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Renal Function-Based Contrast Dosing to Define Safe Limits of Radiographic Contrast Media in Patients Undergoing Percutaneous Coronary Interventions

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Objectives The aim of this study was to evaluate the association between calculated creatinine clearance (CCC)-based contrast dose and renal complications in patients undergoing percutaneous coronary interventions (PCI).

Background Excess volumes of contrast media are associated with renal complications in patients undergoing cardiac procedures. Because contrast media are excreted by the kidney, we hypothesized that a dose estimation on the basis of CCC would provide a simple strategy to define a safe dose of contrast media.

Methods We assessed the association between CCC-based contrast dose and the risk of contrast-induced nephropathy (CIN) and need for in-hospital dialysis in 58,957 patients undergoing PCI and enrolled in the BMC2 (Blue Cross Blue Shield of Michigan Cardiovascular Consortium) registry from 2007 to 2008. Patients receiving dialysis at the time of the procedure were excluded.

Results The risk of CIN and nephropathy requiring dialysis (NRD) was directly associated with increasing contrast volume adjusted for renal function. The risk for CIN and NRD approached significance when the ratio of contrast dose/CCC exceeded 2 (adjusted odds ratio [OR] for CIN: 1.16, 95% confidence interval [CI]: 0.98 to 1.37, adjusted OR for NRD: 1.72, 95% CI: 0.9 to 3.27) and was dramatically elevated in patients exceeding a contrast to CCC ratio of 3 (adjusted OR for CIN: 1.46, 95% CI: 1.27 to 1.66, adjusted OR for NRD: 1.89, 95% CI: 1.21 to 2.94).

Conclusions Our study supports the need for minimizing contrast dose in patients with renal dysfunction. A contrast dose on the basis of estimated renal function with a planned contrast volume restricted to less than thrice and preferably twice the CCC might be valuable in reducing the risk of CIN and NRD. (J Am Coll Cardiol 2011;58:907–14)

Contrast-induced nephropathy (CIN) is a common, serious problem of percutaneous coronary intervention (PCI) that is associated with increased morbidity, mortality, and health care cost (1–4). Conditions that heighten the risk of CIN such as chronic kidney disease, diabetes, congestive heart failure, hemodynamic instability, and anemia are not typically modifiable at the time of cardiac catheterization, but other strategies have emerged to minimize the nephrotoxicity of contrast media (4,5).

Proven effective preventative measures against CIN in PCI patients include hydration with normal saline and minimization of contrast volume (CV) (6,7). The benefit of *N*-acetylcysteine or isotonic sodium bicarbonate remains controversial, with considerable disagreement between various studies and meta-analysis (8–11).

Although the need to minimize contrast is generally recognized, it remains unclear as to what is a safe level of contrast. Prior studies support use of maximal acceptable contrast dose (MACD) to determine the threshold for safe contrast exposure customized to each patient (12). The MACD is calculated by 5 ml of contrast·body weight (kg)/baseline serum creatinine (mg/dl). Although MACD

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Abbreviations and Acronyms

CCC = calculated creatinine clearance
CI = confidence interval
CIN = contrast-induced nephropathy
CV = contrast volume
GFR = glomerular filtration rate
MACD = maximal acceptable contrast dose
MDRD = Modification of Diet in Renal Disease
NRD = nephropathy requiring dialysis
OR = odds ratio
PCI = percutaneous coronary intervention

has been validated by many groups (13,14), it is infrequently used in clinical practice. Furthermore, a significant number of cases of CIN occur even when MACD is not exceeded. Contrast media are excreted via kidneys, and one possible alternative method for contrast dosing would be to calculate CV on the basis of renal function (15).

The purpose of this investigation is: 1) to assess whether contrast dose on the basis of calculated creatinine clearance (CCC) is better than MACD at predicting CIN and need for dialysis; and 2) to define the safe dose of contrast media on the basis of CCC.

Methods

The study cohort for our analysis included patients undergoing PCI in a large regional registry of contemporary PCI in 31 hospitals in Michigan. The details of the registry and of the data collection process have been described previously (16–18). Briefly, procedural data on all patients undergoing elective and nonelective PCI at the participating hospitals are collected with standardized data collection forms. Baseline data include clinical, demographic, procedural, and angiographic characteristics as well as medications used before, during, and after the procedure and in-hospital outcomes. All data elements have been prospectively defined, and the protocol was approved by the local institutional review board at each institution. The data were collected by a dedicated staff member and forwarded to the coordinating center. Medical records of all patients undergoing multiple procedures or coronary artery bypass grafting or of patients who died in the hospital were reviewed to ensure data accuracy. A further 2% of cases were randomly selected for audit.

