

# Clinical Outcomes and Therapeutic Strategy in Patients With Acute Myocardial Infarction According to Renal Function

## — Data From the Korean Acute Myocardial Infarction Registry —

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**Background** The aim of the present study was to evaluate the relationship between clinical outcomes after acute myocardial infarction (MI) and renal function by glomerular filtration rate (GFR) in patients with normal or mildly elevated serum creatinine concentrations.

**Methods and Results** As part of the Korean Acute Myocardial Infarction Registry (KAMIR), 6,834 acute MI patients with a serum creatinine concentration of  $\leq 2.0$  mg/dl were enrolled from November 2005 to December 2006. The renal function was stratified arbitrary to 5 groups: (1) normal function,  $>90.0$ ; (2) preserved function,  $75.0$ – $89.9$ ; (3) mild dysfunction,  $60.0$ – $74.9$ ; (4) moderate dysfunction,  $45.0$ – $59.9$ ; (5) severe dysfunction,  $<45$  ml·min<sup>-1</sup>·1.73 m<sup>-2</sup>. Clinical characteristics, mortality and adverse events were analyzed among each group. Although reperfusion and medical therapies were underused, the rates of mortality and adverse events were increased with declining renal function. After adjustment with confounders, severe and moderate renal dysfunctions were important risk predictors of in-hospital mortality, long-term mortality and adverse events.

**Conclusion** The spectrum of renal function, when it was presented by GFR, is broad and is an important risk predictor for adverse outcomes after acute MI, even in patients with normal or mildly elevated serum creatinine concentrations. Furthermore, standard treatments were underused in any degree of renal dysfunction. (*Circ J* 2008; 72: 1410–1418)

**Key Words:** Glomerular filtration rate; Mortality; Myocardial infarction

The renal dysfunction has been reported as an independent risk factor which has shown worse clinical outcomes after acute myocardial infarction (MI)<sup>1–3</sup>. Previous studies, which have focused on patients with severe and end-stage renal disease, showed that high inci-

dence of mortality and adverse events is observed in those patients who developed acute MI<sup>4,5</sup>. This particularly poor outcome has been explained by facts such as specific pathophysiologic condition, high prevalence of comorbidity and underuse of life-saving treatments, so called ‘therapeutic nihilism’<sup>6</sup>. However, the relationship between clinical outcomes and the utilization of standard therapies after acute MI and renal function is not clear yet in patients with normal or mildly elevated serum creatinine concentrations, because those patients have not been highlighted in studies of this area. In fact, serum creatinine concentration has been known as an insensitive indicator of renal function! Despite a relatively normal range of serum creatinine concentration, some patients might have renal dysfunction or impairment, when renal function is defined by estimated glomerular filtration rate (GFR). Furthermore, any degree of renal dysfunction, as well as end-stage renal disease, might be an indicator of early pathologic changes of vascular wall such as atherosclerosis, and could be associated with poor prognosis after acute MI<sup>7,8</sup>.

Consequently, as part of the Korean Acute Myocardial Infarction Registry (KAMIR) study, the present study aimed to investigate the prognostic impact of renal function

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by estimated GFR, and test the effects of evidence-based therapies in unselected large populations with normal or mildly elevated serum creatinine concentration who developed acute MI, to coincide with real practice.

## Methods

### *Patients and Baseline Characteristics*

The KAMIR study is a retrospective multi-hospital study and collected data from 10,463 patients with acute MI between November 2005 and December 2006. The purpose and methods used to register patients of the KAMIR study have been described previously.<sup>9</sup>

We abstracted 7,411 data that were available to calculate the estimated GFR. Of these patients, we analyzed data of 6,834 eligible patients who were 20 years or older (mean age: 64.1±12.9 years, male: n=5,209). These patients were newly diagnosed with acute MI at 41 primary percutaneous coronary intervention (PCI) facilities and admitted to hospital within 7 days after symptom onset. On the basis of the cut-off value of serum creatinine which was used in the Third National Health and Nutrition Examination Survey (NHANES III),<sup>10</sup> patients with a baseline serum creatinine concentration of more than 2.0 mg/dl, as the index of moderate and severe renal impairment, were excluded. We also excluded patients with a history of previous renal diseases and overt renal failure (defined as renal replacement therapy or GFR of less than 15 ml per min per 1.73 m<sup>2</sup> of body surface area). The clinical data after discharge were obtained from outpatient visits and contacted by telephone at 30, 90 and 180 days.

### *Definition*

Acute MI was defined by World Health Organization criteria incorporating clinical features, elevated biochemistry marker and electrocardiographic findings.<sup>11</sup> ST elevation MI (STEMI) was indicated by new ST elevation in at least 2 contiguous leads, measuring more than 0.2 mV in leads V<sub>1-3</sub>, or 0.1 mV in all other leads. When these findings were compounded, the diagnosis was supported by coronary angiographic (CAG) findings. Killip class was defined at admission. Left ventricular ejection fraction (LVEF) was shown by echocardiography.

### *GFR Measurement*

Renal function was defined by estimated GFR. Of several reliable equations, we used the Mayo clinic quadratic equation (MCQ) because of the following reasons: (1) Cockcroft and Gault formula usually overestimates GFR, especially in low range; and (2) the modification of diet in renal disease equation underestimates high GFR in diabetics.<sup>12</sup> MCQ incorporated age, sex and serum creatinine concentration.

$$\text{MCQ} = \exp [1.911 + 5.249/\text{SCr} - 2.114/\text{SCr}^2 - 0.00686 \times \text{age (years)} - 0.205 \text{ if female}].$$

According to the cut-off value which was used in the Candesartan in heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trial,<sup>13</sup> we stratified a study population into 5 groups as follows: normal renal function, >90.0; preserved renal function, 75.0–89.9; mild renal dysfunction, 60.0–74.9; moderate renal dysfunction, 45.0–59.9; severe renal dysfunction, <45 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup>. Serum creatinine concentration used in this equation was an initial value after presentation and had a normal range from 0.6–1.5 mg/dl.

