Canadian Association of Radiologists Guidance on Contrast Associated Acute Kidney Injury

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Abstract

Iodinated contrast media (ICM) is one of the most frequently administered pharmaceuticals. In Canada, over 5.4 million computed tomography (CT) examinations were performed in 2019, of which 50% were contrast enhanced. Acute kidney injury (AKI) occurring after ICM administration was historically considered a common iatrogenic complication which was managed by screening patients, prophylactic strategies, and follow up evaluation of renal function. The Canadian Association of Radiologists (CAR) initially published guidelines on the prevention of contrast induced nephropathy in 2007, with an update in 2012. However, new developments in the field have led to the availability of safer contrast agents and changes in clinical practice, prompting a complete revision of the earlier recommendations. This revised guidance document was developed by a multidisciplinary CAR Working Group of radiologists and nephrologists, and summarizes changes in practice related to contrast administration, screening, and risk stratification since the last guideline. It reviews the scientific evidence for contrast associated AKI and provides consensus-based recommendations for its prevention and management in the Canadian healthcare context. This article is a joint publication in the Canadian Association of Radiologists Journal and Canadian Journal of Kidney Health and Disease, intended to inform both communities of practice.

Résumé

Les produits de contraste iodés comptent parmi les produits pharmaceutiques le plus souvent administrés. Plus de 5,4 millions de tomodensitométries ont été réalisées en 2019 au Canada et un rehaussement du contraste a été utilisé dans 50 % des cas. Historiquement, une lésion rénale aiguë (LRA) survenant après l'administration d'un produit de contraste iodé était considérée comme étant une complication iatrogénique courante que l'on gérait en sélectionnant les patients, en appliquant des stratégies prophylactiques et par un suivi de l'évaluation de la fonction rénale. L'Association canadienne des radiologistes (CAR) a initialement publié des lignes directrices sur la prévention de la néphropathie induite par produit de contraste en 2007, avec une

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mise à jour en 2012. Cependant, de nouvelles avancées dans le domaine ont conduit à la mise à disposition de produits de contraste plus sécuritaires et à des changements dans la pratique clinique, ce qui a incité la CAR à revoir complètement les recommandations antérieures. Ce document d'orientation révisé a été élaboré par un groupe de travail multidisciplinaire de la CAR constitué de radiologistes et de néphrologues. Il résume les changements de pratique liés à l'administration des produits de contraste, à la sélection et à la stratification du risque qui ont eu lieu depuis les lignes directrices précédentes. Il examine les données probantes scientifiques relatives aux LRA associées aux produits de contraste et fournit des recommandations fondées sur un consensus pour la prévention et la gestion de ces lésions dans le contexte des soins de santé canadiens. Cet article est une publication conjointe du Journal de l'Association canadienne des radiologistes et du *Canadian Journal of Kidney Health and Disease*, et a pour but d'informer les deux communautés concerné.

Keywords
iodinated contrast, prevention, risk stratification, acute kidney injury, contrast medium, contrast-associated AKI, contrast-induced AKI

Introduction

Iodinated contrast medium (ICM) is one of the most frequently administered pharmaceuticals, with an estimated 80 million doses administered globally in 2006. In Canada, over 5.4 million computed tomography (CT) examinations were performed in 2019, of which 50% were contrast enhanced.[1] In addition to CT, ICM is used for angiography and other interventional radiology and cardiology procedures. Acute kidney injury (AKI) occurring after ICM administration has historically been considered a common iatrogenic complication which was managed by screening patients, prophylactic strategies, and follow up evaluation of renal function. Although AKI associated with ICM administration is reversible (returning to baseline creatinine in 1-3 weeks), AKI in this setting is associated with a higher risk of both short- and long-term mortality.[2,3] To date, there have been no adequately-powered clinical trials showing that its prevention results in survival benefit, and the deprivation of contrast enhanced imaging may have important unintended clinical consequences,[4] most importantly a missed or delayed diagnosis.

