Background: The relationship between acute kidney injury (AKI) in the acute phase of acute decompensated heart failure (ADHF) and patient outcome has not yet been reported.

Methods and Results: Data for 625 patients with ADHF admitted to the intensive care unit were analyzed. No AKI occurred in 281 patients (no AKI) during the first 5 days. The AKI patients were assigned to 3 groups based on the timing: AKI present on admission and stable risk, injury, failure, loss, and endstage (RIFLE) class (stable early AKI; n=125), stepped-up RIFLE class (worsening early AKI; n=49), or AKI that occurred after admission (late AKI; n=170). The AKI patients were grouped into another 3 groups based on severity: class R (risk; n=214), class I (injury; n=73), or class F (failure; n=57). A multivariate logistic regression model found class I, class F, late AKI and worsening early AKI to be independently associated with in-hospital mortality. Kaplan-Meier survival curves showed that the survival rate in any-cause death during 2 years was significantly lower in class I, class F and the worsening early-AKI group, and there were significantly more HF events in class F and the worsening early-AKI group. There were significantly more class I and class F patients in the worsening early-AKI group.

Conclusions: The presence of AKI on admission, worsening of AKI, and severe AKI (class I or class F) are associated with a poorer prognosis for ADHF patients. (Circ J. 2013; 77: 687–696)

Key Words: Acute heart failure; Mortality; Renal function

Renal dysfunction is recognized as an independent predictor of poor prognosis in patients with heart failure (HF). Patients with acute decompensated HF (ADHF) sometimes experience acute worsening of renal function, which is associated with poor outcome. To assess the acute worsening of renal function, a system for classifying acute kidney injury (AKI) has been proposed. The risk, injury, failure, loss, and endstage (RIFLE) criteria have been established as the standard method for evaluating AKI in intensive care patients, but the clinical significance of the RIFLE criteria has so far only rarely been investigated in patients with ADHF. In a previous study, we investigated the relationships among in-hospital mortality, long-term prognosis and AKI evaluated using RIFLE criteria in patients with ADHF, and concluded that patients with AKI during hospitalization had a worse in-hospital mortality and a worse long-term prognosis in comparison with no-AKI patients. In contrast, the mean time to worsening of renal function, as defined by an increase in serum creatinine of 0.3 mg/dl from the level on admission, has been reported to be 4 days. There have so far, however, been no reports describing AKI in the early phase of ADHF. In the present study, we therefore examined early-phase AKI in ADHF patients and investigated the relationships among short-term prognosis, long-term prognosis and AKI during the first 5 days of hospitalization.
The serum creatinine level in patients without chronic kidney disease (CKD; according to their medical data) was calculated using the Modification of Diet in Renal Disease (MDRD) equation as recommended by the Acute Dialysis Quality Initiative, by solving the MDRD equation for serum creatinine (CrMDRD) assuming a glomerular filtration rate (GFR) of 75 ml · min–1 · 1.73 m–2.

Baseline creatinine was the lowest value recorded during the admission of patients with CKD. The lower of the lowest creatinine values during hospitalization or the CrMDRD creatinine served as the baseline value for patients without CKD.

CKD was defined as a syndrome consisting of low GFR (<60 ml · min –1 · 1.73 m–2), and history lasting >3 months. Patients who did not have medical records at Chiba Hokusoh Hospital for the 3 months before admission were diagnosed with CKD using another institution’s data for the 3 months before admission or based on the 3 months of data after admission to the hospital.

Kidney damage as identified by abnormal functional class of either III or IV. Patients with HF caused by acute coronary syndrome were excluded from the study, as were patients who had undergone renal replacement therapy before admission. Furthermore, only the first admission was considered for patients who were readmitted to the ICU during the 2-year period after discharge. All data were retrospectively retrieved from hospital medical records.

Evaluation of AKI

Because urine output could not be precisely measured in the general ward, and the majority of patients with ADHF receive diuretics, which influences urine output, AKI was investigated solely on the basis of the creatinine criteria of the RIFLE classification. The RIFLE classification is based on the ratio of the maximum serum creatinine recorded during the first 5 days to the baseline creatinine. Patients were classified as no AKI, class R (risk), class I (injury) or class F (failure).

The RIFLE classification of patients who received renal replacement therapy was class F. Furthermore, the RIFLE classification was evaluated before heart surgery in surgical patients. The serum creatinine level in patients without chronic kidney disease (CKD; according to their medical data) was calculated using the Modification of Diet in Renal Disease (MDRD) equation as recommended by the Acute Dialysis Quality Initiative, by solving the MDRD equation for serum creatinine (CrMDRD) assuming a glomerular filtration rate (GFR) of 75 ml · min–1 · 1.73 m–2. Baseline creatinine was the lowest value recorded during the admission of patients with CKD. The lower of the lowest creatinine values during hospitalization or the CrMDRD creatinine served as the baseline value for patients without CKD.

