The Impact of Renal Tubular Damage, as Assessed by Urinary
$\beta_2$-Microglobulin-Creatinine Ratio, on Cardiac Prognosis in Patients with
Chronic Heart Failure

Otaki et al: Renal Tubular Damage in Heart Failure Patients

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DOI: 10.1161/CIRCHEARTFAILURE.112.000089

Journal Subject Codes: Heart failure: [10] Cardio-renal physiology/pathophysiology
Abstract

Background—Renal dysfunction was reported to be closely associated with clinical outcomes in patients with chronic heart failure (CHF). Renal tubulointerstitial damage has been shown to be an important factor in the development of renal dysfunction as well as glomerular damage. However, it remains to be determined the impact of renal tubular damage on clinical outcomes in patients with CHF.

Methods and Results—Urinary $\beta_2$-microglobulin-creatinine ratio (UBCR) was measured in 315 patients with CHF. Renal tubular damage was defined as a UBCR $\geq$ 300 $\mu$g/g, as previously reported. Patients were prospectively followed for a median period of 1097 days. There were 91 cardiac events, including 16 cardiac deaths and 75 re-hospitalizations for worsening heart failure. $\log_{10}$ UBCR was increased with worsening New York Heart Association (NYHA) functional class. Multivariate analysis revealed that renal tubular damage was an independent predictor of cardiac events. Kaplan-Meier analysis demonstrated that the rate of cardiac events was higher in patients with renal tubular damage compared to those without it. Patients were divided into 4 groups according to the presence of chronic kidney disease and renal tubular damage. The Cox proportional hazard analysis revealed that comorbidity of chronic kidney disease and renal tubular damage was associated with the highest risk for cardiac events compared to other groups.

Conclusions—Renal tubular damage was related to the severity of heart failure and was associated with poor outcomes in patients with CHF. Renal tubular damage could add clinical information to chronic kidney disease in patients with CHF.

Key Words: renal tubular damage, heart failure, urinary $\beta_2$-microglobulin
Despite the reduction in mortality with advances in treatment, comorbidity of renal dysfunction is still indicative of an extremely poor prognosis in patients with chronic heart failure (CHF).\textsuperscript{1,2} Therefore, evaluation of renal function for risk stratification of patients with CHF continues to be important.

Renal tubule cells have diverse regulatory and endocrine functions. Renal tubule plays a pivotal role in modulating acid base balance, active vitamin D synthesis, and reabsorption of sodium, water and bicarbonate.\textsuperscript{3} We have reported that renal tubular damage (RTD) is common and is a risk factor for deterioration of renal function in the general population, suggesting that there is an association between RTD and early abnormality in renal function.\textsuperscript{4} Furthermore, some reports have indicated that in a population living in a cadmium-polluted region, severe RTD is related to future cardiovascular disease, as well as glomerular damage.\textsuperscript{5,6}

Urinary $\beta_2$-microglobulin is a low molecular weight protein, produced by all cells expressing major histocompatibility complex class I antigen.\textsuperscript{7} It is readily filtered through the glomerulus and almost completely reabsorbed by the proximal tubules.\textsuperscript{8} When proximal tubule cells are damaged, an increase in excretion of urinary $\beta_2$-microglobulin results from impaired reabsorption in the proximal tubule. Therefore, urinary $\beta_2$-microglobulin is a reliable marker of RTD.\textsuperscript{9} Excretion of urinary $\beta_2$-microglobulin was reported to be enhanced in patients with CHF as well as urinary albumin and protein.\textsuperscript{10} We reported that urinary
\( \beta_2 \)-microglobulin-creatinine ratio (UBCR) is an independent predictor for deterioration of renal function. However, the impact of RTD on cardiac prognosis in patients with CHF has not yet been fully elucidated. The aim of the present study was to determine whether the comorbidity of RTD, as assessed by UBCR, predicts cardiac prognosis in patients with CHF.