Guidance on this topic requires interprofessional collaboration, given that contrast-enhanced diagnostic and therapeutic procedures are ordered by various specialties, performed by other specialists, and require management by nephrologists in the event that AKI develops. This document, which was

Table 1. Definitions/Terminology.

Term	Definition	Comment
Acute kidney injury (AKI)	Increase in creatinine >26 μmol/L in 48 hours, OR increase by >50%, which is known or presumed to have occurred within the 7 prior days OR urine output <.5 mL/kg/hour for 6 – 12 hours	Defined on basis of KDIGO criteria, with staging by severity[a]
Chronic kidney disease (CKD)	Abnormalities of kidney structure or function, present for >3 months, with implications for health	Defined on basis of KDIGO criteria, with staging by severity[a]
Contrast associated acute kidney injury (CA-AKI)	AKI (as defined above) after a contrast procedure, includes CI-AKI and other causes of AKI such as acute tubular necrosis, acute interstitial nephritis and atheroembolic disease	'Associated' makes the distinction that AKI cannot be directly attributed to contrast
Post contrast acute kidney injury (PC-AKI)	AKI (as defined above) following a contrast procedure same as CA-AKI in definition	Here, 'post contrast' is a descriptive term of chronology, not causation
Contrast induced nephropathy (CIN)	*Increase in creatinine of 44 μmol/L or 25% from baseline after contrast administration*	*Seen in older literature, implies causality which remains unproven; time point not well established, from 24 to 72 hours*
Contrast induced acute kidney injury (CI-AKI)	*AKI (as defined above) after a contrast procedure, which can be attributed to contrast-induced kidney damage*	*Definition assumes that contrast caused AKI, which is now felt to be very rare and/or unproven causality*

Abbreviation: KDIGO, kidney disease improving global outcomes.
See supplementary appendix for actual criteria. *NB: Italicized terms are historical and not recommended for use.*

developed by a multidisciplinary working group of radiologists and nephrologists, reviews the scientific evidence for contrast associated AKI (CA-AKI) and provides consensus-based guidelines for its prevention and management.

A summary of terms used in these guidelines is presented in Table 1. Contrast-associated acute kidney injury (CA-AKI), also known as post-contrast acute kidney injury (PC-AKI), is a general term used to describe a sudden deterioration in renal function that occurs within 48 hours after the intravascular administration of iodinated contrast medium. CA-AKI may occur regardless of whether the contrast medium was, or was not, the cause of the deterioration. Contrast-induced acute kidney injury (CI-AKI), formerly referred to as contrast-induced nephropathy (CIN), is a specific term used to describe AKI that is caused by the ICM administration; therefore, CI-AKI is a subgroup of CA-AKI.[5] Since the causal attribution of contrast leading to AKI is not clear, CA-AKI is the appropriate term used throughout this document, except in the sections describing the causal literature.

The Canadian Association of Radiologists last provided guidance related to CA-AKI in 2012.[6] A summary of what has changed between this document and the 2012 recommendations is detailed in Table 2.

Is Contrast-Induced Acute Kidney Injury a 'Myth'?

Over the last 4 decades, the perception of contrast-induced-AKI (CI-AKI) has evolved from being viewed as a common and widespread complication, to being questioned as a medical 'myth.' In an influential study from 1983, it was reported that contrast media was the third most common cause of AKI in the hospital setting, after hypovolemia and major surgery.[7] Unfortunately, this study was a small case series that included only admitted inpatients, lacked a control group of patients who did not receive contrast, and evaluated high-osmolar contrast media, which is no longer used. A 2006 study reported that of 3081 articles published between 1996 – 2004 and containing keywords such as "contrast" and "kidney failure," only 40 (1.3%) evaluated patients who received intravenous contrast, and only 2 had control groups of patients who did not receive contrast media.[8] Another study of over 32,000 hospitalized patients showed that fluctuations in creatinine levels are quite common: about 27% of inpatients have a 25% or greater rise in creatinine, even in the absence of any ICM administration.[9] A control group is important in such studies, since it allows for assessing the background incidence of AKI, which would be expected in patients who are unwell and undergoing computed tomography (CT) examinations for various indications, such as sepsis, or hypoperfusion. Some patients develop AKI from their underlying disease, or other concomitant causes, such as ischemic acute tubular necrosis due to renal hypoperfusion, drug induced acute interstitial nephritis, and atheroembolic renal disease.[10]

