

A Simple Risk Score for Prediction of Contrast-Induced Nephropathy After Percutaneous Coronary Intervention

Development and Initial Validation

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- OBJECTIVES** We sought to develop a simple risk score of contrast-induced nephropathy (CIN) after percutaneous coronary intervention (PCI).
- BACKGROUND** Although several risk factors for CIN have been identified, the cumulative risk rendered by their combination is unknown.
- METHODS** A total of 8,357 patients were randomly assigned to a development and a validation dataset. The baseline clinical and procedural characteristics of the 5,571 patients in the development dataset were considered as candidate univariate predictors of CIN (increase $\geq 25\%$ and/or ≥ 0.5 mg/dl in serum creatinine at 48 h after PCI vs. baseline). Multivariate logistic regression was then used to identify independent predictors of CIN with a p value < 0.0001 . Based on the odds ratio, eight identified variables (hypotension, intra-aortic balloon pump, congestive heart failure, chronic kidney disease, diabetes, age > 75 years, anemia, and volume of contrast) were assigned a weighted integer; the sum of the integers was a total risk score for each patient.
- RESULTS** The overall occurrence of CIN in the development set was 13.1% (range 7.5% to 57.3% for a low [≤ 5] and high [≥ 16] risk score, respectively); the rate of CIN increased exponentially with increasing risk score (Cochran Armitage chi-square, $p < 0.0001$). In the 2,786 patients of the validation dataset, the model demonstrated good discriminative power (c statistic = 0.67); the increasing risk score was again strongly associated with CIN (range 8.4% to 55.9% for a low and high risk score, respectively).
- CONCLUSIONS** The risk of CIN after PCI can be simply assessed using readily available information. This risk score can be used for both clinical and investigational purposes. (J Am Coll Cardiol 2004;44:1393–9) © 2004 by the American College of Cardiology Foundation
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Radiologic procedures utilizing intravascular iodinated contrast media injections are being widely applied for both diagnostic and therapeutic purposes. This has resulted in an increasing incidence of procedure-related contrast-induced nephropathy (CIN) (1–3). Although the risk of renal function impairment associated with radiologic procedures is low in the general population, it may be very high in selected patient subsets, especially in cardiac procedures. Reported rates from different centers may vary significantly (4–8).

Many individual risk factors for the development of CIN have been reported (1–8). Although the combination of two or more risk factors is rather common in daily practice, the cumulative risk of several variables on renal function is unknown. This dictates the need for global assessment of the impact of these variables on the development of CIN.

The aim of the present study was to develop a simple risk score that could be readily applied by clinicians to evaluate individual patient risk to develop CIN after percutaneous coronary intervention (PCI).

METHODS

Consecutive patients with documented serum creatinine before the procedure and at 48 h after the procedure who underwent PCI over a period of six years were identified from our prospective interventional cardiology data base. Patients with pre-existing end-stage renal disease requiring dialysis and other contrast exposure within one week or less from the index procedure, patients treated with PCI after acute myocardial infarction, and patients in shock were excluded from the analysis.

Patients underwent PCI according to current guidelines after written, informed consent was obtained. Routine hydration was performed with 1 ml/kg/h of half-normal saline for 4 to 12 h before PCI and 18 to 24 h after PCI. All patients received 325 mg/day aspirin at least 24 h before the

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Abbreviations and Acronyms

CIN	= contrast-induced nephropathy
eGFR	= estimated glomerular filtration rate
IABP	= intra-aortic balloon pump
OR	= odds ratio
PCI	= percutaneous coronary intervention

procedure and continued indefinitely. Patients were also treated with an additional antiplatelet agent: either ticlopidine 250 mg twice daily or clopidogrel 75 mg/day for four weeks.

Clinical definitions and follow-up. “Contrast-induced nephropathy” was defined as an increase of $\geq 25\%$ or ≥ 0.5 mg/dl in pre-PCI serum creatinine at 48 h after PCI. “Anemia” was defined using World Health Organization criteria: baseline hematocrit value $< 39\%$ for men and $< 36\%$ for women (9). “Chronic kidney disease” was baseline serum creatinine of > 1.5 mg/dl or an estimated glomerular filtration rate (eGFR) of < 60 ml/min/1.73 m² (Levey modified MDRD formula) (10,11). “Hypotension” was systolic blood pressure < 80 mm Hg for at least 1 h requiring inotropic support with medications or intra-aortic balloon pump (IABP) within 24 h periprocedurally. Serum creatinine was measured before the procedure and at 48 h after the procedure.