### *Treatment*

PCI and coronary artery bypass graft (CABG) surgery were used for reperfusion therapy. As primary reperfusion therapy in STEMI patients, intravenous thrombolytic therapy, primary and facilitated PCI were performed. Early invasive PCI was defined as emergent PCI, which was performed in non-STEMI (NSTEMI) patients with remained symptoms. Treatment strategies were decided by operators, according to the American College of Cardiology and the American Heart Association guidelines for the management of patients with acute coronary syndrome. Furthermore, evidence-based medications were prescribed in a non-randomized unselected condition.

### *Clinical Outcomes*

The primary endpoint was death from any cause. Other major adverse cardiac events such as cardiac death, recurrent MI, repeated coronary revascularization and CABG were defined as secondary endpoints. Cardiac death included sudden death within 1 month after MI onset as well as a known mechanical or arrhythmic cause.

### *Statistical Analysis*

The estimated GFR is presented in categorical value which was suited for our purposes. For continuous variables, comparison among each group was performed by one-way ANOVA and the Kruskal–Wallis test, when appropriate. Pearson's chi-square test was used for the analysis of categorical variables. All p-values were two-sided, and a p-value of less than 0.05 was considered to indicate statistical significance. Univariate and multivariate analyses were performed to determine the prognostic significance of clinical variables for in-hospital and long-term clinical endpoint. Variables with p-values of <0.25 on univariate analysis were entered into multivariate logistic regression models and Cox proportional-hazards models. Multivariate logistic regression modeling was used to compare in-hospital outcomes and candidates for adjustment included age, sex, comorbidities (previous MI, previous PCI, diabetes, hypertension, elevated lipid concentrations, current smoking, previous stroke, previous heart failure, chronic lung disease), 'symptom to door time', Killip class >I, primary ventricular tachyarrhythmia, LVEF <40%, therapeutic modalities and medical treatments during hospitalization, angiographic findings, PCI-related complications, and spectrum of renal function. Cox proportional-hazards modeling was used to compare long-term clinical outcomes. The following variables were included in adjustment: age, sex, comorbidities (previous MI, previous PCI, diabetes, hypertension, elevated lipid concentrations, current smoking, previous stroke, previous heart failure, peripheral vascular disease, malignancy), pre-hospital resuscitation, 'symptom to door time', symptoms and sign at presentation, Killip class >I, atrial fibrillation, primary ventricular tachyarrhythmia, LVEF <40%, therapeutic modalities, medical treatments during hospitalization and at discharge, angiographic findings, PCI-related complications, and spectrum of renal function. We used stepwise elimination and backward selections to select the most powerful predictive variables in both models. Life table estimates, by 5 groups according to the estimated GFR, for long-term mortality and adverse events were determined and presented as event curves. Analyses were performed with the use of SPSS software (version 13.0, SPSS Inc, Chicago, IL, USA).