Subsequent studies using advanced statistical methods to control for confounding variables (propensity score-matched analyses) have failed to find evidence for true CI AKI, with limitations described below. These studies demonstrate that the incidence of AKI associated with contrast enhanced CT scans is no higher than with unenhanced CT scans (Table 3).[11-14] It is important to note that negative propensity score studies cannot be interpreted as 'CI-AKI is a myth'; however, the results do indicate that the incidence of true CI-AKI is far less than previously thought. However, propensity scoring only addresses known bias, and covariates captured in an administrative database; unknown biases and confounders are not accounted for as they would be in a randomized clinical trial (RCT). Although these studies are large (n > 10k), the number of patients with severely reduced kidney function (eg estimated glomerular filtration rate [eGFR] ≤ 30 mL/min/1.73 m^2) who are at highest risk for CI-AKI was low, with uncertainty persisting in this population. Paradoxically, some studies found a lower risk of AKI with contrast, compared to unenhanced scans, which reflects selection bias rather than any nephroprotective effect of contrast.[11,12] In the study by Davenport et al There was a slightly higher risk of AKI when grouping by eGFR (especially when eGFR ≤30 mL/min/1.73m2) but this finding has not been replicated in other studies.[2,14]

In summary, the role of contrast as the cause of AKI remains unproven and the risk of contrast as a cause of AKI is likely very low. However, there is currently insufficient evidence to claim that there is zero risk. **The risk, if any, is only important in patients with severe underlying chronic kidney disease (CKD) with an eGFR ≤ 30 mL/min/1.73m2, those with AKI, and/or those receiving a high volume of contrast especially through the arterial route.** Additionally, the above discussion on AKI after contrast relates to the occurrence of AKI as defined by a small rise in creatinine. The risk of severe AKI, including the need for renal replacement therapy (RRT), is several orders of magnitude lower.

Screening and Risk Stratification

Goals of Screening

The goals of screening are to identify patients at risk of preventable kidney function decline associated with the use of ICM. Since the publication of the 2012 Canadian Association of Radiologists guidelines,[6] new research has significantly reduced our estimates of the risk associated with the use of ICM; and at the same time research has increased our awareness of the negative clinical impacts of delayed imaging or suboptimal imaging done without ICM.[17] The guidance on screening has been summarised in Figure 1.

Table 2. Changes to recommendations between 2012 and 2022 guidelines.

