
ABSTRACT
Iodinated contrast media (CM) are used in many investigations that a patient may undergo during the course of an inpatient stay. For the vast majority of patients, exposure to CM has no sequelae; however, in a small percentage, it can result in a worsening in renal function termed contrast-induced acute kidney injury (CI-AKI). CI-AKI is one of the leading causes of in-hospital renal dysfunction. It is associated with a significant increase in morbidity and mortality as well as an increased length of hospital stay and costs. Unfortunately, the results of extensive research into pharmacological inventions to prevent CI-AKI remain disappointing. In this article, we briefly outline the pathophysiological mechanisms by which iodinated CM may cause CI-AKI and discuss the evidence for reducing CI-AKI by limiting contrast volumes. In particular, we review the data surrounding the use of contrast volume to glomerular filtration rate ratios, which can be used by clinicians to effectively lower the incidence of CI-AKI in their patients.

INTRODUCTION
Almost 60 years ago, the first case of contrast-induced acute kidney injury (CI-AKI) was described in a patient with multiple myeloma receiving intravenous pyelography [1]. Currently, intravascular contrast agents are the third most common cause of AKI in hospitalized patients, accounting for 10–13% of cases [2, 3]. The growth in incidence in CI-AKI over the decades is not surprising. In 2003, ~80 million doses of iodinated contrast media (CM) were prescribed worldwide [4]. The recipients of this contrast have, on average, become older with increased risk factors for CI-AKI such as diabetes mellitus (DM) and baseline chronic kidney disease (CKD).
Patients who develop CI-AKI are at an increased risk of long-term renal impairment and mortality as well as an increased length of stay and costs [5–8]. In a large retrospective analysis of 16 248 patients undergoing procedures involving radiocontrast, the in-hospital mortality for patients who developed CI-AKI was 34%, compared with 7% of matched controls who received contrast, but did not develop AKI [5]. The 2-year survival for patients who develop CI-AKI requiring dialysis following coronary angiography is 18.8% [7].

Therefore, the ongoing dilemma of CI-AKI risk represents a significant problem in contemporary medical care. It is evident that efforts to prevent it need to be intensified.

### PATHOPHYSIOLOGY OF CONTRAST-INDUCED ACUTE KIDNEY INJURY

In spite of the increasing burden of CI-AKI, our understanding of the pathophysiological processes involved is imperfect. Hypoxia, vasoconstriction and cytotoxic effects of the CM themselves all play a significant role.

Oxygen delivery to the outer medulla is poor owing to its distance from the descending vasa recta (DVR), which forms its blood supply. The medulla is therefore particularly at risk of hypoxia. The CM have been shown to directly constrict DVR. Vasodilatory nitric oxide is reduced, while vasoconstrictive superoxides increase [9]. Endothelial and renal tubular cells exhibit evidence of severe toxicity or apoptosis when exposed to CM [10]. This cytotoxicity is putatively iodine mediated. Iodine is a well-documented toxin towards human cells through cell-membrane damage [11]. Due to photolysis, iodine can be released from the CM [12], and even very small amounts can be cytotoxic [13].

Viscous properties of contrast exacerbate the vasoconstrictive and cytotoxic effects above [10, 13, 14]. The contrast is retained and its effects are aggravated, because high viscosity reduces the glomerular filtration rate (GFR) and medullary oxygenation as well as impeding urine flow.

### CONTRAST-INDUCED ACUTE KIDNEY INJURY PREVENTION

Largely, strategies aimed at reducing CI-AKI have targeted two approaches. First, pharmacotherapy aimed at preventing CI-AKI and secondly identifying risk factors. Significant debate and controversy surround prevention strategies despite extensive clinical investigation. Currently, recommended pharmacological prevention strategies for patients at risk include intravascular volume expansion either with isotonic sodium chloride [15–17] or with sodium bicarbonate [16, 17] along with the use of oral N-acetylcysteine [16].

Risk factors for developing CI-AKI may be non-modifiable or modifiable. Non-modifiable influences include the low baseline GFR, presence of DM, advanced age, congestive cardiac failure (CCF) or route of administration. The risk of CI-AKI also appears to be greater for intra-arterial versus intravenous (i.v.) contrast administration. The incidence of CI-AKI following i.v. contrast in patients with moderate renal dysfunction undergoing CT scanning has been reported to be 5% [18]. Factors such as volume of contrast administered, hydration status and anaemia may be considered modifiable in an elective setting, but in an emergency, only volume of contrast could be considered modifiable. The strongest predictors of CI-AKI are creatinine clearance, DM and contrast volume [9, 19] (Figure 1).

