Recent prophylactic strategies and novel biomarkers for contrast-induced acute kidney injury

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Abstract
Introduction
Contrast-induced acute kidney injury (CIAKI), defined as a serum creatinine (Cr) level of ≥ 25% or ≥ 0.5mg/dL from baseline, is a major complication associated with the administration of iodinated contrast media, and often irreversible declines in the kidney function. CIAKI is the major leading cause of acute kidney injury in hospitalized patients and substantially increases the morbidity and mortality. Although numerous studies have addressed the characteristics of patients at risk, neither precipitating factors regarding procedures or renoprotective agents, reliable biomarkers nor prophylactic strategies for CIAKI have yet been established. Assessing patients at risk and providing the early detection of CIAKI is of utmost clinical relevance. Several papers have been published with respect to plasmatic and urinary biomarkers from this point of view, with the utility of an increased urinary neutrophil gelatinase-associated lipocalin (NGAL) level in the early phase as a powerful independent predictor. As no specific treatment for CIAKI has been established, the management of such patients is focused on the clinical importance of prevention with hydration as the only secured protective agent to date. This review summarizes recent evidence and provides a future perspective for clinicians, concerning the pathophysiology of CIAKI, identification of populations at risk, predictive factors, and treatment based on prophylactic strategies.

Conclusion
The recent studies and reports indicated the utility of the urinary NGAL level as a biomarker of early phase of CIAKI. For the purpose of the prevention of contrast-induced renal impairment, the clinicians should mind the established renoprotective strategies of small volume of contrast media and adequate transfusion, with the usage of a novel biomarker.

Introduction
Contrast-induced acute kidney injury (CIAKI), previously known as contrast-induced nephropathy (CIN), a major critical complication of coronary angiography (CAG) and/or percutaneous coronary intervention (PCI) and is associated with increased morbidity and mortality. Multiple studies have demonstrated a 2 to 5-fold increase in risk of both short and long-term mortality among patients with CIAKI. This disease is the third most common cause of in-hospital acute renal failure (12%) and substantially increases the length of hospitalization. Furthermore, the development of CIAKI is associated with a higher risk of myocardial infarction, neurologic complications and the need for revascularization of target vessels.

In the recent literature, CIAKI is generally defined as an increase in the creatinine level of 25% or 0.5 mg/dL from baseline at the maximum value obtained within 48 hours after the procedure, with a peak at 3–5 days followed by a return near to the baseline value within 7–10 days.

CIAKI is defined as an adverse complication of the administration of intravascular contrast media (CM) for imaging procedures. However, irreversible renal dysfunction can occur in rare cases, in which treatment with dialysis is essential. The reported incidence of CIAKI varies based on the definition, population, and clinical setting. In a registry of more than 7,500 patients who underwent coronary intervention, 3.3% developed CIAKI. In particular, among patients with preexisting chronic kidney disease (CKD), the incidence of CIAKI is relatively high, at 10–25%.

The aim of this paper is to summarise the recent evidence and provides a future perspective for clinicians, concerning the pathophysiology of CIAKI, identification of populations at risk, predictive factors, and treatment based on prophylactic strategies.

Pathophysiology
CIAKI involves a reduction in the renal function consequent to renal toxicity to intravascular iodine contrast agents. As previous investigations have demonstrated that elevation of the serum Cr level indicates a compromise in the renal mass of 50% more, CIAKI is fundamentally defined as a transient form of renal injury, with a poor clinical outcome. The physiopathology of CIAKI is multifactorial and not well understood. The following underlying mechanisms are thought to contribute to the development of this disorder.

Renal hypoperfusion and ischemia
Previous investigations have shown an initial increase in the renal blood flow followed by a sustained reduction following CM exposure. This increased blood flow may be the result of blood hyperviscosity and increased intratubular pressure due to CM, leading to a state of renal hypoperfusion.

Several endogenous vasoconstrictors are upregulated by CM, such as adenosine and endothelin, causing a direct vasoconstrictive effect on smooth muscle cells, which induces renal ischemia, resulting in increased tubuloglomerular damage and side effects.

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effects of CM toxicity\(^6\). Such ischemia is obviously worsened by an impaired endothelial function and microvascular regulation, particularly in diabetic and hypertensive patients.

