Moving Points in Nephrology

Contrast-Induced Nephropathy: What Are the True Clinical Consequences?

Michael Rudnick* and Harold Feldman†

*Renal Electrolyte and Hypertension Division, Penn Presbyterian Medical Center, Philadelphia, Pennsylvania; and †Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Background and objectives: Observational studies have demonstrated that short- and long-term mortality is increased in patients who develop contrast-induced nephropathy (CIN). The more clinically relevant questions, and the objectives of this review, are whether CIN is causally related to mortality, and to what extent could mortality in patients undergoing contrast procedures be reduced by preventing CIN.

Design, setting, participants, & measurements: A literature review was conducted, focusing on observational studies that assessed factors associated with mortality in patients with CIN.

Results: The deaths of some patients with CIN are complicated by factors that cannot be directly related to CIN, such as liver disease, sepsis, respiratory failure, bleeding, *etc.* However, it is plausible that CIN contributes to cardiovascular causes of death in patients with CIN.

Conclusions: At the very least, CIN is a marker for increased mortality. More carefully designed prospective studies are needed to fully elucidate the relationship between CIN and death. In the absence of data disproving a causal relationship between CIN and death in all subgroups, reducing its incidence should remain a goal in clinical practice as well as a target for future research.

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Acute kidney injury (AKI) in the setting after contrast media (CM) administration derives from many causes including ischemia, atheroembolism, or nephrotoxicity of the CM itself. The latter is referred to as contrast-induced nephropathy (CIN).

During the past decade, multiple studies have addressed the question of whether patients who develop CIN have a greater risk for other medical complications and for death. Before these studies, most observers viewed CIN as a condition usually characterized by asymptomatic, minor, and transient elevations in the serum creatinine (SCr) without any significant associated morbidity or mortality (1). As reviewed below, recent studies have demonstrated convincingly that patients experiencing CIN have a greater risk of in-hospital and 1-yr mortality. However, the causal nature of this relationship is much less clear. Stated differently, the portion of mortality or morbidity observed after CIN that would be avoided if CIN events were prevented remains unknown because of the potentially confounded nature of these relationships. This article will review recent observational studies and clinical trials to shed light on the nature of the relationship between CIN and mortality.

Risk Factors Associated with CIN

Most of the studies that have evaluated the relationship between CIN and downstream events of morbidity and mortality demonstrate that patients who experience CIN have greater levels of comorbidities at the time of CM administration than patients who do not experience CIN. This raises the question of whether downstream events such as death are caused by the preexisting comorbidities or by CIN itself. Many of these baseline comorbidities have also been demonstrated to be patient or procedural risk factors for CIN. Examination of specific non-traditional risk factors (traditional risk factors are chronic kidney disease (CKD) and diabetes mellitus) identified in these studies provides further clarity as to how these risk factors could contribute to downstream events after contrast administration. For example, Bartholomew *et al.* found significant associations between CIN and chronic medical conditions beyond renal impairment and diabetes to include congestive heart failure (CHF), hypertension, and peripheral vascular disease (PVD) (2). Significant associations also were noted for acute conditions that influence specific procedures such as vascular collapse requiring the use of an intraaortic balloon pump (IABP) and acute vascular and hemodynamic alterations necessitating urgent interventions. The negative impact of many of

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Correspondence: Dr. Michel Rudnick, Associate Professor of Medicine, Chief, Renal Electrolyte and Hypertension Division, Penn Presbyterian Medical Center, Medical Office Building, 39 Market Street, 2nd Floor, Suite 240, Philadelphia, PA 19104. Phone: 215-662-8730; Fax: 215-243-4686; E-mail: rudnickm@uphs.upenn.edu

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these risk factors, especially those that acutely alter hemodynamic stability, on subsequent clinical events makes it difficult to separate out the role, if any, of CIN *per se* in subsequent mortality. As demonstrated in Figure 1, it is not surprising that as the number of risk factors increases, there is a proportional increase not only in CIN but also in mortality. Those patients with the greatest number of risk factors also were the most ill at baseline (2).

Overall, the findings from the study by Bartholomew *et al.* and others showed that increased net baseline morbidity was associated with the development of CIN (2–4). Because baseline net morbidity also negatively impacts survival and hospitalization, it is not surprising that one can readily identify associations between CIN and mortality.

Possible Strategies to Elucidate the Relationship between CIN and Mortality

Study design and data analysis for elucidation of the relationship between CIN and postevent morbidity and mortality present a number of challenges. There are multiple possible strategies that could be used to elucidate this relationship. One strategy would be to compare survival data from patients with CIN to survival data from patients who developed AKI of similar severity but from other causes. With this approach, careful statistical modeling would be needed to control for differences in these patient groups, especially with respect to baseline medical status. The findings from more feasible and interpretable studies and analyses reflecting other strategies in elucidating the CIN–mortality relationship will be covered in the next section. These strategies include comparisons of survival among patients after CIN to survival in patients whose recovery after a contrast-enhanced procedure was not complicated by CIN; comparisons of survival across treatment arms of clinical trials assessing prophylactic agents associated with different rates of CIN; and comparisons of survival across treatment arms of clinical trials assessing different types of contrast agents.

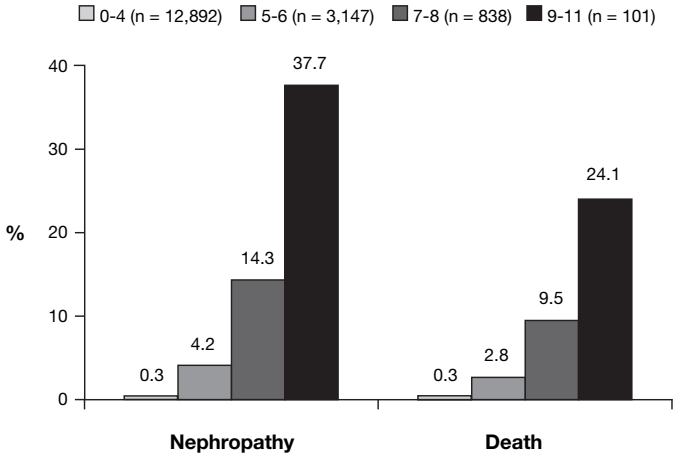


Figure 1. Risk for development of contrast-induced nephropathy (CIN) according to CIN risk score. The CIN risk score was developed from data from a derivation cohort of >10,000 patients undergoing percutaneous coronary interventions (PCI) between 1993 and 1998, with subscores assigned to the following variables significantly associated with CIN: baseline creatinine clearance <60 ml/min, urgent PCI, and intraaortic pump use each receiving 2 points; and diabetes mellitus, congestive heart failure, hypertension, peripheral vascular disease, and contrast volume >260 ml each receiving 1 point. Findings for development of CIN and in-hospital death were combined for the derivation and validation cohorts (>20,000 patients) (2).