**Table 1** Baseline Characteristics According to the eGFR

	Normal renal function	Preserved renal function	Mild renal dysfunction	Moderate renal dysfunction	Severe renal dysfunction	p value
Patients, n	3,441	1,649	881	520	343	
Age, years <sup>¶</sup>	58±11	68±11	71±10	72±11	75±9	<0.001
Male sex, n (%)	3,192 (92.8)	967 (58.6)	548 (62.2)	328 (63.1)	174 (50.7)	<0.001
<b>Comorbidities</b>						
Hypertension, n (%)	1,288 (37.4)	839 (50.9)	505 (57.3)	320 (61.5)	240 (70.0)	<0.001
Diabetes, n (%)	751 (21.8)	405 (24.6)	263 (29.9)	203 (39.0)	149 (43.4)	<0.001
Current smoker, n (%)	2,058 (59.8)	570 (34.6)	270 (30.6)	155 (29.8)	73 (21.3)	<0.001
Elevated lipid concentrations <sup>§</sup> , n (%)	2,418 (70.3)	1,108 (67.2)	547 (62.1)	274 (53.0)	174 (50.7)	<0.001
Previous MI, n (%)	113 (3.3)	74 (4.5)	47 (5.3)	28 (5.4)	21 (6.1)	<0.001
Previous PCI, n (%)	163 (4.7)	101 (6.1)	50 (5.7)	35 (6.7)	26 (7.6)	<0.001
Previous CABG, n (%)	21 (0.6)	16 (1.0)	4 (0.5)	4 (0.8)	6 (1.7)	<0.001
Previous heart failure, n (%)	22 (0.6)	29 (1.8)	35 (4.0)	31 (6.0)	30 (8.7)	<0.001
Previous stroke, n (%)	150 (4.4)	123 (7.5)	81 (9.2)	58 (11.2)	54 (15.7)	<0.001
<b>Initial presentation</b>						
ST elevated MI, n (%)	2,213 (64.7)	1,031 (62.9)	552 (63.3)	305 (59.2)	196 (57.6)	0.021
Non-ST elevated MI, n (%)	1,205 (35.3)	609 (37.1)	320 (36.7)	210 (40.8)	144 (42.4)	0.021
Symptom to door time, min <sup>¶</sup>	713±1,346	707±1,261	761±1,435	757±1,230	1,062±1,614	<0.001
Pre-hospital resuscitation, n (%)	46 (1.3)	45 (2.7)	28 (3.2)	23 (4.4)	21 (6.1)	<0.001
Systolic BP, mmHg <sup>¶</sup>	130±30	127±29	124±42	121±34	119±34	<0.001
Diastolic BP, mmHg <sup>¶</sup>	80±22	77±17	75±36	73±19	74±54	<0.001
Preinfarct angina, n (%)	1,373 (40.5)	710 (43.8)	359 (41.7)	204 (40.0)	144 (42.9)	0.224
Typical chest pain, n (%)	3,043 (88.8)	1,397 (85.4)	712 (81.7)	389 (75.2)	238 (70.0)	<0.001
Dyspnea, n (%)	732 (21.4)	448 (27.4)	325 (37.4)	218 (42.2)	167 (49.3)	<0.001
Killip class >I, n (%)	607 (18.4)	441 (27.9)	288 (34.4)	198 (40.4)	189 (58.3)	<0.001
Q wave infarction, n (%)	576 (16.6)	236 (14.3)	131 (14.9)	79 (15.2)	62 (18.1)	0.133
Atrial fibrillation, n (%)	87 (2.5)	81 (4.9)	53 (6.0)	34 (6.5)	28 (8.2)	<0.001
Primary VT/VF, n (%)	20 (0.6)	20 (1.2)	9 (1.0)	10 (1.9)	6 (1.7)	0.008
<b>Laboratory findings</b>						
LVEF <40%, n (%)	372 (12.0)	212 (14.5)	176 (22.8)	127 (28.7)	90 (31.5)	<0.001
eGFR, ml·min <sup>-1</sup> ·1.73m <sup>-2</sup> <sup>‡</sup>	106.4 (98.1–115.7)	83.3 (79.7–86.6)	68.4 (65.0–72.1)	53.3 (49.0–56.8)	37.7 (34.0–41.3)	<0.001
Creatinine, mg/dl <sup>‡</sup>	0.9 (0.9–1.0)	1.1 (0.9–1.2)	1.2 (1.1–1.3)	1.4 (1.3–1.6)	1.8 (1.6–1.9)	<0.001
Troponin I, ng/ml <sup>‡</sup>	22.8 (5.0–52.2)	18.18 (3.2–50.0)	16.5 (2.5–50.0)	21.7 (3.7–50.0)	14.0 (4.2–44.3)	<0.001
CK-MB, ng/ml <sup>‡</sup>	94.8 (26.0–232.0)	78.7 (19.0–219.5)	65.8 (16.5–193.3)	47.0 (15.0–175.0)	43.3 (11.0–158.9)	<0.001
Total cholesterol, mg/dl <sup>‡</sup>	183.0 (157.0–211.0)	181.0 (155.0–209.0)	177.0 (149.0–209.0)	169.0 (141.0–205.0)	167.0 (138.3–201.5)	<0.001
Triglyceride, mg/dl <sup>‡</sup>	109.0 (72.0–163.0)	101.0 (69.0–146.0)	103.0 (70.0–149.0)	101.0 (71.0–145.0)	96.0 (72.0–138.0)	<0.001
HDL-cholesterol, mg/dl <sup>‡</sup>	43.0 (37.0–51.0)	44.0 (37.0–52.0)	42.0 (35.0–50.0)	42.0 (35.3–51.0)	41.0 (34.0–49.0)	<0.001
LDL-cholesterol, mg/dl <sup>‡</sup>	116.0 (94.0–142.0)	115.0 (92.0–140.0)	110.0 (87.0–136.0)	108.0 (84.0–140.0)	104.0 (80.0–134.0)	<0.001

eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BP, blood pressure; VT/VF, ventricular tachycardia/ventricular fibrillation; LVEF, left ventricular ejection fraction; CK, creatine kinase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

<sup>¶</sup>Data are presented as the means±standard deviation.

<sup>‡</sup>Data are presented as the median with 25–75 percentiles.

<sup>§</sup>Defined as total cholesterol level >240mg/dl or LDL-cholesterol >100mg/dl.

## Results

The median value of estimated GFR and serum creatinine of 6,834 patients were 90.3 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup> (interquartile range: 74.4–106.4) and 1.0 mg/dl (interquartile range: 0.9–1.2), respectively. Although we enrolled acute MI patients with serum creatinine concentration ≤2.0 mg/dl as an object of study and mild elevation of serum creatinine concentration was observed in just 435 (6.4%) patients, 863 (12.6%) patients had estimated GFR of less than 60 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup>.

### Baseline Characteristics

Baseline demography and clinical characteristics of patients are shown in Table 1 by spectrum of renal function. Old age and female sex were more frequently observed in patients with renal dysfunction. Except current smoker and elevated lipid concentration, a prevalence of cardiovascular comorbidities, such as hypertension, diabetes, and heart failure increased with declining renal function. Patients with renal dysfunction were delayed remarkably in 'onset to door time' and more likely to present with heart failure (Killip

class >I). These patients had a higher incidence of pre-hospital resuscitation, lower blood pressure, dyspnea, left ventricular (LV) systolic dysfunction, and arrhythmia than patients with preserved renal function. The rates of STEMI and typical chest pain were significantly higher in the patients with preserved renal function.