**Direct cytotoxicity of CM**

The main target of direct toxicity of CM is tubular epithelial cells. As CM is freely filtered and not resorbed, exposure increases tubular osmolarity. Tubular cells exposed to a high osmotic load have been shown to suffer from impairment in intracellular transport and energy metabolism. These processes induce cytopathological changes called “osmotic nephrosis”, ranging from tubular cell vacuolization to necrosis\(^6\). In addition, renal parenchymal damages may be worsened by CM mediated complement cascade activation and inflammatory cytokine release\(^7\).

**Reactive oxygen species**

The production of reactive oxygen species, which are primarily released during blood flow reperfusion, with subsequent tubular injury has been demonstrated in a number of animal studies. As the antioxidant reserve is decreased in elderly patients and the baseline level of oxidative stress is increased in subjects with CKD or diabetes, these patients are especially vulnerable\(^8\).

**Risk factors**

Risk factors for CIAKI can be divided into patient-related risk factors and procedure-related risk factors. The most prevalent patient-related risk factors include pre-existing renal disorders, concomitant hypotension, congestive heart failure, an older age, anaemia, diabetes mellitus and the concomitant use of nephrotoxic drugs.

On the other hand, procedure-related risk factors include the total amount of CM administered and the use of intra-aortic balloon pumping (IABP) or any type of diuretics. In an attempt to help clinicians to minimize or stratify the risk of CIAKI, Mehran et al. reported the utility of a CIAKI risk stratification score for predicting the occurrence of this disease after PCI based on eight available variables\(^9\). Among these factors, the baseline renal function strongly determines the risk of CIAKI, and the degree of renal impairment at baseline correlates with a proportionate risk of CIAKI\(^10\).

The Minnesota Registry of Interventional Cardiac Procedures reported that, in their series, CIAKI was diagnosed in 22% of patients with a serum Cr level of >2 mg/dL and 30% of patients with a serum Cr level of >3 mg/dL\(^3\).

Concerning glucose intolerance, preprocedural hyperglycaemia has recently been reported to be a significant risk factor for CIAKI. Hyperglycaemia is known to increase oxidative stress and induce endothelial dysfunction in numerous in vitro and animal studies. An acutely elevated blood glucose level in non-diabetic patients has also been reported to increase the risk of CI AKI more significantly than does a chronically elevated blood glucose level in diabetic patients\(^11\). However, the results remain inconsistent as to whether strict glycaemic control helps to prevent CIAKI\(^12\).

**Potential biomarkers**

The diagnosis of CIAKI is made on a change in the serum Cr level; however, this parameter is a delayed and unreliable indicator of acute kidney injury. The lack of early biomarkers has limited the ability to translate promising experimental therapies to the setting of CIAKI. Fortunately, elucidating the early stress response in the kidneys to acute injury has led to the identification of several potential biomarkers in the immediate postprocedural phase of contrast media use.

**Neutrophil Gelatinase-associated Lipocalin (NGAL)**

A recent published meta-analysis of a large number of clinical studies and systematic reviews suggested that neutrophil gelatinase-associated lipocalin (NGAL) is a reliable diagnostic and prognostic biomarker for acute kidney injury, as its serum and urinary levels rise earlier and exhibit better sensitivity than serum Cr alone\(^13,14\). NGAL is emerging as an excellent stand-alone troponin-like structural biomarker in the plasma and urine for the early diagnosis of AKI and the prediction of clinical outcomes, such as the need for dialysis and mortality, in several common clinical scenarios. NGAL is massively and rapidly up-regulated in the kidneys following ischemic or nephrotoxic injury\(^15\). Of note, as a promising biomarker for early detection of acute tubular necrosis, the plasma NGAL level is less specific than its urinary counterpart\(^16\).

Urinary NGAL is reported to be upregulated two hours after tubular injury\(^17\). A data analysis of three studies of up to 191 patients revealed the urinary NGAL level measured within six hours after CM exposure to have good sensitivity (0.78) and specificity (0.96), with an area under the receiver operating characteristic (ROC) curve of 0.894 for predicting CIAKI (cut-off for urinary NGAL: 100 ng/ml)\(^18\).