A dedicated data coordinating center performed all data management and analyses. Prespecified clinical and laboratory demographic information was obtained from hospital charts that were reviewed by independent research personnel who were unaware of the objectives of the study; accumulated data were then entered prospectively in the data base. These methods for data extraction have been published previously (12,13).

Risk score development. Eligible patients from the entire data base were randomized in a 2:1 manner to create a development and validation dataset, respectively. The risk score development dataset was initially used for identifying univariate associations between baseline clinical and key procedural characteristics and CIN. Multivariate logistic regression analysis was then performed to identify independent predictors of CIN and to estimate odds ratios (ORs). Risk factors that were significant in the univariate analysis were available for selection in the final model; a bootstrap method was used to select the best subset of risk factors to avoid overfitting the data. A total of 200 bootstrap samples were selected from the development dataset. For each sample, a stepwise selection procedure was used to choose independent predictors of CIN. Variables that were selected in at least 90% of the bootstrap models were included in the final multivariate models.

Two separate regression models were created: the first accounted for baseline serum creatinine value (model A) and the second accounted for eGFR (model B). The eight variables in each of the final models with $p < 0.0001$ were assigned a weighted integer coefficient value. For this

purpose, the estimated ORs from the logistic model were used, giving an integer of 2 to each 0.5 value of OR; the integer of 1 was given for each 100-ml increment in contrast media administered during the procedure; and the integer of 2, 4, or 6 was assigned for baseline eGFR 40 to 60, 20 to 40, and < 20 ml/min/1.73 m², respectively. The final risk score represented the sum of integer coefficients.

The risk score was tested in the validation dataset. Model discrimination was assessed by the goodness-of-fit Hosmer-Lemeshow statistic, and its predictive performance was assessed with the c -statistic.

Finally, the prognostic significance of risk score on rates of in-hospital dialysis and one-year mortality was estimated.

RESULTS

Patients. Of the 8,443 patients with serum creatinine measured at baseline and 48 h after the procedure, 86 patients were excluded due to exclusion criteria. A total of 5,571 patients were assigned to the development dataset. Baseline clinical and angiographic characteristics, as well as the main procedural data of these patients, are listed in Table 1. Overall, the mean age was 63.6 years old, and there were 28.8% females. The median baseline serum creatinine value was 1.0 mg/dl (interquartile range 0.9 to 1.2). Chronic kidney disease diagnosed by baseline creatinine > 1.5 mg/dl was present in 585 patients (10.5%), whereas 1,473 patients (26.4%) met the National Kidney Foundation cutoff for moderate impairment of eGFR < 60 ml/min/1.73 m².

An IABP was applied in a total of 7.1% of patients: electively (in the setting other than hypotension/congestive heart failure) in 3.5% and emergently in 3.6% of patients. Saphenous vein graft lesions were treated in 15.8% of patients and 4% in conjunction with treatment of a native vessel as well.

Univariate variables associated with CIN are shown in Table 2. A total of 16 variables were significantly associated with the development of CIN. The significant correlates included demographics (age > 75 years and female gender), risk factors for coronary artery disease (hypertension, hyperlipidemia, and diabetes), several co-morbidities (peripheral vascular disease, previous stroke, chronic kidney disease, advanced congestive heart failure [New York Heart Association functional class III/IV], and anemia), acute coronary syndrome at presentation, and several angiographic and/or procedural characteristics (multivessel disease, hypotension, IABP use, contrast media type, and contrast amount > 150 ml).

Multivariate analyses. The multivariate model of predictors of CIN was obtained by using data for all 4,898 patients with no missing co-variate values and included 646 (88.6%) of 729 patients who developed CIN. Hypotension, elective use of IABP, advanced congestive heart failure, impaired renal function, age > 75 years, anemia, diabetes, and increasing contrast media volume were identified as independent predictors of CIN. Given the possible impact of repeat contrast exposure on the development of CIN, a repeat

Table 1. Clinical and Angiographic Data at Baseline and Procedural Characteristics (Development Dataset)

