Cystatin C and Contrast-Induced Acute Kidney Injury

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Background—Cystatin C (CyC) is more sensitive than serum creatinine (sCr) to rapidly detect acute changes in renal function.

Methods and Results—We measured CyC together with sCr in 410 consecutive patients with chronic kidney disease undergoing either coronary and/or peripheral angiography and/or angioplasty. sCr was assessed at baseline and 24 and 48 hours after contrast media exposure. CyC was assessed at baseline and at 24 hours. Major adverse events (including death of any cause and dialysis) at 12 months were assessed. At 48 hours after contrast media exposure, contrast-induced acute kidney injury (defined as a sCr increase ≥0.3 mg/dL) occurred in 34 patients (8.2%). A CyC increase concentration ≥10% at 24 hours after contrast media exposure was detected in 87 patients (21.2%). This was the best CyC cutoff for the early identification of patients at risk for contrast-induced acute kidney injury (negative predictive value=100%; positive predictive value=39.1%). According to the defined cutoffs (that is, increase in CyC ≥10% and sCr ≥0.3 mg/dL), major adverse events occurred in 16 of 297 patients (5.4%) without any cutoffs satisfied (group 1), in 9 of 49 patients (18.4%) with only a CyC increase ≥10% (group 2), and in 9 of 31 patients (29%) with both cutoffs satisfied (group 3). By logistic regression analysis, the independent predictors of major adverse events at 1 year were group 2 (odds ratio=2.52; 95% confidence interval, 1.17 to 5.41; P=0.02), group 3 (odds ratio=4.45; 95% confidence interval, 1.72 to 11.54; P=0.002), and baseline glomerular filtration rate (odds ratio=0.91; 95% confidence interval, 0.88 to 0.95; P<0.001).

Conclusions—In patients with chronic kidney disease, CyC seems to be a reliable marker for the early diagnosis and prognosis of contrast-induced acute kidney injury. **(*Circulation*. 2010;121:2117-2122.)**

Key Words: contrast media ■ kidney ■ prognosis

Contrast-induced acute kidney injury (CI-AKI) is associated with a prolonged in-hospital stay and represents a powerful predictor of unfavorable early and late outcome.[1,2] Therefore, it has been recommended to monitor renal function in all patients at risk with serial measurements of serum creatinine (sCr) after contrast media (CM) exposure.[2,3] However, the delayed increase in sCr is a potential reason for overlooking CI-AKI[4,5] and, on the contrary, for prolonging hospital stay in the vast majority of patients who will not develop CI-AKI.

Clinical Perspective on p 2122

Cystatin C (CyC) is more sensitive than sCr to rapidly detect acute changes in renal function.[6,7] Preliminary data suggest that the increase of CyC achieves a maximum within 24 hours after CM exposure.[8,9] However, limited data exist on whether changes in CyC are superior to sCr in predicting future major adverse events (MAE).[10] Hence, we performed a prospective study comparing changes in sCr and CyC in patients at medium to high risk for CI-AKI undergoing CM administration during coronary or peripheral procedures. The purpose was to assess whether changes in serum CyC at 24 hours after CM exposure are a reliable index (1) for an early diagnosis of CI-AKI and (2) in predicting future MAE.

Methods

Patient Population

From January 2007 to September 2009, we considered all consecutive patients with chronic kidney disease (than is, with an estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m^2) scheduled for coronary and/or peripheral angiography and/or angioplasty procedure. eGFR was calculated by applying the Levey modification of the Modification of Diet in Renal Disease formula: $(186.3 \times \text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times (0.742 \text{ if female})$.[11] Exclusion criteria were preexisting dialysis, multiple myeloma, pulmonary edema, acute myocardial infarction, recent (≤2 days) exposure to CM, pregnancy, and administration of theophylline, dopamine, mannitol,

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Table 1. Clinical Characteristics (n=410)

