfare Scientific Research, has received subsidies or donations from Daiichi Sankyo Co., Ltd, Bayer Holding Ltd, Baxter Ltd, Otsuka Pharmaceutical Co., Ltd, Kyowa Hakko Kirin Co., Ltd, Dainippon Sumitomo Pharma Co., Ltd, Astellas Pharma Inc, Takeda Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd, Teijin Pharma Ltd, Mitsubishi Tanabe Pharma Corporation, Eisai Co., Ltd and ZERIA Pharmaceutical Co., Ltd and belongs to endowed department by MSD K.K. a subsidiary of Merck & Co., Inc. Masaharu Ishihara has received lecture fees from MSD K. K., Bayer Yakuhin, Ltd., Daiichi Sankyo Co., Ltd. Abbott Vascular Japan Co., Ltd., Sanofi K.K. and Kissei Pharmaceutical Co., Ltd, has received research funding from Abbott Vascular Japan Co., Ltd., Boston Scientific Japan K.K., Sanofi K.K., MSDK K.K., Bayer Yakuhin, Ltd., Daiichi Sankyo Co., Ltd., Goodman Co., LTD. and MID, Inc.

Appendix

J-MINUET Investigators: Masaharu Ishihara, Hyogo College of Medicine (principle investigator); Nobuaki Kobuk, Sapporo Medical University; Tadayo Sato, Akita Medical Center; Tero Inoue, Dokkyo Medical University; Shigeru Oshima, Gunma Prefectural Cardiovascular Center; Hiroshi Funayama, Saitama Medical Center Ichiji Medical University; Ken Kozuma, Hinojuki Kyono, Teikyo University; Wataru Shimizu, Nippon Medical School; Satoru Suwa, Juntendo University Shizuoka Hospital; Kengo Tanabe, Mitsui Memorial Hospital; Tetsuya Tobaru, Sakakibara Heart Institute; Kazuo Kimura, Yokohama City University Medical Center; Junya Ako, Kitasato University; Tadaya Sato, Akita Medical Center; Hiroshi Funayama, Saitama Medical Center Ichiji Medical University; Ken Kozuma, Hinojuki Kyono, Teikyo University; Wataru Shimizu, Nippon Medical School; Satoru Suwa, Juntendo University Shizuoka Hospital; Kengo Tanabe, Mitsui Memorial Hospital; Tetsuya Tobaru, Sakakibara Heart Institute; Kazuo Kimura, Yokohama City University Medical Center; Junya Ako, Kitasato University; Mafumi Owa, Suwa Red Cross Hospital; Yasuhiro Morita, Ogaki Municipal Hospital; Yukio Ozaki, Fujita Health University; Satoshi Yasuda, Teruo Noguchi, Masashi Fujiwara, Yoshihiro Miyamoto, Kunihiro Nishimura, National Cerebral and Cardiovascular Center; Junichi Kotani, Osaka University Graduate School of Medi-
References

1. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2013 update: a report from the American Heart Association. Circulation 2013; 127: e6-245.

2. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012; 33: 2560-619.

3. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 267-315.

4. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013; 127: e362-25.

5. ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 130: e344-26.

6. Granger CB, Goldberg RJ, Dabbous O, et al; Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003; 163: 2345-53.

7. Calvin JE, Klein LW, VandenBerg BJ, et al. Risk stratification in unstable angina. Prospective validation of the Braunwald classification. JAMA 1995; 273: 136-41.

8. Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndrome without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. Circulation 2000; 101: 2557-67.

9. Shiraishi J, Nakamura T, Shikuma A, et al. Relationship between mean blood pressure at admission and in-hospital outcome after primary percutaneous coronary intervention for acute myocardial infarction. Int Heart J 2016; 57: 547-52.

10. Lee PT, Chao TH, Huang YL, et al. Analysis of the clinical characteristics, management, and causes of death in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention from 2005 to 2014. Int Heart J 2016; 57: 541-6.

11. Gibson CM, Pinto DS, Murphy SA, et al; TIMI Study Group. Association of creatinine and creatinine clearance on presentation in acute myocardial infarction with subsequent mortality. J Am Coll Cardiol 2003; 42: 1535-43.

12. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004; 351: 1285-95.

13. Al Suwaidi J, Reddan DN, Williams K, et al; GUSTO-IIB, GUSTO-III, PURSUIT. Global Use of Strategies to Open Occluded Coronary Arteries. Platelet glycoprotein Ib/IIa in unstable angina: Receptor suppression using integrilin therapy; PARAGON-A Investigators. Platelet Ib/IIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network. Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. Circulation 2002; 106: 974-80.

14. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ; ADHERE Scientific Advisory Committee, Study Group, and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA 2005; 293: 572-80.

15. Chen CY, Yoshida A, Asakura M, et al. Serum blood urea nitrogen and plasma brain natriuretic Peptide and low diastolic blood pressure predict cardiovascular morbidity and mortality following discharge in acutely decompensated heart failure patients. Circ J 2012; 76: 2372-9.