Variable	Patients (n = 5,571)
Age (yrs)	63.8 ± 11.2
Age >75 yrs	17.1%
African American	6.2%
Male	71.2%
Diabetes mellitus	30.7%
Hypertension	62.1%
Hypercholesterolemia	69.8%
Smoking history	57.7%
Congestive heart failure	6.0%
Body surface area (m ²)	1.95 ± 0.22
Hypotension	8.3%
Acute coronary syndrome	35.7%
Previous myocardial infarction	53.4%
Previous CABG	39.9%
Peripheral vascular disease	18.0%
Previous angioplasty	49.4%
Baseline hematocrit (%)	40.7 ± 4.9
Anemia	25.8%
Baseline serum creatinine (mg/dl)	1.12 ± 0.52
<1.5	89.5%
1.5-2.0	8.2%
>2.0	2.3%
Baseline eGFR (ml/min 1.73 m ²)	72.7 ± 21.1
>60	73.6%
40-60	20.5%
20-40	5.3%
<20	0.7%
Multivessel disease	26.9%
Multivessel PCI	26.9%
Treated saphenous vein graft	15.8%
Intra-aortic balloon pump*	7.1%
Intra-aortic balloon pump†	3.5%
Contrast amount (ml)	260.9 ± 122
Contrast >150 ml	80.4%

*In all patients. †In the setting other than hypotension and/or congestive heart failure. Data are presented as the mean value ± SD or percentage of subjects.

CABG = coronary artery bypass grafting surgery; eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention.

procedure performed within two weeks from the index procedure was forced into the multivariate model as a binary variable and was not found to predict independently CIN (OR 1.28, 95% confidence interval 0.70 to 2.33).

Importantly, the same predictors of CIN were identified by multivariate models, whether baseline plasma creatinine (model A) or eGFR (model B) were used for the definition of chronic kidney disease (Table 3). The power of the statistical association between identified risk factors and CIN assessed by OR was also quite close between the two models.

Development of risk score. Contrast-induced nephropathy occurred in 729 patients, or 13.1% of the development set. The incidence of CIN by risk score assignment is depicted in Figure 1, with significant trends across increasing score values for prediction of CIN (Cochran Armitage chi-square, $p < 0.0001$). Whether the model used serum creatinine or eGFR to define risk attributed to chronic

kidney disease, the c -statistic was very close (0.69 and 0.70, respectively). The Hosmer-Lemeshow statistic was chi-square = 8.05 ($p = 0.43$) for the score with creatinine and chi-square = 8.13 ($p = 0.42$) for the score with eGFR, indicating that a logistic model was appropriate in both analyses.

Based on the obtained frequencies of CIN in relation to different risk score, 4,898 patients were further categorized into four groups: relatively low risk ($n = 2,898$ [59.2%]), moderate risk ($n = 1,555$ [31.7%]), high risk ($n = 389$ [7.9%]), and very high risk ($n = 56$ [1.1%]), corresponding to risk scores of ≤ 5 , 6 to 10, 11 to 15, and ≥ 16 , respectively.

Validation of risk score. Contrast-induced nephropathy occurred in 386 (13.9%) of 2,786 patients of the validation set. The rates of CIN in the validation set were close to those in the development set inside each of the four risk groups (Fig. 2). The developed CIN model demonstrated good discriminative power in the validation population (c -statistic = 0.67).

Risk score and outcome after PCI. The ability of the risk score to predict the rates of post-PCI dialysis and one-year mortality was further evaluated separately in the development and validation sets. Significant increases in rates of dialysis (Fig. 3) and one-year mortality (Fig. 4) were observed with increments of risk score (Cochran-Armitage trend test, $p < 0.0001$) in both sets.

DISCUSSION

Development of CIN after percutaneous endovascular procedures has been associated with several baseline patient characteristics and procedural variables, and confers unfavorable prognosis. The risk of CIN and its detrimental consequences have been shown to be present in both patients with and without chronic kidney disease and to increase in diabetic patients (1-8). However, other reported risk factors for CIN have not been examined as additive to the above, and practical, readily applicable methods to assess the CIN risk in patients undergoing PCI have not been specifically developed.

In the present study, we proposed a CIN risk stratification score based on 8 readily available variables, and we showed that an increasing score number confers exponentially increased CIN risk. The variables included in the CIN risk score are: 1) patient-related characteristics (i.e., age >75 years, diabetes mellitus, chronic congestive heart failure, or admission with acute pulmonary edema, hypotension, anemia, and chronic kidney disease); and 2) procedure-related characteristics (i.e., the use of elective IABP or increasing volumes of contrast media). The main results of this study are also summarized schematically in Figure 5.