Observational Studies on the Effects of CIN on Mortality

Mortality after development of CIN has been assessed in several observational studies that compared mortality from patients developing CIN to mortality without CIN after contrast exposure. Although mortality rates varied from study to study, one consistent finding was that, within these studies, short-term and long-term mortality rates were significantly greater for patients who developed CIN compared with those with stable renal function after contrast-enhanced procedures (Table 1).

McCullough *et al.* reported an analysis of CIN in patients undergoing percutaneous coronary interventions (PCI) between December 1993 and May 1995 (5). A total of 1826 patients were included in a derivation set, and subsequently 2251 patients were included in a validation set. In the derivation set, 14.5% developed CIN and the incidence of CIN requiring dialysis was 0.8%. In-hospital mortality rates (derivation set) were 1.1% for patients without CIN, 7.1% for patients with CIN, and 35.7% for patients with CIN requiring dialysis ($P < 0.0000001$) (Table 1). The adjusted odds ratios for the relationship between renal outcomes and in-hospital mortality were 6.56 (95% confidence interval (CI) 3.34 to 12.62; $P < 0.00001$) for CIN of any severity and 13.54 (95% CI 3.92 to 46.8; $P < 0.00001$) for CIN requiring dialysis. Long-term survival was poor, respectively, for patients with CIN requiring dialysis (the derivation and validation set populations combined); median survival was 2.75 mo, with a 2-yr survival rate of only 18.8%.

Rihal *et al.* conducted a retrospective analysis of 7586 patients from the Mayo Clinic PCI Registry (3). There was a total of 254 patients (3.3%) who developed AKI, 20 of whom (2.6%) required hemodialysis. In-hospital mortality rates were 22.0% for patients with AKI *versus* 1.4% for patients without AKI ($P < 0.001$) (Table 1). One-year mortality rates were 12.1% for patients with AKI *versus* 3.7% for patients without AKI and 44.6% *versus* 14.5% at 5 yr ($P < 0.0001$). In this study a number of risk factors for AKI were identified including age, contrast volume, CHF, acute myocardial infarction (AMI), diabetes mellitus, PVD, and higher baseline SCr. Most of the in-hospital mortality in patients with AKI was the result of cardiac causes. Not surprisingly, preprocedural cardiac morbidity tended to be greater among the patients with AKI who died during hospitalization than among those with AKI who were discharged, as evidenced in the former group by a significantly higher incidence of shock (both pre- and postprocedure), history of CHF, three-vessel coronary disease, AMI within 24 h of the procedure, need for urgent or emergent procedure, and need for IABP assistance. Independent predictors of in-hospital death

Table 1. Mortality Rates Associated with Contrast-Induced Nephropathy

Reference	No. of Patients and Type of Contrast Procedures	CIN Definition (Size of Increase in SCr from Baseline)	In-Hospital Mortality Rates: CIN vs No CIN	Long-Term Mortality Rates: CIN vs No CIN
McCullough *et al.*, 1997 (5)	1826 in a derivation set, 2251 in a validation set; PCI	>25% during first 5 days	7.1% vs 1.1%; 35.7% for dialysis-dependent ($P <$ 0.0000001)	—
Rihal *et al.*, 2002 (3)	254 with CIN, 6890 without CIN; PCI	>0.5 mg/dl during first 48 h	22.0% vs 1.4% ($P < 0.001$)	12.1% vs 3.7% ($P < 0.0001$) (1-yr hospital survivors); 44.6% vs 14.5% ($P <$ 0.0001) (5-yr hospital survivors)
Gruberg *et al.*, 2000 (8)	439 with CKD (SCr ≥1.8 mg/dl) not dialysis-dependent; PCI	≥25% during first 2 days or needing dialysis	14.9% vs 4.9%; 22.6% for dialysis-dependent ($P < 0.001$)	37.7% vs 19.4% ($P = 0.001$) (1-yr cumulative rate)
Gruberg *et al.*, 2001 (9)	7741; PCI	Requiring dialysis	27.5% vs 1.0% ($P < 0.001$)	54.5% vs 6.4% ($P < 0.0001$) (1-yr cumulative rate)
Dangas *et al.*, 2005 (4)	5250 CKD(+), 1980 CKD(−); PCI	≥25% or ≥0.5 mg/dl during first 48 h	6.3% vs 0.8% (CKD(+), $P <$ 0.0001); 2.5% vs 0.1% (CKD(−), $P <$ 0.0001)	22.6% vs 6.9% (CKD(+); $P <$ 0.0001) 8.0% vs 2.7% (CKD(−); $P <$ 0.0001) (1-yr cumulative rate)
Levy *et al.*, 1996 (11)	183 with CIN, 183 matched control subjects; various procedures (about half angiography)	≥25% to ≥2 mg/dl during first 2 days	34% vs 7% ($P < 0.001$)	—

CIN, contrast-induced nephropathy; CKD, chronic kidney disease, defined as an estimated glomerular filtration rate <60 ml/min per 1.73 m^2; PCI, percutaneous coronary intervention; SCr, serum creatinine.

are listed in Table 2. In addition to the higher mortality in patients with AKI *versus* non-AKI patients, after PCI AKI patients had greater increases in systemic complications (*e.g.* stroke, adult respiratory distress syndrome, pulmonary embolus, gastrointestinal bleed), vascular complications (femoral bleeding, pseudoaneurysm), and cardiac complications (procedural failures, coronary artery bypass graft surgery, Q-AMI, shock, cardiac arrest) (Figure 2).

