

# CONTRAST-INDUCED NEPHROPATHY

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## ABSTRACT

**Objectives:** To know the epidemiology, current definitions, pathophysiology, risk factors, contrast media, and preventative strategies of CI-AKI.

**Material & Methods:** Various studies have been reviewed and their conclusion have been discussed in this paper.

**Results:** CIN (Contrast-induced Nephropathy) is one of the complications after PCI that accounts for hospital-acquired renal failure, with adverse effects on prognosis, prolonging hospital stays and health care costs. CIN is most widely defined as an increase in serum creatinine of 0.5 mg/dl (44.2umole/L) or a 25% increase from the baseline value of 48 hours after the procedure. Multiple risk factors are involved in the development of CIN; these factors are divided into the patient- and procedure-related factors.

**Conclusion:** It is recommended that CIN can be prevented by adequate hydration through the IV normal saline.

**Key Words:** Pathophysiology, contrast media, Nephropathy.

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## INTRODUCTION

In recent decades, the interventional cardiology procedure has advanced substantially, resulting in a greater degree of patient safety. PCI and diagnostic catheterization are among the most common procedures interventional cardiology. During these procedures the CM are frequently used for imaging the coronary and other peripheral vasculature, which can cause the CI-AKI. CI-AKI is a significant challenge for cardiologists because PCI or diagnostic catheterization patients most likely have diabetes and CKD, which is a significant risk factor for CI-AKI.

This paper presents an update on the current definitions, pathogenesis, risk factors and impact of heart failures on the CIN and preventive measures of CI-AKI as applied specifically to cardiac intervention. Few consensus statements were developed, after reviewing the literature.

## MATERIAL & METHODS

Literature about the epidemiology, current definitions, pathophysiology, risk factors, contrast media,

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and preventative strategies of CI-AKI was compiled and categorized accordingly.

## RESULT/DISCUSSION

### Epidemiology:

The incidence of the CIN depends on the studies inclusion criteria such as patient populations, risk factors and it also varies on the criteria which it is defined [Figure 1]. The average incidence of the CIN in general population is reported to 1.2 to 1.6% but in some studies it shows up to 50% or more depend on the risk factors and criteria for definition<sup>1,2</sup>. Mayo clinic registry data reported that in 1826 patients, the incidence of CI-AKI was 14.55% who underwent PCI<sup>3</sup> and McCullough et al reported that the incidence of CIN was 14.5% in 1826 patients<sup>4</sup> who underwent percutaneous coronary interventions (PCI). Nash and Colleagues found that the incidence of CIN was 7.2% of 4622 general hospital patients<sup>5</sup>.

### Definitions:

Various kinds of definitions have been used for CIN. CIN is most widely defined as an increase in serum creatinine level of  $\geq 0.5$ mg/dl (26.4  $\mu$ mol/l) or a percentage increase in serum creatinine level of  $\geq 25\%$  from the baseline within 48 hours<sup>6</sup>. The ESUR modified the definition of CIN on the timeline base. The creatinine changes were said to occur within 3 days after intravascular administration of contrast media without an alternative etiology<sup>7</sup>. NCDR defined the CIN on the

**Table 1: Pharmacologic strategies to prevent the CI-AKI**

Potentially Beneficial Methods	Mechanism of the Prevention
Hydration	Increase GFR
Theophylline and aminophylline	Vasodilatory effect
N-acetylcysteine	Antioxidant and Anti-inflammatory
Ascorbic acid	Antioxidant
Statin	Antioxidant
Prostaglandin E1	Vasodilatory effect
Trimetazidine	Antioxidant
No consistent effect	
Calcium channel blocker	Renal Vasodilatory effect
Fenoldopam	Renal Vasodilatory effect
Dopamine	Renal Vasodilatory effect
Potentially detrimental	
Mannitol	
furosemide	
Endothelin receptor antagonists	

basis of AKIN criteria<sup>8</sup>, which is an increase in serum creatinine by 50% or 0.3 mg/dl after PCI compared with the baseline. However, in AKIN the time frame for the post creatinine changes is within 48 hours. According to NCDR, the highest creatinine value, within 30 days after the indexed procedure, should be used for the definition of CIN<sup>9</sup>. The ERBP (European Renal Best Practice) recommends the same definition and grading of AKIN criteria for CIN<sup>10</sup>.