The Mehran et al. [20] risk score involves eight variables (hypotension, intra-aortic balloon pump, congestive heart failure, CKD, diabetes, age >75 years, anaemia and volume of contrast) that were assigned a weighted integer. The total score was calculated as the sum of each of the weighted integers. This score has been widely cited and has also been shown to predict not only CI-AKI, but also poorer short- and long-term outcomes in patients undergoing primary percutaneous coronary intervention (PCI). In spite of this, the Mehran score has not been widely applied in day-to-day practice.

The CM used can also influence the risk of CI-AKI. The use of high-osmolar contrast has been shown to be more nephrotoxic than low-osmolar or iso-osmolar agents in patients with pre-existing CKD [21, 22]. Iso-osmolar and low-osmolar media are recommended in the most recent guidelines [16] and have largely replaced high-osmolar preparations in contemporary practice, except in some developing countries. In comparisons of iso-osmolar and low-osmolar media, some earlier studies reported that iso-osmolar agents reduced the risk of CI-AKI [23, 24]. However, recent studies and meta-analyses have found no significant difference in the rates of AKI between iso-osmolar and low-osmolar CM [25–28].

### ENSURE EVERY MILLILITRE OF CONTRAST COUNTS

Methods have been described, whereby ‘ultra-low’ contrast usage is facilitated [29]. Key components of this method

![Figure 1: Validated risk of acute renal failure requiring dialysis after diagnostic angiography and ad hoc angioplasty. In diabetic and non-diabetic patients, both a mean contract dose of 250 mL and a mean age of 65 years are assumed. CrCl, creatinine clearance; CIN, contrast-induced nephropathy. Data adapted from McCullough et al. [47] and Rihal et al. [19]. Copyright: MedReviews®, LLC. Reprinted with permission of MedReviews®, LLC. Reviews in cardiovascular medicine are a copyrighted publication of MedReviews®, LLC. All rights reserved.](image-url)
include using a smaller (3 cm³) syringe to limit the volume of contrast available to inject, using smaller diameter catheters, biplane angiography and liberal use of intravascular ultrasound among other strategies. By meticulous attention to these points, the authors describe carrying out complete diagnostic procedures with <15 cm³ of contrast. In some cases, where previous angiograms were available, no contrast was used at all.

An extremely high-risk group was studied by Manske et al. [30]. In their cohort of 59 insulin-dependent diabetics with a mean serum creatinine (Scr) of 5.9 mg/dL (522 μmol/L), patients underwent coronary angiography as part of their evaluation for renal transplant surgery. CI-AKI occurred in 50% of patients and no controls. Seven patients required dialysis within 6 days of coronary angiography and two additional patients required dialysis within 14 days. Scr values obtained at baseline and 24 h after angiography were compared, and a value that was >10% above the baseline was considered significantly increased. Patients who developed CI-AKI received significantly more CM than patients who did not develop CI-AKI (P = 0.004). For each 5-mL increment in CM dose, there was a 65% increase in the risk of CI-AKI in these very high-risk patients.

Within radiology, the ongoing development of newer imaging technologies has facilitated faster image acquisition. In addition to reduced radiation exposure, this has enabled radiologists to perform studies with less intravascular contrast, because the duration of time over which contrast needs to be administered has shortened. Other strategies advocated for reduction in contrast include weight-based contrast administration for thin patients, and close scrutiny of each CT requests to examine which studies may be feasible without contrast [16]. It remains to be seen whether the above recommendations translate to a significant reduction in CI-AKI for patients.

**CONTRAST VOLUME LIMITS**

Patients with lower baseline GFR, DM or left ventricular (LV) dysfunction are at highest risk of developing CI-AKI. Unfortunately, these patients are also more likely to have multivessel disease, complex lesions and previous coronary artery bypass grafting [31, 32], all of which demand higher contrast doses. Therefore, formulating a ratio of maximum contrast dose is attractive to cardiologists, and more practical than use of the Mehran risk score. It allows for a predefined target to be set prior to intervention and encourages complex intervention in high-risk patients to be staged.

Such investigations can also be used to further our understanding of what doses of CM can safely be administered to specific subgroups. This knowledge could prevent patients who are felt to be at too high a risk of CI-AKI being denied appropriate investigations. Low rates of angiography have largely focussed on patients undergoing PCI and hence have never widely been embraced as a tool in day-to-day clinical practice. A solution originating from studies in patients more reflective of everyday practice was needed.

A study by Laskey et al. [31] involving 3179 all-comers for PCI advocated the use of a volume of contrast to creatinine clearance (V/CreCl) ratio. The cut-off point for the ratio of V/CreCl was calculated at 3.7. The sensitivity and specificity of this ratio for predicting CI-AKI were 65 and 75%, respectively. After adjustment for other known causes of CI-AKI, V/CreCl >3.7 remained significantly associated with an increase in creatinine secondary to contrast use (OR 3.84; 95% CI: 2.0–7.3). In this study, those who developed AKI were administered with 255 ± 124 mL of contrast, while those who did not develop AKI received 224 ± 112 mL. This difference was not significant (P = 0.06). In additional studies, in 871 consecutive STEMI patients, the contrast medium volume to GFR ratio of 3.7 has been shown to be independently associated with a 3-fold increase in 1-month mortality [42].