**Methods**

**Study subjects**

This was a prospective study of 315 consecutive patients who were admitted to our hospital for the diagnosis or treatment of CHF. Patients were stable for a median 714 days before their admission. The diagnosis of CHF was made by two cardiologists who used the generally accepted Framingham criteria, including a history of dyspnea and symptomatic exercise intolerance, with signs of pulmonary congestion or peripheral edema and radiological or echocardiographic evidence of left ventricular enlargement or dysfunction.

Transthoracic echocardiography was performed by physicians who were blinded to the biochemical data. The diagnoses of hypertension, diabetes mellitus, and hyperlipidemia were established on the basis of the patient’s medical records or history of current or previous medical therapy. Twenty two patients were excluded from the present study due to acute coronary syndrome within 3 months preceding admission, dialysis, active hepatic disease, pulmonary disease or malignant disease.
Demographic and clinical data including age, gender, and New York Heart Association (NYHA) functional class were collected from hospital medical records and patient interviews. Medications at discharge were also collected from hospital medical records.

*Biochemical markers*

Urine and venous blood samples were obtained in the early morning within 24 hours after admission. Urinary \( \beta_2 \)-microglobulin concentrations were determined by the latex agglutination method (BML, Inc., Tokyo, Japan). \( \beta_2 \)-microglobulin levels were corrected for urinary creatinine (UBCR). Since UBCR was not normally distributed, we utilized \( \log_{10} \) UBCR for all analyses. RTD was defined as a UBCR \( \geq 300 \mu g/g \) \( (\log_{10} \text{UBCR} \geq 2.47 \mu g/g) \), as previously reported.\(^4\) We quantitatively measured urinary albumin by immunoturbidimetry in a single spot urine specimen collected in the early morning. Urinary albumin levels were corrected for urinary creatinine in a single manner to urinary microalbumin-creatinine rate (UACR). N-acetyl-\( \beta \)-D-glucosaminidase (NAG) level, a marker of early renal tubular damage, was measured in single spot urine specimens. UACR and NAG were also not normally distributed, we utilized \( \log_{10} \) UACR and \( \log_{10} \) NAG for all analyses. We detected urinary protein with albumin-specific dipsticks at the same time. We defined proteinuria as positive dipstick test (1+ or more). The glomerular filtration rate (GFR) was estimated using the modification of diet in renal disease’s equation with the Japanese coefficient, as previously
reported. Chronic kidney disease (CKD) was defined as a reduced eGFR (< 60 ml/min/1.73m²) or presence of proteinuria according to K/DOQI clinical guideline.14, 15

Endpoints and follow-up

Patients were prospectively followed for a median period of 1097 days (range 794 to 1244). Patients were followed by telephone interview or review of the medical record twice a year until 1250 days. There were 14 patients who were not followed due to non-cardiac death. The endpoints were cardiac death, defined as death due to progressive heart failure, sudden cardiac death, acute myocardial infarction and progressive heart failure requiring re-hospitalization. Sudden cardiac death was defined as death without definite premonitory symptoms or signs, and was confirmed by the attending physician.

The study was approved by the institutional ethics committee and all patients gave written informed consent.

Statistical analysis

All values are expressed as means ± SD or medians. The t-test and chi-square test or linear regression analysis were used for comparison of continuous and categorical variables, respectively. The receiver operating characteristics (ROC) curves for cardiac event were constructed to determine optimal sensitivity and specificity. The area under the ROC curve was calculated by using the trapezoidal rule.16 The Cox proportional hazard analysis was performed to identify the independent predictors for cardiac events. Predictors that were
significant by univariate analysis were entered into the multivariate analysis. Proportionality
assumption in Cox model was evaluated by log-minus-log survival plot. Cardiac event-free
curves were constructed according to the Kaplan-Meier method and were compared using the
log-rank test. Differences among groups were analyzed by analysis of variance (ANOVA)
with Scheffe post hoc test. A P value <0.05 was considered statistically significant. Statistical
analyses were performed using a standard software package (JMP version 8; SAS Institute
Results