These observations clearly demonstrate that AKI after contrast administration during PCI is associated with a high risk of in-hospital and long-term mortality. However, the question as to whether there is a physiological causal relationship between AKI after contrast and postprocedural morbidity or mortality remained unanswered. As demonstrated in the study by Rihal *et al.* (3), many of the correlates for postcontrast AKI could by themselves be associated with increased morbidity and mortality. For many of these downstream events, it is unclear what specific biological pathway would explain the link between mild AKI and the development of the complications in the short- and long-term, which favors the explanation that such cases of AKI are a marker and not a cause of mortality. On the other hand, many of the downstream events (both morbidity and mortality) were cardiac in nature. In this regard, a recent study, in which ischemia-reperfusion renal injury (IRI) was performed in dogs, demonstrated that after AKI, coronary vascular tone, reserve, and vessel reactivity are markedly diminished (6). This could lead to increased mismatching between oxygen supply and demand and ultimately induce subendocardial ischemia, providing one possible explanation for how AKI can cause increased cardiac morbidity and mortality. It should be noted that the experimental AKI in this model was severe (creatinine level, 9 mg/dl), which raises questions about the relevance of this observation to the milder forms of AKI observed in these observational studies. The possibility that ischemic AKI can induce injury in distant organs which in turn may contribute to mortality is further supported by observations that rodents subjected to IRI developed lung injury characterized by increased pulmonary vascular permeability, lung edema, and alveolar hemorrhage (7). These observations were not seen in bilateral nephrectomized rodents, despite similar levels of azotemia, suggesting they were unique to ischemic induced AKI and not the result of uremia or volume overload. These authors further identified several proinflammatory and proapoptotic pathways in the lung transcriptome by global gene expression profiling which were unique only in the rodents with ischemic AKI, suggesting possible mechanistic pathways.

Rihal *et al.* were careful to classify the postprocedural rises as AKI and not CIN, recognizing their inability to determine if the acute creatinine rise was caused by contrast, ischemia, or atheroemboli (3). AKI caused by ischemia or atheroemboli may be associated with significant pre- and postevent comorbidities, which could directly affect short- and long-term mortality. This is an important observation because AKI from these etiologies improperly classified as arising from CM would be expected to overestimate the true mortality rate associated with CIN. Unfortunately, the methodology of these observational studies on contrast and mortality in cardiac patients undergoing PCI does

Table 2. Independent Predictors of Short- and Long-Term Mortality in Patients Undergoing Contrast Procedures in Addition to CIN

Reference	Study Exclusion Criteria	Independent Predictors of In-Hospital Mortality (OR; 95% CI)	Independent Predictors of Long-Term Mortality (OR; 95% CI)
Rihal *et al.*, 2002 (3)	• No medical criteria	• Age (1.03; 1.01 to 1.05) • CHF (2.24; 1.51 to 3.32) • Emergent procedure (3.12; 1.79 to 5.42) • Multivessel procedure (1.85; 1.29 to 2.66) • Preprocedural shock (12.12; 8.11 to 18.13) • PVD (2.08; 1.35 to 3.20) • CIN (10.83; 6.91 to 16.98)	—
Gruberg *et al.*, 2000 (8)	• SCr < 1.8 mg/dl • Dialysis dependence	—	• Creatinine elevation (3.86; 1.96 to 7.58) • Age (1.05; 1.05 to 1.09) • Location of vein graft lesion (1.55; 0.95 to 2.52)
Gruberg *et al.*, 2001 (9)	• Dialysis dependence	• IABP use (1.88; 1.52 to 2.32) • Age increase by 10 yr (2.52; 1.86 to 3.42) • Non–Q-wave infarction (2.76; 1.08 to 7.01) • CK-MB 3× normal (3.98; 1.45 to 10.94) • Dialysis (5.82; 2.22 to 15.26) • Creatinine increase by 5 g/dl from baseline (6.25; 2.25 to 17.80)	• Age increase by 10 yr (1.53; 1.28 to 1.83) • IABP use (1.58 (1.41 to 1.78) • CPK 3× normal (1.64; 1.24 to 2.17) • Vein graft intervention (1.72; 1.28 to 2.31) • Diabetes (2.00; 1.54 to 2.61) • Creatinine increase by 5 mg/dl from baseline (2.86; 1.27 to 6.47) • In-hospital dialysis (4.15; 1.27 to 6.47) • CrCl (0.96; 0.93 to 0.99)
Dangas *et al.*, 2005 (4)	• Acute ST-elevation AMI within 48 h of procedure • Cardiogenic shock • Baseline ESRD	—	• Hypotension (CKD+: 3.18; 2.08 to 4.86) (CKD−: 2.70; 1.76 to 4.14) • Diabetes (CKD+: 1.92; 1.34 to 2.76) (CKD−: 1.56; 1.12 to 2.19) • PVD (CKD+: 1.85; 1.30 to 2.65) (CKD−: 1.78; 1.23 to 2.59) • IABP use (CKD+: 2.49; 1.41 to 4.41) (CKD−: 2.04;1.11 to 3.76) • LVEF <40% (CKD+: 1.66; 1.15 to 2.41) (CKD−: 3.26; 2.32 to 4.58) • Older age (CKD+: 1.03; 1.01 to 1.05) (CKD−: 1.03; 1.01 to 1.04) • eGFR (CKD+: 0.97; 0.96 to 0.99) • Baseline hematocrit (CKD−: 0.90 (0.86 to 0.93) • Previous stroke (CKD−: 1.55; 1.01 to 2.39)
Levy *et al.*, 1996 (11)	• No medical criteria	• Liver disease (18.03; 2.91 to 13.19) • Age >60 yr (4.69; 2.24 to 9.83) • Physiologic Severity Score[b] (1.23; 1.09 to 1.39)	—

[a]CHF, congestive heart failure; CK-MB, creatine kinase-MB fraction; CPK, creatine phosphokinase; CrCl, creatinine clearance; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; AMI, acute myocardial infarction, PVD, peripheral vascular disease.