**Pathophysiology:**

Etiology of CIN is multifactorial. CIN is mostly due to the vasoconstriction and direct cellular toxicity (Figure 2). When the CM is injected to the intra-arterial system, there is transient vasodilation of arterial circuit in the kidney via the release of nitric oxide, followed by sustained arteriolar vasoconstriction by the release of angiotensin, aldosterone, the vasopressin, catecholamine's, endothelin, pro-inflammatory cytokines and decreased nitric oxide (NO) and an increase in sympathetic tone<sup>11,12</sup>. When there is reduced number nephrons in the setting of diabetes and CKD patients, the sustained vasoconstriction can cause ischemia, offering a reason the incidence of CIN is might be higher in CKD and Diabetes patients. The region of the medulla is mostly affected because of the 10% of total renal blood flow that goes to the medulla<sup>13</sup>. High

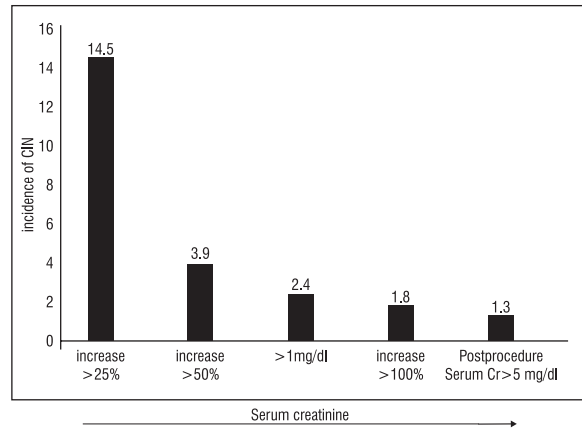


Figure 1: The graph showed that the incidence of the CIN decrease if the cutup value of the post serum creatinine is increased

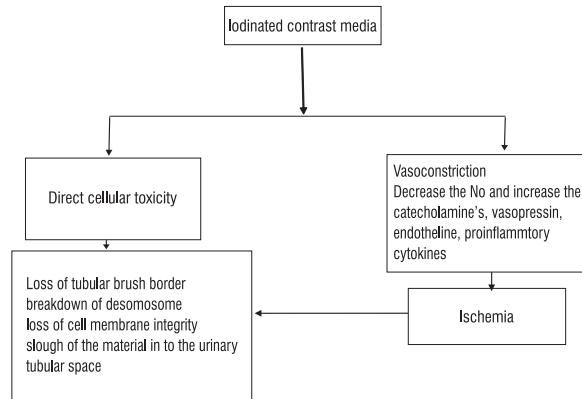


Figure 2: Showed the pathophysiology of the CIN

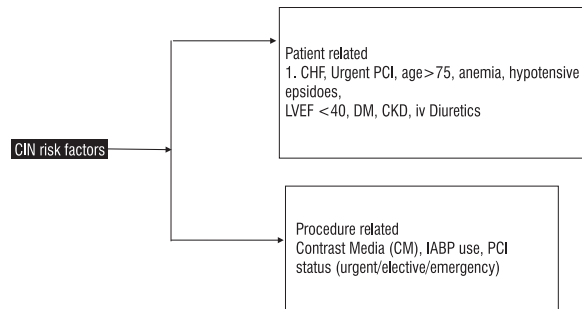


Figure 3: Flowchart for the CIN Risk factors

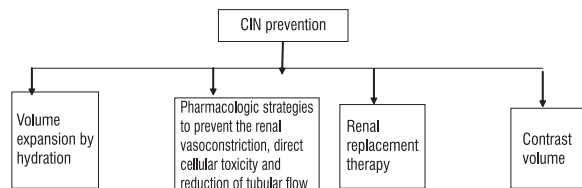


Figure 4: The strategies for the prevention of the CIN concentration of contrast within the tubules cause direct cellular toxicity due to which the integrity of cell membrane loss, desomesome breakdown, and shedding of these dead cells in to tubular space. This phenomenon promotes the stasis of the CM in the urine, which enable the movement of the contrast media in to the interstitial