	2012 CAR Consensus Guidelines for the Prevention of Contrast-Induced Nephropathy(6)	What's New for 2022
Screening: eGFR requirement for outpatients	Serum creatinine (and eGFR) should be obtained within 6 months in the stable out-patient with 1 or more risk factors but without significant renal impairment. (Table 1 from 2012 guidelines with 13 risk factors)	Simple screening questionnaire: "Do you have kidney problems or a kidney transplant?" and "have you seen, or are you waiting to see a kidney specialist or urologist (kidney surgeon)?" Creatinine/eGFR required only if 'yes' to this question
Inpatients	Obtain eGFR within 1 week for in-patients and patients with unstable or acute renal disease	Current eGFR (within 7 days for inpatients, or upon presentation for ER patients), however this should not delay emergent imaging examination
Emergent setting	In patients who are acutely ill, delays in imaging while awaiting serum creatinine level results may adversely affect patient care. In situations in which the contrast procedure cannot be delayed, if the patient's medical history reveals 1 or more risk factors, then preventive measures (particularly preprocedural fluid administration) should be implemented empirically	For emergent presentation an indicated contrast enhanced imaging study should proceed without delay
Contrast use in acute kidney injury	As above	Use of intravenous or intraarterial contrast in the setting of pre-existing AKI should consider the trade-off of overall risk of worsening AKI with contrast against the benefit of improved diagnostic capability and therapeutic intervention
Risk stratification	eGFR >60 mL/min/1.73 m^2: Very low risk eGFR 45 - 59 mL/min/1.73 m^2: Low risk eGFR 30 - 44 mL/min/1.73 m^2: Moderate risk eGFR <30 mL/min/1.73 m^2: High risk	eGFR >30 mL/min/1.73 m^2 then proceed with an indicated contrast imaging study If eGFR ≤30 mL/min/1.73 m^2, individual patient decision to explain and balance the risks of CA-AKI against the risks and uncertainties of delayed or suboptimal imaging
Contrast use in dialysis patients	Patients undergoing hemodialysis need not be fluid loaded before contrast administration. Coordination of contrast administration with the timing of hemodialysis is unnecessary. Nephrotoxicity remains a concern in patients who retain residual function, and in these patients, renal protective measures may be considered	Imaging with ICM can be performed in patients on peritoneal or hemodialysis regardless of residual urine output and no change in dialysis schedule is required
Prophylaxis: Hydration	eGFR >60 mL/min/1.73 m^2: Require no specific prophylaxis or follow up eGFR 45-59 mL/min/1.73 m^2: IV contrast, no specific prophylaxis or follow up. Intraarterial and additional risk factors: Preventative measures are recommended eGFR <45 mL/min/1.73 m^2: Preventive measures are recommended. IV hydration is recommended for patients who receive IA contrast. For IV contrast administration, either oral or IV hydration could be used; eGFR <30 mL/min/1.73 m^2: IV hydration is preferred for prophylaxis	eGFR >30 mL/min/1.73 m^2: No need for hydration eGFR ≤30 mL/min/1.73 m^2, intravenous ICM, there is a lack of evidence on benefit of volume expansion; institutions may choose practices best suited to their local environments eGFR ≤30 mL/min/1.73 m^2, intraarterial ICM, some endorsed a strategy of volume expansion using either intravenous hydration (with .9% saline or 1.26% sodium bicarbonate) or oral salt and water. Given insufficient evidence the use of hydration or not, and the route of hydration was best left to judgment of the practitioner
Pharmacological prophylaxis: N-acetylcysteine	Consider N-acetylcysteine in moderate to high risk (eGFR <45 mL/min/1.73 m^2)	Do not recommend N-acetylcysteine use for the prophylaxis of CA-AKI.

(continued)

Table 2. (continued)