[b]The Physiologic Severity Score was a dimensional variable with values ranging from 0 to 17 and was based on temperature, heart rate, respiratory rate, blood pressure, oxygenation, pH, serum sodium and potassium levels, hematocrit, and white blood cell count.

not permit an identification of the specific role of contrast alone in postprocedural creatinine rises.

Gruberg *et al.* published a retrospective analysis on the effects of CIN after PCI in 439 patients with CKD, approximately half of whom were diabetic (8). A total of 161 patients (37.7%) developed CIN, and 31 of the 439 patients (7.0%) required dialysis. When patients with CIN were compared with patients without CIN, the former group had more diabetics and a lower left ventricular ejection fraction. In-hospital mortality rates were 4.9% for patients without CIN and 14.9% for patients with CIN ($P < 0.001$). In-hospital cardiac death rates were 9.6% for the patients with CIN *versus* 3.3% for those without CIN ($P = 0.003$). Morbidities after PCI, which were significantly greater in CIN patients compared with non-CIN patients, were non-Q AMI, pulmonary edema, and gastrointestinal bleeding. For the 31 patients requiring dialysis, the mortality rate was 22.6% (Table 1). One-year mortality rates were 19.4% for patients without CIN *versus* 37.7% for patients with CIN ($P = 0.001$). In this analysis, a cardiac morbidity factor (the location of the vein graft lesion), a postprocedural renal outcome (creatinine elevation), and age were independent predictors of 1-yr mortality (Table 2) (8).

In a subsequent analysis using data from the same Cardiovascular Research Foundation database, Gruberg *et al.* performed a retrospective evaluation of CIN requiring dialysis among 7741 consecutive patients who underwent PCI (9). Of these patients, 51 developed CIN after PCI that required in-hospital dialysis; the cause(s) of deterioration in renal function

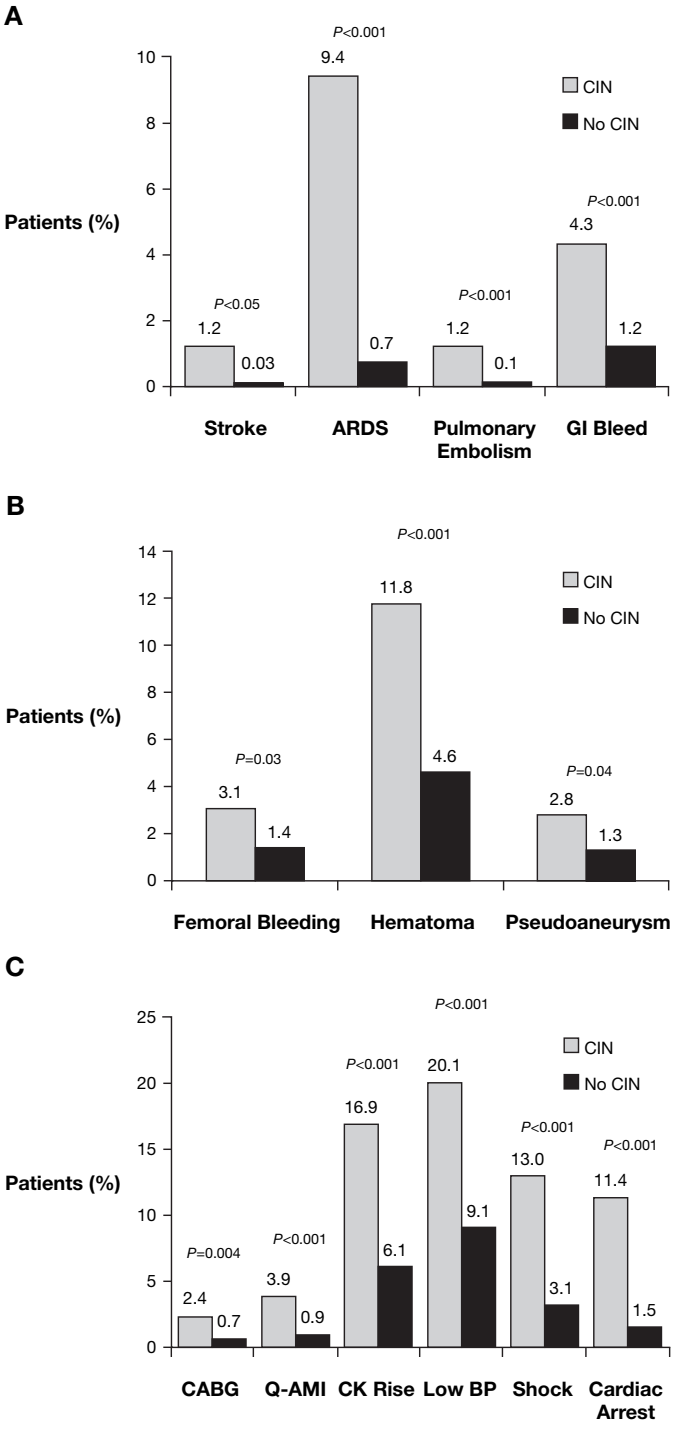


Figure 2. Systemic (A), vascular (B), and cardiac (C) procedural complications in patients with and without CIN from an analysis of data from 7586 patients in the Mayo Clinic PCI Registry (3). ARDS, adult respiratory distress syndrome; GI, gastrointestinal.

was acute tubular necrosis after contrast load in 90% of these patients, shock in 25%, and atheroembolism in 10%. Patients who required dialysis compared with patients who did not were older, more often female, and demonstrated a greater incidence of diabetes mellitus, CKD, prior percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery, had a higher baseline SCr (2.6 mg/dl *versus* 1.1 mg/dl), and a lower ejection fraction (35% *versus* 46%). Patients who developed CIN necessitating dialysis had a significantly higher in-hospital mortality rate (27.5%) compared with patients who did not need postprocedural dialysis (1.0%; $P < 0.0001$) (Table 1). Morbidities of non-Q AMI, CK-MB elevation, pulmonary edema, and vascular complications during the hospitalization were significantly higher in patients who required dialysis post-PCI compared with patients who did not require dialysis. Of the patients who required dialysis and survived the hospitalization, 23% were discharged on permanent dialysis. One-year cumulative mortality rates also were significantly higher for the group that required dialysis: 54.5% *versus* 6.4% for the patients who did not receive dialysis ($P < 0.0001$). Multivariate analysis revealed several cardiac, renal, and other types of independent predictors, such as in-hospital dialysis, that were similar as predictors for both in-hospital dialysis and long-term mortality (Table 2) (9). In addition to the demonstration of increased short-term and long-term morbidity and mortality in patients who required dialysis post-PCI and the increased comorbidities present at baseline in patients who required dialysis, this study also observed (similar to the study by Rihal *et al.* (3)) that not all patients who required dialysis post-PCI had AKI solely as a result of CM, but rather in some cases as a result of ischemia or atheroemboli. This observation once again emphasizes the challenges to interpreting mortality after AKI in the setting of contrast exposure as a reflection of mortality after CIN.