Age, y (range)	70±9 (41–90)
Male	344 (84)
Weight, kg	76±12
Height, m	1.68±0.6
Body mass index, kg/m^2	27±3
Blood pressure, mm Hg	
Systolic	150±19
Diastolic	80±8
Mean	102±10
Left ventricular ejection fraction, %	50.5±10.5
<40%	53 (13)
Systemic hypertension	332 (81)
Diabetes mellitus	161 (39.3)
Non–insulin requiring	80 (19.5)
Insulin-requiring	81 (19.8)
Peripheral chronic artery disease	102 (25)
Thyroid dysfunction	29 (7)
Hypothyroidism	25 (6.1)
On treatment	14 (3.4)
Hyperthyroidism	4 (0.9)
On treatment	3 (0.7)
Drugs	
ACE inhibitors	273 (57.9)
Calcium channel blockers	112 (27.5)
Angiotensin II receptor inhibitors	79 (19.2)
Diuretics	139 (34)
β-blockers	201 (49.2)
Statins	276 (67.5)
Performed procedure	
Coronary angiography	162 (39.6)
PCI	53 (13)
Coronary angiography and ad hoc PCI	167 (40.8)
Peripheral procedures	27 (6.6)
Volume of CM, mL	165±125

Continuous values are expressed as mean±SD; categorical values are expressed as total number and percentage of the global population (in parentheses). ACE indicates angiotensin-converting enzyme; PCI, percutaneous coronary intervention.

Table 2. Biochemical Characteristics (n=410)

sCr, median (IQR), mg/dL	
Baseline	1.64 (1.51–1.90)
After 24 h	1.50 (1.30–1.80)
After 48 h	1.60 (1.40–1.89)
Serum CyC, median (IQR), mg/dL	
Baseline	1.43 (1.16–1.78)
After 24 h	1.42 (1.15–1.74)
eGFR, mL/min per 1.73 m^2	41±10
40–60	234 (57)
20–40	163 (39.8)
<20	13 (3.2)
Contrast nephropathy risk score*	7.9±3.4
≤5	120 (29.3)
6–10	207 (50.5)
11–16	77 (18.7)
>16	6 (1.5)
CI-AKI rate	
sCr increase ≥0.3 mg/dL	34 (8.2)
CyC increase ≥10%	87 (21.2)
Serum sodium, mEq/L	
Baseline	141±3
After 48 h	140±8
Serum potassium, mEq/L	
Baseline	4.5±0.6
After 48 h	4.2±0.6

Continuous values are expressed as median and interquartile range (IQR) (sCr and CyC) or mean±SD; categorical values are expressed as total number and percentage of the global population (in parentheses).

*According to Mehran et al.[14]

or fenoldopam. The local ethics committee approved the study, and all patients gave written informed consent.

All patients were treated by intravenous sodium bicarbonate plus *N*-acetylcysteine before and after administration of the CM.[12] Sodium bicarbonate (154 mEq/L in dextrose and H_2O) infusion was started at least 1 hour before the procedure and lasted 6 hours after administration of the CM.[13] *N*-Acetylcysteine (Fluimucil, Zambon Group SpA, Milan, Italy) was administered orally at a dose of 1200 mg twice daily on the day before and on the day of CM exposure.[12] Diuretics were routinely withheld on the day of the procedure. The risk score for predicting CI-AKI was calculated according to the following algorithm: hypotension (integer score 5), intra-aortic balloon pump support (integer score 5), congestive heart failure (integer score 4), age >75 years (integer score 4), diabetes mellitus (integer score 3), eGFR <60 (integer score 2 to 6), preexisting anemia (integer score 3), and CM volume (integer score 1 for each 100 mL). The global scores ≤5, 6 to 10, 11 to 16, and ≥16 anticipate a CI-AKI risk of 7.5%, 14%, 26.1%, and 57.3%, respectively.[14] Iodixanol (Visipaque, 320 mg iodine/mL, Amersham Health), a nonionic, iso-osmolality (290 mOsm/kg water) CM, was used in all patients.

sCr, serum sodium, and serum potassium were measured 24 hours before and 24 and 48 hours after administration of the CM; additional measurements were performed in all cases of impairment of renal function. Serum CyC was measured 24 hours before and 24 hours after administration of the CM with the use of the Dade Behring N Latex Cystatin C assay (Dade Behring Diagnostics, Marburg, Germany).[15]

Study Purpose

The primary purposes of the study were to assess whether changes in CyC levels at 24 hours after CM exposure (1) anticipate the occurrence of CI-AKI, defined as an increase in sCr concentration of ≥0.3 mg/dL from the baseline value at 48 hours after administration of the CM or the need for dialysis,[16] and (2) predict the occurrence of 12-month MAE, defined as death from any cause and further deterioration of renal function requiring chronic dialysis. Clinical follow-up was performed by a visit at the outpatient clinic or by a telephone interview with the patients or their relatives at 1, 6, and 12 months. For any reported event, all available medical records (ie, case records, dialysis schedules, death certificates) were obtained and reviewed by 2 independent and blinded adjudicators.