This proposed simple risk score for CIN allows for immediate identification of the variables accounted for before the procedure and appropriate (and timely) risk allocation. This is particularly important because treatment

Table 2. Association of Baseline Clinical, Angiographic, and Procedural Characteristics and CIN After Percutaneous Coronary Intervention (Development Dataset, Univariate Analysis)

Variable	Patients (%)	Incidence of CIN (%)	OR	95% CI	p Value
Chronic kidney disease	8.1	30.0	2.89	2.32-3.59	<0.0001
Congestive heart failure*	6.0	38.5	2.68	2.09-3.44	<0.0001
Hypotension	8.3	26.4	2.36	1.89-2.95	<0.0001
Intra-aortic balloon pump use	3.5	24.9	2.05	1.47-2.87	<0.0001
Anemia	25.8	21.4	2.02	1.72-2.36	<0.0001
Age >75 yrs	17.1	21.8	1.90	1.59-2.27	<0.0001
Diabetes mellitus	30.7	19.2	1.73	1.48-2.02	<0.0001
Peripheral vascular disease	18.0	19.6	1.61	1.35-1.93	<0.0001
Female gender	28.8	18.3	1.54	1.31-1.80	<0.0001
Hypertension	62.1	15.9	1.45	1.24-1.71	<0.0001
Prior stroke	11.0	18.0	1.37	1.10-1.71	0.0007
Contrast type (Ioxaglate)	49.9	15.9	1.29	1.09-1.52	0.0006
Multivessel disease	26.5	16.7	1.20	1.03-1.40	0.003
Acute coronary syndrome	35.7	15.8	1.20	1.03-1.40	0.02
Hypercholesterolemia	69.8	13.2	0.75	0.64-0.88	0.0004
Contrast amount	80.4	14.6	1.24	1.01-1.54	0.045

*New York Heart Association functional classification III/IV and/or history of pulmonary edema.
 CI = confidence interval; CIN = contrast-induced nephropathy; OR = odds ratio.

of CIN is rather limited, and the development of this complication is associated with a prolonged hospital stay and unfavorable in-hospital and one-year outcomes (1-8). Once CIN is established, only supportive care is currently provided until renal function resolves; infrequently, hemodialysis may be required, either transiently or even permanently. Although a recent single-center report indicated that peri-PCI hemofiltration starting before PCI and extending for 24 h after the PCI may decrease the incidence of CIN in high-risk patients, this approach has not been yet widely adopted in clinical practice (14). Therefore, presently, the main method to tackle this complication is its

prevention. We believe that adequate risk assessment before PCI offers a greater opportunity to do so, especially because the factors included in the risk score described are readily available.

The methodologic inclusion of two procedural variables with baseline characteristics in the CIN risk score warrants specific mention. Elective IABP insertion may be linked with CIN through various mechanisms: 1) as a marker of significant hemodynamic disturbances during PCI; 2) as a marker of very severe atherosclerotic disease without hypotension; 3) as a source of atheroemboli to the renal circulation during insertion, pulsation, or re-

Table 3. Multivariate Predictors of CIN After Percutaneous Coronary Intervention (Development Dataset)

Variable	Integer Score	Model Coefficient	OR	95% CI	p Value
Model A*					
Hypotension	5	0.9310	2.537	1.973-3.262	<0.0001
Intra-aortic balloon pump use	5	0.8910	2.438	1.677-3.544	<0.0001
Congestive heart failure†	5	0.8111	2.250	1.682-3.011	<0.0001
Serum creatinine >1.5 mg/dl	4	0.7194	2.053	1.586-2.658	<0.0001
Age >75 yrs	4	0.6133	1.847	1.509-2.260	<0.0001
Anemia	3	0.4705	1.601	1.328-1.930	<0.0001
Diabetes mellitus	3	0.4109	1.508	1.260-1.806	<0.0001
Contrast volume	1 for 100 ml	0.2549	1.290	1.210-1.375	<0.0001
Model B†					
Congestive heart failure‡	5	0.9923	2.698	2.019-3.603	<0.0001
Hypotension	5	0.9845	2.676	2.082-3.441	<0.0001
Intra-aortic balloon pump use	5	0.9350	2.547	1.751-3.706	<0.0001
Age >75 yrs	4	0.7861	2.195	1.780-2.706	<0.0001
Anemia	3	0.6028	1.827	1.518-2.199	<0.0001
Diabetes mellitus	3	0.4681	1.597	1.335-1.910	<0.0001
Contrast volume	1 for 100 ml	0.2434	1.276	1.197-1.360	<0.0001
Estimated glomerular filtration rate (ml/min 1.73 m ²)	2 for 40 to 60, 4 for 20 to 40, 6 for <20	0.1772	1.194	1.099-1.297	<0.0001

