ORIGINAL ARTICLE

Impact of contrast-induced acute kidney injury with transient or persistent renal dysfunction on long-term outcomes of patients with acute myocardial infarction undergoing percutaneous coronary intervention

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ABSTRACT

Objective To investigate the long-term prognostic implications of contrast-induced acute kidney injury (CI-AKI) with transient or persistent renal dysfunction in acute myocardial infarction (AMI) patients undergoing percutaneous coronary intervention (PCI).

Design A retrospective observational registry study.

Setting Clinical follow-up after PCI.

Patients and methods A total of 1041 PCI-treated AMI patients from the Infarction Prognosis Study registry. CI-AKI was defined as an increase in serum creatinine ($>25\%$ or >0.5 mg/dl (>44.2 $\mu\text{mol/l}$)) within 2 days after PCI.

Main outcome measures Two-year cumulative event rate of all-cause death or renal failure requiring dialysis.

Results CI-AKI was observed in 148 patients (14.2%). Patients with CI-AKI had a higher rate of death or dialysis (25.4% vs 6.3%, $p<0.001$) at 2 years compared with patients without CI-AKI. CI-AKI was an important independent predictor of death or dialysis (HR 2.76, 95% CI 1.61 to 4.73, $p<0.001$). Persistent renal dysfunction after CI-AKI was documented in 68 patients (45.9%). Patients with transient renal dysfunction showed a lower 2-year event rate of death or dialysis compared with those with persistent renal dysfunction (17.9% vs 34.1%, $p=0.013$); however, they showed a higher event rate compared with those without CI-AKI (17.9% vs 6.3%, $p<0.001$).

Conclusion Transient and persistent renal dysfunction after CI-AKI was associated with increased short and long-term mortality and morbidity in AMI patients treated by PCI. Better preventive strategies are needed to improve clinical outcomes in AMI patients at high risk of developing CI-AKI.

Contrast-induced acute kidney injury (CI-AKI) is generally considered a reversible form of acute renal failure that begins soon after iodinated contrast administration during angiographic procedures. This hospital-acquired complication is of great concern because of its adverse effects on patients' clinical outcomes, including prolonged hospitalisation and increased morbidity and mortality.^{1, 2} Important predisposing factors for CI-AKI include female gender, older age, diabetes mellitus, pre-existing renal insufficiency, advanced heart failure and intravascular volume depletion.^{3–5} The risk of CI-AKI is significantly higher among patients with acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI) than among the general population undergoing elective PCI.^{6–10} The

most likely contributing factors for CI-AKI in patients with AMI are haemodynamic instability or impaired systemic perfusion caused by left ventricular dysfunction, large volume of contrast medium, or insufficient time to perform renal prophylactic therapies during contrast medium exposure.⁷ The purpose of this study was to determine the incidence of CI-AKI in patients with AMI undergoing PCI and to evaluate clinical predictors and long-term prognostic implications of CI-AKI in these patients.

METHODS

Study population

The registry of the Infarction Prognosis Study, a prospective single-centre cohort study, is maintained at the Severance Cardiovascular Hospital following an institutional review board-approved protocol. From the registry, we identified all consecutive patients 20 years of age or older who underwent PCI from May 2005 to July 2009. Patients exposed to contrast medium within 7 days before PCI or patients with end-stage renal disease requiring chronic dialysis treatment were excluded.

Definitions

CI-AKI was defined as a greater than 25% increase in serum creatinine level or greater than 0.5 mg/dl (>44.2 $\mu\text{mol/l}$) serum creatinine within 2 days after intravascular administration of iodinated contrast medium when no other major kidney insult was identified. Recovery of renal function in CI-AKI patients was defined as return to serum creatinine level of 25% or less or 0.5 mg/dl or less (≤ 44.2 $\mu\text{mol/l}$) above the baseline level at 1 month by a single measurement.