Baseline characteristics of the study population

The baseline characteristics of the patients are presented in Table 1. There were 80 patients in New York Heart Association (NYHA) functional class I, 115 in NYHA class II, 82 in NYHA class III and 38 in NYHA class IV. Hypertension, diabetes mellitus, and hyperlipidemia were identified in 194 (62%), 94 (30%), and 95 (30%) patients, respectively. The etiology of heart failure was dilated cardiomyopathy in 61 (19%) patients, ischemic heart disease in 72 (23%) patients, valvular heart disease in 100 (32%) patients, and other conditions in the remaining 82 (26%) patients. The median log_{10} UBCR was 2.25 \mu g/g. The relationships between UBCR and eGFR and UBCR and UACR was weak and moderate, respectively (eGFR; r = -0.232, P < 0.0001, UACR; r = 0.412, P < 0.0001, respectively). RTD was identified in 120 (38%) patients. All CHF patients were divided into two groups according to the presence of RTD. Patients with RTD were older and were in more severe NYHA functional classes than those without RTD. The prevalence of diabetes mellitus and proteinuria were higher in patients with compared to those without RTD. Furthermore, patients with RTD had a lower eGFR and Hb level and higher brain natriuretic peptide (BNP), UACR, and NAG levels. Patients with RTD took more loop diuretics and higher dose of furosemide than those without RTD. There were no significant differences in other variables, including gender, prevalence of hypertension and hyperlipidemia, etiology of CHF, medication excluding loop diuretics and
echocardiographic parameters between patients with and without RTD.

**UBCR and clinical outcomes**

Log$_{10}$ UBCR was increased with advancing NYHA functional class (Figure 1). During the follow-up period, there were 91 cardiac events (29%), including 16 cardiovascular deaths and 75 re-hospitalizations for worsening heart failure. The causes of cardiac death were worsening CHF in 14 patients, sudden cardiac death in 1 patient, and acute myocardial infarction in 1 patient.

To determine the risk factors for cardiac events, univariate and multivariate Cox proportional hazard regression analyses were performed (Table 2). Univariate analysis showed that log$_{10}$ UBCR and RTD were significantly associated with cardiac events. Furthermore, age, NYHA functional class, eGFR, BNP, Hb, UACR, proteinuria, left ventricular ejection fraction (LVEF), NAG, CKD and dosages of furosemide were associated with cardiac events. Multivariate Cox proportional hazard analysis revealed that RTD was an independent predictor for cardiac events after adjustment of age, NYHA functional class, BNP, Hb, proteinuria, dosages of furosemide, and CKD (hazard ratio 3.18; 95% confidence interval, 1.92 – 5.30; $P < 0.0001$) (Table 2). Furthermore, when NAG was substituted for RTD, NAG was also an independent predictor for cardiac events after adjustment for other confounding factors (data not shown).

Kaplan-Meier analysis demonstrated that patients with RTD had a significantly
higher rate of cardiac events compared to those without RTD (Figure 2A). Furthermore, cardiac mortality was higher in patients with compared to those without RTD (Figure 2B).

**Comorbidity of RTD and CKD in patients with CHF**

All patients with CHF were divided into 4 groups according to the presence of CKD and RTD: (1) normal group (n = 110): CKD (-) and RTD (-); (2) CKD group (n = 85): CKD (+) and RTD (-); (3) RTD group (n = 39): CKD (-) and RTD (+); (4) CKD + RTD group (n = 81): CKD (+) and RTD (+). As shown in Table 3, levels of Hb were lower in RTD group than in normal group and CKD group. CKD + RTD group were older and had higher BNP, $\log_{10}$ UBCR and $\log_{10}$ NAG than normal group and CKD group. CKD + RTD group also had lower Hb compared with normal group and CKD group. CKD + RTD group showed higher prevalence of proteinuria, higher $\log_{10}$ UACR and lower eGFR compared with other groups.

