Original Article

Risk Factors and Clinical Outcomes for Contrast-induced Nephropathy After Percutaneous Coronary Intervention in Patients with Normal Serum Creatinine

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Abstract

Introduction: We aim to examine the risk predictors of contrast-induced nephropathy (CIN) in patients with normal baseline serum creatinine (Cr). CIN is an important complication post-percutaneous coronary intervention (PCI). Previous studies examined CIN predictors in patients with chronic renal impairment. No large studies investigated patients with normal renal function which constitute the majority undergoing PCI. We aim to identify risk predictors in this cohort and examine the clinical outcomes. Materials and Methods: A total of 3036 patients with normal baseline Cr (<1.5 mg/dL) who did not receive prophylaxis while undergoing PCI were enrolled. We examined the occurrence of CIN and the mortality outcome at 1 and 6 months. Results: CIN occurred in 7.3% of patients. The median age was 59.5 years (range, 26 to 86), 78.7% men, 34.6% diabetics. Risk predictors for CIN include age [odds ratio (OR), 6.4; 95% CI, 1.01-13.3; *P* = 0.042], female gender (OR, 2.0; 95% CI, 1.5-2.7; *P* = 0.001), abnormal left ventricular ejection fraction (LVEF) <50%(OR,1.02; 95% CI, 1.01-1.04; *P* = 0.01), anaemia with haemoglobin <11 mg/dL (OR, 1.5; 95% CI, 1.01-2.4; *P* = 0.044) and systolic hypotension with blood pressure <100 mmHg (OR, 1.5; 95% CI, 1.01-2.2; *P* = 0.004). Diabetics on insulin therapy were at the highest risk compared with diabetics on oral hypoglycaemics and diet control (18.9% vs 6.8% vs 3.6%; *P* = 0.001). Patients who developed CIN had higher mortality at 1 month (14.5% vs 1.1%; *P* <0.001) and 6 months (17.8% vs 2.2%; *P* <0.001). Conclusions: Subgroups of patients with normal baseline Cr undergoing PCI are at risk of developing CIN with resultant higher mortality. Age, female gender, insulin dependent diabetes mellitus, presence of hypotension, anaemia and low LVEF are predictors of CIN. Prophylaxis may be considered in these patients.

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Key words: Anaemia, Female gender, Haemoglobin, Left ventricular ejection fraction

Introduction

Contrast-induced nephropathy (CIN) is a common complication post-percutaneous coronary intervention (PCI).[1] CIN is associated with increased morbidity, mortality, prolonged hospitalisation and long-term renal impairment.[2] Several predisposing risk factors for CIN have been identified which include baseline renal impairment, diabetes mellitus, congestive heart failure, intravascular volume depletion, and the use of a large volume of contrast agent.[3,4]

Currently, the most recognised risk factor for development of CIN is baseline renal impairment.5 This is conveniently defined as serum creatinine (Cr) level of ≥1.5 mg/dL (132 mmol/dL).[6,7] CIN prophylactic regimes have been used to reduce its occurrence in patients with baseline renal impairment undergoing PCI. These include normal saline hydration and oral N-acetylcysteine.[8-10] CIN prophylaxis is not commonly used in patients with normal baseline Cr below 1.5 mg/dL.

However, despite normal baseline Cr, subgroups of patients undergoing PCI may be at higher risk of developing CIN. Presence of conditions other than elevated baseline Cr can contribute to renal injury. We hypothesise that risk factors such as hypotension,[8] large contrast volume,[11] female gender,[12] diabetes mellitus,[5] old age,[13,14] and acute myocardial infarction (AMI),[15,16] may have significant impact on the development of CIN even in patients with

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normal Cr undergoing PCI. Present CIN studies mainly focused on prophylactic trials,[17,18] and superiority of contrast agents,[19,20] in preventing CIN in high-risk patients with baseline renal impairment. No large studies to-date looked at the risk predictors of CIN and its clinical outcomes in patients with normal baseline Cr.

Hence, the purpose of our study was to determine the incidence, clinical predictors and clinical consequences of CIN in a cohort of patients with normal baseline renal function defined by serum Cr undergoing PCI.