### Reperfusion Therapy and Adjunctive Medical Therapy

PCI and CABG during the index hospitalization were performed in 83.3% and 3.3% of total study population, respectively. PCI was used less frequently in patients with moderate and severe renal dysfunction, whereas the use of CABG showed no significant difference among each group (Table 2). We specified acute MI to STEMI and NSTEMI to show an association between primary reperfusion strategies and renal function (Table 2). The use of thrombolytic therapy was significantly lower in patients with moderate and severe renal dysfunction. However, an incidence of primary and facilitated PCI in STEMI was similar across the spectrum of renal function. Patients with preserved renal function who developed NSTEMI were treated more frequently with early invasive PCI. After adjustment for baseline char-

**Table 2** Treatments of Acute MI According to the eGFR

	Normal renal function	Preserved renal function	Mild renal dysfunction	Moderate renal dysfunction	Severe renal dysfunction	p value
<i>ST elevated MI</i>						
Patients, n	2,213	1,031	552	305	196	
Primary PCI, n (%)	1,653 (73.9)	781 (75.1)	423 (75.4)	233 (75.2)	140 (70.4)	0.625
Facilitated PCI, n (%)	64 (2.9)	30 (2.9)	18 (3.2)	9 (2.9)	5 (2.5)	0.989
Thrombolytic therapy, n (%)	258 (11.5)	97 (9.3)	34 (6.1)	19 (6.1)	12 (6.0)	<0.001
Conservative therapy, n (%)	286 (12.8)	137 (13.2)	84 (15.0)	47 (15.2)	40 (21.1)	0.040
<i>Non-ST elevated MI</i>						
Patients, n	1,205	609	320	210	144	
Early invasive therapy, n (%)	623 (53.8)	274 (47.7)	132 (43.9)	75 (38.5)	45 (33.1)	<0.001
Patients, n	3,441	1,649	881	520	343	
CAG, the index hospitalization, n (%)	3,151 (91.6)	1,449 (87.9)	758 (86.0)	426 (81.9)	257 (74.9)	<0.001
PCI, the index hospitalization, n (%)	3,054 (89.1)	1,387 (84.5)	730 (83.4)	390 (75.4)	231 (67.7)	<0.001
CABG, the index hospitalization, n (%)	7 (0.2)	3 (0.2)	2 (0.2)	1 (0.2)	0	0.625
<i>Medical therapy</i>						
<i>During the index hospitalization, n (%)</i>						
Aspirin	3,389 (98.5)	1,621 (98.3)	860 (97.6)	498 (95.8)	331 (96.5)	<0.001
Thienopyridine	3,341 (97.1)	1,587 (96.2)	838 (95.1)	483 (92.9)	320 (93.3)	<0.001
Cilostazole	1,191 (34.6)	514 (31.2)	242 (27.5)	137 (26.3)	84 (24.5)	<0.001
$\beta$ -blocker	2,532 (73.6)	1,147 (69.6)	599 (68.0)	321 (61.7)	211 (61.5)	<0.001
ACEI/ARB	2,851 (82.9)	1,325 (80.4)	707 (80.2)	390 (75.0)	243 (70.8)	<0.001
Nitrate	2,464 (71.6)	1,111 (67.4)	588 (66.7)	330 (63.5)	211 (61.5)	<0.001
Calcium channel blocker	492 (14.3)	237 (14.4)	127 (14.4)	82 (15.8)	66 (19.2)	0.149
Statin	2,718 (79.0)	1,237 (75.0)	629 (71.4)	346 (66.5)	232 (67.6)	<0.001
Unfractionated heparin	1,981 (57.6)	862 (52.3)	467 (53.0)	261 (50.2)	176 (51.3)	<0.001
LMWH	1,257 (36.5)	623 (37.8)	311 (35.3)	189 (36.3)	123 (35.9)	0.785
Glycoprotein IIb/IIIa inhibitor	433 (12.6)	202 (12.2)	114 (12.9)	56 (10.8)	29 (8.5)	0.171
<i>After discharge, n (%)</i>						
Aspirin	3,179 (92.4)	1,457 (88.4)	747 (84.8)	410 (78.8)	248 (72.3)	<0.001
Thienopyridine	3,059 (88.9)	1,381 (83.7)	711 (80.7)	376 (72.3)	236 (68.8)	<0.001
$\beta$ -blocker	2,329 (67.7)	1,040 (63.1)	535 (60.7)	283 (54.4)	164 (47.8)	<0.001
ACEI/ARB	2,702 (78.5)	1,206 (73.1)	616 (69.9)	331 (63.7)	200 (58.3)	<0.001
Statin	2,579 (74.9)	1,163 (70.5)	569 (64.6)	287 (55.2)	182 (53.1)	<0.001

CAG, coronary angiography; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; LMWH, low molecular weight heparin. Other abbreviations see in Table 1.

**Table 3** Determinants of Primary Reperfusion Therapy

Adjusted results	<i>ST elevated MI</i>		<i>Non-ST elevated MI</i>	
	OR (95%CI)	p value	OR (95%CI)	p value
Chest pain	1.9 (1.4–2.5)	<0.001	2.9 (2.3–3.8)	<0.001
Dyspnea	0.7 (0.6–1.0)	0.028		
Q wave on initial ECG	0.4 (0.3–0.5)	<0.001		
Previous stroke	0.5 (0.3–0.8)	0.002		
Malignancy	0.3 (0.2–0.7)	0.002		
Symptom to door time, min	1.1 (1.0–1.3)	<0.001		
Female sex			0.7 (0.5–1.0)	0.031
LVEF <40%			1.9 (1.3–2.6)	<0.001
Elevated lipid concentrations			1.5 (1.1–2.0)	0.003

Multivariate logistic regression model. Candidates for adjustment: age, sex, weight, abdominal circumference, previous MI, diabetes, current smoker, previous stroke, chronic lung disease, previous heart failure, cancer, symptom at presentation, Killip class >1, Q wave and bundle branch block on initial electrocardiogram, LVEF <40%, spectrum of renal function, 'symptom to door time', heart rate, serum creatinine concentration, CK-MB.