The Cox proportional hazards regression analysis revealed that the CKD + RTD group had the highest risk for cardiac events among 4 groups after adjustment of age, NYHA functional class, BNP, Hb, proteinuria and dosages of furosemide (Figure 3A). Since RTD is a risk factor for deterioration of CKD, new development of CKD is likely to occur in RTD group during follow-up periods. We divided into study patients into the following 3 groups; normal group, CKD or RTD group, and CKD + RTD group. Log-minus-log survival plot showed that hazard ratios of variables were constant overtime. Kaplan-Meier analysis demonstrated that CKD + RTD group had the highest rate of cardiac events in patients with CHF (Figure 3B).
Further, we performed subgroup analysis. Kaplan-Meier analysis showed that the rate of cardiac events was higher in patients with RTD than in those without it irrespective of having CKD (Supplemental Figure 2).

**Comparison of prognostic value between UBCR and traditional markers**

We performed the ROC analyses to evaluate whether log$_{10}$ UBCR could add clinical information to traditional markers such as LVEF, LVEDD, and BNP. As shown in Figure 4, the AUC, sensitivity and specificity of log$_{10}$ UBCR was 0.74, 68% and 77%, respectively. The AUC of UBCR was higher than that of traditional markers of heart failure.
Discussion

The new and important findings from this study were 1) RTD was increased with advancing NYHA functional class; 2) multivariate Cox proportional hazard analysis demonstrated that RTD was an independent predictor of cardiac events; 3) Kaplan-Meier analysis demonstrated that the rate of cardiac events was higher in patients with compared to those without RTD; 4) The Cox proportional hazard regression analysis revealed that comorbidity of RTD and CKD was associated with the highest risk in patients with CHF.

Association between CHF and RTD

A cardio-renal interaction was noted in patients with CHF. Accumulating evidence indicates that renal dysfunction has a close association with cardiac function in patients with CHF through activation of the renin-angiotensin system, volume expansion, cytokine secretion, sympathetic nerve activation and anemia. Cardiac dysfunction with low cardiac output decreases renal perfusion and leads to renal parenchymal hypoxia. Renal parenchymal hypoxia plays a pivotal role in the development of RTD. We previously reported that the prevalence of RTD is approximately 13% in the Japanese general population. In the present study, 38% of patients with CHF were found to have RTD. The prevalence of RTD was higher in patients with CHF than in the general population, suggesting an association between cardiac function and RTD.

Renal parenchymal hypoxia, and in particular, chronic tubulointerstitial hypoxia is
recognized as a final common pathway for end-stage renal dysfunction, that eventually leads to a decreased GFR.\textsuperscript{21, 22} Therefore, CHF patients with RTD may have a poor prognosis due to their renal dysfunction. However, left ventricular ejection fraction was not lower in patients with compared to those without RTD. This may be attributed to the fact that chronic tubulointerstitial hypoxia is induced by several factors, including age, hypertension, diabetes mellitus, and CKD itself.\textsuperscript{23}

Since peritubular interstitial cells produce erythropoietin\textsuperscript{24}, RTD is likely to cause renal anemia. As shown in Table 3, decreased hemoglobin levels were more closely associated with RTD than CKD. Anemia promoted by RTD may deteriorate cardiac prognosis in patients with CHF.

\textit{Differences between NAG and UBCR in patients with CHF}

Both urinary NAG and UBCR are considered to be reliable markers for RTD. NAG is an enzyme which localizes in the lysosomes of proximal tubular cells. Urinary NAG levels often increase through the exocytosis-endocytosis pathway, which is a different pathway from that of RTD.\textsuperscript{25, 26} A previous report suggested that UBCR is superior to NAG for predicting renal dysfunction.\textsuperscript{27} UBCR was considered as a more specific marker than NAG. Damman et al. showed that a high NAG level was a risk factor for future cardiac events in patients with CHF.\textsuperscript{28} Similarly, NAG was also an independent predictor for cardiac events in the present study. These findings supported our hypothesis that the comorbidity of RTD is associated
with a poor prognosis in patients with CHF.

The limitation of this study was relatively high EF in the study population. The relatively high EF (51 ± 17%) observed in this study may primarily be the result of a lower prevalence of ischemic heart diseases in Japan (23%). The prevalence of ischemic heart disease is reportedly relatively lower in Japan compared with the US and European countries. The mean EF in this study is thought to be equivalent to that seen in Japanese heart failure study and the Japanese heart failure registry. Another limitation of the present study was the relatively small number of study subjects.