CKD was defined as a syndrome consisting of low GFR (<60 ml · min –1 · 1.73 m–2), and history lasting >3 months. Patients who did not have medical records at Chiba Hokusoh Hospital for the 3 months before admission were diagnosed with CKD using another institution’s data for the 3 months before admission or based on the 3 months of data after admission to the hospital.

Kidney damage as identified by abnormal

### Table 1. Patient Characteristics, Medications and Short-Term Prognosis vs. Presence of AKI

| Patient characteristics | No AKI (n=281) | Early AKI (n=174) | Late AKI (n=170) | P-value† |
|-------------------------|----------------|-------------------|------------------|---------|
| Age (years)             | 71.2±11.9      | 73.5±11.6         | 71.4±11.1        | 0.040   |
| Male                    | 217 (77.2)     | 95 (54.6)         | 104 (61.2)       | <0.001  |
| New onset               | 202 (71.9)     | 134 (77.0)        | 132 (77.6)       | 0.164   |
| Ischemia                | 116 (43.3)     | 69 (37.7)         | 73 (42.9)        | 0.814   |
| NYHA class IV           | 229 (81.5)     | 139 (79.9)        | 136 (80.0)       | 0.644   |
| BUN (mg/dl)             | 25.1±12.5      | 32.6±21.5         | 23.5±10.4        | 0.003   |
| Creatinine (mg/dl)      | 1.38±0.88      | 1.57±1.02         | 1.21±0.68        | 0.014   |
| Total bilirubin (mg/dl) | 0.76±1.07      | 0.99±1.05         | 0.69±0.87        | 0.019   |
| Urinary acid (mg/dl)    | 6.90±1.91      | 7.37±2.69         | 6.46±1.92        | 0.457   |
| BNP (pg/ml)             | 993.3±871.0    | 1,230.7±1,305.8   | 983.0±1,376.9    | 0.269   |
| Sodium (mmol/L)         | 139.6±3.8      | 138.7±5.1         | 139.5±3.6        | 0.168   |
| Potassium (mmol/L)      | 4.25±0.60      | 4.52±0.88         | 4.15±0.67        | 0.022   |
| Hemoglobin (g/dl)       | 12.8±2.8       | 12.2±2.6          | 12.6±2.8         | 0.045   |
| CRP (mg/dl)             | 1.31±2.27      | 2.68±4.50         | 1.75±3.24        | 0.001   |
| SBP (mmHg)              | 167.4±38.2     | 141.8±39.6        | 168.9±39.7       | <0.001  |
| Heart rate (beats/min)  | 114.1±28.9     | 109.2±35.7        | 115.3±27.5       | 0.257   |
| LVEF (%) on admission   | 36.0±15.3      | 35.8±17.1         | 39.6±16.6        | 0.969   |

### Medication during the first 5 days

| Medication | No AKI (n=281) | Early AKI (n=174) | Late AKI (n=170) | P-value† |
|------------|----------------|-------------------|------------------|---------|
| Furosemide | 269 (95.7)     | 164 (94.3)        | 164 (94.5)       | 0.556   |
| Nitroglycerin | 217 (77.2) | 112 (64.4)        | 134 (78.8)       | 0.008   |
| Nicorandil | 30 (10.7)      | 23 (13.2)         | 24 (14.1)        | 0.343   |
| Carperitide | 168 (59.8)    | 78 (44.8)         | 102 (60.0)       | 0.005   |
| Dopamine   | 63 (22.4)      | 90 (51.7)         | 52 (30.6)        | <0.001  |
| Dobutamine | 42 (14.9)      | 68 (39.1)         | 37 (21.8)        | <0.001  |
| ACEI/ARB   | 130 (46.3)     | 54 (31.0)         | 72 (42.4)        | 0.002   |
| β-blocker  | 75 (26.7)      | 22 (12.6)         | 32 (18.8)        | <0.001  |
| Spironolactone | 106 (37.7) | 48 (27.6)         | 68 (40.0)        | 0.061   |

### Outcomes

| Outcomes | No AKI (n=281) | Early AKI (n=174) | Late AKI (n=170) | P-value† |
|----------|----------------|-------------------|------------------|---------|
| ICU hospitalization (days) | 5.1±5.7 | 10.4±18.3 | 10.3±17.8 | <0.001  |
| Total hospitalization (days) | 29.8±23.1 | 50.9±60.5 | 44.3±42.3 | <0.001  |
| In-hospital mortality | 11 (3.9) | 24 (13.8) | 20 (11.8) | <0.001  |

Data given as mean±SD or n (%). †Jonckheere–Terpstra test.

ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; BNP, B-type brain natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; ICU, intensive care unit; LVEF, left ventricular ejection fraction (measured on echocardiography on admission); NYHA, New York Heart Association; SBP, systolic blood pressure.
findings in urine and imaging tests was diagnosed in some of the present patients; therefore, CKD was diagnosed only by low GFR history lasting >3 months.

**Procedure**

In total, 273 patients had CKD (43.7%), comprising 190 patients (69.4%) diagnosed on the previous 3 months’ data before admission, and 83 patients (30.4%) by the 3 months of data after admission. Therefore, baseline creatinine was defined as the lowest value recorded during admission for these patients. In contrast, 352 patients did not have CKD (56.6%), and thus baseline creatinine was defined as the CrMDRD creatinine for 208 patients (59.1%) and the lowest creatinine value for 144 patients (40.9%).

The occurrence of AKI was evaluated using the RIFLE classification during the first 5 days. We identified AKI in 174 patients on admission, and the number of patients according to class were as follows: class R, n=134; class I, n=32; and class F, n=8. During the first 5 days, AKI developed additionally in 170 patients who were free of AKI on admission. For the 134 patients who were class R at admission, 95 patients remained in class R, while 26 changed to class I and 13 to class F during the first 5 days. For the 32 patients who were class I on admission, 22 patients remained in class I, while 10 patients changed to class F. Moreover, all 8 class F patients at admission continued to be classified as class F. Based on these results, the patients were assigned to each of the 3 groups according to their timing and the degree of AKI during the first 5 days.

No AKI occurred in 281 patients (no AKI), AKI was present on admission in 174 patients (early AKI) and occurred after admission in 170 patients (late AKI). Therefore, AKI patients were also assigned to 2 groups based on the timing of AKI in the first 5 days: an early-AKI group (n=174) and a late-AKI group (n=170). The patients with early AKI were also divided into 2 groups: patients who stepped up a RIFLE class (worsening early-AKI group, n=49) and patients who had a stable RIFLE classification (stable early AKI, n=125). AKI patients were also assigned to 3 categories based on severity of AKI during the first 5 days of the hospital stay: class R (risk; n=214), class I (injury; n=73), or class F (failure; n=57).

### Table 2. Patient Characteristics, Medications and Short-Term Prognosis vs. Timing of AKI

| Patient characteristics | Early AKI (n=174) | Late AKI (n=170) | P-value† |
|-------------------------|------------------|-----------------|---------|
|                         | Stable (n=125)   | Worsening (n=49) |         |
| Age (years)             | 73.8±11.5        | 72.8±12.0       | 0.027   |
| Male                    | 69 (55.2)        | 26 (53.1)       | 0.230   |
| New onset               | 95 (78.0)        | 39 (79.6)       | 0.772   |
| Ischemia                | 48 (38.4)        | 21 (52.9)       | 0.391   |
| NYHA class IV           | 99 (79.2)        | 40 (81.6)       | 0.892   |
| BUN (mg/dl)             | 31.7±20.1        | 34.8±24.6       | <0.001  |
| Creatinine (mg/dl)      | 1.43±0.68        | 1.92±1.53       | <0.001  |
| Total bilirubin (mg/dl) | 0.99±1.12        | 0.99±0.87       | 0.001   |
| Urinary acid (mg/dl)    | 7.44±2.83        | 7.17±2.31       | 0.012   |
| BNP (pg/ml)             | 1,165.4±1,144.0  | 1,413.1±1,684.9 | 0.007   |
| Sodium (mmol/L)         | 139.0±4.6        | 138.0±6.2       | 0.325   |
| Potassium (mmol/L)      | 4.48±0.79        | 4.62±1.06       | <0.001  |
| Hemoglobin (g/dl)       | 12.4±2.5         | 11.6±2.8        | 0.275   |
| CRP (mg/dl)             | 2.30±4.17        | 3.65±5.17       | 0.395   |
| SBP (mmHg)              | 142.3±35.1       | 140.7±49.7      | <0.001  |
| Heart rate (beats/min)  | 110.0±35.7       | 107.1±37.0      | 0.164   |
| LVEF (%) on admission   | 35.8±18.1        | 35.7±13.9       | 0.223   |

### Medication during the first 5 days

| Medication            | Early AKI (n=174) | Late AKI (n=170) | P-value† |
|-----------------------|------------------|-----------------|---------|
| Furosemide            | 117 (93.6)       | 47 (95.9)       | 0.259   |
| Nitroglycerin         | 80 (64.0)        | 32 (65.3)       | 0.004   |
| Nicorandil            | 17 (13.6)        | 6 (12.2)        | 0.874   |
| Carperitide           | 53 (42.4)        | 25 (50.0)       | 0.003   |
| Dopamine              | 62 (49.6)        | 28 (57.1)       | <0.001  |
| Dobutamine            | 44 (35.2)        | 24 (49.0)       | 0.006   |
| ACEI/ARB              | 41 (32.8)        | 13 (26.5)       | 0.052   |
| β-blocker             | 15 (12.0)        | 7 (14.3)        | 0.107   |
| Spironolactone        | 40 (32.0)        | 8 (16.3)        | 0.088   |