ST-segment elevation myocardial infarction was defined as characteristic chest pain with ST-segment elevation of 0.2 mV or greater in two or more contiguous leads or new-onset left bundle branch block observed on electrocardiogram and positive troponin-T. Non-ST-segment elevation myocardial infarction was defined as myocardial infarction without ST-segment elevation. The Mehran score was calculated based on eight clinical and procedural variables such as age greater than 75 years, hypotension, congestive heart failure, intra-aortic balloon pump, serum creatinine, diabetes, anaemia and volume of contrast according to the previous report.⁵

The primary endpoint was defined as a composite of all-cause death and renal failure requiring dialysis. In addition, we also investigated outcomes in all-cause death as well as the composite event of death, dialysis and hospital admission due to cardiovascular events such as myocardial infarction, heart failure, stroke and target vessel revascularisation.

Study protocol

The serum creatinine concentration was routinely measured before PCI and 24 h, 48 h and 1 month after PCI. Creatinine clearance was calculated using the Cockcroft–Gault formula.

Patients received intravenous hydration with 0.9% normal saline (1 ml/kg per hour) for 12 h before and after PCI. However, for patients with ST-segment elevation myocardial infarction undergoing primary PCI, hydration was performed after PCI. In these patients prehydration was not generally performed because of limited time. The hydration rate was reduced to 0.5 ml/kg per hour in patients with left ventricular ejection fraction (LVEF) less than 40%, overt heart failure or volume overload. Relevant baseline and follow-up laboratory and clinical data were recorded during the hospital stay. After hospital discharge, patients were clinically followed up at 1 month and every 3 months thereafter. If the patient did not attend a scheduled visit, outcome variables were obtained by telephone. The present study was approved by the hospital institutional review board and performed according to good clinical practice standards. Written informed consent was obtained from each patient before enrolment.

Percutaneous coronary intervention

PCI was performed with the femoral approach according to standard clinical practice. Patients received 250 mg aspirin, 300 mg clopidogrel (600 mg in case of ST-segment elevation myocardial infarction), and a bolus of 5000 U heparin immediately after diagnosis of AMI, followed by an additional bolus of heparin during the procedure, if necessary. A non-ionic dimeric, iso-osmolality contrast medium, iodixanol (Visipaque, GE Healthcare, Princeton, New Jersey, USA), was used in 1033 patients (99.7%). The other patients received a non-ionic monomeric, low-osmolar contrast medium (Ultravist, Bayer HealthCare Pharmaceuticals, Berlin, Germany). In general, target lesions were predilated with a balloon followed by stent implantation. Supportive pharmacological therapies, mechanical support, contrast medium dose and angioplasty technique were left to the discretion of the operator, according to our institute's clinical protocols and international guidelines.⁸

Statistical analysis

Continuous data are reported as mean±SD, unless otherwise specified. Categorical data are expressed as absolute value and percentage. Continuous variables were compared by Student's *t* test. Categorical variables were compared by χ^2 or Fisher's exact test, as appropriate. A multivariate logistic regression model was used to determine independent risk factors of CI-AKI. The cumulative incidence of clinical events was estimated using the Kaplan–Meier method. The significance of the curves was tested using the log-rank test. Univariate and multivariate Cox regression analyses were performed to identify independent predictors of death and dialysis. Univariate analysis included variables such as age, gender, body mass index, smoking, diabetes mellitus, hypertension, dyslipidaemia, renal failure, past medical history, pattern of AMI (ST-segment elevation vs non-ST-segment elevation myocardial infarction), shock, heart failure, multivessel disease, anaemia, primary PCI, contrast volume and medication. Variables with *p*<0.15 in the univariate analysis

were entered into the multivariate Cox regression analysis by forward stepwise selection. Statistical significance was defined as *p*<0.05. Statistical analysis was performed by SPSS version 18.0.