Statistical Analysis

Continuous variables are given as mean±1 SD or median and interquartile ranges, when appropriate. The Student *t* test and

Table 3. Distribution of Changes in Scr and CyC Plasma Levels After CM Exposure (n=410)

Changes in SCr at 48 h	
Decrease ≥0.3 mg/dL	46 (11.3)
Decrease <0.3 mg/dL to no change	261 (63.7)
Increase <0.3 mg/dL	69 (16.8)
Increase ≥0.3 mg/dL	34 (8.2)
Changes in CyC at 24 h	
Decrease ≥10%	63 (15.5)
Decrease <10% to no change	182 (44.3)
Increase <10%	78 (19)
Increase ≥10%	87 (21.2)

Values in parentheses are percentages.

nonparametric Wilcoxon test were used to determine differences between mean values for normally and nonnormally distributed variables, respectively. Categorical variables were reported as percentages and were analyzed by either χ^2 or Fisher exact test, as appropriate. Receiver operating characteristic curve analysis was performed to establish increment cutoff values of CyC at 24 hours for predicting CI-AKI. The percent increase in CyC was compared against the 0.3-mg/dL sCr increment at ≥1%, 10%, 15%, and 25%, respectively. Subsequently, from the receiver operating characteristic analysis, a CyC cutoff increment value was chosen on the basis of maximum sensitivity and specificity. Logistic regression analysis was performed to assess whether changes in sCr and CyC were predictors of 1-year MAE. In addition, multivariable logistic regression analysis was performed to identify the independent predictors of 1-year MAE. Additionally, to assess the independent predictive power of both sCr ≥0.3 mg/dL and CyC ≥10%, 3 groups were defined: group 1, with increase in sCr <0.3 mg/dL and CyC <10%; group 2, with increase in CyC ≥10% and sCr <0.3 mg/dL; and group 3, with both sCr ≥0.3 mg/dL and CyC ≥10%. Each group was included as covariate in the logistic regression model, along with diabetes mellitus, left ventricular ejection fraction, and eGFR. $P<0.05$ was considered significant throughout the analysis. Data were analyzed with SPSS 13.0 (Chicago, Ill) for Windows and R software, as appropriate. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Results

Clinical and Biochemical Characteristics

Four hundred ten consecutive patients with chronic kidney disease were included in the study. The clinical and biochemical characteristics of the patients are shown in Tables 1 and 2. One patient had a previous exposure to CM 9 days before our observation. Mean contrast nephropathy risk score was 7.9±3.4. A high (≥11) risk score occurred in 83 patients (20.2%) (Table 2). Median baseline CyC level was 1.43 (interquartile range=1.16 to 1.78) mg/dL. History of thyroid dysfunction was present in 29 patients (7%). All of these patients were in a euthyroid state at the time of our observation (Table 1).

Creatinine Kinetic

Median sCr concentration significantly decreased from baseline to 24 hours after CM administration ($P<0.001$) but was unchanged at 48 hours ($P=0.30$) (Table 2). An increase of sCr concentration ≥0.3 mg/dL from baseline value occurred in 16 patients (3.9%) at 24 hours and in 34 patients (8.2%) at 48 hours after CM administration. The distribution of changes in sCr according to a 0.3-mg/dL increase or decrease is summarized in the Table 3.

CyC Kinetic

Median serum CyC concentration did not significantly change from baseline to 24 hours after CM administration ($P<0.38$) (Table 2). At 24 hours, we observed the following changes: (1) any increase above the upper limit of normal in 165 patients (40.2%); (2) an absolute increase ≥0.3 mg/dL in 31 patients (7.5%); (3) a ≥10% increase in 87 patients (21.2%); (4) a ≥15% increase in 52 patients (12.7%); and (5) a ≥25% increase in 16 patients (3.9%).

The relationships between changes of CyC levels and CI-AKI, defined by a sCr increase ≥0.3 mg/dL, are represented in Table 4. A CyC increase ≥10% at 24 hours after administration of the CM was the best increment cutoff value for the early identification of patients at risk for CI-AKI. The distribution of the changes in CyC according to a 10% increase or decrease is depicted in Table 3. By receiver operating characteristic analysis, we found that a CyC increase ≥10% at 24 hours had a 100% sensitivity and a 85.9% specificity for predicting a sCr increase ≥0.3 mg/dL (Figure 1). The negative predictive value was 100%; indeed, none of the 323 patients with CyC increase <10% at 24 hours after administration of the CM had a sCr increase ≥0.3 mg/dL. On the contrary, the positive predictive value of CyC increase ≥10% was 39.1%; indeed, the majority of patients with a CyC increase ≥10% at 24 hours did not eventually develop a sCr increase ≥0.3 mg/dL.