### Outcomes

| Outcome               | Early AKI (n=174) | Late AKI (n=170) | P-value† |
|-----------------------|------------------|-----------------|---------|
| ICU hospitalization   | 8.3±8.5          | 15.9±31.2       | 0.751   |
| Total hospitalization | 46.0±49.2        | 63.7±42.3       | 0.576   |
| In-hospital mortality | 13 (10.4)        | 11 (22.5)       | 0.902   |

Data given as mean±SD or n (%). †Jonckheere-Terpstra test.

Abbreviations as in Table 1.
AKI and Prognosis

The short-term prognosis was evaluated as the length of ICU stay, the length of total hospitalization and the in-hospital mortality. Furthermore, long-term prognosis was also evaluated as any-cause death including non-cardiac death, sudden death and cardiac death without any sudden death, and HF events defined as any-cause death or readmission for HF within 2 years. The patients were clinically followed up at a routine outpatient clinic. In the patients followed up at other institutes, prognosis was determined by telephone contact. All variables on admission, including age, type of HF (new-onset or worsening), etiology of HF (ischemic or non-ischemic), sex, NYHA class (III or IV), blood urea nitrogen, total bilirubin, sodium, potassium, hemoglobin, C-reactive protein, systolic blood pressure (SBP), heart rate, AKI in the first 5 days, and i.v. medication during the first 5 days, including furosemide, nitroglycerin, nitrateril, carperitide, dopamine and dobutamine, which were retrieved from all 625 cases, were selected for inclusion in the multivariate logistic regression model. The continuous variables were evaluated by dividing patients into 2 groups using a cut-off. The cut-off for each of the continuous variables was the median. The analysis was divided into 2 separate parts: comparison of the AKI timing; and RIFLE classification. Survival rate and event-free rate were analyzed using Kaplan-Meier curves according to the timing of AKI and the RIFLE classification.

Statistical Analysis

All data were statistically analyzed using SPSS 16.0 J (SPSS Japan Institute, Tokyo, Japan). All numerical data are expressed as mean±SD. The Jonckheere-Terpstra test was used to compare means between 3 groups. Comparisons of all proportions were done using chi-square analysis. The significant factors indicating in-hospital mortality were determined by the multivariate logistic regression model. P<0.05 was defined as statistically significant. Survival rate and event-free rate were analyzed between groups using Kaplan-Meier curves according to the timing of AKI and the RIFLE classification, and significant differences were calculated using the log-rank test.

Table 3. Patient Characteristics, Medications and Short-Term Prognosis vs. Severity of AKI

| Patient characteristics | AKI (n=344) | P-value† |
|-------------------------|------------|---------|
|                         | Class R (n=214) | Class I (n=73) | Class F (n=57) |
| Age (years)             | 72.7±11.5 | 71.5±12.0 | 73.1±10.0 | 0.690 |
| Male                    | 121 (58.5) | 36 (49.3) | 42 (73.7) | 0.209 |
| New onset               | 166 (77.6) | 60 (82.2) | 40 (70.2) | 0.610 |
| Ischemia                | 84 (39.3) | 33 (45.2) | 25 (43.9) | 0.360 |
| NYHA class IV           | 165 (77.1) | 61 (83.6) | 49 (86.0) | 0.086 |
| BUN (mg/dl)             | 24.2±12.4 | 26.8±16.3 | 44.5±24.8 | <0.001 |
| Creatinine (mg/dl)      | 1.14±0.48 | 1.32±0.85 | 2.42±1.29 | <0.001 |
| Total bilirubin (mg/dl) | 0.76±0.53 | 1.02±1.71 | 0.94±0.98 | 0.499 |
| Urinary acid (mg/dl)    | 6.71±2.28 | 7.06±2.22 | 7.56±2.88 | 0.036 |
| BNP (pg/ml)             | 984.7±1,313.7 | 1,133.5±1,129.8 | 1,537.0±1,635.1 | <0.001 |
| Sodium (mmol/L)         | 139.6±3.9 | 138.6±4.6 | 138.2±5.9 | 0.069 |
| Potassium (mmol/L)      | 4.20±0.68 | 4.41±0.63 | 4.78±1.18 | <0.001 |
| Hemoglobin (g/dl)       | 12.8±2.7 | 12.2±2.5 | 11.5±2.6 | <0.001 |
| CRP (mg/dl)             | 1.79±3.24 | 1.95±3.83 | 4.17±5.82 | 0.001 |
| SBP (mmHg)              | 159.6±40.2 | 147.1±39.3 | 149.1±48.9 | 0.021 |
| Heart rate (beats/min)  | 114.8±30.8 | 112.9±31.1 | 101.7±35.7 | 0.043 |
| LVEF (%) on admission   | 38.7±17.7 | 35.2±15.6 | 36.7±15.1 | 0.281 |