This figure allows facilitates a more generous administration of contrast for angiography than a similar study by Gurm et al. [43]. They found that, below a ratio of contrast to
creatinine clearance of 2.0, CI-AKI was a rare complication of PCI, but it increased dramatically at a ratio of 3.0 (Figure 2). At 2.0, the OR for CI-AKI was 1.16 (95% CI: 0.98–1.37), increasing to 1.46 at 3.0 (95% CI: 1.27–1.66). Episodes of NRD followed a similar trend. Their findings, therefore, advocate a ratio of <3.0, but preferably to keep the ratio <2.0. They also demonstrated that, even at a GFR of <30 mL/min, by using a contrast volume/calculated creatinine clearance (CV/CCC) ratio of <2.0, the incidence of contrast-induced nephropathy is less than half of that at higher ratios (Figure 3).

The reasons underlying why two different studies on similar patients have inconsistent conclusions are not immediately apparent. Both papers involved patients undergoing PCI. Gurm’s study involved a higher percentage of patients with CKD at baseline (10.1 versus 7.2%) had more episodes of CI-AKI (3.2 versus 1.5%) and perhaps most significantly was in much larger patient population (45,429 versus 3,179), and therefore is likely to be more reliable a figure. Laskey et al. [31] also recognized that, below their CV/CCC level of 3.7, a small but significant number of patients still developed CI-AKI.

Evolving from the view that a contrast volume to an estimated GFR (eGFR) should guide contrast doses, other groups have suggested that grams of iodine to the eGFR ratio (g-I/eGFR) would be superior. Reporting g-I is a logical step in formulating a ratio to guide contrast use. There is a wide range of iodine concentrations available and used from one department to the next throughout hospitals (140–400 mg-I/mL). Universally accepting g-I as a reference would allow for easier comparison of CI-AKI rates with different procedures in different settings.

Using this annotation, Yoon and Hur [44] prospectively examined the relationship between iodine and CI-AKI in 226 patients undergoing elective PCI. In their analysis, a ratio of 1.42 was determined to have a sensitivity and specificity of 81.3 and 80%, respectively, for CI-AKI, with an area under the curve of 0.867. These results would suggest that their ratio of 1.42 g-I/eGFR is the best solution to a contrast limit for preventing CI-AKI. However, other figures have been borne out of studies involving significantly larger patient numbers, with emergency PCI, and therefore it would need to be validated further before being accepted in clinical practice.

The danger in suggesting a maximum contrast dose for the prevention of CI-AKI is that we suggest a ‘one size fits all’ solution. This is a dramatic oversimplification of the cases we deal with in clinical practice, particularly with emergency PCI. Patients may present with hypotension and with reduced LV systolic function. To account for these situations and the obvious negative impact that they have on development of renal dysfunction, Nyman et al. [45] have described the effect of various ratios of g-I/eGFR on incidence of CI-AKI in 391 STEMI patients with and without shock, further subdividing patients into those with an ejection fraction of more or less than 50% (Figure 4).

They developed a regression model encompassing gram-iodine dose, eGFR, LV ejection fraction and shock. For predicting CI-AKI, the area under the receiver operating curve for this model was 0.87. Another model with area under the curve of 0.80 was also described. This model only included gram-iodine dose and eGFR.

Additionally, over a wide range of renal dysfunction (eGFR 30–90 mL/min), in patients with no shock and normal LV function, a 1:1 eGFR ratio gave reassuringly low risk of CI-AKI (4–7%). Their work elegantly illustrates that, even at low doses of contrast, rates of CI-AKI are exceptionally high in the setting of shock and LV dysfunction. At a 1:1 ratio, for a patient undergoing PCI, the risk of CI-AKI was 6% if there

![Figure 2](image-url)
**FIGURE 3:** Incidence of CI-AKI by categories of CV/CCC across different categories of baseline GFR. The baseline GFR is a key determinant of risk and NRD with higher risk patients having a low baseline GFR. From Gurm et al. [43], with permission.