Materials and Methods

Study Population

For the period between May 1996 and March 2007, we enrolled all consecutive patients with baseline Cr <1.5 mg/dL admitted to the National University Hospital undergoing PCI. Prior to PCI, metformin was routinely withheld. The use of beta-adrenergic blockers, angiotensin-converting enzyme inhibitors, platelet glycoprotein IIb/IIIa receptor inhibitors (abciximab, eptifibatide), diuretics, or the indication for intra-aortic balloon pump or inotropic drugs support, were left to the discretion of the interventional cardiologists in accordance to guidelines.[21,22] Patients who had end-stage renal failure receiving dialysis were excluded. The study was approved by the ethics committee of our institution.

Study Protocol

A total of 5058 consecutive patients with normal baseline Cr were enrolled. Three thousand and thirty-six patients completed serum Cr test pre- and post-PCI and clinical follow-up. Patients' data were extracted from the institution's cardiac database. The database was designed and maintained by a dedicated group of doctors and database technologists. The database was prospectively designed and contained 201 data columns which include patient's baseline bio-data and procedural details. The interventional cardiologists entered the data into predesigned data templates. Important blood results peri-procedure include Cr, haemoglobin (Hb), prothrombin (PT), partial thromboplastin time (PTT), creatinine kinase (CK) and CKMB and so on were entered by independent research nurses. Echocardiogram evaluation was performed for patients during hospitalisation or early discharge. Serum Cr was measured at baseline (immediately prior to emergency PCI and within 2 weeks prior to elective PCI). Serum Cr was obtained on the day after PCI and daily after if it was necessary to further monitor the renal function. AMI patients were managed in the coronary care unit (CCU). Serum Cr was taken in day 1 and day 2 post-PCI. Complications during hospitalisation, 1 month and 6 months post-discharge were assessed by research nurses. Mortality was assessed at 1 month and 6 months via clinical appointments and telephone calls.

Percutaneous Coronary Intervention

PCI was performed according to standard clinical practice.[23] The National University Hospital offered 24 hour PCI service. We used low osmolality, low ionic contrast Iohexol (Omnipaque®). Contrast dose, angioplasty technique, and use of adjunctive pharmacologic therapies were left to the discretion of the interventional cardiologists. Because of normal baseline Cr, patients did not receive hydration or prophylaxis prior to PCI. All patients received 300 mg loading dose of aspirin before the procedure and followed by 100 mg/day. Patients were treated with the recommended dual antiplatelet regime according to guidelines.

Clinical Definitions and Follow-up

CIN was defined as ≥25% or ≥0.5 mg/dL increase from baseline Cr within 48 hours after PCI.[8,24] The highest post-procedural Cr was used for the calculation. Anaemia was defined as serum Hb <11g/dL. Renal impairment was defined as baseline Cr ≥1.5 mg/dL. Hypotension was defined as systolic blood pressure <100 mmHg by aortic opening pressure during coronary angiogram. Cardiogenic shock was defined as sustained hypotension for greater than 30 minutes with clinical evidence of tissue hypoxia.[25] Pre-specified clinical, laboratory and demographic information were obtained from case notes by independent research nurses who were unaware of the objectives of the study. Data were entered prospectively into the database.

Statistical Analysis

Continuous data were reported as mean value ± SD, unless otherwise specified. Categorical data were presented as absolute values and percentages. Comparison of continuous variables was performed by Student's *t*-test. Chi-square and Fisher's Exact tests were performed for comparison of categorical variables as appropriate. Multivariate analysis with an enter model including variables of age, gender, AMI, renal impairment, diabetes mellitus, cardiac enzymes level, contrast volume, left ventricular ejection fraction (LVEF) and cardiogenic shock was performed. $P < 0.05$ was considered statistically significant. Analyses were conducted using SPSS statistical software (Version 16.0, SPSS Institute Inc, Chicago, Illinois).

Results

Incidence of CIN and Clinical Characteristics

Baseline clinical characteristics are listed in Table 1. Consecutive patients (n = 3036) with biochemical and clinical follow-up data who underwent PCI were included. Patients who underwent only diagnostic coronary angiogram without PCI due to either insignificant coronary lesions or referral for bypass surgery were excluded from the study.