*Using serum creatinine as a criterion for renal function. †Using estimated glomerular filtration rate as a criterion for renal function. ‡New York Heart Association functional classification III/IV and/or history of pulmonary edema.
 Abbreviations as in Table 2.

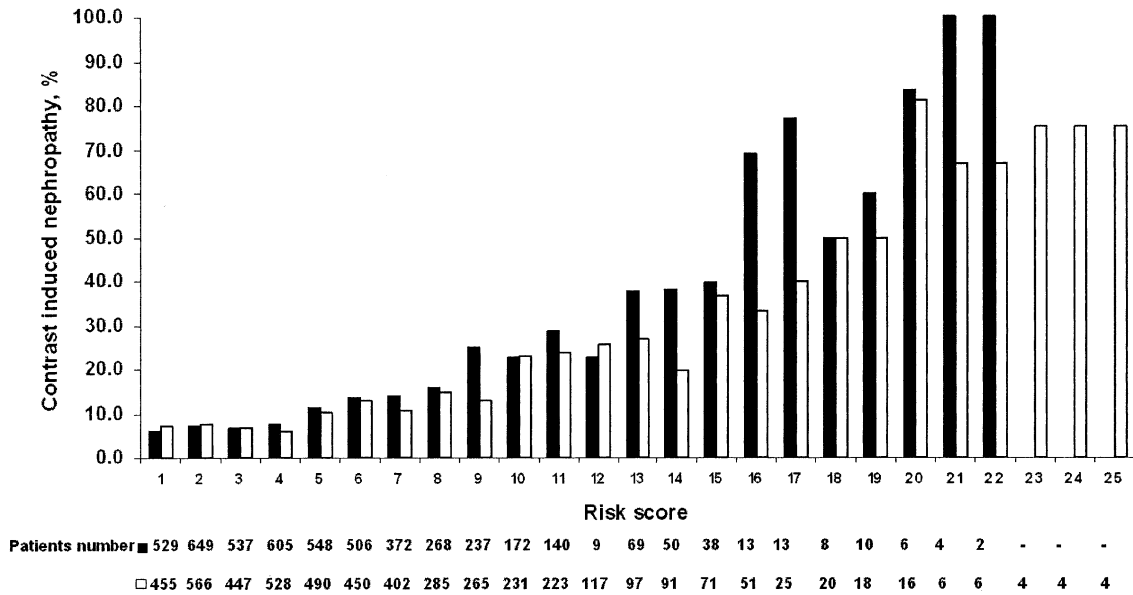


Figure 1. Risk score development dataset. Increasing risk of contrast-induced nephropathy with increasing risk score is evident with inclusion of either baseline serum creatinine value or estimated glomerular filtration rate in the multivariate model. **Solid bars** = serum creatinine-based model; **open bars** = estimated glomerular filtration rate-based model.

moval; 4) as a partial occlusion of the renal blood flow if it is positioned too low (i.e., in the abdominal instead of the descending thoracic aorta); and 5) as a marker of increased vascular complications and post-PCI hypotension. We have shown in another report that both peri-PCI hypotension and use of IABP without hypotension are powerful predictors of CIN (15); inclusion of elective IABP use for any reason in the risk score estimation essentially addresses both of these factors.

Contrast media volume has been linked to CIN after PCI in several studies, but without a firm description of the nature of the association. We previously reported that the ratio of contrast volume over body surface area may be of particular importance (15). In this analysis, both the volume and the ratio could have been used in the CIN risk score with essentially interchangeable results. We opted for inclusion of the total volume because it is more easily applicable and allows for practically easier risk score calcu-

lation. Given not only the absence of therapeutic measures for CIN but also the very small number of preventive measures that have been proven effective in randomized trials (4), it is important to understand that avoidance of IABP and use of lower volume of contrast media, when possible, may afford a sufficient reduction in the patient's CIN risk with a potentially rewarding outcome. This intriguing observation should be further explored prospectively.