In conclusion, RTD, as assessed by UBCR, was related to the severity of heart failure and was associated with a high risk of cardiac events in patients with CHF. The comorbidty of RTD could add clinical information to CKD and may be a crucial risk factor for cardiac events in patients with CHF.

**Sources of Funding**

This study was supported, in part, by a grant-in-aid for Scientific Research (No. 21590923, 24591033 and 24659380) from the Ministry of Education Culture, Sport, Science and Technology and a grant-in-aid from the global century center of excellence (COE) program of the Japan Society for the Promotion of Science.

**Disclosures**

None.
References


<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients</th>
<th>RTD (-)</th>
<th>RTD (+)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72 ± 11</td>
<td>69 ± 12</td>
<td>76 ± 10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Men/women</td>
<td>181 / 134</td>
<td>117 / 78</td>
<td>64 / 56</td>
<td>0.2452</td>
</tr>
<tr>
<td>NYHA functional class (I/ II/ III/ IV)</td>
<td>80/ 115/ 82/ 38</td>
<td>68/ 71/ 39/ 17</td>
<td>12/ 44/ 43/ 21</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>194 (62%)</td>
<td>114 (58%)</td>
<td>80 (67%)</td>
<td>0.1460</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>94 (30%)</td>
<td>50 (26%)</td>
<td>44 (37%)</td>
<td>0.0378</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>95 (30%)</td>
<td>56 (29%)</td>
<td>39 (33%)</td>
<td>0.4775</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td>0.1979</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>61 (19%)</td>
<td>43 (22%)</td>
<td>18 (15%)</td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>72 (23%)</td>
<td>38 (19%)</td>
<td>34 (28%)</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>100 (32%)</td>
<td>64 (26%)</td>
<td>36 (30%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>82 (26%)</td>
<td>50 (33%)</td>
<td>32 (27%)</td>
<td></td>
</tr>
<tr>
<td>Blood examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>64 ± 26</td>
<td>68 ± 22</td>
<td>57 ± 31</td>
<td>0.0003</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>362 (129 - 875)</td>
<td>252 (101 - 529)</td>
<td>619 (294 - 1260)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>12.3 ± 2.3</td>
<td>13.1 ± 2.1</td>
<td>11.1 ± 2.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urinalysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log₁₀ UBCR (µg/g)</td>
<td>2.25 ± 0.95</td>
<td>1.69 ± 0.57</td>
<td>3.21 ± 0.62</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log₁₀ UACR (mg/g)</td>
<td>1.50 ± 0.65</td>
<td>1.27 ± 0.53</td>
<td>1.88 ± 0.66</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Proteinuria (%)</td>
<td>58 (18%)</td>
<td>18 (9%)</td>
<td>40 (33%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log₁₀ NAG (U/g)</td>
<td>1.05 ± 0.32</td>
<td>0.95 ± 0.27</td>
<td>1.23 ± 0.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CKD (%)</td>
<td>166 (53%)</td>
<td>85 (44%)</td>
<td>81 (68%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>54 ± 10</td>
<td>54 ± 10</td>
<td>55 ± 10</td>
<td>0.5627</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>51 ± 17</td>
<td>52 ± 18</td>
<td>49 ± 15</td>
<td>0.1433</td>
</tr>
<tr>
<td>Medicine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEIs or ARBs</td>
<td>239 (76%)</td>
<td>141 (72%)</td>
<td>98 (82%)</td>
<td>0.0594</td>
</tr>
<tr>
<td>β-blockers</td>
<td>212 (67%)</td>
<td>124 (64%)</td>
<td>88 (73%)</td>
<td>0.0734</td>
</tr>
<tr>
<td>Aldosterone blockers</td>
<td>99 (31%)</td>
<td>62 (32%)</td>
<td>37 (31%)</td>
<td>0.8583</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>207 (66%)</td>
<td>118 (61%)</td>
<td>89 (74%)</td>
<td>0.0132</td>
</tr>
<tr>
<td>Doses of furosemide</td>
<td>20 (0 – 20)</td>
<td>10 (0 – 20)</td>
<td>20 (0 – 30)</td>
<td>0.0103</td>
</tr>
<tr>
<td>Statins</td>
<td>109 (35%)</td>
<td>67 (34%)</td>
<td>42 (35%)</td>
<td>0.9075</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD, number (percentage), or median (interquartile range).