In the study cohort, the majority were men. The most

Table 1. Baseline Clinical and Procedural Characteristics of the Study Patients

Baseline characteristics	No. of patients (%) (n = 3036)
Age (range), y	59.5 (26-86)
Gender/female	807 (26.6%)
Hypertension	1840 (60.6%)
Diabetes mellitus	1090 (35.9%)
Smoking	1466 (48.3%)
Hyperlipidaemia	2316 (76.3%)
Acute coronary syndrome	1126 (37.1%)
Primary PCI	514 (16.9%)
Hypotension with aortic systolic BP <100 mmHg	389 (12.8%)
Anaemia (haemoglobin <11 g/dL)	259 (8.5%)

PCI: percutaneous coronary intervention

Table 2. Comparison of Baseline Characteristics between Patients who Developed CIN [CIN (+)] and who did not Develop [CIN (-)]

Baseline characteristics	CIN (+) n = 222/3036 (7.3%)	CIN (-) n = 2814/3036 (92.7%)	*P*
Age (range), y	68.2 (50-86)	58.9 (26-81)	0.04
Gender/Female	34.7%	25.9%	<0.001
Diabetes mellitus	40.1%	35.6%	0.18
Hypertension	60.4%	60.6%	0.93
Anaemia (Hb <11 g/dL)	12.2%	8.2%	0.04
Hypotension (Systolic BP <100 mmHg)	17.5%	12.5%	0.04
Mean LVEF	45%	50%	0.01
Primary PCI	21.1%	16.6%	0.02

BP: blood pressure; Hb: haemoglobin; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention

common age group was 50 to 60 years old. Many patients had multiple coronary risk factors which include 35.9% diabetes mellitus and 37.1% patients presented with acute coronary syndrome.

In the cohort, 222 patients [7.3%; 95% confidence interval (CI), 3.8-9.6] developed CIN. We compared baseline characteristics of patients who developed CIN {CIN (+)} and patients who did not develop CIN {CIN (-)}. We hypothesised that these different risk characteristics were potential CIN predictors. The baseline comparisons between CIN (+) and CIN (-) groups are shown in Table 2.

CIN (+) patients were older and more likely to be females. They were more frequently presented with AMI and underwent primary PCI. CIN (+) patients had higher CK peak levels and lower LVEF compared to CIN (-) patients. In addition, CIN (+) patients received significantly larger contrast volume during PCI. They were also more likely to have underlying anaemia.

CIN occurred in 8.2% (95% CI, 5.2-14.4) of patients with diabetes mellitus vs 6.8% (95% CI, 3.2-7.9) in patients without diabetes mellitus. Although diabetic patients showed the trend of a higher CIN rate, this was not statistically significant ($P = 0.180$). However, analysis of diabetic subgroups according to different treatment regimes showed that insulin dependent diabetics (IDDM) had significantly higher risks of developing CIN compared to diabetics taking oral hypoglycaemic medication or on diet control alone (18.9% vs 6.8% vs 3.6%; $P = 0.001$) (Fig. 1).

Independent Risk Predictors of CIN

Based on the potential CIN predictors from the above comparison, we performed further statistical analysis to confirm their significance. By using the stepwise logistic regression statistical model, we identified that the significant CIN predictors were old age ≥70 years, AMI with shock, female gender, large contrast agent volume, presence of anaemia, hypotension and abnormal LVEF (<50%). Table 3 shows the univariate and multivariate analysis results of these CIN predictors with corresponding odds ratio and 95% CI.

Mortality Rates and Predictor of Mortality

We looked at the mortality rate at 1 month and 6 months post-PCI and assessed its relation to the development of CIN. CIN (+) patients suffered more complicated in-hospital clinical course with longer hospitalisation. The mortality rate was significantly higher in CIN (+) patients compared to CIN (-) patients (14.5% vs 1.1%) at 1 month and (17.8% vs 2.2%) at 6 months (Fig. 2).

Among the mortality patients, cardiovascular causes including heart failure, myocardial infarction and ischaemic cardiomyopathy documented according to hospital mortality codes were the most common. The documented causes of mortality at 1 and 6 months between CIN (+) and (-) patients are shown in Table 4. It was noted that 2 patients in the CIN (+) group suffered advanced renal failure which attributed to the cause of mortality.