	2012 CAR Consensus Guidelines for the Prevention of Contrast-Induced Nephropathy(6)	What's New for 2022
Pharmacological prophylaxis: Other drugs	No recommendations	Do not recommend initiating statins specifically for prevention of CA-AKI. Do not recommend use of other pharmacological agents, including theophylline, prostaglandin E1, nicorandil, ascorbic acid, allopurinol, alpha-tocopherol, fenoldopam, natriuretic peptides, and trimetazidine
Choice of contrast	Use an iso-osmolar or low-osmolar CM in patients with eGFR <45 mL/min/1.73 m^2 for IV CM use and eGFR <60 mL/min/1.73 m^2 for IA CM studies A higher risk of iohexol compared with iodixanol cannot be entirely ruled out	Do not recommend preferential use of iso-osmolar ICM for reducing risk of CA-AKI. We recommend decisions about low-osmolar or iso-osmolar ICM be made based on other factors (e.g., cost and availability)
Volume of contrast	If possible, reasonable attempts to minimize contrast volume should be made. Use of the lowest concentration of iodinated contrast, in mg/mL, required to achieve satisfactory image quality is encouraged	Reduced dosing of IV contrast administration for CT examinations is discouraged because it will lower parenchymal enhancement; use the appropriate IV dose for high quality CT imaging in all patients For IA interventions a pragmatic approach is recommended using the necessary dose to achieve the diagnostic and therapeutic results but judiciously reducing dose when adjunctive imaging and doses are low yield or can be delayed
Repeat contrast exposure	If possible, reasonable attempts to avoid repeated injections within 72 hours should be made	Do not recommend restricting medically indicated repeat contrast doses in lower risk patients (eGFR >30, no AKI, IV route) Avoid repeated contrast exposures within 48 hours for elective procedures if the patients at higher risk of CA-AKI (GFR ≤30, AKI, intraarterial ICM administration) However, in the face of life-threatening illness, repeat dosing of ICM may be necessary and justified to establish a confident diagnosis and treatment plan
Dialysis prophylaxis	In patients who are already receiving renal replacement therapy, dialysis after CM administration may be helpful in individual situations only if volume loading has occurred	Do not recommend any form of post ICM administration renal replacement therapy, either dialysis or continuous renal replacement therapy
Metformin	In patients with eGFR <45 mL/min/1.73 m^2, metformin should be stopped at the time of contrast injection and should not be restarted for at least 48 hours and only then if renal function remains stable (<25% increase compared with baseline creatinine) It generally is unnecessary to stop metformin 48 hours before contrast injection, but special care should be taken in patients with severe or acute renal dysfunction	Do not recommend stopping metformin for patients with eGFR >30 mL/min/1.73 m^2 In patients with eGFR ≤30 mL/min/1.73 m^2 or AKI, metformin should be held at the time of, or prior to, ICM administration, and should not be restarted for at least 48 hours and only then if kidney function remains stable (<25% increase compared with baseline creatinine) and the ongoing use of metformin has been re-assessed by the patient's clinical team
Other drugs	Hold nephrotoxic drugs	Do not recommend routinely discontinuing renin angiotensin system inhibitors (ACEi and ARBs) or diuretics prior to, or after, ICM administration

(continued)

Table 2. (continued)

	2012 CAR Consensus Guidelines for the Prevention of Contrast-Induced Nephropathy(6)	What's New for 2022
Follow up kidney function	A follow-up creatinine level measurement is recommended 48-72 hours after CM injection in all patients who receive IA CM	Recommend a follow-up serum creatinine measurement 48 to 72 hours only after intra-arterial ICM injection in all patients with eGFR ≤30 mL/min/1.73 m^2
	A follow up creatinine level measurement should be considered in those who receive IV CM with eGFR <45 mL/min	For the remainder of patients, the risk of AKI is extremely low, and routine testing is not warranted
		However, any at-risk patient should be instructed to seek medical attention and kidney function testing if they develop increased shortness-of-breath, peripheral edema, or note a marked decline in urine output in the days following the imaging test

Abbreviations: eGFR, estimated glomerular filtration rate; CM, contrast media; ICM, intravascular contrast media; CIN, contrast induced nephropathy; CA-AKI, contrast associated acute kidney injury; AKI, acute kidney injury; IA, intraarterial; IV, intravenous; ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.
Notes on changes in terminology: CIN (2012) to CA-AKI (2022); eGFR units ml/min (2012) and ml/min/1.73 m^2 (2022); CM (2012) and ICM (2022).

Table 3. Major Epidemiological Studies of Contrast and Acute Kidney Injury.