Finally, use of the CIN risk score described offers a great investigational tool in future studies regarding CIN prevention. It is possible that certain measures may be very effective in the prevention of CIN only in certain risk score-based patient subsets. For example, debate already exists on whether *N*-acetyl-L-cysteine is effective in high-risk patients (large contrast volume, complex angioplasty procedures), whereas data are more supportive of its utility in patients at relatively low risk of CIN (low contrast volume,

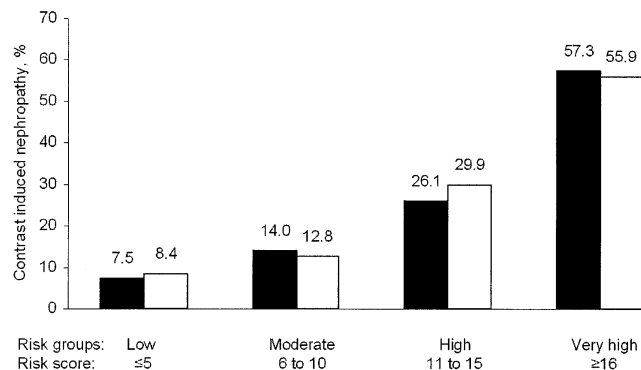


Figure 2. The contrast-induced nephropathy risk score derived from the development dataset predicted this complication in the validation set, as well. **Solid bars** = development dataset; **open bars** = validation dataset.

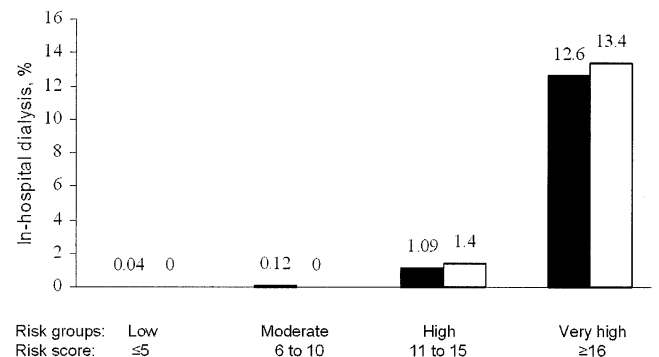


Figure 3. In-hospital hemodialysis can be predicted by a high or very high risk score value similarly in the development and validation datasets. **Solid bars** = development dataset; **open bars** = validation dataset.

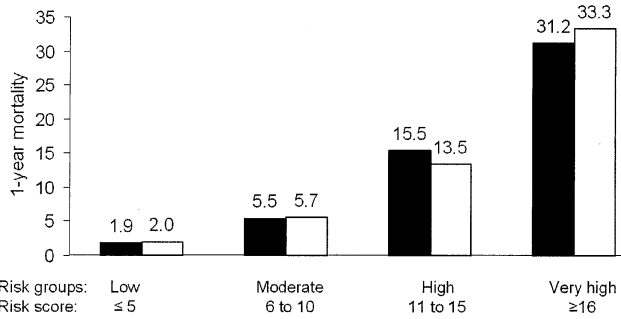


Figure 4. The prognostic significance of the proposed risk score for contrast-induced nephropathy extended to prediction of one-year mortality, as indicated by the results obtained from both the development and validation datasets. **Solid bars** = development dataset; **open bars** = validation dataset.

diagnostic procedures) (4,16–18). On one hand, it would be detrimental to entirely dismiss a preventive measure because it may not prevent CIN in high-risk subsets, but it would also be inappropriate to apply universally a preventive measure to all patients receiving contrast media if it is only effective in a certain subgroup. Use of the CIN risk score may help clarify such controversial issues and potentially lead to patient subset-oriented recommendations.