The study population for this analysis included 58,957 patients who underwent PCI from 2007 to 2008. We excluded patients with a prior history of renal failure requiring dialysis and patients with missing baseline or post-procedural creatinine measurement. All procedures were performed with standard coronary intervention technique. The choice of contrast media was at the discretion of the operating physician within the dictates of the individual hospital policy.

The primary endpoints for this analysis were CIN and nephropathy requiring dialysis (NRD). CIN was defined as impairment in renal function resulting in $\geq$0.5 mg/dl absolute increase in serum creatinine from baseline. Peak creatinine was defined as the highest value of creatinine in the week after the procedure and was ascertained as per local clinical practice. A follow-up creatinine was collected at least 1 day after the procedure but varied, depending on length of stay. NRD was defined as new need for hemodialysis in patients due to worsening of renal function after PCI. The CCC was calculated with the Cockcroft-Gault equation (19). We also assessed the utility of using contrast dose on the basis of glomerular filtration rate (GFR) as estimated by the Modification of Diet in Renal Disease (MDRD) equation (20). Because Cockcroft-Gault equation has been conventionally used for renal dosing of medications, these results are preferentially reported (21).

Continuous variables are expressed as mean $\pm$ SD, and discrete variables are expressed as frequency counts and percentages. The differences in discrete variables between groups were evaluated by the chi-square test and Fisher's exact test. Continuous variables were analyzed with the *t* test and Wilcoxon rank-sum test as needed. We estimated area under the receiver-operator characteristic curve (a plot of sensitivity vs. 1-specificity) for comparing MACD and CV/CCC and CV/MDRD GFR for CIN and NRD and compared them with bootstrapping (22,23). We then plotted the occurrence of CIN and NRD by deciles of CV/CCC. On the basis of the results of this analysis and to develop a clinically easy-to-use tool, we divided the cohort into patients on the basis of CV/CCC of $<$2, 2 to 2.9, and $\geq$3. Rates of CIN were calculated for these categories in the entire cohort, patients undergoing primary PCI for ST-segment elevated myocardial infarction or non–ST-segment elevated myocardial infarction (excluding shock), patients with cardiogenic shock, patients undergoing PCI for stable disease, and patients categorized by baseline CCC. Patients with stable disease were defined as patients who did not have a myocardial infarction within 7 days; were not in cardiogenic shock; and had not had a recent cardiac arrest or had not needed intravenous nitroglycerine, intravenous unfractionated heparin, low molecular weight heparin, or platelet glycoprotein IIb/IIIa inhibitors before the procedure. Finally, we calculated the odds of CIN and NRD at CV/CCC ratio of 2, 2.5, and 3 in unadjusted and fully adjusted hierarchical models. All analysis was performed with SAS software (version 9.2, SAS, Cary, North Carolina).

Results

A total of 58,957 patients underwent PCI during the study period. Patients with end-stage renal disease requiring dialysis and patients with CV/CCC $\geq$10 were excluded from the analysis, and therefore the total cohort comprised 54,526 patients. A total of 9,097 patients were excluded from the CIN calculation, because the post-procedural creatinine was not drawn. Patients who were excluded were, in general, less sick, less likely to present with acute coronary syndromes, and had less-advanced coronary artery disease, compared with the study cohort (Online Table 1). Overall CIN occurred in 1,470 patients, whereas NRD developed in 142 patients.

The mean contrast dose was 205 ml, whereas the median contrast dose was 200 ml (interquartile range: 100 ml) and ranged from 5 to 900 ml. The baseline characteristics of patients who developed CIN compared with those who did not develop CIN are listed in Table 1. Patients who developed CIN were typically older, female, and less likely to be current smokers. The CIN patients were more likely to have hypertension, prior myocardial infarct, diabetes, chronic heart failure, extra-cardiac vascular diseases, significant valve diseases, history of gastrointestinal bleeding, atrial fibrillation, and chronic obstructive airways disease. The CIN patients were more likely to have worse renal function at baseline, anemia, and a lower ejection fraction. They were more likely to be undergoing PCI as an emergency and to have more extensive coronary artery disease and to be undergoing PCI for cardiogenic shock. Patients who developed NRD were more likely to have a higher preponderance of these comorbidities and worse cardiovascular profile (Table 1).

A comparison of area under the receiver-operator characteristic curve demonstrated that CV/CCC was a better predictor of CIN compared with MACD ($c = 0.667$ vs. $c = 0.632$, $p < 0.05$), as well as NRD ($c = 0.729$ vs. $c = 0.583$, $p < 0.05$). The CV/CCC was similar to CV/MDRD GFR with respect to predicting CIN ($c = 0.667$ vs. $c = 0.661$, $p > 0.05$) and NRD ($c = 0.72$ vs. $c = 0.77$, $p > 0.05$).