RTD, renal tubular damage; NYHA, New York Heart Association; GFR, glomerular filtration rate; BNP, brain natriuretic peptide; Hb, hemoglobin; UBCR, urinary \( \beta_2 \)-microglobulin-creatinine ratio; UACR, urinary microalbumin-creatinine ratio; NAG, N-acetyl-beta-D-glucosaminidase; LVEDD, Left ventricular end diastolic dimension; LVEF, Left ventricular ejection fraction; CKD, chronic kidney disease; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.
Table 2. Univariate and multivariate Cox proportional hazard analysis of predicting cardiac events in patients with chronic heart failure.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio</th>
<th>95% confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Per 1-year increase)</td>
<td>1.04</td>
<td>1.02 – 1.07</td>
<td>0.0002</td>
</tr>
<tr>
<td>Gender (women vs. men)</td>
<td>0.98</td>
<td>0.65 – 1.50</td>
<td>0.9597</td>
</tr>
<tr>
<td>NYHA (II vs. I)</td>
<td>1.95</td>
<td>0.99 – 3.82</td>
<td>0.0524</td>
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<tr>
<td>NYHA (III vs. I)</td>
<td>3.44</td>
<td>1.77 – 6.71</td>
<td>0.0003</td>
</tr>
<tr>
<td>NYHA (IV vs. I)</td>
<td>4.55</td>
<td>2.19 – 9.50</td>
<td>&lt;0.0001</td>
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<tr>
<td>Hypertension</td>
<td>1.18</td>
<td>0.78 – 1.78</td>
<td>0.4475</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.79</td>
<td>0.51 – 1.23</td>
<td>0.2970</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.82</td>
<td>0.53 – 1.27</td>
<td>0.3790</td>
</tr>
<tr>
<td>Estimated GFR (Per 1-SD increase)</td>
<td>0.50</td>
<td>0.39 – 0.64</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BNP (Per 1-SD increase)</td>
<td>1.30</td>
<td>1.10 – 1.48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hb (Per 1-SD increase)</td>
<td>0.55</td>
<td>0.44 – 0.67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log10 UBCR (Per 1-SD increase)</td>
<td>2.01</td>
<td>1.65 – 2.44</td>
<td>&lt;0.0001</td>
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<tr>
<td>Log10 UACR (Per 1-SD increase)</td>
<td>1.87</td>
<td>1.50 – 2.41</td>
<td>&lt;0.0001</td>
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<tr>
<td>Proteinuria</td>
<td>2.44</td>
<td>1.56 – 3.82</td>
<td>0.0003</td>
</tr>
<tr>
<td>Log10 NAG (Per 1-SD increase)</td>
<td>1.63</td>
<td>1.34 – 1.98</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEDD (Per 1-SD increase)</td>
<td>1.19</td>
<td>0.97 – 1.47</td>
<td>0.1016</td>
</tr>
<tr>
<td>LVEF (Per 1-SD increase)</td>
<td>0.74</td>
<td>0.60 – 0.90</td>
<td>0.0026</td>
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<tr>
<td>Furosemide (Per 1-mg increase)</td>
<td>1.02</td>
<td>1.01 – 1.03</td>
<td>&lt;0.0001</td>
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<tr>
<td>CKD</td>
<td>3.43</td>
<td>2.12 – 5.55</td>
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<td>RTD</td>
<td>5.08</td>
<td>3.24 – 8.00</td>
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</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Per 1-year increase)</td>
<td>1.02</td>
<td>0.99 – 1.04</td>
<td>0.1819</td>
</tr>
<tr>
<td>NYHA (II vs. I)</td>
<td>1.13</td>
<td>0.57 – 2.27</td>
<td>0.7245</td>
</tr>
<tr>
<td>NYHA (III vs. I)</td>
<td>1.89</td>
<td>0.92 – 3.89</td>
<td>0.0829</td>
</tr>
<tr>
<td>NYHA (IV vs. I)</td>
<td>2.33</td>
<td>1.08 – 5.05</td>
<td>0.0309</td>
</tr>
<tr>
<td>BNP (Per 1-SD increase)</td>
<td>0.96</td>
<td>0.82 – 1.10</td>
<td>0.6202</td>
</tr>
<tr>
<td>Hb (Per 1-SD increase)</td>
<td>0.81</td>
<td>0.63 – 1.07</td>
<td>0.1563</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1.12</td>
<td>0.67 – 1.85</td>
<td>0.6668</td>
</tr>
<tr>
<td>Furosemide (Per 1-mg increase)</td>
<td>1.01</td>
<td>0.99 – 1.02</td>
<td>0.0995</td>
</tr>
<tr>
<td>CKD</td>
<td>2.05</td>
<td>1.18 – 3.55</td>
<td>0.0110</td>
</tr>
<tr>
<td>RTD</td>
<td>3.18</td>
<td>1.92 – 5.30</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviation as in Table 1.
Table 3. Clinical characteristics of the 4 subgroups of CHF