space. The contrast causes further direct cellular toxicity there<sup>14</sup>. The histopathologic changes in the tubules due to the contrast is called "osmotic nephrosis"<sup>15</sup>. It has been hypothesized that hydration by normal saline may attenuate the risk of CI-AKI by expanding intravascular volume, reducing the production of reactive oxygen species, reducing the renin-angiotensin activation and increasing the nitric oxide production and dilution of the contrast medium within the tubular lumen<sup>16,17</sup>. In addition, the hydration attenuates the urine viscosity, which speeds up the excretion of the contrast medium within the tubules<sup>18</sup>.

### Risk factors:

There are two kinds of risk factors, patient related and procedure related (Figure 3)<sup>14</sup>.

### Contrast media:

Three kinds of contrasts are used during angiography on the basis of the osmolality: Isosmolal [IOCM] 290mosm/kg, low osmolal [LOCM] 600 to 800mosm/kg and high osmolal [HOCM] 2000mosm/kg<sup>19</sup>. Studies have proven that the incidence of CIN is lower with IOCM than with LOCM in high-risk patients who underwent cardiac catheterization. However, the incidence of CIN is equal among IOCM and LOCM in low-risk patients undergoing CT<sup>19,20</sup>. The incidence of CIN after PCI is related to the dose of CM. Therefore, CM should be used in low dosages in all patients, especially in at high-risk patients. These recommendations cannot be applied to directly intravenous such as an intravenous urography or enhanced CT. A safe route does not exist for the IV use of CM.

The incidence of the CI-AKI after the PCI and diagnostic Ca this related to the amount of CM used. CM should be used in low dosages in all the patients. A safe route and recommendation does not exist for the IV use of CM<sup>23</sup>. The incidence of CIN was reported as low in the IV used CM patients who underwent enhanced CT as compared to the patients who had the 1 intra-arterial administration of CM for PCI or angiography<sup>21,22</sup>. The Contrast Media Safety Committee (CMSC) concluded that the risk of CI-AKI is significantly lower because risk factors for CIN is higher in intra-arterial procedure than the intravenous procedures. Studies mentioned that the rate of CIN was high if the GFR was decreased<sup>21</sup> in the patients who underwent IV procedures such as enhanced CT. Contrast Media even up to 30 ml can cause CIN in high risk patients like those with diabetes and CKD. Multivariate analyses have shown that those patients who have CIN, usually high contrast were used in these patients<sup>23,24</sup>.

Studies have mentioned that maximum amount of the contrast should be safely administered during

the cardiac procedures. Some studies mentioned the dose of contrast should be equal to the GFR in high risk patients<sup>25</sup> but as a general rule the volume of the amount of contrast media during the PCI and cardiac catheterization should not more than twice of the GFR of the patient<sup>26</sup>.

### Consensuses statement:

1. CIN is a serious complication, the third leading cause of hospital-acquired renal failure, following the cardiac catheterization using the contrast media in high-risk patients.
2. The most common definition used for the CI-AKI is an increase in serum creatinine level of  $\geq 0.5$ mg/dl (26.4  $\mu$ mol/l) or a percentage increase in serum creatinine level of  $\geq 25\%$  from the baseline within 48 hrs, but the most recent NCDR definition for the CI-AKI is an increase in serum creatinine by 50% or 0.3 mg/dl after PCI compared with the baseline.
3. The rate of CIN is lower in the intravenous administration of the contrast as compared to the intra-arterial.
4. The pathophysiology of the CIN is mostly due to the direct cellular toxicity of the CM and vasoconstriction from hormones and cytokines, which release due to CM.
5. Higher contrast volume shows the association of higher incidence of CI-AKI in patients at high risk. However, small volumes up to 30 ml can cause the CIN incidence in high risk patients.
6. Adequate hydration with normal saline or isotonic crystalloid can lower the incidence of CI-AKI, if the hydration is properly done for 4hrs before the procedure and continued for 8-24 hrs after the procedure.
7. No pharmacologic treatment is better than the normal saline or isotonic crystalloid.