Table 1 Baseline Characteristics of Patients Who Developed CIN or NRD

Risk Factor	CIN (n = 1,470)	No CIN (n = 43,959)	p Value	NRD (n = 142)	No NRD (n = 54,384)	p Value
Demographic						
Age (60–69 yrs)	25.6	28.6	0.01	33.1	28.7	0.25
Age (70–79 yrs)	29.1	22.8	<0.0001	28.9	23.2	0.11
Age (80+ yrs)	25.0	12.0	<0.0001	16.9	11.9	0.07
Female	45.3	33.7	<0.0001	40.9	34.0	0.09
Current smoking	21.8	27.7	<0.0001	23.2	27.4	0.26
Lean (BMI <25 kg/m^2)	20.0	18.5	0.13	19.0	18.2	0.79
Overweight (BMI 25–29.9 kg/m^2)	32.2	35.5	0.009	28.9	35.3	0.11
Obese (BMI ≥30 kg/m^2)	48.0	46.1	0.16	52.1	46.6	0.18
Historical						
Hypertension	89.1	83.4	<0.0001	84.5	83.8	0.05
Prior MI	39.8	34.4	<0.0001	44.4	34.9	0.005
Diabetes	55.2	34.9	<0.0001	63.4	35.2	<0.0001
Congestive heart failure	38.3	15.2	<0.0001	45.1	15.2	<0.0001
Extracardiac vascular disease	43.6	25.7	<0.0001	45.1	25.8	<0.0001
Significant valve disease	10.7	3.8	<0.0001	14.8	3.7	<0.0001
Gastrointestinal bleeding	4.4	1.6	<0.0001	4.9	1.5	0.0009
Atrial fibrillation	22.8	10.1	<0.0001	25.4	10.0	<0.0001
Cardiac arrest	1.4	1.3	0.65	0.7	1.3	0.54
Prior PCI	40.1	44.3	0.001	34.5	45.5	0.009
Prior CABG	21.2	19.4	0.09	23.2	19.6	0.27
COPD	31.5	19.2	<0.0001	30.3	19.5	0.001
Laboratory						
Baseline creatinine ≥1.5 mg/dl	33.3	9.7	<0.0001	62.0	9.6	<0.0001
Anemia	55.7	27.2	<0.0001	65.5	26.7	<0.0001
Ejection fraction <50%	61.7	31.0	<0.0001	73.2	30.3	<0.0001
Procedural						
Emergency PCI	36.7	15.4	<0.0001	52.1	14.0	<0.0001
MI (prior 7 days)	62.6	32.3	<0.0001	73.9	30.1	<0.0001
Acute MI (<24 h)	38.3	19.5	<0.0001	51.4	17.9	<0.0001
Recent cardiac arrest	6.3	1.3	<0.0001	11.3	7.3	<0.0001
Cardiogenic shock	14.1	1.3	<0.0001	28.2	1.5	<0.0001
Ventricular tachycardia/fibrillation	5.9	1.2	<0.0001	10.6	1.2	<0.0001
Exceeding MACD	15.0	4.5	<0.0001	21.1	4.5	<0.0001
Left main stenosis >70%	7.6	3.6	<0.0001	11.3	3.6	<0.0001
Restenotic lesion	9.7	10.3	0.40	8.5	10.3	0.48
Visible thrombus	24.6	12.4	<0.0001	35.2	11.5	<0.0001
Calcification	16.6	12.2	<0.0001	12.7	12.7	0.98
Chronic total occlusion	1.6	2.1	0.69	3.5	2.1	0.25

Values are %. Baseline characteristics of patients who developed contrast-induced nephropathy (CIN) or nephropathy requiring dialysis (NRD). Patients with a prior history of renal disease requiring dialysis are excluded.

BMI = body mass index; CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; MACD = maximal acceptable contrast dose; MI = myocardial infarction; PCI = percutaneous coronary intervention.