Our study revealed the urinary NGAL level at two hours after the procedure to be an independent predictor of a decline in the eGFR after CM use in CKD patients. The combined predictive value of an increase in NGAL and a higher baseline urinary albumin creatinine ratio (UACR) is associated with a higher incidence rate of kidney injury, up to 83.9%\(^18\). However, proper randomized clinical trials of renal injury are still lacking, and investigations of systemic outcomes comparing the use of NGAL vs. standard clinical practice are expected.

**Urinary Interleukin-18 (IL-18)**

IL-18 is a widely expressed pro-inflammatory cytokine. In addition to its involvement in the immune response, animal studies have confirmed a key role for IL-18 in ischemic kidney injury. In human adult population, it has been reported that the urinary IL-18 levels increase prior to the Cr levels in patients with AKI and that an elevated IL-18 level is independently associated with mortality\(^19\). The urinary IL-18 levels at 24 hours after PCI are significantly increased in patients who develop CIAKI compared to that observed in...
controls, reducing the diagnostic delay by 24 hours\textsuperscript{20}. However, conflicting results have been reported regarding the predictive ability of IL-18 for CIAKI. Although the urinary IL-18 level is an earlier predictor of AKI than the serum Cr level and has been found to be an independent predictor of later major cardiac events, it has not been recognized as a reliable biomarker for CIAKI.

**Urinary Liver-type Fatty Acid-Binding Protein (L-FABP)**

L-FABP is a cytoplasmatic protein that facilitates long-chain fatty acid transport from the plasma membrane and reduces oxidative stress by binding fatty acid oxidation products. Urinary L-FABP is undetectable in healthy control urine, whereas the urinary L-FABP levels are reported to be significantly elevated in patients with acute kidney disorders\textsuperscript{21}.

Although several small studies have reported the early diagnostic ability of L-FABP, the predictive value of this parameter for CIAKI has not been established. In addition, our study demonstrated that the predictive value of L-FABP for eGFR reduction two hours after CM exposure is inferior to that of NGAL\textsuperscript{18}.

**Urinary Kidney Injury Molecule-1 (KIM-1)**

KIM-1 is a transmembranous protein that is normally not detectable in urine, although it is expressed at very high levels in proximal tubular epithelial cells soon after ischemic or toxic injury. KIM-1 is reported to have the ability to detect AKI rapidly\textsuperscript{22}. In adult cardiac surgery patients, the predictive value of urinary KIM-1 for post-operative AKI is superior to that for NGAL\textsuperscript{23}.

Additionally, a study of adult cardiac surgery patients illustrated that the preoperative KIM-1 level can be used to predict the development of AKI\textsuperscript{24}. Although a few papers have reported the diagnostic value of KIM-1 for CIAKI, the use of this biomarker appears to be limited in this particular context, since the pathogenesis of CAKI is multifactorial\textsuperscript{22}.

**Preventive & therapeutic strategies**

**Contrast Media (CM)**

With regard to the type of CM, early studies have demonstrated an increased risk of CIAKI associated with high-osmolality contrast agents. The results of several recent studies have shown conflicting findings as to which is more beneficial, iso-osmolar contrast medium (IOCM) or low-osmolality contrast medium (LOCM), for preventing CIAKI, especially in patients with underlying CKD.

Considering the accumulated findings of recent comparative studies, including a meta-analysis that enrolled 16 separate trials\textsuperscript{25}, the Cin Consensus Working Panel concluded that “Current evidence suggests that for intra-arterial administration in high risk patients with CKD, particularly those with diabetes mellitus, nonionic, iso-osmolar contrast is associated with the lowest risk of Cin.”\textsuperscript{26}

The dose of CM administered also contributes to the risk of renal toxicity. According to the volume to risk correlation, the calculation of a contrast volume limit [\(\text{ml} = 5 \times \text{body weight (kg)} / [88.4 \times \text{SCR (μmol/ l)}]\)] has been proposed. The results of previous studies have demonstrated that patients receiving more than the limit volume of CM are more likely to develop CIAKI, resulting in a higher OR of 1.75\textsuperscript{27}. However, the occurrence of CIAKI is not always dependent on the use of a large amount of CM. For example, our data revealed a rate of CIAKI of 5.7\% among CKD patients who underwent coronary angiography or intervention with a minimum volume of CM (64.8±20.5 ml)\textsuperscript{28}.