Study limitations. Although the data were collected prospectively by independent monitors and entered into a dedicated database, this was a post hoc analysis. Due to

limited availability of data fields, we could not consider periprocedural hydration volume, proteinuria, urine output, and nephrotoxic medications for inclusion in the risk score parameters. We did not use creatinine clearance value based on 24-h urine collection during a true baseline clinical condition, and our eGFR calculation is subject to limitations due to the formula used and the possibility that patients may not be at their true baseline condition before PCI because of dehydration or cardiac illness; however, we believe that the assessment of CIN risk based on the utilized cutoffs of serum creatinine and eGFR is fairly accurate for the clinical purposes of this study and certainly more practical and readily available than direct measurement of creatinine clearance. Although the rise in serum creatinine occurs within the first 24 h after exposure to contrast media in 80% of the patients, the absence of data on serum creatinine later than 48 h after PCI in the present study might result in the slight underestimation of CIN (19). However, it is doubtful that a delayed creatinine elevation in patients without a significant rise within 48 h after PCI may be at all clinically significant (20). Finally, prospective validation of the proposed CIN risk score is warranted in other data bases that may provide such ability.

Conclusions. Individual patient risk for CIN after PCI can be globally assessed with the calculation of a simple risk score based on readily available information. This CIN risk

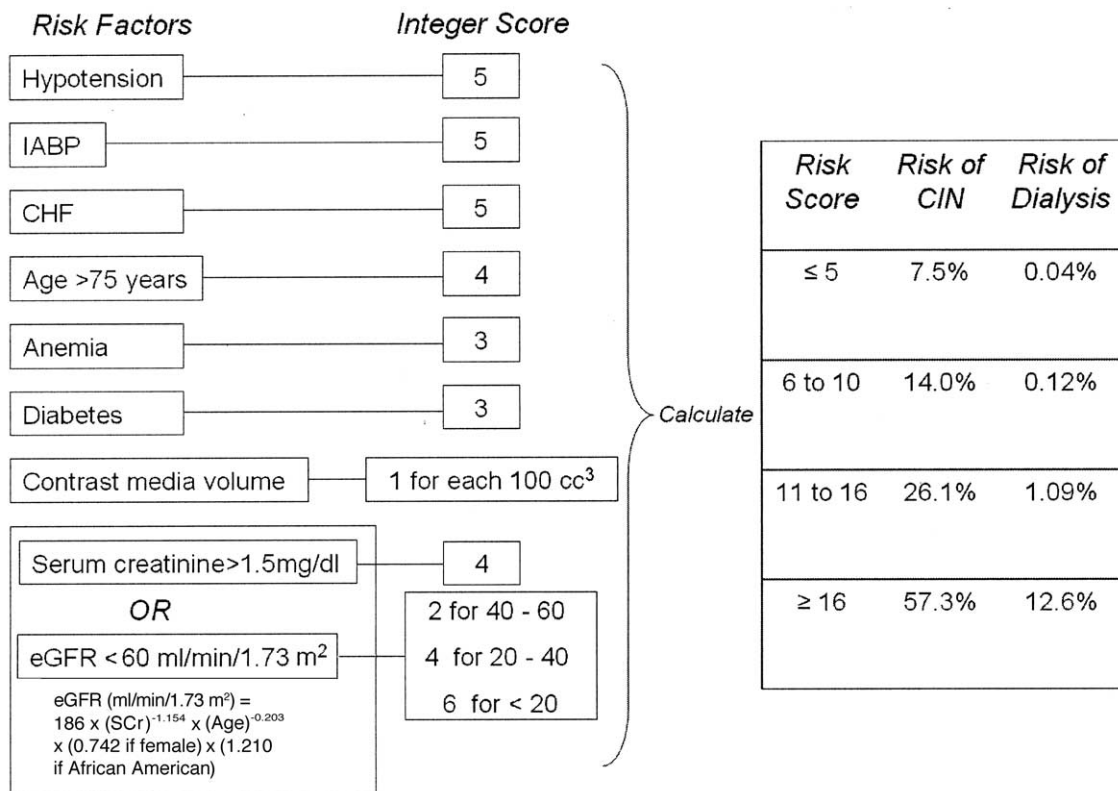


Figure 5. Scheme to define contrast-induced nephropathy (CIN) risk score. Anemia = baseline hematocrit value <39% for men and <36% for women; CHF = congestive heart failure class III/IV by New York Heart Association classification and/or history of pulmonary edema; eGFR = estimated glomerular filtration rate; hypotension = systolic blood pressure <80 mm Hg for at least 1 h requiring inotropic support with medications or intra-aortic balloon pump (IABP) within 24 h periprocedurally.

score can be used for both clinical and investigational purposes.

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