Data given as mean±SD or n (%). †Jonckheere-Terpstra test.
Class F, failure; class I, injury; class R, risk. Other abbreviations as in Table 1.
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Nippon Medical School approved the study protocol. The institutional review board at Chiba Hokusoh Hospital, Ethics

Benign hypertension (23.5 ± 10.4 mg/dl, 1.21 ± 0.68 mg/dl) was significantly higher in the late-AKI group (30.6% and 21.8%, respectively, P<0.001). The length of ICU hospitalization and total hospitalization were both longer in the early-AKI and late-AKI groups than in the no-AKI group. The in-hospital mortality rate was also significantly higher in the early-AKI and late-AKI groups than in the no-AKI group (Table 1).

Table 1. Serum blood urea nitrogen and creatinine were significantly higher in the class F patients (44.5±24.8 mg/dl, 2.42±1.29 mg/dl, respectively) than in those in classes R and I (R, 24.2±12.4 mg/dl, 1.14±0.48 mg/dl; I, 26.8±16.3 mg/dl, 1.32±0.85 mg/dl, respectively; P<0.001). Dobutamine was used more frequently during the acute phase in the class F patients (52.6%) than in the class R and I patients (R, 22.0%; I, 38.4%; P<0.001).

Outcomes and AKI

The length of ICU hospitalization and total hospitalization were both significantly longer in the early-AKI and late-AKI groups than in the no-AKI group. The in-hospital mortality rate was also significantly higher in the early-AKI and late-AKI groups than in the no-AKI group (Table 1).

The length of ICU hospitalization and total hospitalization were both longer in the worsening early-AKI group than in the stable early-AKI group and late-AKI group. The in-hospital mortality rate tended to be higher in the worsening early-AKI group than in the stable early-AKI group (Table 2).

The length of ICU hospitalization and total hospitalization were significantly longer in class F patients than in class R and I patients. The in-hospital mortality rate was also significantly higher in the class F patients than in the class R and I patients.

Table 2. Multivariate Analysis of In-Hospital Mortality

| Data                        | In-hospital mortality | In-hospital mortality |
|-----------------------------|-----------------------|-----------------------|
|                            | OR (95% CI)           | P-value               |
|                            | OR (95% CI)           | P-value               |
| BUN (>21.9 mg/dl)           | 1.919 (0.881–4.181)   | 0.101                 |
| Creatinine (>1.11 mg/dl)    | 2.192 (0.995–4.382)   | 0.052                 |
| Sodium (>140 mmol/L)        | 1.068 (0.554–2.059)   | 0.843                 |
| Potassium (>4.2 mmol/L)     | 0.836 (0.425–1.643)   | 0.603                 |
| Hemoglobin (<12.5 g/dl)     | 1.551 (0.783–3.071)   | 0.208                 |
| CRP (>0.59 mg/dl)           | 1.901 (0.937–3.855)   | 0.075                 |
| SBP (<160 mm/Hg)            | 1.538 (0.733–3.225)   | 0.255                 |
| Pulse (<116 beats/min)      | 0.606 (0.306–1.203)   | 0.153                 |

RIFLE timing

Stable early-AKI 1.066 (0.412–2.762) 0.895
Worsening early-AKI 2.881 (1.007–8.243) 0.049
Late AKI 3.192 (1.369–7.443) 0.007

RIFLE classification

Class R 1.054 (0.425–2.612) 0.012
Class I 3.654 (1.424–9.377) 0.007
Class F 4.361 (1.653–11.506) 0.003

Medication

Furosemide 0.221 (0.068–0.719) 0.012
Nitroglycerin 0.469 (0.231–0.953) 0.036
Nicorandil 1.123 (0.483–2.613) 0.787
Carperitide 1.410 (0.722–2.753) 0.315
Dopamine 1.480 (0.676–3.239) 0.327
Dobutamine 2.205 (0.995–4.886) 0.051

BUN, blood urea nitrogen; CI, confidence interval; OR, odds ratio; RIFLE, risk, injury, failure, loss, and endstage. Other abbreviations as in Tables 1, 3.

Results

Patient Characteristics and AKI

The patient cohort consisted of 66.6% men, with a mean age of 71.9±11.6 years, and 468 patients (74.9%) had new-onset HF: 258 (41.3%) of the patients had ischemic heart disease, and 367 (58.7%) had non-ischemic heart disease, including cardiomyopathy (n=99), hypertensive heart disease (n=116), valvular disease (n=136), and other heart diseases (n=16). The etiology of HF was similar in the 2 groups. Most patients were in NYHA class IV (80.6%), and the average left ventricular ejection fraction on admission was 36.9±16.2%.