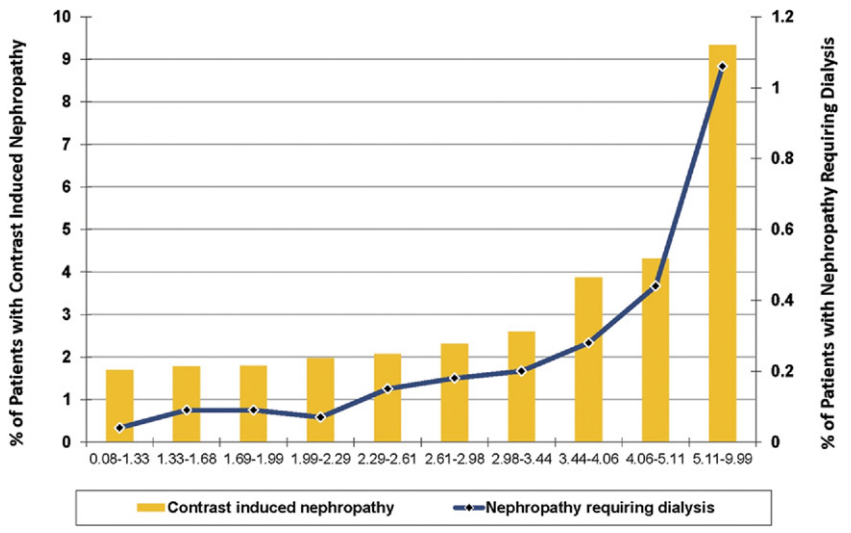

Figure 1 The Incidence of Contrast-Induced Nephropathy and Nephropathy Requiring Dialysis by Deciles of CV/CCC

The **numbers under the solid bars** reflect the contrast volume/calculated creatinine clearance (CV/CCC) in each decile.

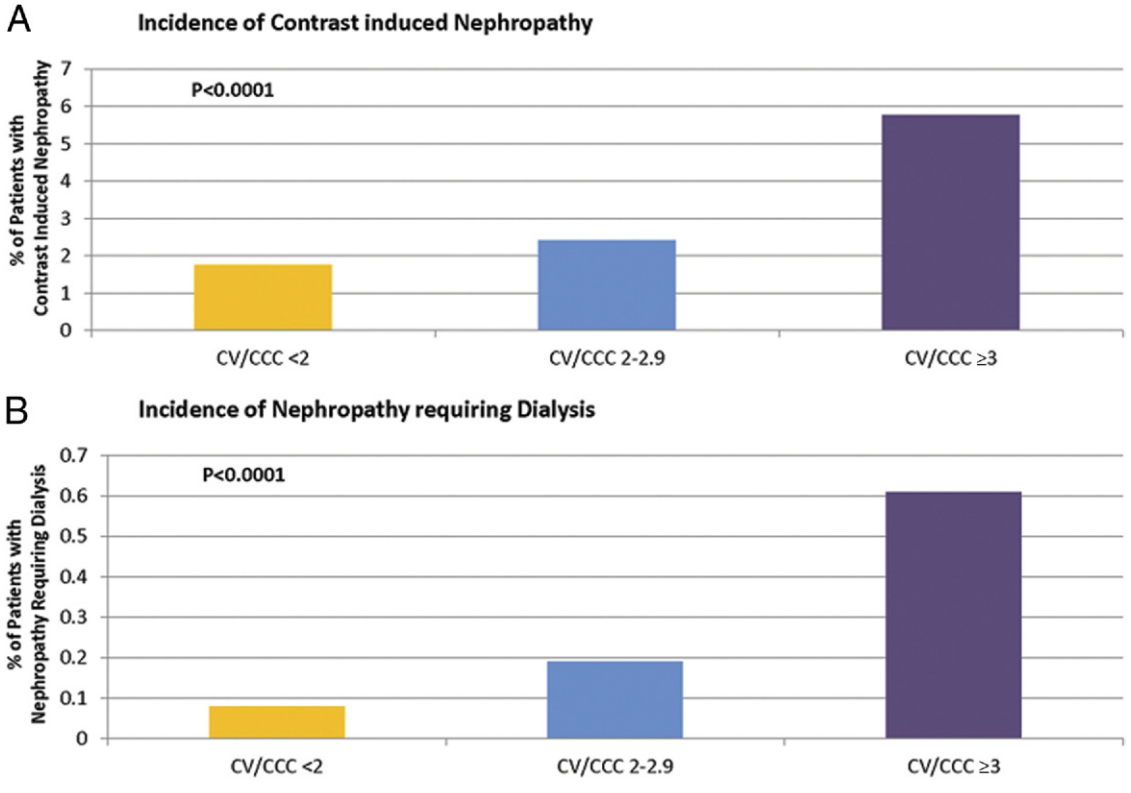

Figure 2 Incidence of CIN and NRD

Incidence of contrast-induced nephropathy (CIN) **(A)** and nephropathy requiring dialysis (NRD) **(B)** by categories of contrast volume/calculated creatinine clearance (CV/CCC) of <2, 2 to 2.9, and ≥3 in the entire study population.