Study	Major Finding	Comments
Hou et al (1983)[7]	N = 129 contrast (16/129) was identified as the third most common cause of AKI in the hospital setting	Applied only to inpatients; in 1983 awareness of CI-AKI was lower than now for patient selection; high osmolar contrast media were used
Newhouse et al (2008)[9]	N = 32,161 Retrospective study that demonstrated that 25% increase in creatinine is common (27%) in hospitalized patients, even without contrast use	First major study to question the true incidence of 'CI-AKI'
McDonald et al (2013)[11]	N = 53,439 patients and 157,140 scans propensity score matched analysis reported no difference in AKI risk with/without contrast	Large, well-done study reporting no increase in AKI risk with contrast; cannot rule out residual confounding and underlying selection bias
Davenport et al (2013)[14]	N = 17,652 patients propensity score matched analysis reported increased incidence of AKI with underlying CKD	Large, well-done study reporting graded small increase in AKI risk with contrast only in those with underlying severe CKD eGFR >60 mL/min/1.73 m^2; OR 1.00, 95% CI 0.86 – 1.16 eGFR 45 – 59 min/1.73 m^2; OR 1.06, 95% CI 0.82 – 1.38 eGFR 30 - 44 mL/min/1.73 m^2; OR 1.40, 95% CI 1.00 -1.97 eGFR ≤30 mL/min/1.73 m^2; OR 2.96, 95% CI 1.22 – 7.17
Wilhelm-Leens et al (2017)[12]	N = 5,922,537 hospitalized patients Incidence of AKI with contrast was 5.5%, with no contrast 5.6%	Largest study, however timing of contrast and AKI unclear Adjusted analysis reported lower risk of AKI with contrast (OR .93, 95% CI 0.88 to .97)
Aycock et al (2018)[15]	N = 28 studies, 107,335 patients Contrast CT scans not associated with AKI, need for RRT or all-cause mortality	Meta-analysis of observational studies, susceptible to same biases as underlying studies
Goulden et al (2021)[16]	N = 29,830 in emergency getting a D-Dimer tested CTPA not associated with long term kidney function, or need for dialysis	Using regression discontinuity methodology reduced residual confounding and selection bias; CTPA typically requires smaller amount of contrast, and mean eGFR was 86 in this cohort

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CI-AKI, contrast induced acute kidney injury; CT, computed tomography; OR, Odds Ratio; CI, confidence interval; CTPA, computed tomography pulmonary angiogram; eGFR, estimated glomerular filtration rate.