Patient characteristics, including baseline values on admission, medications prescribed during the first 5 days, vs. the presence of AKI are listed in Table 1. Serum levels of blood urea nitrogen and creatinine were significantly higher in the early-AKI group (32.6±21.5 mg/dl, 1.57±1.02 mg/dl) than in the late-AKI group (23.5±10.4 mg/dl, 1.21±0.68 mg/dl, P=0.003, P=0.144). Nitroglycerin and carperitide were used less frequently in the early-AKI group (64.4% and 44.8%, respectively) than in the late-AKI group (78.8% and 60.0%, respectively, P=0.008, P=0.005), and dopamine and dobutamine were used more frequently during the acute phase in the early-AKI group (51.7% and 39.1%, respectively) than in the late-AKI group (30.6% and 21.8%, respectively, P<0.001).

The patient characteristics, including baseline data on admission and medications prescribed during the first 5 days, according to AKI timing, are listed in Table 2. The serum creatinine was significantly higher in the worsening early-AKI group (1.92±1.53 mg/dl) than in the stable early-AKI group (1.43±0.68 mg/dl, P<0.001). The other factors were not significantly different between the stable early-AKI and worsening early-AKI groups.

Patient characteristics vs. RIFLE classification are listed in Table 3. Serum blood urea nitrogen and creatinine were significantly higher in the class F patients (44.5±24.8 mg/dl, 2.42±1.29 mg/dl, respectively) than in those in classes R and I (R, 24.2±12.4 mg/dl, 1.14±0.48 mg/dl; I, 26.8±16.3 mg/dl, 1.32±0.85 mg/dl, respectively; P<0.001). Dobutamine was used more frequently during the acute phase in the class F patients (52.6%) than in the class R and I patients (R, 22.0%; I, 38.4%; P<0.001).

Ethics

The institutional review board at Chiba Hokusoh Hospital, Nippon Medical School approved the study protocol.
The Kaplan-Meier survival curves showed that the prognosis, including any-cause death, was significantly poorer for early-AKI than for late-AKI and no-AKI patients, and was significantly poorer for late-AKI than for no-AKI patients (Figure 1A). Furthermore, the prognosis was significantly poorer for patients with worsening early AKI than for those with stable early AKI and late AKI (Figure 1B). The HF events had significantly poorer prognosis in the early-AKI group than in the no-AKI group (Figure 1C); moreover, prognosis was significantly poorer in patients with worsening early AKI than in those with late AKI (Figure 1D). The Kaplan-Meier survival curves showed that the prognosis, including any-cause death, was significantly poorer for early-AKI than for late-AKI and no-AKI patients (Figure 1A). Furthermore, the prognosis was significantly poorer for patients with worsening early AKI than for those with stable early AKI and late AKI (Figure 1B). The HF events had significantly poorer prognosis in the early-AKI group than in the no-AKI group. (Figure 1C); moreover, prognosis was significantly poorer in patients with worsening early AKI than in those with late AKI (Figure 1D). The Kaplan-Meier survival curves showed that the prognosis, including any-cause death, to be significantly poorer in the class I group than in the no-AKI and class R patients (Table 3).

The multivariate logistic regression model for in-hospital mortality with AKI timing showed that the specific predictive factors from the clinical information on admission and i.v. medications prescribed during the first 5 days were as follows: worsening early AKI (P=0.049, odds ratio [OR], 2.881; 95% confidence interval [CI]: 1.007–8.243), and late AKI (P=0.007, OR, 3.192; 95% CI: 1.369–7.443). Meanwhile, the multivariate logistic regression model for in-hospital mortality based on the RIFLE classification identified the specific factors as class I status (P=0.007, OR, 3.654; 95% CI: 1.424–9.377) and class F status (P=0.003, OR, 4.361; 95% CI: 1.653–11.506; Table 4).

HF events occurred in 206 of the 625 patients (33.0%), and included 114 any-cause deaths, 92 readmissions to hospital during the 2-year follow-up. One hundred and fourteen deaths included 9 non-cardiac deaths, 9 sudden deaths and 96 cardiac deaths without any sudden death.
Acute Phase AKI and ADHF

often refer to worsening renal function as a 0.3–0.5-mg/dl rise in serum creatinine compared with the baseline value.\[^{16,17}\] Cowie et al reported that 33% of patients developed worsening renal function as defined by an increase in serum creatinine of 0.3 mg/dl from baseline during their hospital admission.\[^{8}\] The epidemiology and definition of worsening renal function, however, are not well defined in the literature, and there is no universally accepted definition. In defining worsening renal function, the most important factor is the baseline creatinine level, which most studies have determined to be the level on admission.