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal</th>
<th>CKD</th>
<th>RTD</th>
<th>CKD + RTD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 110</td>
<td>n = 85</td>
<td>n = 39</td>
<td>n = 81</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 ± 11</td>
<td>72 ± 10</td>
<td>73 ± 12</td>
<td>77 ± 10†</td>
</tr>
<tr>
<td>Blood examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>81 ± 16</td>
<td>51 ± 15†</td>
<td>87 ± 29†</td>
<td>42 ± 20†</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>186 (67 – 397)</td>
<td>414 (167 – 1106)</td>
<td>395 (161 – 1238)</td>
<td>694 (409 – 1270)†</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>13.3 ± 2.0</td>
<td>12.8 ± 2.3</td>
<td>11.7 ± 2.3†</td>
<td>10.8 ± 1.9†</td>
</tr>
<tr>
<td>Urinalysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log₁₀ UBCR (µg/g)</td>
<td>1.8 ± 0.5</td>
<td>1.5 ± 0.6</td>
<td>3.0 ± 0.5†</td>
<td>3.3 ± 0.7†</td>
</tr>
<tr>
<td>Log₁₀ UACR (mg/g)</td>
<td>1.18 ± 0.49</td>
<td>1.39 ± 0.57</td>
<td>1.47 ± 0.43</td>
<td>2.09 ± 0.65††</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0 (0%)</td>
<td>18 (31%)</td>
<td>0 (0%)</td>
<td>40 (69%)§</td>
</tr>
<tr>
<td>Log₁₀ NAG (U/g)</td>
<td>0.94 ± 0.29</td>
<td>0.94 ± 0.25</td>
<td>1.20 ± 0.34†</td>
<td>1.22 ± 0.29†</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD, number (percentage), or median (interquartile range). CKD, chronic kidney disease; RTD, renal tubular damage; GFR, glomerular filtration rate; BNP, brain natriuretic peptide; Hb, hemoglobin; UBCR, urinary β₂-microglobulin-creatinine ratio; UACR, urinary microalbumin-creatinine ratio; NAG, N-acetyl-beta-D-glucosaminidase. *p < 0.05 vs. normal group, †p < 0.05 vs. CKD group, ‡p < 0.05 vs. RTD group, §p < 0.05 by chi-square test.
Figure Legends

Figure 1. The association between urinary $\beta_2$-microglobulin-creatinine ratio (UBCR) and New York Heart Association (NYHA) functional class. Log$_{10}$ UBCR was increased with worsening NYHA functional class (Kruskal-Wallis test, $P < 0.0001$).

Figure 2. (A) Kaplan-Meier analysis of all cardiac events in patients with and without renal tubular damage. (B) Kaplan-Meier analysis of cardiac deaths in patients with and without renal tubular damage.