Using the same database as Gruberg *et al.*, Dangas *et al.* reported a retrospective analysis of clinical outcomes in 7230 patients with or without CKD who underwent PCI (4). CIN (defined as an increase in SCr from baseline of ≥25% or ≥0.5 mg/dl) developed in 1069 (14.8%) patients. Those who developed CIN included 688 of 5250 patients without CKD (13.1%) and 381 of the 1980 patients with CKD (19.2%). The higher than expected CIN rate in patients without CKD raises the possibility that AKI in this population may not, as previously discussed, be related solely to contrast nephrotoxicity. A number of baseline and procedural variables were significantly more prevalent in patients with CIN compared with patients without CIN, irrespective of their being in the CKD or non-CKD groups. These variables were older age, hypertension, diabetes mellitus, PVD, prior AMI, coronary artery bypass graft surgery, or PCI, ejection fraction <40%, multivessel PCI performed, and pre-, intra-, or postprocedure hypotension. CIN patients received more contrast and had a lower eGFR and hematocrit compared with non-CIN patients. Again, these differences suggest that patients who developed CIN were sicker at baseline than patients who did not develop this complication and that hemodynamic changes during PCI may have contributed to AKI. In a multivariate logistic regression analysis, most of these variables were found to be significant independent predictors of CIN. Postprocedure morbidities more frequent in patients with CIN compared with patients without CIN were bypass surgery, bleeding, vascular complications, longer postprocedure hospital stay, and non-Q AMI. In-hospital mortality rates were greatest for patients with CKD who developed CIN, 6.3%; the rate

for patients with CKD who did not develop CIN was 0.8% ($P < 0.0001$). Among the patients without CKD, in-hospital mortality rates were significantly higher for those with CIN (2.5%) than for those without CIN (0.1%, $P < 0.0001$) (Table 1). These observations support previous observations that CKD itself is associated with increased in-hospital mortality in a cardiac setting (9) and also demonstrate that CIN is associated with poor outcomes even in patients without baseline CKD. Cumulative 1-yr death rates among patients with CKD were significantly greater for those with CIN compared with those without CIN (22.6% *versus* 6.9%; $P < 0.0001$), as were 1-yr death rates for patients discharged from the hospital (16.3% *versus* 6.1%; $P < 0.0001$). A similar pattern emerged for the 1-yr death rates among patients without CKD: 8.0% in CIN patients *versus* 2.7% in patients without CIN for the cumulative 1-yr rate and 6.5% *versus* 2.6% for the out-of-hospital rate; $P < 0.001$) (Table 1). Not surprisingly, 1-yr mortality remained greater for CIN patients *versus* non-CIN patients when stratified according to baseline GFR, and with worsening baseline GFR, mortality rose proportionately (Figure 3A). Furthermore, with increasing clinically significant definitions of CIN, there was a proportional rise in mortality (Figure 3B). Independent predictors of 1-yr mortality are listed in Table 2. These observations suggest that 1-yr mortality appears to be a function of both CKD and CIN, emphasizing the difficulty in ascertaining how much of the observed mortality in other studies is caused by the underlying CKD and not the CIN.

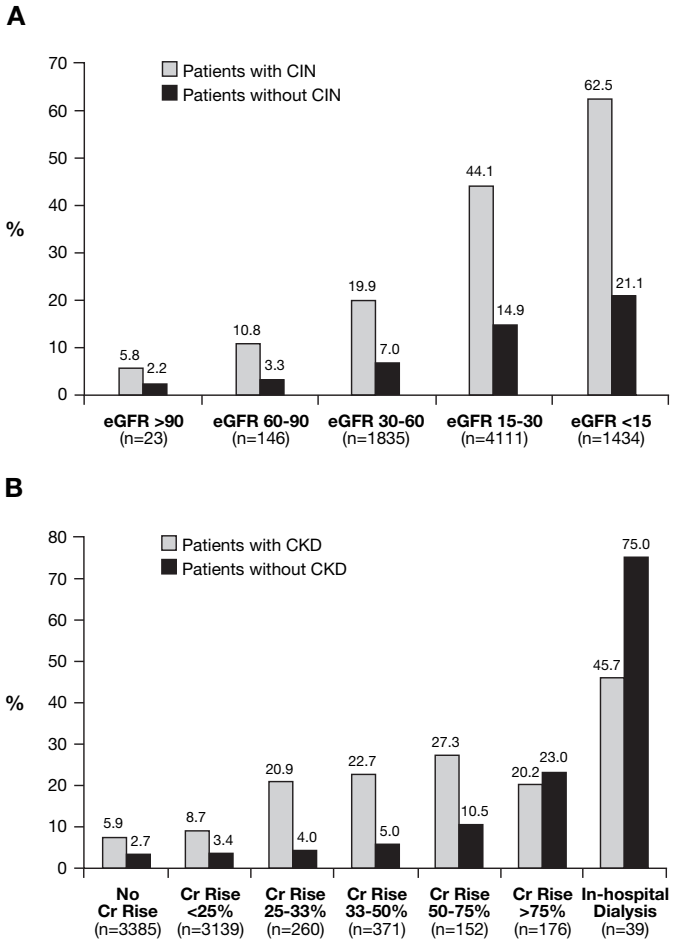


Figure 3. (A) One-year mortality stratified by baseline estimated GFR (eGFR) in patients with or without CIN. (B) One-year mortality stratified by magnitude of postprocedure serum creatinine (Cr) increase in patients with or without baseline CKD (4).