We analysed various clinical predictors of mortality and tested the hypothesis of whether development of CIN was predictive of mortality. We examined several potential mortality predictors for causing 6 months mortality. These included CIN, age, gender, anaemia, hypotension, LVEF, diabetes mellitus, AMI and high CK level. Univariate analysis showed that CIN alone was a significant predictor for mortality with an odds ratio of 5.8 (95% CI, 1.94-17.36). However, multivariate analysis of mortality at 6

Table 3. Univariate and Multivariate Analysis of Clinical Predictors of Contrast-induced Nephropathy (CIN)

	Univariate analysis			Multivariate analysis		
Significant clinical predictors of CIN	**Odds ratio**	**95% CI**	***P***	**Odds ratio**	**95% CI**	***P***
Age (>70 years)	6.40	1.01-13.3	0.042	2.21	1.09-4.51	0.04
Female gender	2.00	1.50-2.70	0.001	1.89	1.10-3.22	0.02
Abnormal LVEF (<50%)	1.02	1.01-1.04	0.010	1.02	1.01-1.05	0.05
Hypotension – Systolic BP <100 mmHg	1.50	1.01-2.20	0.004	1.50	1.01-2.20	0.05
Contrast amount (per mL)	1.003	1.001-1.008	0.010	1.004	1.001-1.007	0.002
Anaemia (Hb <11 g/dL)	1.50	1.01-2.40	0.044	1.50	1.01-2.40	0.04
AMI with shock	7.41	3.39-16.2	<0.001	27.7	2.24-32.90	0.01
AMI without shock	1.07	0.72-1.58	0.74	0.33	0.32-1.47	0.33

95% CI: 95% confidence interval; AMI: acute myocardial infarction; BP: blood pressure; Hb: haemoglobin; LVEF: left ventricular ejection fraction

Table 4. Causes of Mortality in CIN (+) and CIN (-) Groups at 1 and 6 Months

Causes of mortality	**1 month CIN (+) n = 31/222**	**1 month CIN (-) n = 27/2582**	**6 months CIN (+) n = 33/185**	**6 months CIN (-) n = 44/2006CIN**
Cardiovascular death	29	25	29	35
Renal failure	1	0	2	0
Ischaemic bowel	1	0	1	0
Pneumonia	0	1	0	2
Stroke	0	1	1	2
Cancer	0	0	0	2
Unknown	0	0	0	3

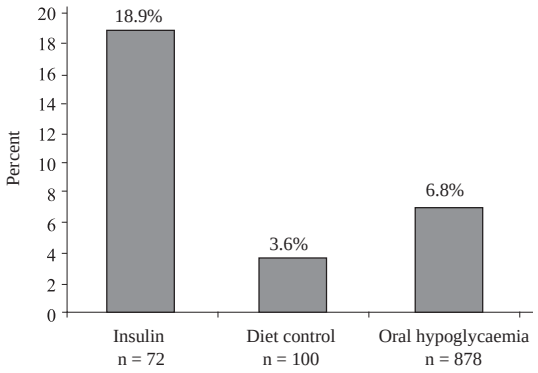

Fig 1. Incidence of CIN among diabetics on insulin therapy (± oral hypoglycaemics) vs diet vs oral hypoglycaemic alone therapy.

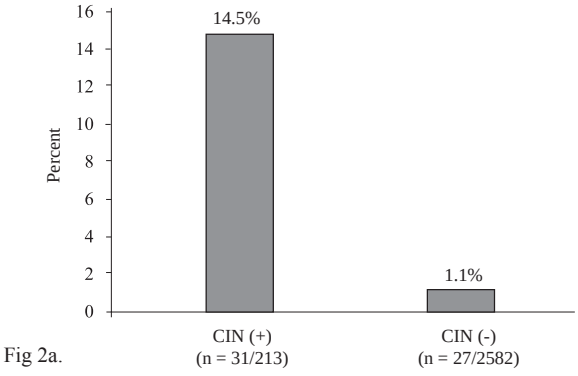

Fig 2a.

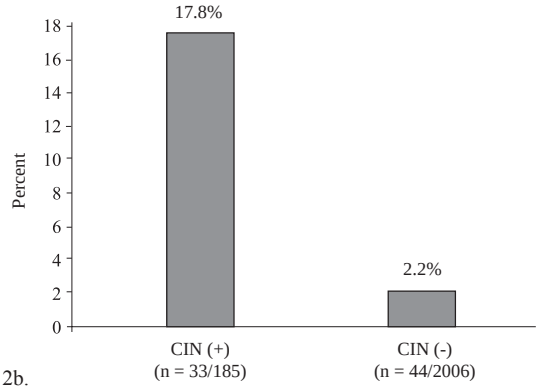

Fig 2b.