Figure 3. (A) The Cox proportional hazard regression analysis of 4 groups. Hazard ratio relative to normal group. *$P < 0.05$ vs. normal group. (B) Kaplan-Meier analysis of all cardiac events among 3 groups.

Figure 4. The receiver operating characteristics curves of log$_{10}$ UBCR, BNP, LVEF, and LVEDD for cardiac events.
Figure 1

Log\textsubscript{10} UBCR (\(\mu\text{g/g}\))

<table>
<thead>
<tr>
<th>NYHA Stage</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA I</td>
<td>80</td>
</tr>
<tr>
<td>NYHA II</td>
<td>115</td>
</tr>
<tr>
<td>NYHA III</td>
<td>82</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>38</td>
</tr>
</tbody>
</table>

n = number of patients in each NYHA stage.
Figure 2

(A) 

Event free rate (%)  

0 250 500 750 1000 1250 Follow-up period (days) 

Log rank test, P < 0.0001 

RTD (-)  
n = 195 18/194 24/185 25/168 26/131 

RTD (+)  
n = 120 34/119 50/117 58/108 60/92 

(B) 

Event free rate (%)  

0 250 500 750 1000 1250 Follow-up period (days) 

Log rank test, P < 0.0001 

RTD (-)  
n = 195 1/194 1/183 1/164 2/118 

RTD (+)  
n = 120 6/112 10/104 12/91 12/63
Figure 3

(A) Hazard ratio

Renal tubular damage
- - + +
Chronic kidney disease
- + - +

Normal group
n = 110
CKD group
n = 85
RTD group
n = 39
CKD + RTD group
n = 81

Hazard ratio

1 3.3 5.5 8.3

*
Figure 3

(B) Event free rate (%) vs. Follow-up period (days)

Log rank test, P < 0.0001

Normal group
n = 110

RTD or CKD group
n = 124

CKD + RTD group
n = 81

Follow-up period (days)

5/110 6/105 7/96 7/72
18/122 28/117 31/107 33/87
29/81 40/80 45/73 46/64
Figure 4.

Log$_{10}$ UBCR; AUC = 0.74, sensitivity 68%, specificity 77%.

BNP; AUC = 0.66, sensitivity 66%, specificity 61%.

LVEF; AUC = 0.59, sensitivity 61%, specificity 55%.

LVEDD; AUC = 0.57, sensitivity 67%, specificity 47%.
The Impact of Renal Tubular Damage, as Assessed by Urinary $\beta_2$-microglobulin-creatinine Ratio, on Cardiac Prognosis in Patients with Chronic Heart Failure
Yoichiro Otaki, Tetsu Watanabe, Tetsuro Shishido, Hiroki Takahashi, Akira Funayama, Taro Narumi, Shinpei Kadowaki, Hiromasa Hasegawa, Shintaro Honda, Shunsuke Ntsu, Mitsunori Ishino, Takanori Arimoto, Takehiko Miyashita, Takuya Miyamoto, Tsuneo Konta and Isao Kubota

Circ Heart Fail. published online May 14, 2013;
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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Supplemental Figure 1

(A) $r = -0.232$
$p < 0.0001$

(B) $r = 0.412$
$p < 0.0001$
Supplemental Figure 2

(A) Normal group
n = 110

Log rank test, P < 0.0001

RTD group
n = 39

Event free rate (%)

Follow-up period (days)

5/110 6/105 7/96 7/72

(B) CKD group
n = 85

Log rank test, P < 0.0001

CKD+RTD group
n = 81

Event free rate (%)

Follow-up period (days)

13/84 18/80 18/72 19/59

Normal group
n = 110

RTD group
n = 39

5/38 10/37 13/35 14/28

5/38 10/37 13/35 14/28
Supplemental figure 1.
(A) The relationship between log$_{10}$ UBCR and eGFR.
(B) The relationship between log$_{10}$ UBCR and log$_{10}$ UACR.

Supplemental figure 2.
(A) Kaplan-Meier analysis of all cardiac events between normal group and RTD group.
(B) Kaplan-Meier analysis of all cardiac events between CKD group and CKD + RTD group.