**Intravascular Transfusion**

As volume depletion has been identified to be a risk factor for the development of CIAKI, intravascular transfusion is strongly recommended and the best-proven prophylaxis against development of CIAKI. The intravenous administration of isotonic saline (NaCl 0.9\%) is preferred over hypotonic solutions for reducing the risk of CIAKI\textsuperscript{26}. Recently, the use of sodium bicarbonate (NaBic 1.4\% or NaHCO3 154 to 166 mEq/l) has received attention, as alkalinization of tubular fluid is thought to diminish tubular toxicity and decrease free radical generation. The individual results of trials comparing the effects of isotonic saline to sodium bicarbonate have shown contradictory results. For example, a single-centre trial of 502 CKD patients scheduled for elective coronary angiography demonstrated that hydration with sodium bicarbonate is not more effective than hydration with isotonic saline for CIAKI prophylaxis\textsuperscript{29}. On the other hand, a recent meta-analysis revealed the benefits of sodium bicarbonate\textsuperscript{30}.

**N-acetylcysteine (NAC)**

NAC, a precursor of glutathione synthesis, has the potential to diminish oxidative stress by directly scavenging free radicals and increasing intracellular glutathione. In addition, NAC improves renal circulation by combining and stabilizing bioavailable nitric oxide. Although the efficacy of N-acetylcysteine in preventing CIAKI has been studied in multiple trials, the results have been remarkably varied, with some studies finding great efficacy, although most showing no significant benefits. Significantly, the two most recently published randomized clinical trials (RCTs) failed to prove any beneficial effects of NAC\textsuperscript{31,32}.

**Renal Vasodilators**

Since the pathogenesis of CIAKI is considered to be primarily dependent on renal vasoconstriction and ischemia in the renal medulla, the administration of vasodilators, with consequent improvements in renal perfusion, is expected to be beneficial for preventing CIAKI. Carperitide, a renal-specific vasodilator, has been reported to have a beneficial effect on the renal function with low-dose administration maintained for up to one month after contrast medium use\textsuperscript{33}.

However, contrary to the findings of that study, our current results did not demonstrate any advantages of carperitide for CIAKI in CKD patients undergoing coronary angiography, concomitant with other previously published results. Our subanalysis

appeared to support the impact of hypotension induced by carperitide, which has been suggested to disturb the renoprotective effects of this drug.\textsuperscript{34}

**Discussion**

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

As above described, substantial inconsistent findings have been reported concerning the predictors and prophylaxis of CIAKI. One reason for this is the fact that the epidemiology and prognosis of CIAKI are variable in relation to the criteria applied to determine the diagnosis and severity of disease. In addition to a conventional definition of AKI, recent classifications include even slight changes in the serum Cr level as low as 0.3 mg/dl, which are associated with worse outcomes.\textsuperscript{34}

The new KDIGO definition of AKI applies to CIAKI, which is defined as any of the following (not graded): an increase in the serum Cr level of \( \geq 0.3 \) mg/dl (\( \geq 26.5 \) \( \mu \)mol/l) within 48 hours, an increase in the serum Cr level to \( \geq 1.5 \) times the baseline value, which is known or presumed to have occurred within the prior seven days or a urine volume of \(<0.5 \text{ ml/kg/h}\) lasting for six hours. Data relevant to predictors and prophylaxis should be carefully evaluated in light of these new criteria.

**Conclusion**

To date, since NAC, as well as all other drugs, has failed to demonstrate any beneficial preventive effects in randomized studies, only two treatments have been proven to be effective: optimal hydration and reducing the CM volume. As there is currently no established treatment specifically targeting CIAKI, the main goal for the clinician remains prevention. In practice, serum Cr monitoring plays a pivotal role in accessing renal dysfunction after CM exposure; however, this parameter is insensitive and slow to be upregulated.

Therefore, there is an urgent need to develop novel tools permitting the early and accurate detection of CIAKI. Current research is exploring new diagnostic and therapeutic targets in this clinical domain, which will undoubtedly open a new frontier for the creation of systematized preventive strategies for treating cases of CIAKI.

**Abbreviations list**

CIAKI = contrast-induced acute kidney injury

AKI = acute kidney injury

Cr = creatinine

CM = contrast media

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

NGAL = neutrophil gelatinase-associated lipocalin

**References**