Long-Term Outcome

One-year outcome was available in 377 patients (92%). Globally, MAE occurred in 34 patients (9.0%). In particular, death occurred in 26 patients (6.9%) and chronic dialysis in 8 patients (2.1%). MAE occurred in 16 of 297 patients (5.4%) in group 1 (that is, a CyC <10% and sCr increase <0.3 mg/dL), in 9 of 49 patients (18.4%) in group 2 (that is, a CyC ≥10% and sCr increase <0.3 mg/dL) (unadjusted odds ratio

Table 4. Relationship Between CI-AKI and Changes in CyC Plasma Levels at 24 Hours After CM Exposure

Changes in CyC at 24 h	Creatinine Increase ≥0.3 mg/dL at 48 h (n=34)	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
Any CyC increase (n=165)	34/34	100	65.2	20.6	100
CyC increase ≥10% (n=87)	34/34	100	85.9	39.1	100
CyC increase ≥15% (n=52)	14/34	41.2	89.9	26.9	94.4
CyC increase ≥25% (n=16)	5/34	14.7	97.1	31.3	92.6
CyC increase ≥0.3 mg/dL (n=31)	18/34	58.1	95.8	52.9	96.5

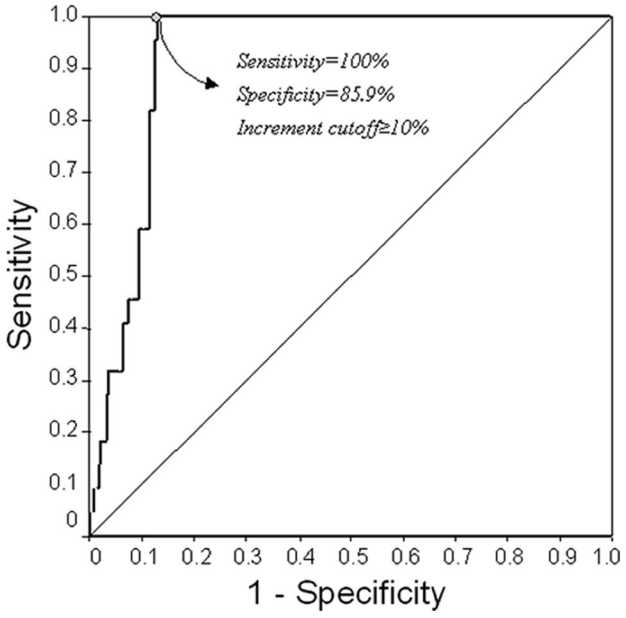

Figure 1. Receiver operating characteristic curve showing correlation between percent CyC increase at 24 hours and CI-AKI, defined as a creatinine increase ≥0.3 mg/dL at 48 hours. Area under the curve=0.92; asymptotic significance <0.001.

[OR] versus group 1=3.95; 95% confidence interval [CI], 1.67 to 8.54; $P=0.001$) and in 9 of 31 patients (29%) in group 3 (that is, a CyC ≥10% and sCr increase ≥0.3 mg/dL) (unadjusted OR versus group 1=7.18; 95% CI, 2.85 to 18.11; $P=0.001$) (Figure 2). By logistic regression analysis, the independent predictors of MAE at 1 year were a CyC ≥10% alone (as shown in group 2) (OR=2.52; 95% CI, 1.17 to 5.41; $P=0.02$) and associated with a sCr increase ≥0.3 mg/dL (as shown in group 3) (OR=4.45; 95% CI, 1.72 to 11.54; $P=0.002$) and baseline eGFR (OR=0.91; 95% CI, 0.88 to 0.95; $P<0.001$) (Table 5).