In one of the few studies that was not restricted to patients undergoing PCI, Levy *et al.* retrospectively analyzed mortality findings in 16,248 in-patients who underwent contrast procedures (half of the patients underwent angiography; the other patients underwent computed tomography and other miscellaneous contrast procedures) between 1987 and 1989 at Yale-New Haven Hospital using a matched-pairs cohort design (11). A total of 174 patients developed CIN. Index subjects (with AKI) were matched with control subjects (no AKI) for age, baseline SCr, and type of contrast-enhanced procedure. Mean Scr was 1.6 mg/dl in both index and control subjects. When compared with control subjects, index subjects had significantly more acute comorbid conditions such as sepsis, mental status changes, liver disease, and gastrointestinal bleeding. The in-hospital mortality rate for the index patients was 34% compared with 7% for the matched subjects ($P < 0.001$). The odds ratio associated with in-hospital mortality for the patients developing AKI after a contrast procedure was 5.77 (95% CI 2.91 to 13.19; $P < 0.001$). Mortality rates also were higher in index patients compared with control patients when both groups were matched for Physiologic Severity Scores. Three baseline variables were found to influence the odds ratio by >5% for mortality in patients with CIN: liver disease, age >60 yr, and Physiologic Severity Score. The clinical course of CIN in these patients was atypical: 29% developed oliguria and 12% underwent renal replacement therapy. Mortality was 62% in the renal replacement patients. The clinical course of the index patients was marked by sepsis, bleeding, delirium, and respiratory failure, usually with onset after the development of CIN. The authors concluded that although all of the case subjects had AKI, "most could not be considered to have contrast nephropathy, since other risk factors for renal failure (both comorbid and iatrogenic) were present" (11) Despite this, they also concluded that AKI in this setting is directly associated with increased mortality, even when comorbidities are adjusted for by matching Physiologic Severity Scores.

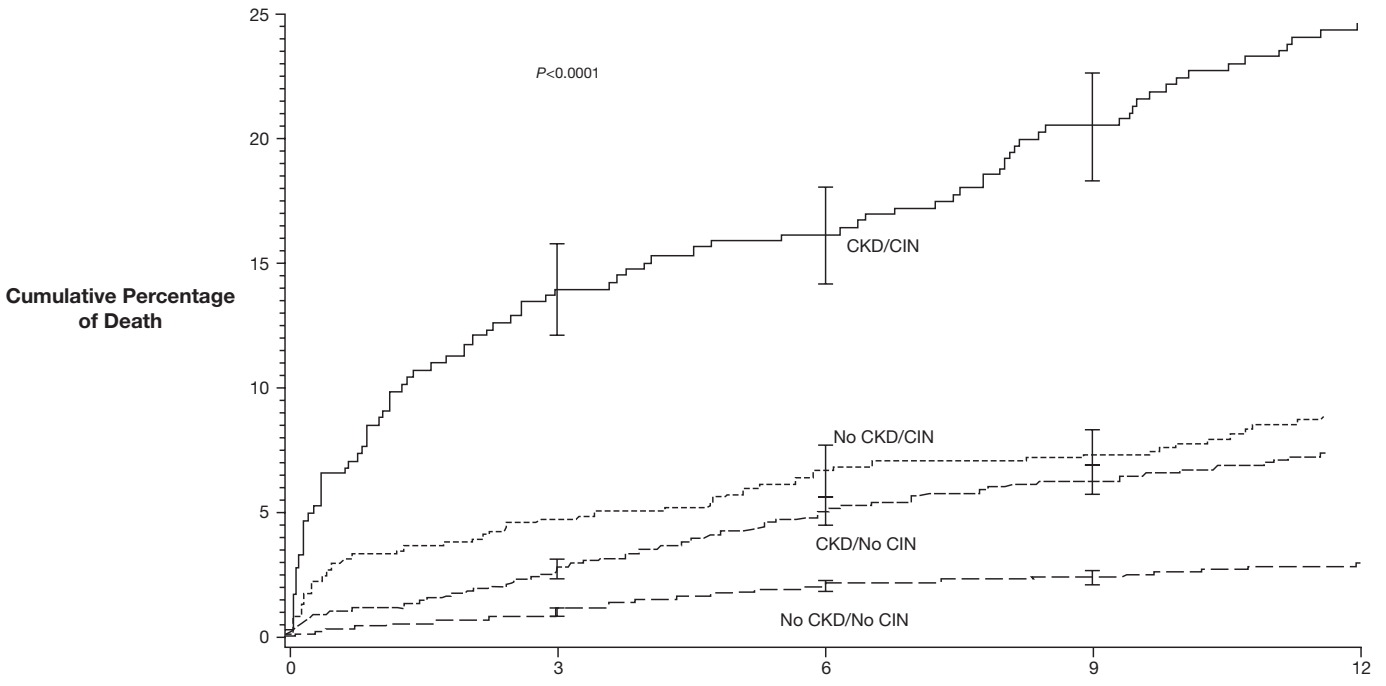
To summarize at this point, many observational studies confirm a higher rate of death in patients with CIN compared with patients without CIN. Clearly, CIN events identify individuals at very high risk for diminished survival. However, observational studies cannot definitively establish whether CIN causally contributes to mortality. The results of these studies are consistent with the hypotheses that CIN development is a risk marker for mortality and/or CIN may modify subsequent therapies that influence mortality. The plausibility of a causal connection between CIN and subsequent mortality is greatest for complications associated with renal and hemodynamic instability. It is more difficult to causally associate CIN with downstream events such as liver disease, sepsis, respiratory failure, delirium, bleeding/hematoma, pseudoaneurysm, *etc.*, as re-

ported by Rihal *et al.* (3) and Levy *et al.* (11). In patients whose death is related to these factors, CIN may be a marker for increased mortality risk rather than a contributing cause of death.

