The aim of this study was to elucidate whether renal tubulointerstitial damage is associated with the occurrence of MACE in patients with STEMI undergoing percutaneous coronary intervention.

Methods and Results: The degree of renal tubulointerstitial damage was evaluated by measuring the U-β2MG level in 89 consecutive STEMI patients. There were 22 MACEs during the follow-up period. Patients with MACE had higher U-β2MG levels than those without MACE, and the U-β2MG level was an independent predictor for MACE. A Kaplan-Meier analysis revealed that the group with higher U-β2MG levels corrected for urinary creatinine was associated with a greater risk for MACE.

Conclusions: An elevated U-β2MG level was associated with the occurrence of MACE in STEMI patients who underwent PCI. Renal tubulointerstitial damage is therefore considered to be associated with the occurrence of MACE.

Key Words: Percutaneous coronary intervention; Secondary prevention; Tubulointerstitial damage

The prevalence of chronic kidney disease (CKD) is an independent risk factor for cardiovascular disease. The most predictive factors for progression to renal dysfunction are glomerular injury and tubulointerstitial damage. Urinary β2 microglobulin (U-β2MG) is a more sensitive and accurate marker of tubulointerstitial damage, and its excretion predicts a rapid 1-year decline in renal function. Thus, an increased U-β2MG level is an independent risk factor for rapid renal deterioration.

The etiology of glomerular damage is related to the occurrence of major adverse cardiovascular events (MACE) in patients with myocardial infarction (MI). Renal tubular damage is associated with impaired outcomes in chronic heart failure patients, even when the estimated glomerular filtration rate (eGFR) is normal, implying that tubulointerstitial damage might be a risk factor for mortality after MI. However, the prognostic importance of tubulointerstitial damage in patients with ST-segment elevation MI (STEMI) has not been established. The aim of this study was to examine whether the level of U-β2MG, a marker for tubulointerstitial damage, is associated with the onset of MACE in patients with STEMI after successful percutaneous coronary intervention (PCI).

Study Population
This study evaluated 95 consecutive patients who underwent PCI between May 2008 and April 2011 for STEMI within 24 h of the onset of symptoms at the Yamagata University Hospital. PCI was successfully carried out in all patients with the use of bare metal stents. STEMI was diagnosed by (1) typical chest pain lasting ≥30 min, (2) ST-segment elevation in at least 2 contiguous leads or left bundle-branch block on ECG, and (3) typical increase and decrease in the serum creatine kinase concentration above twice the upper limit of normal. The exclusion criteria were eGFR <30 (mL·min⁻¹·1.73 m⁻²), acute kidney injury (within 48 h, increase in serum creatinine concentration of ≥0.5 mg/dl from baseline), and data unavailability.
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Therefore 89 patients were included in the present study. Written informed consent was given by all the patients before the study. The protocol was approved by the institutional human investigations committee.

U-β2MG and Other Biochemical Analyses
U-β2MG was measured in a single spot urine specimen collected at admission after PCI. U-β2MG levels corrected for urinary creatinine (UBCR) were used for all analyses. The general biochemical parameters were measured using routine laboratory methods. The eGFR was calculated using the abbreviated Modification of Diet in Renal Disease equation with the Japanese coefficient as described previously.

Gensini Score
To assess the severity of coronary artery disease (CAD), we used the Gensini scoring system: coronary artery score = sum of all segment scores (where each segment score equals segment weighting factor multiplied by severity score). Severity scores assigned to the specific percentage luminal diameter reduction of the coronary artery segment are 32 for 100%, 16 for 99%, 8 for 90%, 4 for 75%, 2 for 50%, and 1 for 25%.

Endpoints and Follow-up
No patients were lost to follow-up (mean follow-up period, 342±220 days) after admission. Clinical follow-up data were obtained from either outpatient record reviews or telephone interviews. The occurrence of MACE included cardiac death, rehospitalization for congestive heart failure, target lesion revascularization (TLR), target vessels revascularization or disabling stroke.

Statistical Analysis
The results are presented as the mean±SD for continuous variables and as percentages of the total number of patients for categorical variables. Skewed values are expressed as medians and the interquartile range. Student’s unpaired t-test and the chi-square test were used for comparisons of continuous and categorical variables, respectively. If the data were not normally distributed, then the Mann-Whitney U test was used. A Cox proportional-hazards regression analysis was performed to evaluate the associations between MACE and measurements. The cardiac-event-free curve was computed according to the Kaplan-Meier method and compared using the log-rank test. The optimal cut-off value for UBCR was determined as that with the largest sum of sensitivity plus specificity on each of the receiver-operating characteristic (ROC) curves.