OR, odds ratio; CI, confidence interval; ECG, electrocardiogram. Other abbreviations see in Table 1.

acteristics, renal function was not presented as a determinant of primary reperfusion strategy in STEMI and early invasive therapy in NSTEMI (Table 3).

Adjunctive medical therapy was recorded and analyzed (Table 2). Standard medications such as antiplatelet agents,  $\beta$ -blocker, statin, unfractionated heparin and angiotensin-converting enzyme (ACE) inhibitor/angiotensin-receptor blocker (ARB) during the index hospitalization were used less frequently in patients with renal dysfunction. These trends were persisted with medical therapy at hospital discharge.

#### Angiographic Findings

Angiographic findings are shown in Table 4. CAG was performed in 6,041 (88.4%) of total study population and patients with renal dysfunction were less likely to undergo CAG. Of infarct-related arteries, right coronary artery (RCA) and left main trunk increased with declining renal function. Multivessel disease on CAG had remarkably high incidence in patients with renal dysfunction. However, complex lesion (type C) and Thrombolysis In Myocardial Infarction (TIMI) flow of grade 0 at initial CAG had fairly similar incidence among each group.

**Table 4 CAG and PCI According to the eGFR**

	Normal renal function	Preserved renal function	Mild renal dysfunction	Moderate renal dysfunction	Severe renal dysfunction	p value
<i>CAG during the index hospitalization</i>						
Patients, n	3,151	1,449	758	426	257	
Diseased vessel >1, n (%)	1,665 (52.9)	879 (60.5)	507 (67.0)	307 (71.9)	189 (73.8)	<0.001
Target vessel, n (%)						<0.001
Left anterior descending	1,606 (51.0)	698 (48.2)	326 (43.0)	192 (45.1)	100 (38.9)	
Left circumflex	521 (16.5)	223 (15.4)	128 (16.9)	62 (14.6)	25 (9.7)	
Right coronary	982 (31.2)	496 (34.2)	284 (37.5)	161 (37.8)	119 (46.3)	
Left main	42 (1.3)	32 (2.2)	20 (2.6)	11 (2.6)	13 (5.1)	
Lesion type C, n (%)	1,456 (49.2)	718 (52.4)	383 (53.6)	219 (54.6)	132 (53.9)	0.098
TIMI flow grade 0 at initial CAG, n (%)	1,319 (43.1)	648 (45.9)	312 (42.3)	189 (46.6)	121 (48.2)	0.314
<i>PCI during the index hospitalization</i>						
Patients, n	3,054	1,387	730	390	231	
Stent implantation, n (%)	2,790 (91.2)	1,242 (89.3)	651 (89.2)	353 (90.3)	213 (92.2)	0.160
Kind of implanted stents, n (%)						0.265
Sirolimus eluting stent	1,342 (48.6)	586 (48.1)	306 (47.8)	165 (47.4)	94 (44.8)	
Paclitaxel eluting stent	928 (33.6)	391 (32.1)	211 (33.0)	120 (34.5)	81 (38.6)	
Other drug-eluting stent	284 (10.3)	167 (13.7)	74 (11.6)	38 (10.9)	17 (8.1)	
Bare metal stent	208 (7.5)	74 (6.1)	49 (7.7)	25 (7.2)	18 (8.6)	
Stent length >30 mm, n (%)	702 (25.5)	333 (27.3)	192 (30.0)	90 (25.8)	59 (28.0)	0.172
Stent diameter ≤3.0 mm, n (%)	514 (18.6)	259 (21.2)	163 (25.5)	80 (23.0)	65 (30.8)	<0.001
Multiple stents, n (%)	932 (34.2)	422 (35.2)	260 (41.0)	130 (38.6)	78 (37.7)	0.016
Final TIMI flow grade 3, n (%)	2,778 (94.2)	1,234 (92.0)	653 (92.4)	339 (88.7)	213 (90.6)	0.004
PCI-related complication, n (%)	275 (8.1)	230 (14.2)	168 (19.4)	111 (21.7)	111 (33.1)	<0.001

TIMI, Thrombolysis In Myocardial Infarction. Other abbreviations see in Table 1.

**Table 5 Outcome Data According to the eGFR**

	Normal renal function	Preserved renal function	Mild renal dysfunction	Moderate renal dysfunction	Severe renal dysfunction	p value
Patients, n	3,441	1,649	881	520	343	
In-hospital Death, n (%)	45 (1.3)	63 (3.8)	65 (7.4)	57 (10.9)	58 (16.9)	<0.001
Cardiac death, n (%)	32 (0.9)	51 (3.1)	56 (6.4)	47 (9.0)	47 (13.7)	<0.001
Total MACE at 180 days, n (%)	166 (4.8)	144 (8.7)	117 (13.3)	83 (16.0)	84 (24.5)	<0.001
Overall mortality, n (%)	53 (1.5)	85 (5.2)	82 (9.3)	70 (13.5)	69 (20.1)	<0.001
Cardiac mortality, n (%)	38 (1.1)	65 (3.9)	67 (7.6)	58 (11.2)	53 (15.5)	<0.001
Recurrent MI, n (%)	24 (0.7)	15 (0.9)	10 (1.1)	7 (1.4)	14 (4.1)	<0.001
Repeated PCI, n (%)	90 (2.6)	47 (2.9)	27 (3.1)	11 (2.1)	9 (2.6)	0.137
CABG, n (%)	19 (0.5)	11 (0.6)	5 (0.6)	3 (0.6)	1 (0.3)	0.627

MACE, major cardiac adverse event. Other abbreviations see in Table 1.