RESULTS

Patient characteristics

Of the total of 1200 patients from the Infarction Prognosis Study registry cohort, 159 patients were excluded from analysis for the following reasons: PCI was not performed (*n*=59), serum creatinine level was not properly checked after PCI (*n*=76), or chronic dialysis was performed because of end-stage renal disease (*n*=24). Therefore, 1041 patients (751 men (71.9%), mean age 62.7±12.2 years) were included in this study. Among them, ST-segment elevation myocardial infarction was diagnosed in 515 (49.5%) patients and non-ST-segment elevation

Table 1 Baseline clinical characteristics of patients

Variables	CIN (n=148)	Non-CIN (n=893)	p Value
Men	83 (56.1%)	665 (74.5%)	<0.001
Age, years	67.6±11.8	61.8±12.1	<0.001
Age >75 years	44 (29.7%)	127 (14.2%)	<0.001
BMI, kg/m ²	23.5±3.2	24.2±3.5	0.047
BMI <24 kg/m ²	92 (62.2%)	421 (47.1%)	0.002
Smokers	48 (32.4%)	346 (38.7%)	0.170
Diabetes mellitus	57 (38.5%)	212 (23.7%)	<0.001
Hypertension	85 (57.4%)	424 (47.5%)	0.023
Dyslipidaemia	49 (33.1%)	348 (39.0%)	0.175
Renal failure, SCr >1.5 mg/dl (>132.6 µmol/l)	31 (20.9%)	58 (6.5%)	<0.001
Previous stroke	9 (6.1%)	52 (5.8%)	0.899
Previous MI	10 (6.8%)	49 (5.5%)	0.536
Previous PCI	19 (12.8%)	118 (13.2%)	0.900
Previous CABG	5 (3.4%)	17 (1.9%)	0.225
Clinical presentation			
STEMI	66 (44.6%)	449 (50.3%)	0.200
NSTEMI	82 (55.4%)	444 (49.7%)	0.200
Cardiogenic shock	37 (25.0%)	129 (14.4%)	0.001
Use of IABP	17 (11.5%)	42 (4.7%)	0.001
Heart failure (LVEF <40%)	54 (36.5%)	160 (17.9%)	<0.001
Mean LVEF, %	42.6±13.1	49.3±12.4	<0.001
Multivessel disease	101 (68.2%)	531 (59.5%)	0.043
Anaemia*	49 (33.1%)	159 (17.8%)	<0.001
Haemoglobin, g/dl	13.1±2.3	14.1±2.0	<0.001
Primary PCI	55 (37.2%)	375 (42.0%)	0.269
Contrast volume, ml	229±74	217±72	0.071
Contrast volume >300 ml	39 (26.4%)	141 (15.8%)	0.002
Renal function			
Pre-PCI SCr, mg/dl (µmol/l)	1.25±0.76 (110.5±67.2)	1.03±0.31 (91.1±27.4)	0.001
Pre-PCI CCr, ml/min	59.3±30.1	71.9±25.7	<0.001
Pre-PCI CCr <60 ml/min	85 (57.4%)	292 (32.7%)	<0.001
Post-PCI peak SCr, mg/dl (µmol/l)	1.91±1.23 (168.8±108.7)	1.04±0.31 (91.9±27.4)	<0.001
Mehran score	9.4±6.8	5.4±4.9	<0.001
Medication			
Aspirin	145 (98.0%)	866 (97.0%)	0.789
Thienopyridine	127 (85.8%)	807 (90.4%)	0.091
Beta blocker	112 (75.7%)	717 (80.4%)	0.197
ACE inhibitor/ARB	118 (79.7%)	756 (84.7%)	0.130
Statin	123 (83.1%)	787 (88.1%)	0.088

*Defined as haemoglobin <13 g/dl for men and <12 g/dl for women.

ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CCr, creatinine clearance; CIN, contrast-induced nephropathy; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SCr, serum creatinine; STEMI, ST-segment elevation myocardial infarction.