Results
The clinical characteristics of the patients with and without MACE are shown in Table 1. Patients with MACE had lower left ventricular ejection fraction (LVEF) (47.8±14.4 vs. 57.4±9.8, P<0.05), Thrombolysis In Myocardial Infarction (TIMI) flow after the procedure (0/0/6/16 vs. 0/0/5/62 in TIMI flow 0, 1, 2, and 3, respectively, P<0.05), higher Gensini score (70.5±37.4 vs. 53.7±24.9, P<0.05), higher urinary N-acetyl-β-D-glucosaminidase (NAG; 16.5±12.0 vs. 11.9±6.8, P<0.05) and UBCR levels [0.427 (0.278–1.037) vs. 0.149 (0.052–0.264), P<0.05] in comparison with those without MACE. Patients with MACE were less frequently administered angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) [17 (77%) vs. 65 (97%) P<0.05] and statins [15 (68%) and 60 (90%), P<0.05] in comparison with those without MACE. Patients with MACE were less frequently administered angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) [17 (77%) vs. 65 (97%) P<0.05] and statins [15 (68%) and 60 (90%), P<0.05] in comparison with those without MACE. Patients with MACE had higher Gensini score (70.5±37.4 vs. 53.7±24.9, P<0.05), higher urinary N-acetyl-β-D-glucosaminidase (NAG; 16.5±12.0 vs. 11.9±6.8, P<0.05) and UBCR levels [0.427 (0.278–2.037) vs. 0.149 (0.052–0.264), P<0.05] in comparison with those without MACE. Other variables, including age, sex, numbers of patients (those with hypertension, hyperlipidemia, and diabetes mellitus), eGFR (71.5±19.3 vs. 76.7±22.9), prevalence of proteinuria [5 (23%) vs. 13 (19%)], urinary pH, and contrast media volume on PCI [133 (110–210) vs. 150 (100–170)] were not different between patients with and without MACE. There were no significant differences in the use of diuretics and/or nonsteroidal antiinflammatory drugs between the 2 groups in the present study.

Univariate and multivariate Cox proportional-hazards re-
gression analyses were performed to determine the risk factors for predicting MACE. The univariate analysis revealed that the UBCR level was significantly associated with the occurrence of MACE. Variables with P<0.05 in the univariate analysis were entered into the multivariate Cox proportional hazards analysis (Table 2). The use of ACEIs or ARBs [hazard ratio (HR) 0.116, 95% confidence interval (CI) 0.016–0.589, P<0.05], TIMI flow after procedure (HR 5.272, 95% CI 1.384–20.076, P<0.05) and UBCR (HR 7.714, 95% CI 1.405–42.39, P<0.05) were the independent predictors of MACE.

The patients were divided into 2 groups based on the UBCR cut-off values determined by ROC curves (Figure 1A): high UBCR group (n=30) and low UBCR group (n=59). Kaplan-Meier analysis demonstrated that the high UBCR group had a significantly higher event rate than the low UBCR group (Figure 1B). The high UBCR group had significantly greater Gensini scores than the low UBCR group (67.3±33.9 vs. 53.0±25.4, P<0.05) (Figure 2A). The level of serum creatinine at 6 months after discharge was significantly higher in the high UBCR group than in the low UBCR group. The eGFR after discharge was significantly lower in the high UBCR group than in the low UBCR group. However, there were no significant differences in the level of serum creatinine or the eGFR.

### Table 1. Clinical Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Factors</th>
<th>MACE (–) (n=67)</th>
<th>MACE (+) (n=22)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, years</td>
<td>65.9±11.8</td>
<td>66.2±10.3</td>
<td>0.91</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>55 (82)</td>
<td>18 (82)</td>
<td>0.98</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>49 (73)</td>
<td>17 (77)</td>
<td>0.70</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>35 (52)</td>
<td>14 (64)</td>
<td>0.35</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>19 (28)</td>
<td>6 (27)</td>
<td>0.92</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>57.4±9.8</td>
<td>47.8±14.4</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Medications**

- Aspirin, n (%) 67 (100) 22 (100) 0.05
- Clopidogrel, n (%) 66 (99) 21 (95) 0.44
- ACEIs or ARBs, n (%) 65 (9) 17 (77) <0.05
- β-blockers, n (%) 39 (58) 9 (41) 0.16
- Statins, n (%) 60 (90) 15 (68) <0.05