Of patients who underwent PCI, plain balloon angioplasty and stent implantation were conducted in 442 (7.8%) and 5,249 (92.2%) patients, respectively. The rates of stent implantation were similar across the spectrum of renal function. Bare metal stent, sirolimus-eluting stent (Cypher<sup>®</sup>, Cordis, Johnson & Johnson, New Brunswick, NJ, USA), paclitaxel-eluting stent (Taxus<sup>®</sup>, Boston Scientific, Boston, MA, USA) and other drug-eluting stents were analyzed and compared with implanted stent during PCI, but there was no significant differences according to type of stent in among each group. The use of stent with small diameter (≤3 mm) was increased with declining renal function. Final TIMI flow of grade 3, as index of successful result of PCI, was obtained less frequently in the patients with moderate renal dysfunction. PCI-related complications including cardiogenic shock needing intra-aortic balloon counter-pulsation, heart failure class III or IV, secondary ventricular tachyarrhythmia, major bleeding and stroke had 4-fold increment of incidence rates between patients with normal renal function and those with severe renal dysfunction.

#### Clinical Outcomes According to Renal Function and Predictors of Clinical Outcomes

Of the total 6,834 patients, in-hospital mortality was recorded in 288 (4.3%) patients. Long-term mortality and adverse events were developed in 359 (5.3%) and 594 (8.7%) patients, respectively.

During the index hospitalization, overall mortality was observed more frequently in patients with renal dysfunction (Table 5). These findings were persisted in long-term mortality and adverse events. Increments of long-term mortality and adverse event rates began even at patients with mild renal dysfunction as compared with those with normal renal function (Fig 1). A stepwise increment of risk ratio for mortality and adverse events according to renal function was shown at Table 6. However, statistical significance of increased risk ratio for in-hospital mortality was observed in just 2 groups with moderate and severe renal dysfunction. Also, only 1 group of severe renal dysfunction had significance in increased risk ratio for long-term mortality and adverse events.

Predictors of in-hospital mortality were diabetes, lung disease, Killip class >I, LVEF <40%, and moderate and severe renal dysfunction (Table 7). Prescription of β-blocker and

ACE inhibitor/ARB improved survivals during hospitalization. Factors associated with an increased risk for long-term mortality included advanced age, previous MI, Killip class >I and LVEF <40%, PCI-related complications and severe renal dysfunction. RCA infarction and the use of statin (in-hospital), thienopyridine and  $\beta$ -blocker reduced long-term mortality. The risk for long-term adverse events was increased by severe renal dysfunction, multi-vessel disease, previous PCI and PCI-related complication.

### Discussion

#### Serum Creatinine and Estimated GFR in Acute MI

Although enrolled patients have serum creatinine concentrations of  $\leq 2.0$  mg/dl as mild degree renal impairment, this work shows that renal function by estimated GFR has broad spectrum, and some patients have moderate or severe renal impairments. Our finding is consistent with some previous studies. With comparison between serum creatinine and estimated GFR, the incidence of renal impairment has been underestimated by serum creatinine in same populations with acute MI.<sup>14</sup> For example, Gibson et al showed that 74% of patients had a normal creatinine concentration of 1.2 mg/dl or less; however, nearly 60% had any degree of renal dysfunction (estimated GFR  $\leq 90$  ml·min<sup>-1</sup>·1.73 m<sup>-2</sup>) with 20% having moderate or severe renal dysfunction.<sup>14</sup> Also, previous studies showed that the incidence of renal impairment, reflected by estimated GFR, was remarkably high in patients with acute MI.<sup>15</sup> This observation seems to be important because we should avoid underscoring renal function by solely use of serum creatinine in real practice. Consequently, physicians have to rely on estimated GFR, as an index of renal function, rather than serum creatinine concentrations in patients with acute MI.

#### Renal Function and Clinical Outcomes After Acute MI

Furthermore, the present study shows that estimated GFR has a significant impact on survival rates after acute MI, even in patients with normal or mildly elevated value of serum creatinine. The gradient of long-term survival rates is observed in patients with mild renal dysfunction. We observe a similar gradient of rates in overall adverse events. This finding is consistent with previous works showing greater mortality rates in severe and end-stage renal disease.<sup>14,16-18</sup> Explanations for more adverse outcomes have included several factors such as advanced age, excessive comorbidities, special pathophysiologic factors and 'therapeutic nihilism' associated with renal dysfunction.<sup>6,17,19</sup> These associations are confirmed and extended in our study by showing other clinical factors as follows: (1) remarkably higher incidence of hypertension, diabetes, stroke and previous heart failure; (2) underuse of reperfusion therapies

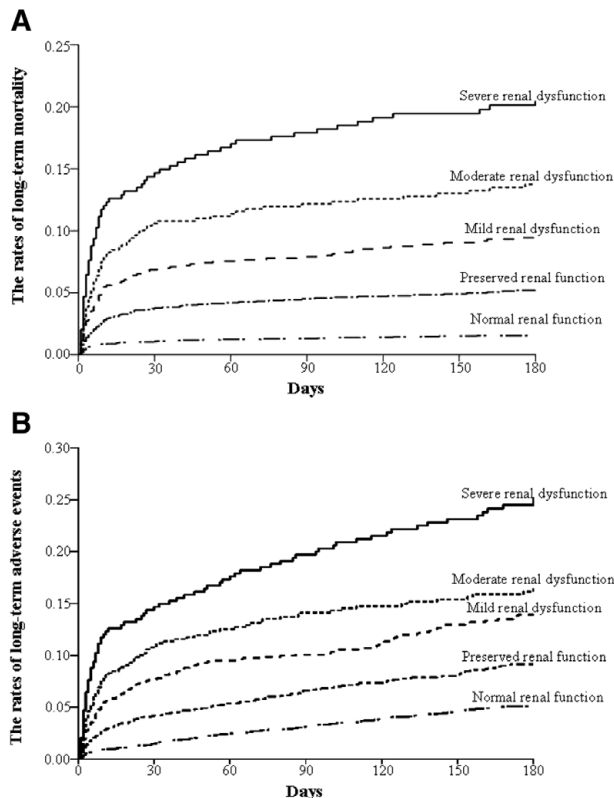


Fig 1. Life table estimates of the rates of long-term mortality (A) and of long-term adverse event (B) according to spectrum of renal function at 180 days.

