

# Diabetic patients with normal baseline renal function are at increased risk of developing contrast-induced nephropathy post-percutaneous coronary intervention

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## ABSTRACT

**Introduction:** We hypothesised that diabetic patients with normal baseline renal impairment who do not receive prophylaxis before percutaneous coronary intervention (PCI) are at an increased risk of developing contrast-induced nephropathy (CIN).

**Methods:** We conducted a cohort study involving 839 patients who underwent PCI between 2004 and 2006, and divided them into three groups: Group A (304 diabetics with normal baseline serum creatinine [Cr] of less than 1.5 mg/dL); Group B (465 non-diabetics with normal Cr); Group C (70 patients with impaired baseline renal function with Cr more than or equal to 1.5 mg/dL). CIN prophylaxis, including oral N-acetylcysteine and saline hydration, were administered only to Group C patients.

**Results:** The median age for Groups A, B and C was 58, 56 and 64 years, respectively. The prevalence of hypertension in Groups A, B and C was 76.3, 56 and 85.7 percent, respectively. Baseline demographics were comparable among the three groups with regard to gender, left ventricular systolic function and contrast volume use. Incidences of CIN in Groups A, B and C were 8.9 percent, 4.3 percent and 4.5 percent, respectively (p-value is 0.042). The incidence of CIN in diabetic patients with a normal baseline Cr who did not receive prophylaxis (Group A) was significantly higher than in the other two groups (p-value is less than 0.001).

**Conclusion:** Our findings suggest that diabetic patients, despite having a normal baseline Cr, are at an increased risk of developing CIN post-PCI. Routine prophylaxis in this cohort may be beneficial.

**Keywords:** contrast-induced nephropathy, diabetes mellitus, percutaneous coronary intervention, renal function

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## INTRODUCTION

Percutaneous coronary intervention (PCI) utilises a significant amount of contrast media that causes an increased incidence of contrast-induced nephropathy (CIN).<sup>(1,2)</sup> CIN is commonly defined as a 25% or 0.5 mg/dL rise from the baseline creatinine (Cr) within 48 hours post-PCI or contrast procedures.<sup>(3,4)</sup> CIN is an adverse event that results in increased morbidity including the need for renal dialysis and mortality.<sup>(5)</sup> The most widely recognised risk predictor of CIN is baseline renal impairment. In clinical practice, renal impairment is commonly defined as serum Cr  $\geq$  1.5 mg/dL or glomerular filtration rate, GFR  $\leq$  60 ml/min/1.73m<sup>2</sup>.<sup>(6)</sup>

Several reports of CIN prophylactic therapies have been published.<sup>(7)</sup> These include pre-saline hydration,<sup>(8)</sup> high-dose oral N-acetylcysteine (NAC),<sup>(9)</sup> the use of an iso-osmolar contrast agent<sup>(10)</sup> and prophylactic haemofiltration.<sup>(11)</sup> In our centre, patients with baseline Cr  $\geq$  1.5 mg/dL receive routine oral NAC and saline pre-hydration prior to PCI. Patients with normal baseline Cr do not receive prophylaxis. Many diabetic patients have subclinical nephropathy despite a normal baseline Cr and hence may be predisposed to a higher risk of developing CIN.<sup>(12)</sup> We aimed to examine the risk and incidence of CIN in diabetic patients with a normal baseline Cr and who did not receive prophylaxis undergoing PCI, and compared them to non-diabetics and patients with baseline renal impairment. We also examined the adverse events associated with the development of CIN.

## METHODS

We conducted a cohort study involving all consecutive patients who underwent PCI in our institution from July 2004 to April 2006. Patients with documented serum Cr taken within two weeks prior to and 48 hours after PCI were

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identified from our cardiac database. We excluded patients who had end-stage renal disease and required dialysis, patients who had recent contrast exposure before PCI, patients who underwent primary PCI or were in cardiogenic shock. A total of 1,158 patients were screened and 839 patients were enrolled into the final analysis.