16. Kajimoto K, Sato N, Takano T, investigators of the Acute Decompensated Heart Failure Syndromes (ATTEND) registry. Relation between elevated blood urea nitrogen, clinical features or comorbidities, and clinical outcome in patients hospitalized for acute heart failure syndromes. Int J Cardiol 2015; 201: 311-4.

17. Kishi T. Heart failure as a disruption of dynamic circulatory homeostasis mediated by the brain. Int Heart J 2016; 57: 145-9.

18. Ishihara M, Fujino M, Ogawa H, et al; J-MINUET investigators, clinical presentation, management and outcome of Japanese patients with acute myocardial infarction in the troponin era - Japanese Registry of Acute Myocardial Infarction Diagnosed by Universal Definition (J-MINUET). Circ J 2015; 79: 1255-62.

19. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012; 60: 1581-98.

20. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000; 36: 959-69.

21. American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 61: e78-140.

22. Little RJA, Rubin DB. Likelihood-based approaches to the analysis of missing data: applications to some common models. In: Statistical analysis with missing data. 2nd edn. New Jersey: Wiley-InterScience; 2002: 65-83.

23. Rubin DB. Inference and missing data. Biometrika 1972; 63: 59-121.

24. Sabatine MS, Morrow DA, Giugliano RP, et al. Implications of upstream glycoprotein Iib/IIa inhibition and coronary artery stenting in the invasive management of unstable angina/non-ST-elevation myocardial infarction: a comparison of the Thrombolysis In Myocardial Infarction (TIMI) IIIB trial and the Treat angina with Aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy (TACTICS)-TIMI 18 trial. Circulation 2004; 109: 874-80.

25. Hsu CY, Chertow GM, Curhan GC. Methodological issues in studying the epidemiology of mild to moderate chronic renal insufficiency. Kidney Int 2002; 61: 1567-76.

26. Kimura K, Morita H, Daimon M, et al. Utility of cystatin C for estimating glomerular filtration rate in patients with muscular dystrophy. Int Heart J 2016; 57: 386-8.

27. Conte G, Dal Canton A, Terribile M, et al. Risk factors of acute heart failure syndromes. Int J Cardiol 2015; 201: 311-4.

28. Uberti M, Federico S, Di Minno G, et al. Effects of angiotensin II on plasma ADH, prostaglandin synthesis, and water
excretion in normal humans. Am J Physiol 1985; 248: F254-9.
29. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984; 311: 819-23.
30. Dal Canton A, Fuiano G, Conte G, et al. Mechanism of increased plasma urea after diuretic therapy in uraemic patients. Clin Sci (Lond) 1985; 68: 255-61.
31. Aronson D, Mittleman MA, Burger AJ. Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure. Am J Med 2004; 116: 466-73.
32. Cauthen CA, Lipinski MJ, Abbate A, et al. Relation of blood urea nitrogen to long-term mortality in patients with heart failure. Am J Cardiol 2008; 101: 1643-7.
33. Kazory A. Emergence of blood urea nitrogen as a biomarker of neurohormonal activation in heart failure. Am J Cardiol 2010; 106: 694-700.
34. Kirtane AJ, Leder DM, Waikar SS, et al; TIMI Study Group. Serum blood urea nitrogen as an independent marker of subsequent mortality among patients with acute coronary syndromes and normal to mildly reduced glomerular filtration rates. J Am Coll Cardiol 2005; 45: 1781-6.
35. Saygitov RT, Glezer MG, Semakina SV. Blood urea nitrogen and creatinine levels at admission for mortality risk assessment in patients with acute coronary syndromes. Emerg Med J 2010; 27: 105-9.
36. Smith GL, Shlipak MG, Havranek EP, et al. Serum urea nitrogen, creatinine, and estimators of renal function: mortality in older patients with cardiovascular disease. Arch Intern Med 2006; 166: 1134-42.
37. Barbash GI, Reiner J, White HD, et al. Evaluation of paradoxical beneficial effects of smoking in patients receiving thrombolytic therapy for acute myocardial infarction: mechanism of the “smoker’s paradox” from the GUSTO-I trial, with angiographic insights. Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol 1995; 26: 1222-9.
38. Violaris AG, Thury A, Regar E, Melkert R, Serruys PW. Influence of a history of smoking on short term (six month) clinical and angiographic outcome after successful coronary angioplasty. Heart 2000; 84: 299-306.
39. Andrikopoulos GK, Richter DJ, Dilaveris PE, et al. In-hospital mortality of habitual cigarette smokers after acute myocardial infarction: the “smoker’s paradox” in a countrywide study. Eur Heart J 2001; 22: 776-84.
40. Zhang YJ, Iqbal J, van Klaveren D, et al. Smoking is associated with adverse clinical outcomes in patients undergoing revascularization with PCI or CABG: the SYNTAX trial at 5-year follow-up. J Am Coll Cardiol 2015; 65: 1107-15.