**Laboratory data**

- Peak creatine kinase, IU 2,379 (1,208–4,006) 2,533 (1,322–5,258) 0.38
- Serum creatinine, mg/dl 0.80±0.27 0.86±0.24 0.38
- eGFR, ml·min⁻¹·1.73m⁻² 76.7±22.9 71.5±19.3 0.35
- Proteinuria, n (%) 13 (19) 5 (23) 0.06
- UBCR, mg/g 0.149 (0.052–0.264) 0.427 (0.278–2.037) <0.05
- Urinary NAG, U/L 11.9±6.8 16.5±12.0 <0.05
- Urinary pH 6.51±0.88 6.21±0.75 0.15

**Infarct-related vessel, n (%)** 0.86

- LAD 38 (57) 11 (50)
- LCX 5 (7) 2 (9)
- RCA 24 (36) 9 (41)

**No. of diseased vessels (1/2/3)** 0.79

- 57/7/3 17/4/1

**Thrombectomy, n (%)** 0.69

- 60 (89) 19 (86)

**No. of stents** 0.66

- 1.13±0.43 1.18±0.16

**Stent diameter, mm** 0.14

- 3.52±0.43 3.37±0.35

**Stent length, mm** 0.52

- 20.3±4.71 21.0±3.6

**TIMI flow before procedure (0/1/2/3)** 0.24

- 54/8/3 21/0/1

**TIMI flow after procedure (0/1/2/3)** <0.05

- 0/0/5/62 0/0/6/16

**Contrast media volume on PCI (ml)** <0.05

- 150 (100–170) 133 (110–210)

**Gensini score** <0.05

- 53.7±24.9 70.5±37.4

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate; LAD, left descending artery; LCX, left circumflex artery; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; NAG, N-acetyl-β-D-glucosaminidase; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, Thrombolysis In Myocardial Infarction; UBCR, urine β2 microglobulin-creatinine ratio.

### Table 2. Factors Associated With MACE (Multivariate Cox Proportional-Hazards Analysis)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Multivariate</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF*</td>
<td>0.602</td>
<td>0.249–1.442</td>
<td>0.26</td>
</tr>
<tr>
<td>ACEIs or ARBs</td>
<td>0.116</td>
<td>0.016–0.859</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Statins</td>
<td>0.492</td>
<td>0.056–4.343</td>
<td>0.52</td>
</tr>
<tr>
<td>UBCR*</td>
<td>7.714</td>
<td>1.405–42.39</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Urinary NAG*</td>
<td>1.571</td>
<td>0.771–3.216</td>
<td>0.21</td>
</tr>
<tr>
<td>TIMI flow after procedure</td>
<td>5.272</td>
<td>1.384–20.076</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Per 1-SD increase.

Cl, confidence interval; HR, hazard ratio; SD, standard deviation. Other abbreviations as in Table 1.
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Discussion

The present study found the UBCR level was increased in patients with MACE. Multivariate Cox proportional hazard regression analysis demonstrated the UBCR level to be an independent and strong factor that could predict the risk of MACE in patients with STEMI.

It is widely accepted that both glomerular injury and tubulointerstitial damage are involved in the progression to renal dysfunction, which is associated with progressive cardiovascular disease. Although the UBCR level was increased in patients with MACE, there was no difference in the eGFR between patients with and without MACE. One possible reason for this result is that the causes of renal tubular damage are different from those of decreased eGFR, and those differences might be associated with the occurrence of MACE. β2MG is readily filtered through the glomerulus and is completely reabsorbed by the proximal tubules. The reabsorption of β2MG is impaired when brush border cells in the proximal tubules are damaged, leading to increased U-β2MG excretion. Another possibility is that the sensitivity to detect silent renal insufficiency might differ between eGFR and UBCR. Importantly, the prevalence of increased UBCR levels (≥300 μg/g creatinine) is higher than the prevalence of renal insufficiency diagnosed by the presence of albuminuria or decreased eGFR, indicating that the UBCR level might be superior for stratifying the risk for MACE in STEMI patients after PCI.