Patients underwent PCI according to the current guidelines.<sup>(13)</sup> Patients with baseline renal impairment ( $\text{Cr} \geq 1.5 \text{ mg/dL}$ ) received CIN prophylaxis. Intravenous hydration was administered at a rate of 1 ml/kg/hour of normal saline for 6–12 hours prior to, and 12–24 hours after, PCI unless contraindicated due to fluid overload or pulmonary congestion. Patients received oral NAC 1.2 g bid from the day before PCI till the day after. Patients received 300 mg aspirin loading before PCI and were continued at 100 mg om. All patients received low osmolality non-ionic contrast iohexol (Omnipaque®) during PCI. The administration of oral metformin was stopped before PCI and for at least two days after PCI. Serum Cr was measured within two weeks before PCI, one day post-PCI and daily thereafter if deemed necessary to monitor renal function by the cardiologist.

CIN in our study was defined as an increase of  $\geq 25\%$  or  $\geq 0.5 \text{ mg/dL}$  from the baseline serum Cr within 48 hours after PCI.<sup>(2,3)</sup> Baseline renal impairment was defined as serum creatinine  $> 1.5 \text{ mg/dL}$  or an estimated glomerular filtration rate ( $\text{GFR}$ )  $< 60 \text{ ml/min/1.73m}^2$  (Levey modified MDRD [modification of diet in renal disease] formula).<sup>(14,15)</sup> Procedural data was entered by the interventional cardiologists performing the PCI. The patient's medical records and clinical follow-up details were entered into the computer database in a prospective manner by research coordinators. Patients were followed up for six months via clinic appointments. Mortality and recurrent hospitalisation information post-PCI were obtained by the research coordinators and recorded in the database.

Demographical data was expressed as mean  $\pm$  standard deviation or median and range. Differences between continuous variables were determined using ANOVA when normality and homogeneity assumptions were satisfied. Otherwise, the equivalent non-parametric Mann-Whitney U or Kruskal-Wallis test was used. Associations between categorical variables were assessed using chi-square or Fisher's exact tests. The potential CIN predictors tested included age, gender, ethnic group, presence of diabetes mellitus, hypertension, smoking, hyperlipidaemia, myocardial infarction, abnormal left ventricular ejection fraction (LVEF) and large contrast volume use. Logistic regression analysis was used to test the significance of important CIN predictors. Statistical analysis was performed using the Statistical Package for Social Sciences version 16.0 (SPSS Inc, Chicago, IL, USA). Statistical significance was defined as a two-tailed p-value  $< 0.05$ .

**Table I. Three groups of patients undergoing percutaneous coronary intervention.**

Group (no. of patients)	Group characteristics
A (304)	Diabetics with normal renal function.
B (465)	Non-diabetics with normal renal function.
C (70)	Impaired baseline renal function $\text{Cr} \geq 1.5 \text{ mg/dL}$ . 45 (64%) patients who had diabetes mellitus.

## RESULTS

The 839 patients included in the final analysis were divided into three groups (Table I). Groups A (diabetic) and B (non-diabetic) patients had a normal baseline Cr and did not receive CIN prophylaxis. Group C patients had impaired baseline renal function ( $\text{Cr} \geq 1.5 \text{ mg/dL}$ ) and received prophylaxis. Group C included 64% diabetics and 36% non-diabetics. Baseline clinical and angiographic characteristics, as well as the selected procedural details, are listed in Table II. Group C renal impaired patients were older and more likely to have hypertension and depressed LVEF. The demographical differences were expected, as renal impaired patients were likely to have more comorbidities. Baseline demographics were otherwise comparable among the three groups. A comparable amount of contrast was used in the three groups.

The baseline serum Cr levels and GFR values in the three groups are shown in Table III. The baseline renal function was moderately impaired in Group C. The incidence of CIN in the three groups is: Group A 8.9%, Group B 4.3% and Group C 4.5% ( $p = 0.042$ ). The incidence of CIN in Group C patients who had baseline renal impairment treated with CIN prophylaxis was comparable to that in Group B (low-risk patients without diabetes mellitus and renal impairment) (4.5% vs. 4.3%,  $p = 0.789$ ). Logistic regression models adjusted for age, hypertension, hyperlipidaemia, smoking status, LVEF and contrast volume, confirmed a significant difference in CIN incidence among the three groups. Diabetic patients with a normal serum Cr who did not receive prophylaxis (Group A) had significantly higher risks of developing CIN compared with non-diabetics with normal renal function (Group B) ( $p = 0.031$ , odds ratio 2.036, 95% confidence interval 1.069–3.878).