Discussion

The main results of the present study are that serum CyC seems to be a reliable marker (1) for an early (24-hour) diagnosis of CI-AKI and (2) for predicting the occurrence of MAE at follow-up in patients with chronic kidney disease undergoing CM exposure.

sCr as a Marker of CI-AKI

Although in 80% of CI-AKI cases, sCr starts rising within the first 24 hours after CM exposure,[17] the sCr typically peaks 2 to 5 days after CM and returns to baseline or near baseline within 1 to 3 weeks.[2,3] Therefore, in all patients at risk, a follow-up sCr should be obtained at 48 to 72 hours after CM exposure.[2–4,18] This implies an intrinsic delay of treatment of patients who will develop CI-AKI and, on the contrary, a prolonged hospital stay in patients who will not develop CI-AKI. Furthermore, creatinine suffers from 2 significant limitations.[4] First, creatinine excreted in the urine is not solely a result of glomerular filtration but also of renal tubular secretion.[19] This means that changes in sCr will underestimate the true fall in GFR. Second, after an acute fall in GFR, less creatinine is excreted. The retained creatinine is distributed in total body water. Thus, the serum level can be expected to rise slowly and will continue to rise until a new steady state has occurred. Therefore, although the injury induced by CM impairs GFR almost immediately, it requires 24 to 48 hours for the fall in GFR to be reflected in an elevated level of sCr.

Serum CyC as a Marker of CI-AKI

CyC is a 122–amino acid, nonglycosylated protein that is a member of the family of cysteine proteinase inhibitors.[20] It is produced at a constant rate by all nucleated cells, representing in the true sense of the word a "housekeeping gene product." CyC concentration is independent of age, sex, changes of muscle mass, and nutrition. CyC levels are lower in the hypothyroid and higher in the hyperthyroid state compared with the euthyroid state.[21] It is found in relatively high concentrations in many body fluids, and its low molecular weight (13.3 kDa) and positive charge at physiological pH levels facilitate its glomerular filtration. It is later reabsorbed and almost completely catabolized in the proximal renal tubule.[22] Because of its constant rate of production, its serum concentration is therefore determined by glomerular filtration. Indeed, CyC does not undergo tubular secretion and appears in the urine solely through filtration.[6,23] For these reasons, CyC has the potential to be a useful marker in detecting both chronic and acute changes in GFR.[24–26] The shorter (1.5-hour) half-life of CyC compared with creatinine accounts for the more rapid rise and the earlier attainment of a new steady state.[27] CyC is distributed in the extracellular volume,[28] whereas sCr is distributed in the total body water,[29] a volume that is 3 times larger. Therefore, the half-life of creatinine compared with CyC will be 3 times longer, and the time to achieve a new steady state will increase proportionally, implying that sCr will rise more slowly.

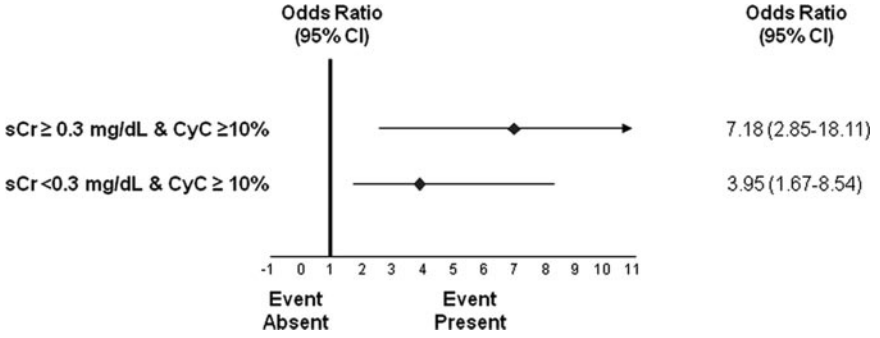

Figure 2. Prediction of MAE (ie, cardiac death and chronic dialysis) at 12 months by creatinine increase ≥0.3 mg/dL at 48 hours and cyC ≥10% increase at 24 hours. The groups of patients with both sCr ≥0.3 mg/dL and CyC ≥10% (n=31) and with increase in sCr <0.3 mg/dL and CyC ≥10% (n=49) were compared with the reference group (that is, patients [n=297] with increase in sCr <0.3 mg/dL and CyC <10%). The symbols indicate the unadjusted ORs; the horizontal lines indicate the 95% CIs.