Figure 1 Cumulative event rates stratified by the presence or absence of contrast-induced acute kidney injury: (A) death or dialysis; (B) death; (C) death, dialysis, or hospital admission due to cardiovascular events. CI-AKI, contrast-induced acute kidney injury.

myocardial infarction was diagnosed in 526 (50.5%) patients. Overall CI-AKI was observed in 148 (14.2%) patients. Table 1 shows the baseline clinical characteristics of patients with and without CI-AKI. There were notable significant clinical and procedural differences between subjects with and without CI-AKI. Patients with CI-AKI were older and more likely to be female. Certain comorbid conditions such as diabetes, hypertension and chronic renal failure were also observed more frequently in the CI-AKI group. Patients with CI-AKI exhibited more multivessel coronary artery disease and cardiogenic shock at initial presentation, and showed lower LVEF than patients without CI-AKI. Patients with CI-AKI had higher baseline serum creatinine levels (1.25 ± 0.76 vs 1.03 ± 0.31 , $p=0.001$) and were more frequently exposed to a high contrast medium volume (>300 ml) during PCI (39 (26.4%) vs 141 (15.8%), $p=0.002$). The Mehran score was higher in the patients with CI-AKI than those without CI-AKI (9.4 ± 6.8 vs 5.4 ± 4.9 , $p<0.001$).

Clinical outcomes: patients with CI-AKI versus patients without CI-AKI

Patients were clinically followed up for a mean duration of 22.8 ± 15.9 months. Patients developing CI-AKI had a significantly longer hospital stay than patients without CI-AKI (14.7 ± 17.9 vs 8.5 ± 9.1 days, $p<0.001$), and the in-hospital mortality rate was also markedly higher for patients developing CI-AKI (14.2% vs 2.5%, $p<0.001$). The 2-year cumulative event rate of death or dialysis was higher in the CI-AKI group compared with the group without CI-AKI (25.4% vs 6.3%, log rank, $p<0.001$), and the 2-year mortality rate was 24.9% in the CI-AKI group versus 6.3% in the non-CI-AKI group (log rank, $p<0.001$) (figure 1). The 2-year cumulative rate of death, dialysis or hospital admission due to cardiovascular events was also higher in the CI-AKI group compared with the group without CI-AKI (31.5% vs 16.7%, log rank, $p<0.001$). In the overall population, all-cause mortality occurred in 84 patients (8.1%), re-infarction in 25 (2.4%), target-vessel revascularisation in 31 (3.0%), heart failure requiring hospital admission in 20 (1.9%), cerebrovascular events in 11 (1.1%) and renal failure requiring dialysis in five (0.5%). The cause of death was cardiogenic in 52 patients (61.9%), cerebrovascular in five (5.9%), infection or malignancy in 15 (17.9%) and unknown in 12 (14.3%). Multivariate Cox regression analysis revealed that CI-AKI was an independent predictor of the rate of death or dialysis (HR 2.76, 95% CI 1.61 to 4.73, $p<0.001$) after adjusting for confounding variables such as gender, age, baseline serum creatinine level,

LVEF and comorbidities (table 2). Elevated pre-PCI serum creatinine level (>1.5 mg/dl, HR 3.82, 95% CI 2.12 to 6.90, $p<0.001$), previous stroke (HR 2.34, 95% CI 1.20 to 4.57, $p=0.013$), body mass index less than 24 kg/m² (HR 1.99, 95% CI 1.08 to 3.66, $p=0.028$), decreased LVEF ($<40\%$, HR 1.89, 95% CI 1.10 to 3.25, $p=0.021$) and anaemia (haemoglobin <13 g/dl for men and <12 g/dl for women, HR 1.85, 95% CI 1.04 to 3.27, $p=0.035$) were other independent predictors.