The incidence of CIN developing in the three groups was further analysed by using  $\text{GFR} \leq 60 \text{ ml/min/1.73m}^2$  for the definition of baseline renal impairment. The result was similar to that when using the Cr value as a definition and confirmed that diabetic patients with normal renal function who did not receive prophylaxis had a higher risk of developing CIN. We compared the clinical outcomes of patients who developed CIN and did not develop CIN (CIN vs. No-CIN) at six months (Figs. 1-3). We examined the

**Table II. Baseline demographics of the three groups of patients.**

Baseline demographics	Group A	Group B	Group C	p-value
Male gender	229 (75.3)	381 (81.9)	59 (84.3)	0.051
Age (years)*	58 (26–86)	56 (25–90)	64 (33–89)	< 0.001
Race				
Chinese	178 (58.6)	328 (70.5)	45 (64.3)	0.001
Indian	65 (21.4)	61 (13.1)	7 (10.0)	
Malay	42 (13.8)	40 (8.6)	13 (18.6)	
Others	19 (6.2)	36 (7.7)	5 (7.1)	
Hypertension	232 (76.3)	260 (56.0)	60 (85.7)	< 0.001
Smoker	130 (42.8)	242 (52.0)	21 (30.0)	0.003
Hyperlipidaemia	232 (76.3)	356 (76.7)	56 (81.2)	0.680
Stroke	11 (3.6)	16 (3.4)	4 (5.7)	0.792
Myocardial infarction	68 (22.4)	103 (22.2)	15 (21.4)	0.985
Left ventricular ejection fraction (%)	49.4 ± 14.7	52.7 ± 13.2	45.9 ± 15.9	0.005
Contrast volume (ml)	223 ± 89	222 ± 86	194 ± 51	0.262
AHA B2/C classification	256 (84.8)	378 (80.9)	59 (85.5)	0.318
Stents used				
1	180 (73.5)	316 (80.4)	42 (70.0)	0.164
2	55 (22.4)	68 (17.3)	16 (26.7)	
≥ 3	10 (4.1)	9 (2.3)	2 (3.3)	
Vessels stented				
1	210 (69.3)	326 (70.7)	46 (65.7)	0.953
2	78 (25.7)	116 (25.2)	18 (25.7)	
3	15 (5.0)	19 (4.1)	6 (8.6)	

Data is expressed either as no. (%) of cases or mean ± standard deviation unless otherwise indicated.

\* data is expressed as mean (range).

**Table III. Baseline serum creatinine and estimated glomerular filtration rate values in the three groups of patients.**

Baseline values	Group A	Group B	Group C	p-value
Creatinine (mg/dL)	0.96 ± 0.23	0.99 ± 0.19	2.49 ± 2.06	< 0.0005
Creatinine (mmol/dL)	84.7 ± 20.0	87.5 ± 16.9	220.4 ± 181.9	< 0.0005
Glomerular filtration rate (ml/min/1.73m <sup>2</sup> )	84.1 ± 55.5	83.4 ± 126.8	34.9 ± 12.8	0.001

Data is expressed as mean ± standard deviation.

Glomerular filtration rates were calculated using the MDRD formula (The MDRD GFR calculator is available at: [www.nephron.com/cgi-bin/MDRD\\_GFR.cgi](http://www.nephron.com/cgi-bin/MDRD_GFR.cgi)).

mortality rate, recurrent hospitalisation rate due to acute coronary syndrome, heart failure, angina, arrhythmias and repeat coronary revascularisation procedures. We analysed the major adverse cardiac event (MACE) rate at six months. MACE was defined as a composite end-point of death, non-fatal myocardial infarction and repeat coronary revascularisation.<sup>(16)</sup>

CIN patients had significantly higher mortality (11.8% vs. 1.5%,  $p = 0.004$ ), MACE (11.1% vs. 4.1%,  $p = 0.046$ ) and recurrent hospitalisation rates (32.4% vs. 13.2%,  $p = 0.005$ ) compared to No-CIN patients. The increased adverse clinical outcome in CIN patients has been shown in several published studies.<sup>(17,18)</sup> We then examined the Group A patients (Table IV). We compared the baseline characteristics of CIN and No-CIN patients in this group. There was no significant difference between the two groups. Multivariate analysis, after accounting for age, gender, hypertension, LVEF and presence of myocardial infarction, showed that the development of CIN was an independent risk factor of mortality at six months.