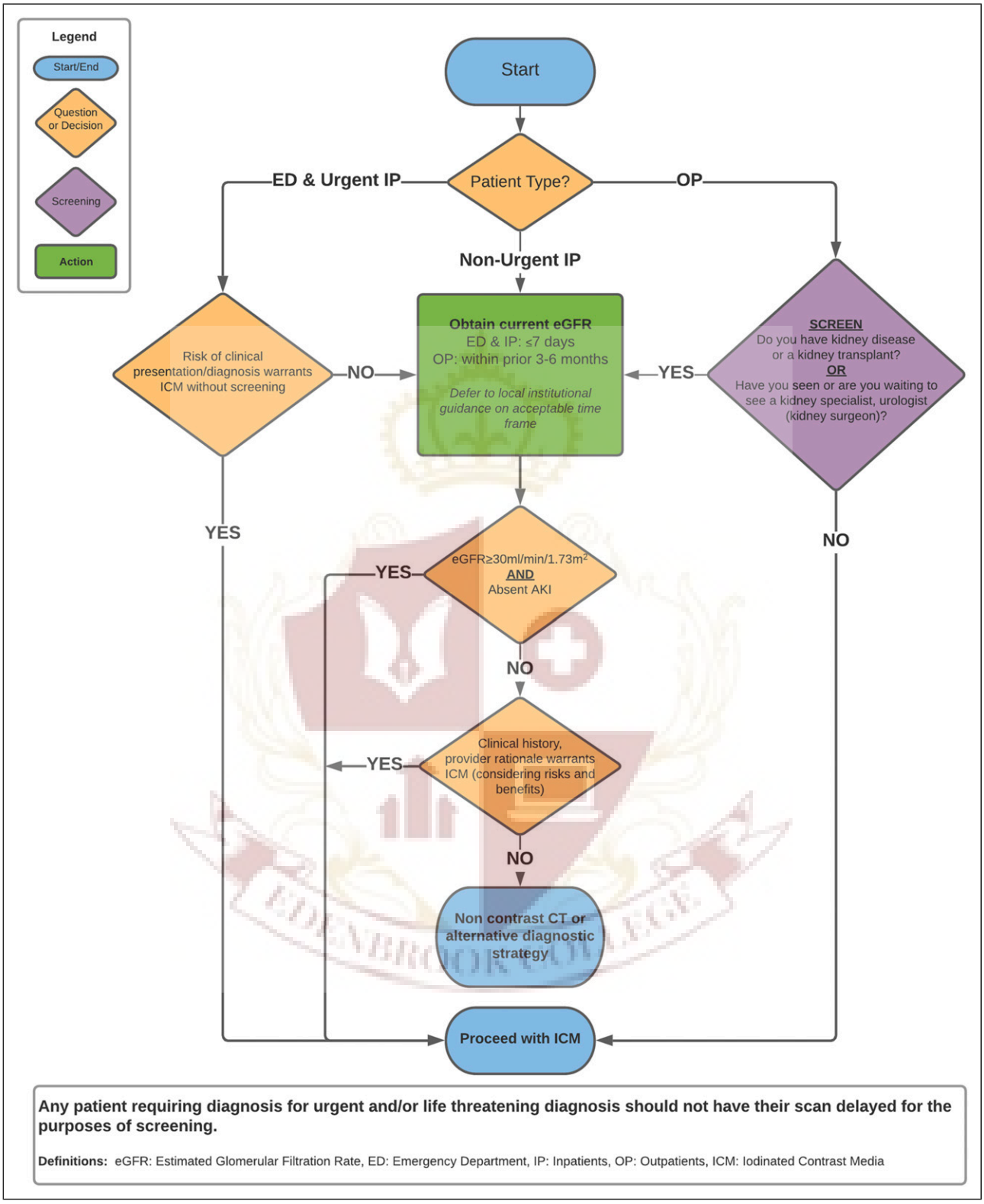


Figure 1. Iodinated contrast media guide.

Chronic Kidney Disease

The most important predictors of CA-AKI are the presence of CKD, and AKI from other causes. Risk can be stratified according to the Kidney Disease Improving Global Outcomes (KDIGO) staging (see Supplementary Table 1). Comorbidities, such as diabetes, exposure to nephrotoxic agents, hypovolemia, and congestive heart failure (CHF), are associated with CA-AKI. Similarly, having a single kidney, including a transplant kidney, can help to identify patients more likely to have CKD, However, none of these factors have been shown to be independent of eGFR.[2,43]

Patients with normal kidney function and those with stable mild or moderate CKD are considered at negligible risk regardless of other factors. Only those with severe CKD (eGFR ≤30 mL/min/1.73 m^2), and those with pre-existing AKI are at risk of CA-AKI.

The process of screening should allow the triage of most patients with small or negligible risk to receive a medically indicated contrast enhanced CT scan without undue cost or delay. The screening should also flag those with an increased risk to a more intensive screening and prevention process with 3 targeted interventions:

1. Measure kidney function using eGFR
2. Decide whether ICM or an alternate imaging strategy can best address the clinical question
3. In at-risk patients that require ICM, consider prophylactic strategies

Specific Risk Groups

Outpatients with known eGFR: When the eGFR is known it should be used in the decision regarding the use of ICM. When the requisition indicates a history of kidney disease and no eGFR is available, the working group recommends that there be an automatic trigger for ordering an eGFR. For a stable outpatient, an eGFR within 3-6 months was considered acceptable by the workgroup. However, if the history indicates kidney injury, then a shorter interval would be more appropriate, and if the history indicates stability in renal function, then a longer interval may be appropriate.

Outpatients without a known eGFR: For patients without an eGFR and without a reported history of kidney disease, we recommend a simple screening questionnaire such as: *"Do you have kidney problems or a kidney transplant? Have you seen or have you been referred to see a kidney specialist (nephrologist) or a urologist?"* If the answer is *YES,* an eGFR is required before protocoling the study with ICM. If the answer is *NO,* an indicated ICM examination can proceed without an eGFR value.