The incidence of CIN and need for dialysis in patients who underwent PCI was directly but nonlinearly associated with increasing CV adjusted for renal function (Fig. 1). When the cohort was divided into deciles of CV/CCC, a low risk of CIN was evident even among patients exposed to very low volume of contrast/CCC. The risk for CIN and need for dialysis increased when the ratio of contrast dose/CCC exceeded 2 and was dramatically elevated in patients with a contrast/CCC ratio of ≥3 (Figs. 2A and 2B).

When the risk for CIN and NRD was assessed in the subsets of patients presenting with shock, those undergoing primary PCI for ST-segment elevated myocardial infarction and those undergoing elective PCI, similar relationship was observed—although the absolute incidence of CIN was lower in more stable patients (Fig. 3).

When the patients were categorized by baseline GFR (≤30, 30 to 59, 60 to 89, or ≥90 ml/min), the incidence of CIN and NRD increased with worsening GFR (Fig. 4). Within each sub-cohort defined by baseline GFR, the incidence of CIN and NRD was the highest in patients with CV/CCC ratio ≥3. No significant interaction was observed between the categories of CV/CCC and the categories of GFR.

After adjusting for baseline clinical and other procedural variables and for clustering, the CV/CCC ratio remained an independent predictor of CIN and NRD with worsening odds of CIN and NRD with rising CV/CCC (Fig. 5). The risk for CIN and NRD approached significance when the ratio of contrast dose/CCC exceeded 2 (adjusted odds ratio [OR] for CIN: 1.16, 95% confidence interval [CI]: 0.98 to 1.37, $p = 0.08$; adjusted OR for NRD: 1.72, 95% CI: 0.9 to 3.27, $p = 0.10$) and was dramatically elevated in patients exceeding a contrast/CCC ratio of 3 (adjusted OR for CIN: 1.46, 95% CI: 1.27 to 1.66, $p < 0.0001$; adjusted OR for NRD: 1.89, 95% CI: 1.21 to 2.94, $p = 0.005$).

When the same analysis was repeated with MDRD equation-derived GFR, the results were similar (Online Figs. 1 and 2).

Discussion

The key finding of our study is that the CV/CCC ratio is a simple tool that can help guide contrast dosing in patients undergoing PCI. The CV/CCC ratio was superior to MACD in discriminating between patients most likely to develop CIN, and a CV/CCC ratio of under 2 is associated with a low