## DISCUSSION

The development of CIN post-PCI is a well-recognised adverse event that frequently leads to an unfavourable outcome.<sup>(1-3)</sup> The risk of CIN and its detrimental consequences have been associated with mainly baseline renal impairment.<sup>(17,18)</sup> Other risk factors of CIN include old age, the presence of myocardial infarction and diabetes mellitus.<sup>(3,19)</sup> Patients with diabetic nephropathy undergoing PCI have a very high risk of developing CIN and therefore prophylaxis is routinely indicated prior to PCI.<sup>(10,20)</sup> There is no conclusive evidence as to whether the presence of diabetes mellitus with normal renal function should be offered routine CIN prophylaxis. Some authors have suggested that diabetes mellitus alone is an independent risk factor for CIN.<sup>(21,22)</sup> Another study suggested that diabetics with normal renal function does not confer an excessive risk of developing CIN.<sup>(20)</sup> Minimal data exists on the effectiveness of prophylactic treatment in the subgroup of diabetic patients with normal renal function and the associated adverse events.

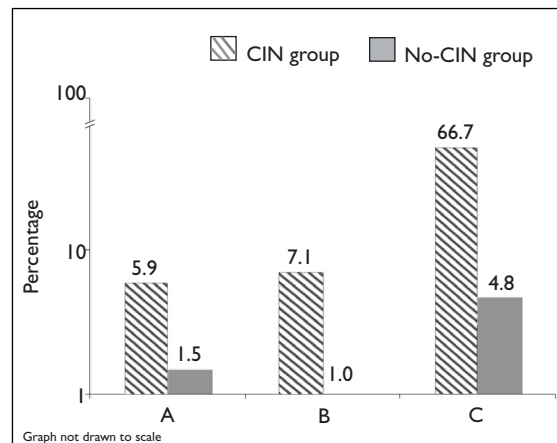
**Table IV. Baseline demographic comparison of Group A patients, CIN (+) versus CIN (-) patients.**

	CIN(+) (%) (n = 24)	CIN(-)(%) (n = 246)	p-value
Gender			
Male	83.3	74.4	0.333
Female	16.7	25.6	
Hypertension	70.8	75.6	0.605
Hyperlipidaemia	91.7	75.6	0.074
Age > 70 years	8.9	9.1	1.000
Mean rank	128.19	136.21	0.631
Smoking			
Current	25.0	22	0.183
Ex-smoker	33.3	19.1	
Insulin	4.2%	2.8	0.716

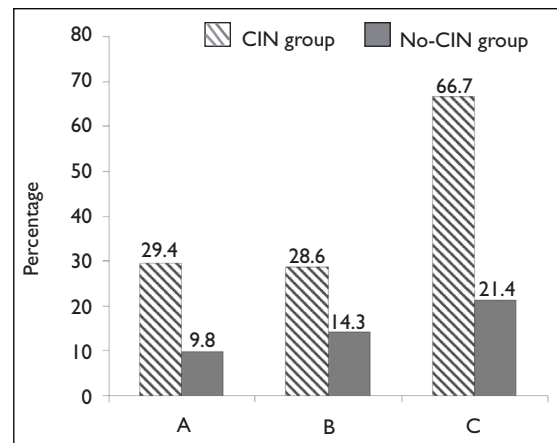
Our study divided patients into three groups. Group C consisted of patients with moderate baseline renal impairment with a mean estimated GFR < 40 ml/min/1.73m<sup>2</sup>. More than half (64%) of the patients in Group C also had diabetes mellitus. Hence, Group C patients would be at a higher risk of developing CIN compared to Groups A and B. The reported incidence of CIN in patients with baseline renal impairment was about 10%–20% without prophylaxis and 5% after prophylaxis.<sup>(23,24)</sup> Our results were fairly consistent with those of the published CIN prophylactic trials.<sup>(25,26)</sup> The routine saline prehydration and high-dose oral NAC treatment were offered to Group C patients. The incidence of CIN in Group C was comparable to that in Group B, which consisted of low-risk patients without diabetes mellitus or baseline renal impairment. This result suggests the presence of a beneficial reno-protective effect of the prophylactic regime.