One might hypothesize that short-term mortality data are more valid because it becomes more difficult to control for other downstream events between the patient groups in the long-term analysis without access to a rich dataset that contains covariates updated over time. Furthermore, Kaplan-Meier mortality curves presented by Gruberg *et al.* and Dangas *et al.* (Figure 4) showed that the most dramatic increase in the death rate for the highest-risk patients occurred during the first few months after CIN (4,8,9). However, the effects of CIN on long-term mortality may be more relevant in low-risk patients than in high-risk patients, as demonstrated in the study by Dangas *et al.* (4) For patients with CKD, 1-yr mortality rates did not appear to correlate with greater postprocedural increases in SCr. On the other hand, 1-yr mortality rates rose with increasing magnitude of change in postprocedure SCr in patients without CKD (Figure 3B).

Randomized Clinical Trials

Thus, how can we gain further insights into whether CIN plays a causal role in mortality? It is unlikely that additional retrospective observational studies in which mortality is compared between CIN and no CIN groups will provide greater insight in answering this question. One approach to additional insight is to consider how much mortality could be avoided if we could reduce the occurrence of CIN. Randomized controlled trials comparing preventive strategies or different contrast agents, although not designed for the purpose of evaluating mortality, may provide us with this further insight. To be of value, these trials would have to record mortality and ideally other morbidities, have a different CIN rate between the two arms, be large enough so that baseline comorbidities are balanced between groups by random allocation, and have follow-up periods of sufficient duration to detect mortality differences associated with differences in CIN rates. Most of these trials that involve CIN as an outcome have assessed the value of a specific intervention to prevent CIN. For the data from these trials to be valuable in elucidating the role of CIN itself on mortality, it would be necessary for the intervention not to have, either directly or indirectly, any effect on morbidity and mortality. As described below, this was not likely the case for the limited number of prospective randomized trials that have been performed to determine the incidence of CIN in which mortality data are available. One possible way around this obstacle would be to look at prospective randomized trials that compare different contrast agents. Although it is unlikely that CM themselves will have an effect on mortality, there



Number at risk

CKD/CIN	364	313	305	289	251
CKD/No CIN	1641	1599	1560	1539	1378
No CKD/CIN	637	608	595	591	542
No CKD/No CIN	4906	4858	4805	4786	4375

Figure 4. One-year survival after percutaneous coronary intervention in patients with or without CKD and with or without CIN (4).

are minimal mortality data in most of the prospective randomized trials comparing different contrast agents.

Marenzi *et al.* reported findings from a randomized, controlled trial comparing the efficacy of hemofiltration with that of hydration using isotonic saline for preventing CIN in 114 consecutive PCI patients with moderately severe CKD, a third of whom were diabetic (12). Hemofiltration was performed in an intensive care unit while hydration was conducted in a step-down unit using a rate of 1 ml/kg body weight per h. Hemofiltration was started 4 to 6 h before PCI, discontinued during angiography, and restarted after the procedure for another 18 to 24 h. Hydration was started 6 to 8 h before and continued for 24 h after angiography.

The in-hospital mortality rate was 2% for the hemofiltration group, which was significantly lower than the 14% rate observed for the hydration (control) group ($P = 0.02$). The cause of death of the patient who received hemofiltration was cardiogenic shock; the cause of death among patients in the hydration group included AMI complicated by cardiogenic shock, multiple organ failure, refractory heart failure, and ischemic stroke. Mortality was not compared between patients with or without CIN, although there was a reduced incidence of CIN in the hemofiltration group that paralleled the reduced mortality in this group. Of the postprocedural complications reported, significant differences between the hemofiltration and hydration groups were noted for pulmonary edema (0% *versus* 11%; $P = 0.02$), development of CIN (5% *versus* 50%; $P < 0.001$), and need for renal replacement therapy (3% *versus* 25%; $P < 0.001$). The cumulative 1-yr mortality rate was 10% for the hemofiltration group and 30% for the hydration group ($P = 0.01$). Among the 19 patients who died during the first year after hospitalization, the cause of death was primarily related to cardiopulmonary events: for patients in the hydration group with a baseline SCr <4 mg/L, the relative risk for death by 1 yr was 1.16 (95% CI 0.96 to 1.40; $P = 0.11$); it was 3.53 (95% CI 1.08 to 11.20; $P = 0.002$) for those with baseline SCr ≥4 mg/dl. Although CIN was less frequent in the hemofiltration group, this was likely confounded by the removal of creatinine by hemofiltration impairing the ability to diagnose CIN. Furthermore, one cannot exclude the possibility that placement of the hemofiltration patients in the intensive care unit or other influences of hemofiltration on acute and chronic pathophysiologies in these patients may have been responsible for the reduction in mortality or postprocedural complications, rather than as a result of the prevention of CIN, *per se*.

In another randomized controlled clinical trial, Marenzi *et al.* assessed the efficacy of N-acetylcysteine (NAC) for reducing morbidity and mortality in 354 consecutive patients undergoing primary angioplasty for ST-segment elevation AMI (13). Patients were randomized to three groups: 600 mg NAC in an intravenous bolus before angioplasty followed by 600 mg NAC orally twice a day during the 2 d after the procedure; 1200 mg NAC by intravenous bolus before the procedure and 1200 mg NAC orally twice a day for 2 d after the procedure; and placebo. After the angioplasty, all three groups received intravenous normal saline (1 ml/kg per h) for 12 h. Baseline demographic and clinical factors, which included renal function and infarct size, were similar in the three groups. A creatinine clearance ≤60 ml/min was present in approximately one third of the patients. Overall, CIN developed in 19% of patients and was related to the presence of reduced left ventricular function and renal function at baseline. Development of CIN was associated with a significantly higher in-hospital mortality rate: 26% for patients with CIN compared with 1.4% for patients without CIN ($P < 0.001$). In-hospital mortality rates were significantly lower for the patients receiving NAC (4% and 3% for the 600-mg and 1200-mg groups, respectively) than for the placebo group (11%; $P = 0.02$ and $P = 0.001$ for trend). The odds ratio for in-hospital death for the control group compared with the NAC 600-mg dose group was 1.85 (95% CI 0.54 to 6.37; $P = 0.32$), and compared with the NAC 1200-mg dose group it was 5.43 (95% CI 1.24 to 23.81; $P = 0.03$). Causes of in-hospital death were similar among the NAC and control patients and included cardiogenic shock, heart failure, multiple organ failure, cardiac rupture, arrhythmias, and noncardiac causes. Complications that ensued during hospitalization at significantly different rates for the control and NAC groups included acute pulmonary edema requiring mechanical ventilation (2% for the NAC 600-mg and 1200-mg groups *versus* 8% for control; $P = 0.03$, $P = 0.02$ for trend), CIN (≥25% increase in SCr from baseline; 8% for the NAC 600-mg group, 15% for the NAC 1200-mg group, and 33% for control; $P < 0.001$, $P < 0.001$ for trend), and CIN requiring replacement therapy (1% for the NAC 600-mg group, 2% for the NAC 1200-mg group, and 5% for control; $P = 0.14$, $P = 0.04$ for trend). The antioxidant and vasodilatory effects of NAC may have directly influenced subsequent mortality in these patients with cardiac disease. More specifically, NAC administration in patients with AMI has been associated with diminished oxidative stress, more rapid coronary reperfusion, preservation in ventricular function, and a decrease in the size of infarct (14,15). Furthermore, the incidence of CIN was somewhat higher than expected given the relatively preserved renal function of the study population and a 15% prevalence of diabetes. Thus the AKI after angioplasty in these hemodynamically unstable patients may in fact have been the result of ischemic causes instead of CIN. Furthermore, mortality rates in the three groups were not reported for those with and without CIN, although the lower mortality in NAC-treated patients did parallel a reduction in CIN. Given these observations, any direct palliative effect on mortality from a lower rate of CIN in this study is difficult to evaluate.