Fig 2. One month and 6 months mortality rates comparing CIN (+) and CIN (-) patients.

months failed to show a statistically significant association with the development of CIN. The most important mortality predictors were elevated CK level, presence of "hypotension" and depressed LVEF (Table 5). Although the development of CIN could predict a higher mortality, CIN alone did not cause mortality independently in this cohort.

Discussion

Our study demonstrated that CIN was a common complication with 7.3% incidence in patients undergoing

Table 5. Univariate and Multivariate Analysis of Clinical Predictors of Mortality at 6 Months

	Univariate analysis			Multivariate analysis		
Clinical predictors of mortality	**Odds ratio**	**95% CI**	***P***	**Odds ratio**	**95% CI**	***P***
Age >70	5.50	2.32-12.90	0.001	Not sig.	Not sig.	Not sig.
Female gender	2.98	1.49-5.95	0.001	Not sig.	Not sig.	Not sig.
Abnormal LVEF (<50%)	5.79	1.28-26.10	0.010	2.94	1.52-0.66	0.010
HypotensionSystolic BP <100 mmHg	5.18	2.92-9.17	<0.001	10.91	2.17-54.99	0.004
CIN	5.80	1.94-17.36	<0.001	Not sig.	Not sig.	Not sig.
Diabetes mellitus	1.79	0.90-3.56	0.095	Not sig.	Not sig.	Not sig.
Anaemia (Hb <11 g/dL)	7.38	2.91-18.60	<0.001	Not sig.	Not sig.	Not sig.
AMI with shock	11.2	5.90-21.30	<0.001	Not sig.	Not sig.	Not sig.
Creatinine kinase level(every 500 U/L) rise	1.13	1.10-1.18	<0.001	1.72	1.07-5.65	0.001

95% CI: 95% confidence interval; AMI: acute myocardial infarction; BP: blood pressure; CIN: contrast-induced nephropathy; Hb: haemoglobin; LVEF: left ventricular ejection fraction

PCI even if they have normal baseline Cr. The study also showed that patients who developed CIN tend to have increased mortality in the intermediate term.

We identified several independent risk predictors of CIN besides baseline renal impairment. These risk predictors include old age (≥70 years), AMI particularly with cardiogenic shock, large contrast volume exposure, female gender, insulin dependent diabetes mellitus, presence of anaemia (Hb <11 g/dL) and reduced LVEF. The presence of these clinical predictors increased risk of CIN occurrence.

Chronic renal impairment has been seen as the most recognised risk factor for CIN. Presence of renal failure often predisposed to adverse clinical outcomes.[26,27] The risk of CIN increased further with worsening degrees of baseline renal impairment.[28] Some of the CIN risk predictors being identified in our study have been reported previously including diabetes mellitus and high contrast volume.[7,8,29] In our institution, only patients with elevated baseline Cr received CIN prophylaxis before PCI. Patients with normal Cr value did not receive prophylaxis as they were thought to be at low risk. The commonly used prophylactic regime consisted of intravenous saline prehydration and high-dose oral N-acetylcysteine as antioxidant.[20] Our study results suggested that even in the normal Cr cohort, prophylaxis for CIN could be potentially beneficial in subgroups of patients with additional CIN risk predictors.

Patients with diabetes mellitus as well as elevated baseline Cr confer the highest risk of developing CIN as reported in literatures.[5,30] This association has not been shown in diabetic patients with normal baseline Cr in our study. However, when the diabetic cohort was subdivided according to different treatment groups, we found that insulin dependent diabetics (IDDM) despite normal Cr had significantly higher incidence of CIN compared to diabetics on oral hypoglycaemic agents and dietary control. It was likely that the IDDM subgroup suffered from higher sub-clinical renal impairment. Insulin dependence generally infer to a more severe insulin resistant status and longer duration of diabetic status.[31] Careful assessment of renal function by measurement of creatinine clearance and proteinuria would be helpful in determining renal dysfunction and further risk stratification. Closer monitoring and priority prophylaxis may be warranted in the IDDM patients.[32]

Females had been shown to have a higher risk of developing CIN than males.[12] The exact mechanism remains unknown. Females tend to have lower eGFR value given the same Cr when comparing to males. Our analysis using Cr <1.5 mg/dL as cut off confirmed that female gender was an important independent predictor of CIN. Other underlying mechanisms might explain the gender difference in CIN.