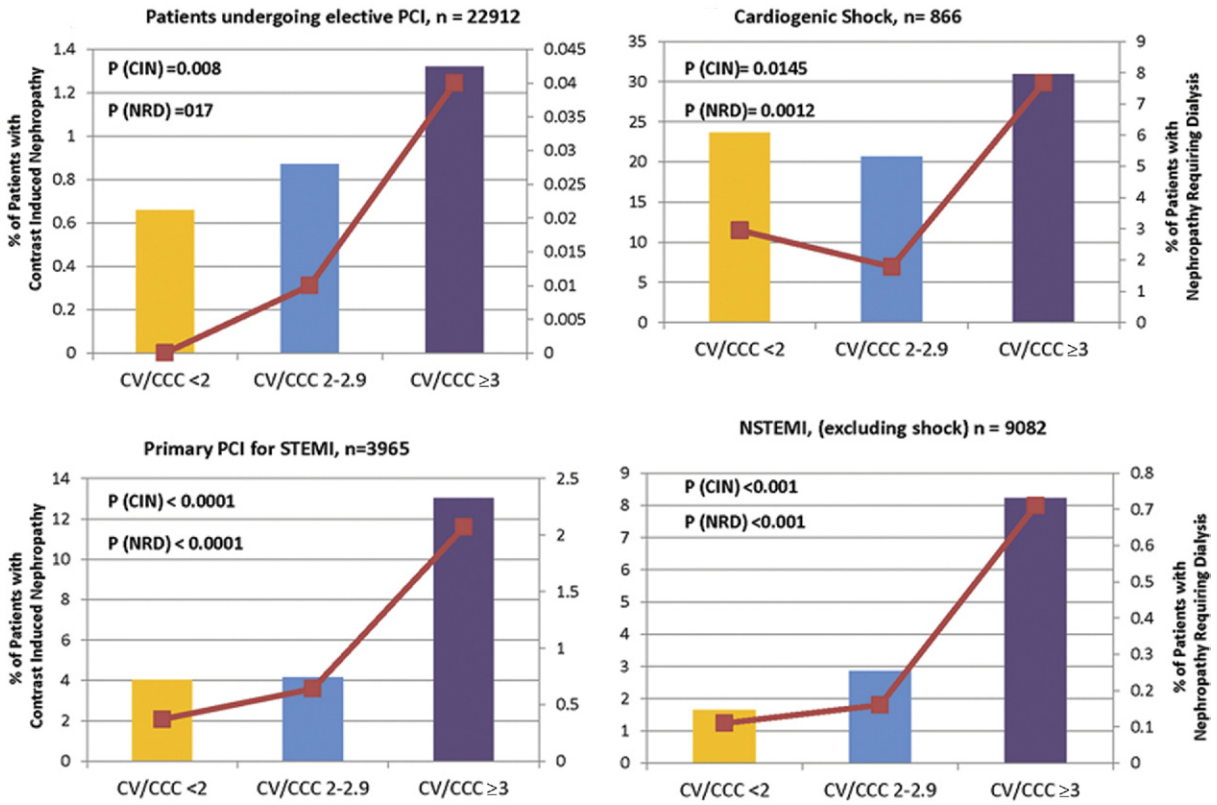

Figure 3 Incidence of CIN and NRD by Categories of CV/CCC in Various Subgroups

The Y axis scale is different in each category and reflects the difference in baseline risk among different subgroups. GFR = glomerular filtration rate; NSTEMI = non–ST-segment elevated myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevated myocardial infarction; other abbreviations as in Figure 2.

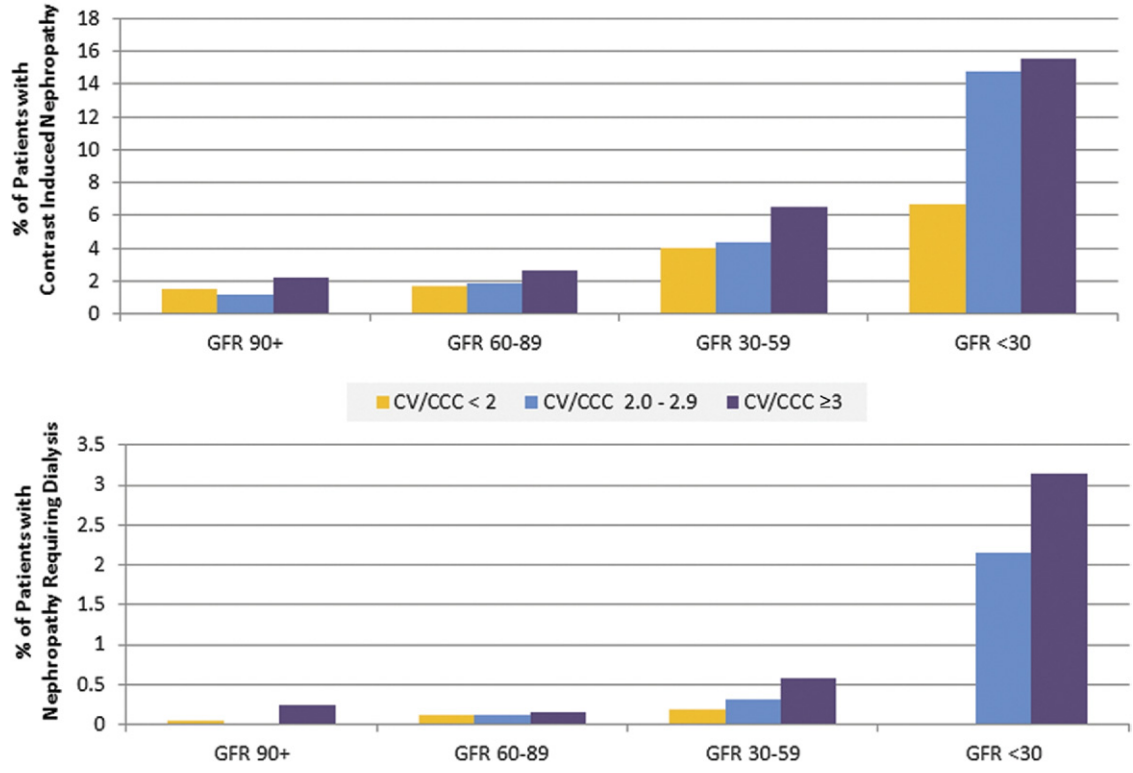

Figure 4 **Incidence of CIN and NRD by Categories of CV/CCC Across Different Categories of Baseline GFR**

The baseline glomerular filtration rate (GFR) is a key determinant of risk of CIN and NRD with higher risk in patients with low baseline GFR. Abbreviations as in Figure 2.

incidence of CIN, whereas the risk of CIN and NRD is markedly increased when the ratio exceeds 3. Our findings corroborate and significantly extend prior work in the field. Because creatinine clearance is routinely calculated for patients undergoing invasive cardiac procedures, use of CV/CCC ratio can be easily incorporated into clinical practice and has the possible implication of impacting patient outcome.