The Acute Dialysis Quality Intensive (ADQI) represents a published consensus definition of acute renal failure as AKI, using a set of criteria called RIFLE.\[^{3}\] The degree of worsening renal failure therefore can be subdivided based on this component of the RIFLE criteria. Moreover, the RIFLE criteria have been recognized as the standard guideline for defining acute renal failure for the past few decades in patients who require intensive care. It was reported that the RIFLE classification

### Timing of AKI vs. RIFLE Classification

The relationship between the timing of AKI and the RIFLE classification is shown in Table 5. There were significantly more class R patients than class I and F patients in the stable early-AKI and late-AKI groups. In contrast, there were no class R patients in the worsening early-AKI group; therefore, there were significantly more class I and F patients than class R patients in the worsening early-AKI group. The timing of AKI was thus found to be associated with RIFLE classification.

### Discussion

**Definition of Worsening Renal Function in ADHF**

Many investigators have reported that “worsening renal function” was common at presentation in patients with ADHF during hospitalization, and leads to an adverse outcome.\[^{1,2,8,15}\] They

#### Table 5. Severity vs. Timing of AKI

|                      | Class R (n=214) | Class I (n=73) | Class F (n=57) | P-value† |
|----------------------|----------------|---------------|---------------|----------|
| Early AKI (n=174)    |                |               |               |          |
| Stable (n=125)       | 95 (76.0)      | 22 (17.6)     | 8 (6.4)       | <0.001   |
| Worsening (n=49)     | 0 (0.0)        | 26 (53.1)     | 23 (46.9)     | <0.001   |
| Late AKI (n=170)     | 119 (70.0)     | 25 (14.7)     | 26 (15.3)     | 0.008    |

Data given as n (%). †Jonckheere-Terpstra test. Abbreviations as in Tables 1, 3.
was a significant predictive factor for long-term mortality in intensive care patients. A more recent classification for AKI based on the RIFLE system has been proposed by the Acute Kidney Injury Network (AKIN), and Kidney Disease Improving Global Guidelines (KDIGO) recommended that clinicians effectively adopt the AKIN criteria. It could not improve the sensitivity of the AKI diagnosis in comparison to the RIFLE criteria, however, and, furthermore; it could not improve the ability of the RIFLE criteria to predict the in-hospital mortality of intensive care patients. The number of studies that have evaluated such validity was higher for the RIFLE criteria than for the AKIN criteria, we therefore adopted the RIFLE criteria to evaluate the AKI.

Meanwhile, the significance of the RIFLE criteria has not yet been discussed for ADHF patients, we therefore previously demonstrated that AKI patients with ADHF had poor outcome. Moreover, the optimal timing of AKI for ADHF patients has not yet been elucidated. The mean time until worsening of the renal function, as defined by increase in serum creatinine of 0.3 mg/dl from the level on admission, has been reported to be 4 days. Furthermore, we previously reported that 125 of 376 ADHF patients (33.2%) had AKI on admission. The RIFLE criteria originally required 7 days of observation, but AKI for ADHF tends to occur at an earlier stage in ADHF patients than in other patients. We therefore evaluated AKI during the first 5 days of observation.

The most important factor affecting the accuracy of the RIFLE classification is the method used to determine the baseline creatinine level. In the present study, the lowest creatinine level recorded during hospitalization, or the CrMDRD creatinine level, served as the baseline for patients without CKD. Bagshaw et al., however, performed a comparison of observed premorbid vs. estimated (using CrMDRD) baseline creatinine levels for the determination of the RIFLE classification in a study of 1,300 patients, and concluded that the use of the estimated baseline creatinine level missclassified 18.8% of patients as having AKI. In a similar study, the estimated baseline creatinine level was shown to primarily affect the classification of class R patients, with both under- and over-classification occurring. In the present retrospective study, 74.9% of patients had new-onset HF, so we did not observe premorbid creatinine level in most of these patients. We therefore evaluated the effect of the RIFLE criteria on ADHF using baseline creatinine level estimated by the CrMDRD. This was also likely to be more accurate because AKI was already present at admission in some ADHF patients.

**Timing of AKI and Medications Used by ADHF Patients**

Worsening renal function is common in ADHF patients and may be a key cause of the cascade involving fluid retention, decompensation, and eventual hospital admission. The etiology is complex.

A multifactorial pathogenesis of AKI has been considered in patients with ADHF, wherein medication might also be associated with late AKI. In general, i.v. diuretics are needed in decompensated HF patients, and potent diuretics are needed during the treatment of ADHF in the acute phase. Diuretics therefore remain the mainstay of treatment in patients with ADHF. A number of studies have also shown that potent diuretics are associated with worsening renal function. It is clear that patients with pre-existing renal dysfunction are vulnerable to developing worsening renal function after using diuretics. Furthermore, bolus infusions do not promote gradual diuresis, and therefore do not allow time for the fluid in the periphery to move from the extravascular to the intravascular space, which leads to a significant decrease in renal perfusion and, as a result, worsening renal function.

The angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blocker (ARB) are recommended for use with regard to the associated components of the pathogenesis, and patients with renal impairment might derive greater benefit from ACEI and ARB, because they are at a higher absolute mortality risk. Suppression of the rennin-angiotensin system by ACEI or ARB improves survival and reduces length of hospitalizations in patients with chronic HF, and it is recommended even in patients with elevated serum creatinine. Creatinine level, however, often increases after the initiation of ACEI or ARB in patients with decompensated HF, especially with pre-existing renal impairment. Therefore, physicians tend to hesitate to use ACEI and ARB for the treatment of existing renal impairment, such as early AKI (especially worsening early AKI) and severe AKI (class I and F). Based on the pathogenesis, however, the use of ACEI or ARB may therefore be indicated for such patients. The clinical importance of each mechanism is likely to vary from patient to patient and situation to situation, and many mechanisms resulting in AKI are intermixed in patients with ADHF.

**AKI and Prognosis for ADHF Patients**

Acute worsening of renal function during hospitalization for ADHF is an important and consistent independent predictor of adverse outcome. Furthermore, those with worsening renal function often require a longer hospital stay. Worsening renal function is defined in most reports as a change in serum creatinine 20.3 mg/dl during hospitalization, and it has been reported to be associated with an increased risk for long-term all-cause/cardiovascular mortality and morbidity in ADHF patients. In a retrospective study of 200,063 hospitalized ADHF patients, Kociol et al found that 17.8% developed worsening renal function, with 64.5% of these patients being readmitted and 35.4% dying within 1 year. Cowie et al defined worsening renal function as an increase in serum creatinine of 0.3 mg/dl from baseline, and reported that the mortality rate was higher in the worsening renal function group than in the without renal dysfunction group during admission (12% vs. 2%), rising to 15% by 30 days and 28% in total by 6 months, compared with 5% and 18%, respectively, in patients without renal dysfunction. The length of hospital stay was also significantly longer at 13 days vs. 9 days. Heywood analyzed patients from the ADHERE registry database with cardiorenal syndrome, and found that even a small rise in creatinine (<0.3 mg/dl) in hospitalized patients predicted an increased risk of death and prolonged hospitalization.

An increasing body of evidence has consistently shown that worsening renal function in HF is a strong and independent predictor of poor outcome and prognosis. Larger increases in creatinine predict the highest risk of death, but even minor changes in renal function are associated with adverse outcome. Smith et al defined worsening renal function as an increase in serum creatinine of 0.1 mg/dl, a relatively small decline in renal function that might be overlooked or dismissed in clinical practice, and found that even this small increase was of great significance in ADHF patients.

In the present study, class R status (ie, mild AKI), characterized by an increase in serum creatinine more than 1.5-fold from baseline, was not found to be associated with a worse outcome. Only class I or F status, both of which were characterized by a creatinine increase of more than 2-fold from baseline, were associated with any-cause death based on a multivariate logistic regression model. Increase in the serum
creatinine level by more than 1.5-fold from baseline was a larger increase of the creatinine level in comparison with the previous definition of 0.3 mg/dl from baseline in most cases, but class R status was not significantly associated with a poor prognosis in ADHF patients based on the RIFLE criteria, which is in contrast to the findings of previous studies.

We also demonstrated in the present study that early AKI, especially worsening early AKI, was more commonly observed in patients with poor in-hospital mortality and led to an adverse long-term outcome. This is the first report to show that early AKI, which indicates the presence of AKI on admission, was a factor predicting adverse outcome for patients with ADHF. The presence of AKI on admission, and the worsening of AKI during the first 5 days after admission, was found to be a more important factor for poor prognosis than the occurrence of AKI after admission.

Study Limitations
First, the ratio of the maximum serum creatinine to baseline creatinine was underestimated in patients with CKD because of their high baseline creatinine level. The serum creatinine level was significantly higher in the no-AKI group compared with the class R group. The serum creatinine level on admission might be associated with the in-hospital mortality based on the results of the multivariate logistic regression model. Second, we could not obtain the previous medical records in all cases, which might be associated with the in-hospital mortality.

The presence of AKI on admission, and the worsening of AKI during the first 5 days after admission, was found to be a more important factor for poor prognosis than the occurrence of AKI after admission.

Conclusions
The presence of AKI on admission (early AKI), especially early AKI with step-up RIFLE classification during the first 5 days of hospitalization, was found to be associated with poorer short-term and long-term prognosis. The presence of severe AKI (class I or F) during the first 5 days was also associated with poorer short-term and long-term prognosis for ADHF patients. Furthermore, there were significantly more class I and class F patients in the worsening early-AKI group. The RIFLE criteria should, therefore, be developed into a clinically applicable and standardized method of assessing ADHF patients.

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