Clinical outcomes: patients with transient versus persistent renal dysfunction

Of 148 patients with CI-AKI, 80 patients (54.1%) showed partial or complete recovery of renal function to the baseline level within 1 month, whereas impaired renal function after angiography remained unchanged in 68 patients (45.9%). Baseline characteristics of the two subgroups did not differ significantly, except for hypertension, which was more frequently found in patients with persistent renal dysfunction (47.5% vs 69.1%, $p=0.008$). Overall, patients with persistent renal dysfunction after CI-AKI had a higher 2-year death or dialysis rate (34.1% vs 17.9%, $p=0.013$), a higher mortality rate (34.6% vs 16.7%, $p=0.012$) and a higher death, dialysis, or hospital admission due to cardiovascular events rate (42.1% vs 22.9%, $p=0.021$) than those with transient renal dysfunction (figure 2). However, in comparison with patients without CI-AKI, patients with transient renal dysfunction after

Table 2 Independent predictors of mortality or dialysis: multivariate cox regression analysis using forward stepwise selection

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Pre-PCI SCr >1.5 mg/dl	7.93 (5.17 to 12.15)	<0.001	3.82 (2.12 to 6.90)	<0.001
CIN	4.39 (2.88 to 6.70)	<0.001	2.76 (1.61 to 4.73)	<0.001
Previous stroke	2.51 (1.53 to 4.14)	<0.001	2.34 (1.20 to 4.57)	0.013
BMI <24 kg/m ²	3.54 (2.15 to 5.85)	<0.001	1.99 (1.08 to 3.66)	0.028
LVEF $<40\%$	3.78 (2.58 to 5.55)	<0.001	1.89 (1.10 to 3.25)	0.021
Anaemia*	4.05 (2.87 to 5.70)	<0.001	1.85 (1.04 to 3.27)	0.035
Age >75 years	2.99 (2.09 to 4.26)	<0.001		
Female gender	1.68 (1.18 to 2.38)	0.004		
Diabetes mellitus	1.56 (1.09 to 2.23)	0.016		
Hypertension	1.62 (1.14 to 2.29)	0.008		
Shock	3.47 (2.44 to 4.94)	<0.001		

*Defined as haemoglobin <13 g/dl for men and <12 g/dl for women.

BMI, body mass index; CIN, contrast-induced nephropathy; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SCr, serum creatinine level.

Figure 2 Cumulative event rates for patients with transient versus persistent renal dysfunction: (A) death or dialysis; (B) death; (C) death, dialysis, or hospital admission due to cardiovascular events. CI-AKI, contrast-induced acute kidney injury.

CI-AKI still had a higher 2-year death or dialysis rate (17.9% vs 6.3%, $p<0.001$), a higher mortality rate (16.7% vs 6.3%, $p=0.001$) and a higher death, dialysis, or hospital admission due to cardiovascular events rate (22.9% vs 16.7%, $p=0.035$) than those with transient renal dysfunction.

DISCUSSION

The major findings of the present study were that patients with AMI who underwent PCI and subsequently developed CI-AKI had poorer short and long-term outcomes in the composite event of all-cause death and renal failure requiring dialysis than patients who did not develop CI-AKI. CI-AKI was an important independent predictor of the long-term event of mortality or dialysis in AMI patients treated with PCI. An additional finding of our study was that 45.9% of CI-AKI patients developed persistent renal functional impairment. Patients who experienced transient renal dysfunction showed better clinical outcomes than those with persistent renal dysfunction, but poorer outcomes than patients who did not develop CI-AKI.

CI-AKI is generally associated with increased short and long-term morbidity and mortality, although acute haemodialysis was uncommon except in patients with severe chronic kidney disease.^{1 2 4 11–13} However, only a small number of studies have focused on the clinical implications of CI-AKI in AMI. Marenzi *et al*⁶ and Wickenbrock *et al*¹⁰ reported that CI-AKI was associated with a higher in-hospital complication rate and mortality in patients with AMI undergoing PCI. In the present study, we found that CI-AKI was not only associated with short-term adverse outcomes, but also higher 2-year rates of mortality, dialysis or other cardiovascular events. The question of whether CI-AKI directly contributes to these adverse events is confounded by the findings of previous studies demonstrating that pre-existing renal insufficiency is associated with an increased risk of death in patients undergoing PCI.¹⁴ In our study, multivariate Cox regression analysis revealed that CI-AKI was an important independent predictor of death and dialysis after adjusting for confounding variables. Recently, Sgura *et al*¹⁵ reported that the Mehran score was a good predictor of the risk of developing major cardiovascular and cerebrovascular events in patients with ST-segment elevation myocardial infarction. The Mehran score was initially developed to predict CI-AKI after non-urgent PCI and includes eight clinical and procedural variables: age greater than 75 years; hypotension; congestive heart failure; intra-aortic balloon pump; serum creatinine; diabetes;