The morbidity and health care cost associated with CIN has been highlighted in many studies (4,24–26). Methods to reduce CIN aside from saline hydration and avoidance of high osmolar contrast media remain controversial, despite extensive clinical investigation. There are conflicting data on use of iso-osmolar contrast media, *N*-acetylcysteine, ascorbic acid, fenoldopam, sodium bicarbonate infusion, atrial natriuretic peptide infusion, and prophylactic hemodialysis (25,27,28).

Multiple moderate-sized studies have implicated CV as a key risk factor for CIN in patients undergoing PCI and have supported the use of a threshold of 5× body weight/serum creatinine as the safe upper limit for contrast (13,14). However, contrast-induced injury has been anecdotally demonstrated at lower doses of contrast, and the need for better dosing strategy has been recognized for a long time. Laskey et al. (15) were the first to propose the use of CV/creatinine clearance ratio and suggested that volume/creatinine clearance >3.7 had the most optimal sensitivity and specificity for defining CIN. Our study, however, focused on defining a dose range where patient safety could be optimized further, because even Laskey et al. (15) recognized that a small but significant number of patients will develop CIN when the CV/CCC ratio is <3.7. Our data suggest that efforts to reduce contrast nephrotoxicity need to focus on efforts to implement a policy of as low as reasonably possible for contrast media.

Use of CV/CCC ratio follows from basic pharmacological principles, and our data demonstrate a consistent relationship between CV/CCC ratio and the risk of CIN and NRD in multiple subgroups. Furthermore, the inherent simplicity of calculating CV/CCC ratio makes this an easy construct to implement in routine clinical practice.

Measures to reduce CV have been described by many authors in the past and have been a major quality effort for the BMC2 (Blue Cross Blue Shield of Michigan Cardiovascular Consortium) registry (17). Recently, Nayak et al. (29) reported an ultra-low contrast technique that further extends this principal to prevent CIN. Their technique employs routine biplane angiography, use of adjunctive imaging such as intravascular ultrasound guidance, "dry" fluoroscopic imaging, and careful minimization of the contrast administered/injection. They report completion of diagnostic and therapeutic coronary procedure with extremely low volume of contrast media, and wider adoption of their methodology needs to be explored.

Dose of contrast media is but one of the factors that influences the risk of CIN in this patient population. Baseline