Although several reports have demonstrated the importance of evaluating proximal tubular injury in predicting the development of renal insufficiency, the importance of tubular damage in patients with STEMI has not been established. We found that proximal tubular damage evaluated by the level of UBCR was an independent predictor of MACE. Tubular damage is thought to be triggered by renal hypoxia induced by reduced renal perfusion, inflammation, and hypertension. Fujii et al have showed the involvement of inflammation during tubulointerstitial injury. Moreover, Tran et al have demonstrated the association of systemic inflammation in regulating global and tubular damage. Therefore, we speculate that evaluation of tubular damage in STEMI patients contributes to the assessment of vascular inflammation, which is strongly associated with MACE.

Tubular injury is both a marker and a mediator of CKD progression. The cardiovascular events associated with atherosclerosis are more often fatal in patients with CKD than in individuals without CKD. It has been reported that the most predictive factor for progression to CKD is not only the etiology of glomerular injury, but also the degree of tubulointerstitial damage. The present study showed that a high UBCR was associated with worsening renal function after discharge. In addition, the present study showed that a high UBCR at ad-
mission was associated with the severity of CAD and the occurrence of MACE. Therefore, it is important to attenuate the tubulointerstitial damage of patients after STEMI even if serum creatinine and eGFR are preserved. The key role of inflammation and oxidative stress in the pathogenesis of atherosclerosis and acute MI has become increasingly apparent in recent years, based on the results of experimental, epidemiologic and clinical studies.\(^7\) Previous studies have shown that tubulointerstitial damage is associated with factors such as oxidative stress and inflammation. The renin-angiotensin system is one of the most important causes of producing oxidative stress and inflammation of the renal tubules.\(^8\) Interestingly, recent studies have reported that ACEIs and angiotensin II type 1 (AT1) receptor blockade reduced tubular damage.\(^9\) ACEIs and AT1 receptor blockers may be of potential value in patients with high UBCR among patients with STEMI, because we found that patients with MACE were less frequently administered ACEIs or ARBs compared with those without MACE; however, further research is required to demonstrate that the use of those drugs has the potential to prevent tubulointerstitial damage in patients who undergo PCI after STEMI.

The current study measured urinary NAG in addition to UBCR. The urinary NAG levels were not an independent risk factor for predicting MACE in this study, although patients with MACE demonstrated a trend toward higher levels of urinary NAG in comparison with those without MACE. Although the cause of β2MG appearance in the urine is dysfunctional absorption in the tubules, urinary NAG is released as a result of direct renal tubular injury,\(^4\) although the detailed mechanism is still unknown, beyond these differences already discussed. Of note, UBCR has been postulated to be superior to urinary NAG for predicting the prognosis in idiopathic membranous nephropathy.\(^4\) There is increasing evidence that urinary liver-type fatty acid binding protein (L-FABP) is a new marker for tubulointerstitial damage.\(^18\)\(^,\)\(^19\) Because the current study did not evaluate the levels of L-FABP in this series, a comparison between UBCR and L-FABP is therefore still required in a future study.

The current study had a comparatively large population of MACE patients because it included TLR. The UBCR levels of patients with MACE were significantly higher than in those without MACE, even if the patients with TLR in MACE are excluded (n=12), and the UBCR levels were almost the same at the time of rehospitalization in TLR patients (data not shown). Therefore, the measurement of UBCR at admission may be a highly reliable method of risk stratifying patients with MI after PCI.

Recently, Ishibashi et al have shown that pravastatin attenuates proximal tubular cell apoptosis by inhibiting the expression of oxidative stress and advanced glycation endproducts.\(^31\) Erythropoietin, some statins and calcium-channel blockers (CCBs) protect against tubulointerstitial injury.\(^31\)\(^-\)\(^34\) However, the drugs to reduce UBCR and which statins or CCBs have clinical benefit for tubulointerstitial damage remains unknown, and further study is required to demonstrate which drugs have the potential to preserve and improve tubular damage in STEMI patients.

In this study, coronary risk factors such as hypertension, hyperlipidemia, and diabetes mellitus were not associated with the rate of MACE after STEMI. Therefore, further studies including a large number of patients are needed to investigate the relationship between classical risk factors and tubulointerstitial damage.

Conclusions

The current data suggest that the UBCR level might be superior for stratifying the risk for MACE in STEMI patients who undergo PCI. The results of this study demonstrate that renal tubulointerstitial damage is associated with short-term cardiovascular events in patients with MI. Further studies with a larger number of patients and a longer follow-up are thus required to evaluate the usefulness of the U-β2MG level for predicting MACE.

Acknowledgments

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Disclosures

The authors declare no conflicts of interest with regard to this study.

References

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