Table 5. Predictors of MAE at 1 Year by Logistic Regression Analysis

	Multivariable Analysis	
Variable	OR (95% CI)	*P*
Baseline eGFR	0.91 (0.88–0.95)	<0.001
Group 2: sCr <0.3 mg/dL and CyC ≥10%	2.52 (1.17–5.41)	0.02
Group 3: sCr ≥0.3 mg/dL and CyC ≥10 %	4.45 (1.72–11.54)	0.002
Left ventricular ejection fraction	0.97 (0.94–1.01)	0.10
Diabetes mellitus	1.22 (0.58–2.58)	0.59

Variables entered into the model were diabetes mellitus, baseline eGFR, left ventricular ejection fraction, and groups (defined according to the presence or not of sCr increase ≥0.3 mg/dL and CyC increase ≥10%).

In the present study, we observed that (1) a CyC increase <10% at 24 hours is a reliable marker for ruling out CI-AKI and (2) a CyC increase ≥10% at 24 hours is an independent predictor of 1-year MAE. The first observation may allow physicians an earlier discharge of the majority (>80%) of patients, thus avoiding an unnecessary prolonged hospitalization with associated practical and economic advantages.[30] The second observation identifies a subgroup of patients at higher risk for future MAE.[10,31,32] This observation may be explained by 2 reasons. First, CyC seems to be a better measure of kidney function than sCr and eGFR.[6,7,30] Second, CyC may provide prognostic information beyond its role as an index of kidney function and also may be a better overall measure of the spectrum of pathophysiological abnormalities that accompany kidney disease. CyC seems to be a potential predictor of the presence or development of cardiac structural abnormalities.[33] Indeed, the Dallas Heart Study showed that CyC is independently associated with left ventricular mass, concentricity, and wall thickness.[34] Some studies have also found a relationship between CyC and C-reactive protein[35] and inducible myocardial ischemia.[36]

Study Limitations

CyC levels have been assessed only at 24 hours, and therefore its trajectory cannot be defined. We chose to control the CyC level at 24 hours because elective patients are usually discharged the day after the procedure. We cannot exclude the possibility that an earlier rise (within hours) may occur. Further studies are necessary to test whether an early CyC rise (ie, at 6 or 12 hours) may be diagnostic. CyC is a sensitive marker of reduction in GFR and not a marker of kidney injury. Other biomarkers (such as kidney injury molecule 1, neutrophilin gelatinase-associated lipocalin, and interleukin-18) identify tubular injury and have been shown to rise much more quickly in response to acute kidney injury (hours instead of days).[37] However, these markers of injury have not been validated as predictors of long-term outcome.

In conclusion, the assessment of CyC at 24 hours after CM exposure allows an early diagnosis of CI-AKI and predicts the occurrence of future MAE. Although more expensive than sCr, measurement of CyC should be adopted not only as a diagnostic test for kidney function but, more importantly, as a prognostic tool for future MAE among patients with chronic kidney disease undergoing CM exposure.

Disclosures

None.

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CLINICAL PERSPECTIVE

Contrast-induced acute kidney injury represents a powerful predictor of unfavorable outcome. Serum creatinine (sCr) suffers from several limitations. Cystatin C (CyC) is more sensitive than sCr to rapidly detect acute changes in renal function. Preliminary data suggest that the increase of CyC achieves a maximum within 24 hours after contrast media exposure. We measured CyC together with sCr in 410 consecutive patients with chronic kidney disease undergoing contrast media exposure. Contrast-induced acute kidney injury (defined as sCr increase $\geq$0.3 mg/dL at 48 hours) occurred in 34 patients (8.2%). A CyC increase in concentration $\geq$10% at 24 hours after CM exposure was the best CyC cutoff for the early identification of patients developing contrast-induced acute kidney injury (negative predictive value=100%; positive predictive value=39.1%). Major adverse events (including death from any cause and dialysis) at 12 months occurred in 5.4% of patients with increase in CyC $<$10% and sCr $<$0.3 mg/dL (group 1), in 18.4% of patients with only a CyC increase $\geq$10% (group 2), and in 29% of patients with both CyC $\geq$10% and sCr $\geq$0.3 mg/dL (group 3). By logistic regression analysis, the independent predictors of major adverse events at 1 year were criteria of group 2 (odds ratio=2.52; 95% confidence interval, 1.17 to 5.41; P=0.02), criteria of group 3 (odds ratio=4.45; 95% confidence interval, 1.72 to 11.54; P=0.002), and baseline glomerular filtration rate (odds ratio=0.91; 95% confidence interval, 0.88 to 0.95; $P<0.001$). In patients with chronic kidney disease, CyC seems to be a reliable marker for the early diagnosis and prognosis of contrast-induced acute kidney injury.