anaemia and volume of contrast.⁵ Therefore, the development of CI-AKI in the acute phase of AMI may be considered a surrogate for more severe atherosclerosis and haemodynamic instability regardless of the underlying mechanism.^{15 16}

In the present study, we also investigated whether the reversibility of renal function after the development of CI-AKI has any implication for clinical outcomes among AMI patients treated with PCI. CI-AKI is generally reversible and non-oliguric, with peak serum creatinine levels typically occurring at days 2 or 3 and returning to normal in most cases within 2 weeks.^{12 17} Persistent serum creatinine level elevation is considered to be rare.^{18 19} However, recent data from the Dartmouth Dynamic Registry showed that renal function of 54.6% of the patients with CI-AKI did not return to baseline after 2 weeks.²⁰ Both transient and persistent postprocedural renal dysfunction were prognostically significant for mortality during extended follow-up in that study; however, the researchers observed no significant difference in the survival rate of patients with transient renal dysfunction caused by CI-AKI compared with those with persistent renal dysfunction.

In the present study, renal function was not restored to baseline at 1 month in 45.9% of patients who developed CI-AKI. In contrast with the previous study, CI-AKI patients with persistent renal functional impairment experienced worse short and long-term clinical outcomes than those with transient renal dysfunction. However, patients with transient renal dysfunction experienced more adverse clinical events than patients who did not develop CI-AKI. This may reflect that patients with persistent or transient renal dysfunction caused by CI-AKI have a different degree of atherosclerotic burden and haemodynamic instability. However, this could not be proved in our study. The clinical characteristics of the patients with persistent versus transient renal dysfunction were in general similar except for hypertension, which was more frequently observed in patients with persistent renal dysfunction.

CI-AKI often goes unnoticed by patients and physicians. Physicians tend to disregard mild or transient serum creatinine level elevation after coronary procedures that use contrast medium, especially when the serum creatinine level remains within the normal range or renal dysfunction improves rapidly. However, the results of our study indicate that CI-AKI unfavourably influences both short and long-term clinical outcomes in patients with AMI, even when renal function recovers rapidly. Once CI-AKI develops, treatment is limited to supportive

measures while waiting for the renal impairment to resolve. Therefore, better preventive strategies and monitoring are needed to improve clinical outcomes in AMI patients at high risk of developing CI-AKI.

Study limitations

The present study had some limitations. First, our study is a post-hoc analysis of existing data. There was no adjudication process for clinical events. The need for dialysis or the use of hospital admission due to cardiovascular events as outcomes was limited by the unblinded nature of the data. Second, it was a moderate sized registry study in a single centre. Our findings need to be confirmed in a larger multicentre trial. Third, the incidence of CI-AKI in our study might have been underestimated because patients in whom creatinine was not adequately checked and patients with cardiogenic shock not surviving the first 48 h were excluded from the analysis. Fourth, the cause of renal function impairment after PCI (ischaemic, nephrotoxic, or atheroembolic) could not be determined precisely. Furthermore, because of methodological limitations inherent in retrospective registry analyses, our data cannot establish a definite aetiological link between worsening renal function after PCI and the increased risk of major adverse cardiorenal events and death. Finally, we were unable to determine whether patients had acute renal dysfunction, chronic kidney disease, or a combination of these two conditions. The serum creatinine level during hospitalisation may not reflect the steady state concentration in some patients with AMI and may be affected by non-renal factors such as hydration status.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Institutional Review Board of Yonsei University Health System.

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