Critical Review Form

Clinical Prediction or Decision Rule

A Simple Risk Score for Prediction of Contrast-Induced Nephropathy After Percutaneous Coronary Intervention, *J Am Coll Card* 2004; 44: 1393-1399

Objective: **"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)." (p. 1393)**

Methods: **Consecutive elective PCI patients with documented serum creatinine before and 48 hours after PCI were identified from an interventional cardiology data base collected prospectively over a six year period. Exclusion criteria included dialysis-dependent renal disease, other contrast exposure within one week, PCI for acute myocardial infarction, and patients in shock.**

All patients were pre-treated with 1mg/kg/hour half-normal saline for 4- to 24-hours before the PCI and 18-24 hours after the PCI. All patients also received anti-platelet therapy before the PCI. For derivation of the risk score the database was randomized in 2:1 manner into derivation and validation sets. Univariate analysis identified significant associations between hypothesized risk factors and CIN. Multivariate logistic regression analysis including variables significant on univariate analysis was performed to yield independent predictors of CIN with odds ratios. Bootstrapping with 200 samples was used to avoid overfitting the model and variables selected in 90% of the models were included in the final multivariate models. Integers were assigned from the odds ratio with 2 for each 0.5unit odds ratio and 1 for each 100 mL increment of contrast material.

Two regression models were created. One used baseline serum creatinine, while the other used eGFR to define renal function. The risk scores created were tested in the validation set and model discrimination was assessed by the Hosmer-Lemeshow goodness-of-fit statistic and predictive performance assessed by the c-statistic. The investigators also assessed the prognostic accuracy of their model for in-hospital dialysis and one-year mortality.

Definitions:

CIN – a 48-hour post-contrast increase in the pre-PCI serum creatinine by ≥ 25% or ≥ 0.05 mg/dl;
Anemia – Hematocrit <39% in men or < 36% in women;

<u>Chronic Kidney Disease</u> – a baseline serum creatinine > 1.5 mg/dl or eGFR < 60 ml/min/1.73 m^2;

<u>Hypotension</u> - systolic blood pressure < 80 mm/Hg for at least one hour requiring inotropes or a balloon pump.

Guide		Comments
I.	**Is this a newly derived instrument (level IV)?**	
A.	Was validation restricted to the retrospective use of statistical techniques on the original database? (If so, this is a Level IV rule & is not ready for clinical application).	No, independent randomly selected subset of same PCI population – so Level III CDR.
II.	**Has the instrument been validated? (Level II or III). If so, consider the following:**	
1a	Were all important predictors included in the derivation process?	No. "Due to the 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." (p. 1398) Other potential risk factors to consider would include solitary kidney patients or prior CIN. In general, when deriving a clinical decision rule the initial set of predictor variables should be explicitly defined and all-inclusive (see Stiell 1999).
1b	Were all important predictors present in significant proportion of the study population?	Yes. Table 1 (p. 1395) demonstrates prevalence of risk factors ranging from 3% to 71%.

1c	Does the rule make clinical sense?	Yes. Each of the risk factors has face validity as a contributory agent for CIN.
2	Did validation include prospective studies on several different populations from that used to derive it (II) or was it restricted to a single population (III)?	Restricted to a single registry of PCI patients so Level III CDR and results may not apply to other populations. For example, this was predominately male (71%) and non-African American (93.8%).
3	How well did the validation study meet the following criteria?	
3a	Did the patients represent a wide spectrum of severity of disease?	Uncertain. Investigators do not report the severity of CIN or the proportion of patients requiring post-PCI dialysis. Pragmatists might argue that if none of the patients suffer permanent kidney damage, what difference does it make?
3b	Was there a blinded assessment of the gold standard?	Yes. The gold standard was the change between pre- and 48 hour post- PCI creatinine. "Pre-specified 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." (p. 1394)
3c	Was there an explicit and accurate interpretation of the predictor variables & the actual rule without knowledge of the outcome?	Probably. The definitions above are clear, but the authors did not assess the raters' ability to differentiate individual risk factor accuracy or reliability.
3d	Did the results of the assessment of the variables or of the rule influence the decision to perform the gold standard?	No – all patients had a 48-hour creatinine (the gold standard) as part of the inclusion criteria.
4	How powerful is the rule (in terms of sensitivity & specificity; likelihood ratios; proportions with alternative outcomes; or relative risks or absolute outcome rates)?	• 8443 patients are in the database but 86 were excluded (numerical breakdown of reasons for exclusion were not included) leaving 5571 in the derivation set 2786 in the validation set. • CIN occurred in 729/5571 (13.1%) of the derivation set and 13.9% of the validation set. • 16 variables were associated with CIN on univariate analysis and the same 8 variables were

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.

independently associated with CIN on both multivariate models (using different definitions for renal function).

Risk Factor	Score
Hypotension	5
Intra-aortic balloon pump	5
CHF (NYHA Class III or IV)	5
Age > 75 years	4
Anemia	3
Diabetes	3
Contrast Volume	1 for every 100 ml
Serum creatinine < 1.5 mg/dl*	4
eGFR <60 ml/min/1.73 m^2*	2 for 40-60 4 for 20-40 6 for <20

Interpretation Risk Factor	Risk of CIN	Risk of dialysis	% of patients
≤5	7.5%	0.04%	59.2%
6-10	14%	0.12%	31.7%
11-16	26%	1.09%	7.9%
≥16	57.3%	12.6%	1.1%

- The above rule should use either the serum creatinine or the eGFR not both.
- The logistic regression model had good fit (not over fitted) using Hosmer-Lemeshow (p = 0.43 for model A, 0.42 for model B).
- C-statistic = 0.67 for the validation set.

III.	**Has an impact analysis demonstrated change in clinical behavior or patient outcomes as a result of using the instrument? (Level I). If so, consider the following:**	
1	How well did the study guard against bias in terms of differences at the start (concealed randomization, adjustment in analysis) or as the study proceeded (blinding, co-intervention, loss to follow-up)?	There have been no impact factor analyses performed for this instrument. Therefore, we are not sure if clinicians would (a) use the instrument; (b) accurately and reliably interpret the instrument's clinical implications; or (c) modify their clinical behavior in response to the instrument's results.

2	What was the impact on clinician behavior and patient-important outcomes?	No physician behavior was tested or observed. There are several procedural changes that could be tested based upon this rule. 1. "peri-PCI hemofiltration starting before PCI and extending for 24 hours after the PCI may decrease the incidence of CIN in high-risk patients." (p. 1396) 2. "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, 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." (p. 1397)

Limitations

1) **Use of logistic regression rather than recursive partitioning. The former will build a model that simultaneously maximizes sensitivity and specificity. For ED risk stratification, we generally prefer to maximize sensitivity at the expense of specificity so recursive partitioning is often preferred.**

2) **Reporting c-statistic (think ROC AUC) rather than sensitivity/specificity so no way to apply to individual patients using Bayesian logic.**

3) **No confidence intervals are reported.**

4) **Single data source, the source of which (single hospital?) is unclear so not ready for prime-time application. The CDR needs prospective validation on a distinct patient population.**

5) **Exclusion of important risk factors so not following CDR methods.**

6) **These were non-urgent cardiac cases so the results have limited external validity for ED.**

Bottom Line

Simple numeric score from variables unavailable at the bedside can identify subset of patients at risk for CIN and dialysis. Future research is needed to validate this score in distinct populations while reporting sensitivity/specificity for the overall rule and individual provider's accuracy and reliability prospectively applying the rule in the care of patients who may be exposed to PCI CIN. The association of these risk factors with non-PCI CT-based CIN should also be assessed.