**FIGURE 4:** The risk of CI-AKI (according to Nyman’s model) as a function to the 1:2, 1:1, 2:1 and 3:1 ratio between contrast medium dose (grams of iodine) and eGFR, with LVEF set to 50% and no shock (A), LVEF set to 25% and no shock (B), LVEF set to 50% and shock (C) and LVEF set to 25% and shock (D). Solid vertical line corresponds to the minimum eGFR (25 µmol/min) and dashed line to the median eGFR (73 µmol/min) in the present study cohort. LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate. From Nyman et al. [45], with permission.
was no shock and an ejection fraction of 50%. This jumped to 80% in the presence of shock and LV dysfunction. Hypotension and LV dysfunction are themselves risks for AKI. However, they are both regularly included as risk factors and risk scores (Mehran) as they may exacerbate the nephrotoxic effects of contrast. Additionally, Nyman et al. [45] also outline that, even with LV dysfunction and shock as well as with increasing contrast volumes, the incidence of CI-AKI rose further. In this high-risk setting, they advocated a contrast volume, which is ‘as low as reasonably achievable’, a phrase that classically applies to radiation dose. The avoidance of left ventriculography and deferring treatment of non-culprit coronary lesions in emergency settings aids contrast limitations.

**LIMITATIONS OF STUDIES TO DATE**

The most striking weakness in the studies conducted, to date, (see Table 1 for summary) is that they are predominantly generated in populations with low rates of baseline CKD. The rate of CKD (defined as SCr >1.5 mg/dL) in the largest study (Gurm et al., 45 429 patients) was only 10.4%. In Cigarroa’s study, all patients had a creatinine level >1.8 mg/dL and the mean creatinine was 2.6 mg/dL, but this study only involved 115 patients. There is also a lack of uniformity within these studies regarding the definition of CI-AKI. The most commonly used definition in this review was a 50% increase in baseline creatinine. The timescale over which this may occur has also varied. Recently, the Kidney Disease: Improving Global Outcomes (KDIGO) [16] group have endorsed the definition initially proposed by the Society for Urogenital Radiology [46]. They define CI-AKI as a rise in SCr of ≥0.5 mg/dL (≥44 µmol/L) or 25% of baseline. KDIGO advocate that this creatinine measurement should be taken at 48 h rather than the 3 days suggested by the Society of Urogenital Radiology. Universally adopting, this definition would facilitate easier comparison of results between future work in the field.

**CONCLUSION**

CI-AKI can be reduced by reducing contrast volumes administered. Doctors should remain cognizant of the risk of AKI during procedures involving CM and restrict contrast doses accordingly. Evidence to date would suggest that contrast doses should be limited to the g-I/GFR ratio of 1, which will minimize, but not nullify the risk of CI-AKI. This should be even less in the presence of additional risk factors. Further improvement on the contrast ratios would be welcomed, but should concentrate on those most at risk of developing CI-AKI, for example, those with baseline CKD.

<table>
<thead>
<tr>
<th>First author (reference)</th>
<th>Patient cohort</th>
<th>CI-AKI definition</th>
<th>Percentage cases of CI-AKI (%)</th>
<th>Contrast volume limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarroa [34]</td>
<td>115 patients with renal dysfunction (SCr &gt;1.8 g/dL) undergoing diagnostic coronary angiography</td>
<td>Creatinine increase of 1 mg/dL over 5 days</td>
<td>6.9</td>
<td>5 mL/kg/creatinine</td>
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<tr>
<td>Marenzi [41]</td>
<td>561 patients with STEMI</td>
<td>&gt;25% increase over 72 h</td>
<td>20.5</td>
<td>5 mL/kg/creatinine</td>
</tr>
<tr>
<td>Laskey [31]</td>
<td>3179 consecutive patients undergoing PG</td>
<td>Creatinine increase of 0.5 mg/dL or 25%</td>
<td>1.5</td>
<td>CV/CrCL &lt;3.7</td>
</tr>
<tr>
<td>Gurm [43]</td>
<td>45 429 patients with PCI 16.1% emergency 20.2% acute MI (&lt;24 h)</td>
<td>Creatinine increase of 0.5 mg/dL</td>
<td>3.2</td>
<td>CV/CCC ratio &lt;2</td>
</tr>
<tr>
<td>Mager [43]</td>
<td>871 patients with STEMI</td>
<td>Creatinine increase of 0.5 mg/dL or 25% in 48 h</td>
<td>8.3</td>
<td>CV/GFR &lt;3.7</td>
</tr>
<tr>
<td>Nyman [45]</td>
<td>391 with STEMI</td>
<td>&gt;44.2 µmol/L rise in creatinine</td>
<td>16.6</td>
<td>g-I/GFR Ratio grades from 1:2 to 3:1 mainly advocated ratio of 1:1</td>
</tr>
</tbody>
</table>

STEMI: ST segment elevation MI; PCI: percutaneous coronary intervention; CV/CrCL: ratio of the volume of contrast (in millilitres) to creatinine clearance (in millilitres per minute); MI: myocardial infarction; GFR: glomerular filtration rate in millilitres per minute; g-I: grams of iodine.
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