and standard medications; (3) serious angiographic findings; and (4) development of more PCI-related complications with declining renal function.

With other conventional risk predictors, we identify moderate and severe renal dysfunction as the most significant risk predictor for in-hospital mortality after adjustment for confounding factors. However, only severe renal dysfunction is represented as a prognostic factor in long-term mortality and adverse outcome. This might be explained by the specific pathologic conditions playing an important role over a longer period of time, in patients with severe renal dysfunction. These include a greater comorbidity and accelerated atherosclerosis by enhanced oxidation of low-density lipoprotein-cholesterol, endothelial dysfunction and pathologic arterial calcification!<sup>6,20</sup> Previous investigators reported that these potential mechanisms attribute to complications from acute MI.<sup>21,22</sup> In this work, the proportion of PCI-related complications has abrupt increase between

**Table 6 The Increased Risk for Death and MACE After MI According to the eGFR**

Adjusted results	Severe renal dysfunction	Moderate renal dysfunction	Mild renal dysfunction	Preserved renal function	Reference <sup>‡</sup>
In-hospital mortality <sup>#</sup> OR (95% CI)	7.0 (3.2–18.2)	5.2 (2.1–13.5)	2.2 (0.7–6.7) <sup>§</sup>	1.5 (0.5–4.3) <sup>§</sup>	1.0
Long-term mortality <sup>†</sup> HR (95% CI)	4.2 (1.6–10.8)	1.5 (0.6–3.5) <sup>§</sup>	1.3 (0.5–3.4) <sup>§</sup>	0.8 (0.3–1.8) <sup>§</sup>	1.0
Long-term adverse events <sup>†</sup> HR (95% CI)	4.0 (2.3–7.1)	1.5 (0.9–2.6) <sup>§</sup>	1.4 (0.9–2.3) <sup>§</sup>	1.0 (0.7–1.5) <sup>§</sup>	1.0

HR, hazard ratio. Other abbreviations see in Tables 1,3,5.

<sup>#</sup>Multivariate logistic regression model.

<sup>†</sup>Cox proportional-hazards modeling.

<sup>§</sup>p-value is more than 0.05 for comparisons among all groups and for comparisons between individual groups.

<sup>‡</sup>Reference indicates normal renal function group.

**Table 7 Predictors of Clinical Outcomes**

Adjusted results	In-hospital mortality <sup>#</sup>		Long-term mortality <sup>†</sup>		Long-term adverse event <sup>†</sup>	
	OR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
Moderate renal dysfunction	5.2 (2.1–13.5)	0.005				
Severe renal dysfunction	7.0 (3.2–18.2)	0.001	4.2 (1.6–10.8)	0.003	4.0 (2.3–7.1)	<0.001
LVEF, <40%	3.4 (1.7–6.8)	0.001	1.8 (1.0–3.1)	0.040		
Killip class >I	2.8 (1.3–5.7)	0.007	2.4 (1.3–4.6)	0.005		
Age			1.1 (1.0–1.3)	<0.001		
Diabetes	2.2 (1.1–4.6)	0.033				
Chronic lung disease	4.2 (1.2–15.0)	0.026				
Previous MI			3.4 (1.6–7.1)	0.001		
Previous PCI					2.5 (1.4–4.8)	0.003
Diseased vessel >1					1.9 (1.3–2.7)	<0.001
RCA infarction			0.5 (0.2–0.9)	0.014		
Primary VT/VF	3.5 (1.5–7.9)	0.003				
PCI-related complications			6.2 (3.4–11.5)	<0.001	2.2 (1.6–3.2)	<0.001
Aspirin (in-hospital)					0.3 (0.1–0.7)	0.011
$\beta$ -blocker (in-hospital)	0.3 (0.1–0.6)	0.001				
ACEI/ARB (in-hospital)	0.3 (0.2–0.7)	0.005				
Statin (in-hospital)			0.4 (0.2–0.6)	<0.001	0.6 (0.5–0.9)	0.016
Aspirin at discharge					0.5 (0.2–1.0)	0.040
Thienopyridine at discharge			0.1 (0.05–0.2)	<0.001	0.3 (0.1–0.5)	<0.001
$\beta$ -blocker at discharge			0.2 (0.1–0.4)	<0.001		

RCA, right coronary artery. Other abbreviations see in Tables 1–3, 6.

<sup>#</sup>Multivariate logistic regression model.

<sup>†</sup>Cox proportional-hazards modeling.

severe and moderate renal dysfunction, and these complications are one of the important predictors in long-term mortality.