### Preventive measures:

#### A. Hydration:

CIN is prevented by the following four-way (Figure 4), but volume expansion is the most critical measure for reducing CIN and should be used in all high-risk patients undergoing contrast media procedures.

The most recent guidelines for the prevention of CI-AKI in patients with chronic kidney disease are increasing volume expansion by adequate hydration 12 hours before and 24 hours after diagnostic cardiac catheterization and PCI, at speed of 1 ml/kg per hour<sup>27,28</sup>. However, there is very limited data which shows that

these guidelines are used in clinical practice. The most frequently used protocol for adequate hydration with normal saline in clinical practice is fluid supplementation for 12 hours before and after the procedure at speed of 1 ml/kg per hour.

Recently, faster and shorter procedural hydration with normal saline ( $\geq 3$  mL/h) has demonstrated remarkable benefits in reducing the risk of CI-AKI. Moreover, the REMEDIAL II study and Mythous study investigated the effects of fast hydration with the Renal Guard and found that the incidence of the CI-AKI was lower in Renal Guard group as compared to the control group<sup>27-29</sup>.

The POSEIDON study conducted by Brar et al assessed the efficacy of a new fluid protocol based on the left ventricular end-diastolic pressure (LVEDP)<sup>30</sup>. LVEDP is a good predictor for the pre-load and shows a good clinical correlation of volume status. The POSEIDON study found that low intravascular volume status patients got a high volume of normal saline infusion based on the hemodynamically guided strategy. The POSEIDON study showed the lower rate of CIN in the intervention group as compare to the control group.

### **B. Contrast Media:**

Using a low volume of contrast to prevent CI-AKI is also an interesting principal of prevention. IOCM is safe in all high-risk patients even in CKD and diabetes<sup>23-26</sup>. IOCM should be used in all high risk patients to decrease the rate of CI-AKI.

### **C. Pharmacologic strategies:**

There are standard drugs for the prevention of CI-AKI. The pharmacologic agents and strategies which were used in the small clinical trials are listed in the Table 1.

#### **Sodium Bicarbonate:**

Sodium bicarbonate may decrease the incidence of CIN by alkalizing the urine, which decreases the formation of free radicals and increases the neutralization of the oxygen radicals. Efficacy of bicarbonates in the prevention of CIN is controversial. Studies have mentioned that the IV sodium bicarbonate can decrease the rate of CIN more as compared to the intravenous isotonic saline with or without NAC<sup>31</sup>. Meanwhile, other studies did not show any significant risk reduction<sup>32</sup>. One retrospective study at Mayo Clinic found that the rate of CIN increase with IV sodium bicarbonate<sup>33</sup>.

#### **N-acetyl cysteine (NAC)**

N-acetyl cysteine (NAC) N-acetylcysteine (NAC) has been used in different studies during the last few decades. NAC is a cheap and safe drug which has vasodilatory and antioxidant properties. There were different protocols used in the selection of an ideal regime of NAC, but the most widely used protocol was 600

mg oral regimen twice daily. More than 30 randomized trials were conducted to determine the role of NAC in preventing CI-AKI. The result of these studies conflict with some studies reporting a decrease in the incidence of CIN, while some studies show no significant benefits.

It has been noticed in some studies that higher doses of NAC give better protection<sup>34,35</sup>. A meta-analysis has been performed and their results are also conflicting. The current guidelines mentioned that NAC is not used in the prevention of CIN. In conclusion, the current opinion for the use of the NAC is that it should not be used for the prevention of CI-AKI.