Our study showed a significantly higher incidence of CIN in Group A. Group A patients were diabetics with a normal baseline Cr < 1.5 mg/dL. Despite having a lower baseline risk predisposition to CIN than Group C patients, Group A patients showed a nearly twofold higher incidence of CIN than Group C patients. The development of CIN was associated with unfavourable clinical outcomes at six months. These included higher mortality, MACE and recurrent hospitalisation rates. This finding suggests that the presence of diabetes mellitus increased the risk of renal dysfunction during PCI. One explanation would be that many diabetic patients had subclinical renal impairment which was not well represented by the serum Cr value alone. If these patients were subjected to a more detailed assessment, such as 24-hour proteinuria quantification and serum albumin/Cr ratio, subclinical renal dysfunction might be detected. Acute hyperglycaemia insult during contrast procedure has also been postulated as a potential cause of renal dysfunction during cardiac catheterisation.<sup>(27)</sup>

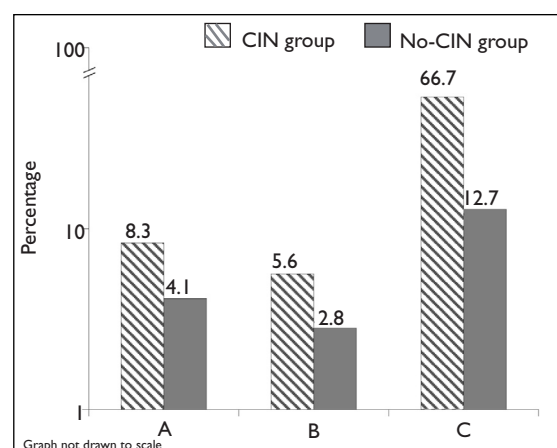
CIN was identified as an important predictor of mortality in addition to several other traditional risk predictors that include old age, depressed LVEF and the presence of myocardial infarction.<sup>(28)</sup> Logistic regression

**Fig. 1** Bar chart shows the clinical outcome of mortality at six months.

Overall incidence of mortality: 11.8% in the CIN group vs. 1.5% in the No-CIN group.

**Fig. 2** Bar chart shows the clinical outcome of recurrent hospitalisation at six months.

Overall incidence of recurrent hospitalisation: 32.4% in the CIN group vs. 13.2% in the No-CIN group.

**Fig. 3** Bar chart shows the clinical outcome of major adverse cardiac events at six months.

Overall incidence of MACE: 11.1% in the CIN group vs. 4.1% in the No-CIN group.

adjusted to these potentially confounding risk factors confirmed that CIN was independently associated with a higher mortality at six months in our study. This supported the hypothesis that acute deterioration of renal function in patients with underlying ischaemic heart disease conferred a worse prognosis. Hence, it would be prudent to prevent



the development of CIN in patients undergoing PCI. At the moment, many patients with a normal baseline Cr do not receive routine CIN prophylaxis before PCI. We propose a more careful assessment of renal function with measurement of the GFR, proteinuria and albumin/Cr ratio in patients with diabetes mellitus. CIN prophylactic therapy could be considered in diabetic patients even without abnormal serum Cr.

Our study was a post-hoc analysis. Due to the limited availability of data fields, we could not consider the periprocedural hydration volume, presence of proteinuria, urine output and HBA1c levels for inclusion in the analysis. The estimated GFR calculation is subjected to a few limitations from the MDRD formula used and the possibility that patients may not be at their true baseline condition before PCI because of hydration or cardiac illness.<sup>(14,15)</sup> However, the assessment of CIN risk, based on the utilised cutoffs of serum Cr of 1.5 mg/dL and GFR of 60 ml/min/1.72m<sup>2</sup>, is fairly accurate for the clinical purpose of this study and certainly more practical and readily available than the direct measurement of Cr clearance. These cut-off points have been used in a number of published studies.<sup>(2,3,5)</sup>

In conclusion, the development of CIN increased the morbidity, mortality and recurrent hospitalisation rates of patients. Our study suggests that diabetic patients without baseline renal impairment are also at an increased risk of developing CIN and that renal protection treatment prior to PCI may routinely be considered. The current prophylaxis regime using saline prehydration and high-dose oral NAC appears to be effective in patients with mild to moderate renal impairment undergoing elective PCI. Finally, prospective validation of the proposed CIN risk in diabetics with normal renal function is warranted in the future.

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