#### Renal Function and Use of Medical Therapy

Previous studies which performed in randomized controlled trials have shown underuse of standard medications in patients with renal dysfunction.<sup>23–25</sup> This work confirms those findings in unselected patients, despite considerable advances of modern pharmaceutical treatment in acute MI. We show that, as well as thrombolytic agent, medications with risk benefit after MI, are used less frequently during the index hospitalization and follow-up periods with declining renal function. Also, several medications have a significant impact on risk reduction of mortality and adverse outcome. The use of aspirin, thienopyridine, statin,  $\beta$ -blocker and ACE inhibitor have a favorable benefit to risk ratio for mortality and adverse events across the spectrum of renal function.

McCullough et al reported that prescription of standard medications is limited by lack of evidence in patients with renal dysfunction, because these patients have been excluded from randomized trials.<sup>26</sup> In real practice, physicians might be reluctant to prescribe drugs such as ACE inhibitors and  $\beta$ -blockers for patients with some degree of renal dysfunction because of the concern that they may worsen renal function. Also, aspirin and thienopyridine in those patients are commonly withheld as a result of increased risk for bleeding. However, it has been shown that the reduction of mortality after acute MI by prescription of these drugs might be even greater in high-risk patients.<sup>25</sup> Some studies have shown that ACE inhibitors and  $\beta$ -blockers have a survival benefit in acute MI patients with LV dysfunction, even in the presence moderate renal dysfunction.<sup>25</sup> Recently, in 2006, Hou et al reported the safety and utility of ACE inhibitor in advanced renal dysfunction, stage III and IV.<sup>27</sup> We suggest that more aggressive prescription of proven medications should make survival rates even in patients with severe renal dysfunction to be improved.

#### Renal Function and the Use of Reperfusion Strategy

Previous studies have shown that coronary reperfusion therapies during the index hospitalization are used less frequently in patients with renal dysfunction who develop acute MI.<sup>17,22,23</sup> As a medical treatment, this is partly associated with advanced age, increased comorbidity and more compromised hemodynamic status in decreased renal function.<sup>26</sup> Wright et al described that patients with any degree of renal dysfunction are more likely to have contraindications to thrombolytic therapy than those without renal dysfunction.<sup>28</sup> We partly ascertained previous works; however, primary and facilitated PCIs in patients with STEMI are performed with similar rate among each group. When acute MI is specified to STEMI and NSTEMI, renal function does not seem to be considered as determinant of early and primary reperfusion therapy in both subgroups of acute MI. As compared with early reports, which described primary reperfusion therapy, we think more aggressive therapy has been accomplished, at least in primary reperfusion regardless of renal function.

It has not been conclusive that PCI reduces risk ratio of mortality after acute MI in populations with lower spectrum of renal function. Al Suwaidi et al showed that invasive reperfusion therapy, PCI and CABG, is not a significant predictor of 30-day mortality model.<sup>22</sup> However, other studies reported that reperfusion therapies have the benefits to risk for long-term mortality and improve survival rates.<sup>16,28</sup> In this work, we found that reperfusion therapies represent no impacts on risk for mortality, despite remarkable advances in PCI and more aggressive approach. We cannot fully explain why these strategies are not associated with risk reduction. It is partly explained by some factors that PCI-related complications might counterbalance the benefits from early reperfusion.<sup>28</sup> Also, contrast induced worsening renal function and volume status during and after PCI might be attributed to those results.<sup>29</sup> Dragu et al reported that survival rates in patients who underwent primary PCI are the lowest as compared with those with thrombolysis and even in those without reperfusion therapy.<sup>30</sup> We think

that a randomized trial is needed to elucidate the impact of primary PCI on clinical outcome in acute MI patients with renal dysfunction.

We extend previous work by evaluating the factors related with CAG and PCI according to the spectrum of renal function. Of these factors, multivessels disease and RCA infarction increase risk of long-term adverse events. Coronary stents, especially drug-eluting stent, are used mainly in PCI rather than plain balloon angioplasty in most patients. Inaguma et al showed that stent implantation is associated with risk reduction of overall mortality.<sup>21</sup> However, this work shows no impact on prognosis of stent implantation, even with a drug-eluting stent. This disparate finding might be a result from differences of study population. They enrolled patients with angina pectoris or MI, who underwent PCI. The success of PCI is less likely to be obtained and PCI related complications are more likely to be developed with declining renal function. It seems that these findings may be attribute to diminishing the effect of PCI in mortality and adverse events in this work.

#### Study Limitations

This study has some limitations. First, this work has a potential bias because we excluded patients with serum creatinine of more than 2.0mg/dl and previous renal disease such as renal failure on dialysis. This exclusion might reduce the strength of risk associated with renal dysfunction. Second, GFR is not measured directly and measured by MCQ equation which has not been tested in oriental populations. Also, GFR might be affected by compromised hemodynamic status because creatinine concentration incorporated in MCQ is initial value. Finally, long-term adverse events including revascularization might be underestimated because we could not perform follow-up CAG in patients without symptoms.

### Conclusion

Although serum creatinine concentrations of patients with acute MI did not exceed 2.0mg/dl, the present study showed that renal function, which is presented by estimated GFR, has broad spectrums. The current study also showed that the mortality rates are strongly affected by the spectrum of renal function. Also, we confirmed 'therapeutic nihilism' in patients with any degree of renal dysfunction, although life-saving medications had a benefit to risk ratio. Several clinical factors including higher prevalence of comorbidities, compromised hemodynamic status, serious angiographic findings and complications might attribute to these association. Even though patients with acute MI have normal or mildly elevated serum creatinine concentrations, renal function must be reflected by GFR and be considered as an independent risk factor in practice. Also, the constructive utilization of standard treatments for acute MI might be associated with better prognosis in patients with any degree of renal dysfunction.

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## Appendix 1

### *Korea Acute Myocardial Infarction Registry Investigators*

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