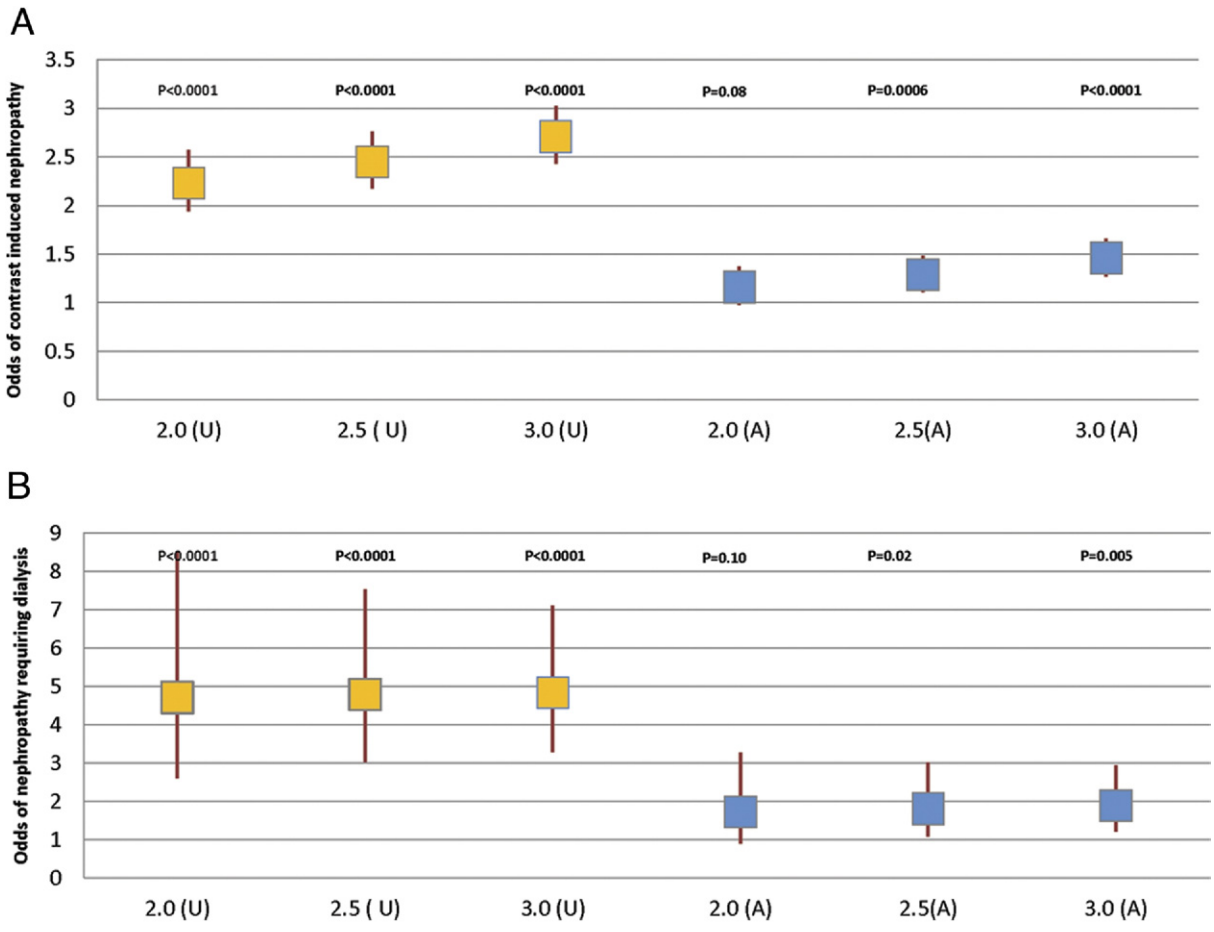

Figure 5 **Unadjusted and Adjusted Odds of CIN and NRD When CV/CCC Exceeds Given Threshold**

The unadjusted (U) **(yellow)** and adjusted (A) **(blue)** odds of CIN **(A)** and NRD **(B)** when the CV/CCC exceeds a given threshold. The adjusted risk of renal complications approaches significance when CV/CCC >2 and is strongly predictive when the ratio >3. Abbreviations as in Figure 2.

comorbidities, hemodynamic instability, use of other nephrotoxic agents, and additional patient specific factors probably interact in a unique fashion to increase the risk of CIN for a given patient. The results of our study suggest that the baseline risk of CIN is further influenced by the volume of contrast media administered and is higher when large volumes of adjusted contrast media are used.

Study limitations. The BMC2-PCI registry is a regional database from the state of Michigan with an active focus on multicentric quality improvement and might or might not be representative of the wider population of patients undergoing PCI. Data were limited to in-hospital information, serum creatinine was not collected in a standardized fashion, and only the highest post-PCI value was recorded. It is likely that a number of patients were discharged before peaking of the serum creatinine, and our study might underestimate the occurrence of CIN. Furthermore, patients who were excluded due to absence of post-PCI serum creatinine ascertainment were, in general, healthier than the study cohort, and this introduces potential selection bias. However, we observed a similar relation in patients who underwent elective PCI and had a low baseline risk of renal complications, and thus our overall findings are likely extant. The total number of patients with NRD was low, despite the overall large cohort, and our study might be underpowered to detect differences in the discriminatory ability of different dosing definitions that were evaluated. The term CIN implies that contrast media are solely responsible for all cases of renal dysfunction occurring in this population, although this is probably incorrect. However, we elected to use this term because there is no widely accepted alternative term. Different contrast media have different iodine concentration, and the total dose of iodine/CCC might be a better strategy for contrast dosing. This measure is not routinely assessed in clinical practice, and these data were not available for this cohort. Our study is observational in nature and cannot ascribe causality.

In our study, over 65% of cases of CIN and 75% of NRD occurred in the little over one-third of the patients whose contrast dose exceeded a CV/CCC ratio of 3. Further research is warranted to assess whether routine incorporation of CV/

CCC ratio in clinical practice and dedicated measures to limit CV/CCC to <3 can translate into a reduction in CIN and NRD.

Conclusions

Our study supports the need for minimizing contrast dose in patients undergoing invasive cardiac procedures. A contrast dose on the basis of CCC with a planned CV restricted to <2× CCC and not to exceed 3× CCC might be valuable in reducing the risk of CIN and NRD.

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Key Words: contrast media ■ percutaneous coronary intervention ■ renal function.

APPENDIX

For supplementary text, table, and figures, please see the online version of this article.