In contrast to these studies, Miner *et al.* performed a randomized trial of high-dose NAC *versus* placebo in 180 patients undergoing PCI or coronary angiography with a high likelihood of PCI (16). CIN occurred in 9.6% of NAC-treated patients and 22.2% of patients assigned to placebo ($P = 0.04$). Despite a reduction in CIN in the NAC-treated population, the in-hospital composite adverse events of death, MI, or urgent dialysis was similar in the two groups: NAC, 7.4%; placebo, 3.5% (P = ns). There were only two deaths, both in

the placebo group and both unrelated to AKI (P = ns). A telephone survey for long-term adverse clinical end points evaluated 171 patients 9.5 ± 2.7 mo after PCI. The primary composite end point of death, MI, need for dialysis, or repeat hospitalization for cardiac causes occurred in 24.2% of NAC-treated patients and 21.2% of placebo-treated patients (P = ns). The authors noted that in patients developing CIN, there was no increase in adverse clinical outcomes on long-term follow-up. The failure to demonstrate an increase in short-term or long-term morbidity or mortality in NAC in this study could mean that none exists (patients with shock or hemodynamic instability were excluded), or such failure could be related to small numbers of patients studied and subsequent adverse effect as well as to missing follow-up data.

Aspelin *et al.* compared the nephrotoxicity of the isoosmolar, nonionic CM iodixanol with that of the low-osmolar, nonionic CM iohexol in a randomized, double-blind, prospective, multicenter study that enrolled 129 patients with diabetes and a SCr of 1.3 to 3.5 mg/dl (17). The incidence of CIN was 26% for the iohexol group and 3% for the iodixanol group (P = 0.002). There were six cases of AKI (all in the iohexol patients) that were clinically significant enough to be classified as a serious adverse event. Two deaths occurred in these six patients. These numbers of events are too small to arrive at any conclusions about CIN and mortality.

Summary and Conclusions

The available literature has consistently shown that patients who develop CIN have a greater risk for dying, both during the short-term period of hospitalization and for up to a year or more after the contrast-enhanced procedure. The data demonstrating a temporal association between CIN and death, however, do not prove a causal relationship. A critical question is whether a reduction in CIN occurrence will result in a reduction in morbidity and mortality. Most of the patients in these observational studies have underlying risk factors that, in addition to increasing the patient's risk of CIN, can directly increase mortality. Putative mechanisms for how CIN, especially when patients are nonoliguric and do not require hemodialysis, is able to cause death or other serious complications have not been elucidated. Furthermore, given the hemodynamic instability and comorbidities of the patients in these observational studies, it is likely that AKI in many instances was incorrectly classified as solely caused by contrast when other pathogenetic mechanisms such as ischemia were also present, and this contributes to an overstatement of mortality rates associated with pure CIN. These data argue for cautious interpretation of observational studies with respect to the reported magnitude of the relationship between CIN and death.

Prospective randomized clinical trials that evaluate the effect of an intervention on CIN occurrence and capture downstream morbidity and mortality provide another useful tool to explore for potential causal relationships between CIN and downstream events. The value of these trials is that baseline comorbidities that may impact morbidity and mortality should be equally distributed between treatment and control groups as a result of randomization. For these trials to provide valid data on CIN and mortality, it is necessary that the intervention itself have no direct or indirect effect on morbidity and mortality. This is difficult to achieve and is very unlikely to be the case in the few intervention trials (hemofiltration, NAC) in which mortality data has been captured. Trials that compare nephrotoxicity and mortality in patients receiving different types of CM may get around this obstacle but have not answered the critical question because either mortality rates have been too low or mortality data were not reported.

Published data to date indicate that, at the very least, CIN is a marker for increased mortality. As such, patients with CIN should be carefully monitored during their hospital stay and after discharge. More carefully designed studies are needed to fully elucidate the relationship between CIN and mortality. Additional randomized comparisons between intervention and control groups with mortality end points are needed in which the interventions, *per se*, are unlikely to directly affect the risk of death (*e.g.*, bicarbonate). In these studies, non-CM causes of AKI need to be excluded. Even if mortality is not a prespecified end point of these studies, mortality data (at least while hospitalized) should be reported by all prospective randomized trials. Although many may cling to the view that relatively healthy patients with asymptomatic transient increases in SCr are not at risk for mortality from CIN, this view may lead to a failure to study such patients with minimal comorbidities and hence impede a better understanding of the relationship between mortality and CIN. Some interventions in certain high-risk groups may reduce mortality even if the mechanism is not by direct prevention of CIN. In these cases it may not be critical to define the exact role of CIN in the mortality. In the absence of clear data disproving a causal relationship between CIN and death, efforts devoted to reducing incidence of CIN remain a valuable clinical and a research goal.

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