#### **Ascorbic acid:**

Spargies et al conducted study in which the effect of ascorbic acid was investigated. The study showed that the incidence of CI-AKI was 20% in the placebo group and 9% in the ascorbic group,  $p < 0.02$ . This decrease incidence in the ascorbic group was due to the antioxidant activity<sup>35</sup>.

#### **Trimezadine:**

Studies demonstrated that trimezadine has antioxidant activity especially in renal and other vital organs. A clinical trial was conducted in which trimezadine was compared to the IV saline hydration group in patients with chronic renal failure undergoing elective procedure. The incidence of the CI-AKI was significantly higher in the patients receiving only intravenous normal saline group<sup>35</sup>.

#### **D. Hemodialysis:**

Hemodialysis before the procedures are not effective in preventing the incidence of CIN<sup>35</sup>.

#### **E. Others:**

##### **Statins:**

Statins are effective in decreasing the prevention of the CI-AKI. Statin may decrease the rate of CIN in several ways, including decrease the uptake of the contrast media in to the tubular cells, endothelial dysfunction, attenuation of free radical, protection of podocyte, and decreasing inflammation. Studies have reported that patients who were on statins during the PCI or other cardiovascular procedures have low rates of CI-AKI<sup>36</sup>. All randomized trials have confirmed that this concept is right. Thus, statins should be used at the baseline of any cardiac catheterization procedure and continue for the long-term course of the care, provided that the patient tolerated the statin very well.

##### **Renin-angiotensin system inhibitors**

Some patients are on RASIs during the cardiovascular procedure because of diabetic nephropathy, hypertension, and heart failure. RASIs cause deleterious effects during acute cardiovascular procedures,

because it vasodilates the renal efferent arteriole, which decreases the pressure in the glomerulus and decreases GFR. Due to decreased flushing of the contrast in the tubules of the nephron, the most recent study of the CAPTAIN trial demonstrated that patients with CKD, continuing ACEI/ARBs compared with holding ACEI/ARBs prior to the cardiac catheterization, the group withholding ACEI/ARBs experienced a significant reduction in post-procedural rise of creatinine and a nonsignificant reduction in CIN<sup>37</sup>. These ACEI/ARBs should be stopped or discuss the cardiac Cath physician before catheterization.

**Nephrotoxic drugs:**

The use of the diuretics especially loop diuretics, NSAID, Coxibs, amphotericin or antibiotics like aminoglycosides showed a higher incidence of the CI-AKI<sup>35</sup>.

The contrast media safety committee, suggested that the nephrotoxic drugs should be discussed with referring physicians and withdrawal of these drugs before catheterization should be on the basis of their benefits and harms. The incidence of the CI-AKI is largely due to the frequent use of the CM for intervention procedures in high risk patients.

The use of loop diuretics, non-steroidal anti-inflammatory drugs, coxibs, aminoglycosides, or amphotericin showed a higher incidence of CIN<sup>35</sup>. In the previous guidelines, nephrotoxic drugs withdrawal was recommended for at least 24 hrs before the procedure. In clinical practice, this guideline is poorly followed.

The contrast media safety committee, therefore, suggested that the possible withdrawal of nephrotoxic drugs before contrast medium in a high-risk patient should be discussed with their referring physicians, and their removal should balance the relative benefits and harms.

**CONCLUSION**

The Incidence of the CI-AKI is largely due to the frequent use of the CM for intervention procedures like PCI and diagnostic catheterization in high risk patients. These CIN patients may also have other risk factors, which may be attributed to CIN.

**RECOMMENDATIONS**

The incidence of CIN can be decreased by adequate hydration, pharmacologic methods, use of a low dose of CM and renal replacement therapy, but the most adequate and efficient way for prevention of CIN is adequate hydration by intravenous normal saline.

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### AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

**Khan MZ:** Main idea, manuscript writing.

**Faruqi R:** Editing.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.