Prior data have confirmed the causative relationship between cardiac and renal dysfunction.[6,13] There were reports on the negative impact on survival from the development of renal disease in patients with coronary artery disease undergoing PCI.[6,7] Renal function has been shown to be a major determinant of cardiovascular outcome in a variety of settings particularly in chronic heart failure,[30] acute coronary syndromes and PCI.[16,33,34] It is hence important to risk stratify patients prior to PCI and take measures to prevent its occurrence.

In our study, CIN was shown as mortality predictor in univariate analysis but not after adjustment by stepwise logistic regression. The overall best mortality predictors found after multivariate analysis were hypotension, rise in cardiac enzymes and depressed LVEF. CIN has been shown to be an important mortality predictor in a high-risk cohort with baseline renal dysfunction.[34-36] Hence we thought the failure of CIN to stand out as an independent

mortality predictor was due to the low-risk cohort in our study. CIN would most likely correlate to higher mortality when developing in a higher risk cohort such as patients with chronic renal failure. Upon developing CIN, the absolute Cr jump would be much higher in the high-risk cohort compared to the low-risk normal renal function cohort. This could explain why we failed to demonstrate the causative relationship between CIN and mortality in the multivariate analysis.

Prophylactic measures would be particularly relevant in patients with an elevated number of CIN risks despite normal baseline Cr. These risk predictors can be easily recalled in the initial hours of hospital presentation and used to predict CIN risk and the associated adverse event in patients undergoing PCI. Moreover, it may help us to better identify patients with normal Cr who will still be likely at risk of developing CIN. We would be alerted to further assess the renal function by using eGFR and urinary analysis. Prophylactic therapies including saline prehydration,[10] pharmacological or non-pharmacological strategies which showed benefits of CIN prevention in patients undergoing PCI should be considered.[35,36]

Study Limitations

Although the data were collected prospectively by independent monitors and entered into the database, this was a post-hoc analysis. We did not consider the presence of proteinuria and urine output prior to PCI. We did not use Cr clearance value based on 24-hour urine collection. However, we believe that the assessment of CIN risk based on the commonly used cut off value of serum Cr was accurate for the clinical purposes of this study and certainly more practical and readily available during clinical work.

Although the rise in serum Cr occurs within the first 24 hours after exposure to contrast media in most of the patients, the absence of data on serum Cr later than 48 hours after PCI in the present study might result in the slight underestimation of CIN.[28] However, we believe that the incidence of delayed Cr rise after 48 hours in our low-risk cohort would be low. It is also doubtful that delayed Cr elevation without a significant rise within the first 48 hours after PCI may be at all clinically significant.[37]

Our study only included a single centre. The findings should be confirmed and the application of risk predictors validated in a large multicentre trial. We could not assess the influence of haemodynamic instability on the development of renal failure in a subgroup of patients with hypotension. These might have contributed, at least in part, to renal impairment via renal ischaemia mechanism and hence influenced the clinical outcome of our patients.[2,3,13] Indeed, in addition to contrast agent volume, other factors reflecting cardiocirculatory impairment, such as AMI and hypotension, were independently related to the development of renal dysfunction.[15,16] This suggests that kidney hypoperfusion, resulting in ischaemic renal injury also play a major role. However, despite the fact that no firm conclusions can be drawn at this stage, our data suggest that the potential exists for further prevention of CIN in patients with normal baseline Cr and potential reduction of mortality after PCI.

Conclusions

CIN is a common complication in patients undergoing PCI. Our data demonstrated that even in patients with normal serum Cr, CIN could still develop and would associate with more complicated clinical outcomes. Thus, despite a normal baseline Cr, elderly female patients with risk factors of IDDM, anaemia, depressed LVEF and presenting with AMI with large enzyme rise and cardiogenic shock might be considered for renal prophylactic therapy to reduce the occurrence of CIN.

We have no potential conflicts of interest.

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