Emergency patients: In the emergency setting, a detailed history and eGFR may not be immediately available. Attempts should be made to determine the exam urgency, patient prognosis, and obtain the current, and baseline renal function. **When a patient is facing a life-threatening illness indicated examinations with ICM should not be withheld for fear of CA-AKI.** Referring healthcare providers and radiologists must weigh the benefits of a contrast enhanced CT versus the very small, theoretical risk of a transient AKI. In patients in whom that risk is considered to outweigh the benefits of ICM administration, other options to consider are the use of non-enhanced CT with a radiologist check, or other imaging modalities. When other imaging strategies are inferior or impractical, ICM use may be the best option for the patient. Meta-analyses from the emergency medicine and stroke literature suggest that there is minimal AKI risk with ICM use in these settings.[12,18,19]

Inpatients: the working group recommends that the decision to proceed with ICM is made after reviewing the most current eGFR obtained not more than 7 days prior to the planned injection. When eGFR ≤30 mL/min/1.73 m^2 or if AKI is suspected then the inpatient care team or ordering physician should clearly indicate in the requisition that the study should proceed with ICM if needed for diagnosis. When this is unclear, the radiologist may proceed with ICM if the condition is urgent (e.g. stroke code, pulmonary embolism, other high-risk unstable presentations) or if there is no practical substitute for ICM enhanced scan.[20] If the scenario is uncertain, then the radiologist should contact the referring physician to discuss the urgency of the test and weigh the potential benefits and harms of administering vs with-holding ICM.

Contrast use in AKI setting: In patients with AKI, risk stratification according to kidney function is not possible as eGFR measurement is unreliable.[21] While patients with AKI might be more susceptible to nephrotoxin induced kidney damage than those without AKI, no controlled studies report on this risk. Given the current paucity of evidence,[5] a cautious approach might favour avoiding ICM. Nonetheless, in these patients, the potential risk of developing CA-AKI must again be weighed against the risk from delayed or missed diagnoses by avoiding ICM. Regarding the use of intra-arterial contrast in such patients, although the risk of CA-AKI may be higher overall, it is frequently indicated in the acute setting for potentially life- or limb-saving diagnostic and therapeutic procedures. Under these circumstances, the overall benefits are likely to outweigh the risks. Thus, as is the case in any clinical context, the use of contrast in patients with pre-existing AKI requires clinical judgement with respect to the overall risks, benefits and available alternatives.

Chronic dialysis patients: It is widespread practice to use ICM for indicated examinations in *anuric* dialysis patients as the risk of loss of renal function is nonexistent. There is no

need to change the dialysis schedule; dialysis at the usual predetermined timing is the least disruptive and customary practice. Some dialysis patients have residual urine output ('residual renal function') such as peritoneal dialysis patients, or patients within the first few months of starting hemodialysis. Historically, it was believed that ICM could further reduce renal function in this setting. However, a systematic review of 9 studies reveals that there is little effect of ICM on residual renal function (weighted difference in means −.16 mL/min, 95% confidence interval −.66 to .34 mL/min; P = .53).[20] Thus, the presence or absence of residual urine output should not influence the decision to use ICM in dialysis patients. **In summary, ICM can be given to patients on peritoneal or hemodialysis regardless of residual urine output and no change in dialysis schedule is required.**

Safety of Repeat Contrast Administration

Two studies have demonstrated the occurrence of CA-AKI in patients that received a second dose of CM within 48 hours of their first.[22,23] Neither of these studies specifically examined whether the risk of CA-AKI was increased relative to having had only a single contrast exposure or none at all.[5]

Given the lack of evidence in this area, the working group considered it prudent to avoid repeated contrast exposures for 48 hours for elective procedures in patients considered at higher risk of CA-AKI (eGFR ≤30, AKI, high-volume intra-arterial ICM administration).[24] The working group did not recommend restricting repeat contrast doses in lower risk patients (eGFR ≥ 30, no AKI, IV route). The working group did not recommend withholding repeat doses for emergency or inpatients who have life-threatening, or acute presentation of illness. Examples include a nondiagnostic CT pulmonary angiogram, short-term repeat evaluations of trauma, surgical complications and during vascular interventions. **In the face of life-threatening illness, repeat dosing of ICM may be necessary and justified to establish a confident diagnosis and treatment plan.**

Summary

Screening for at-risk patients is thought to be beneficial. . However, this must be balanced with the significant benefits of contrast enhanced diagnostic and therapeutic procedures. These screening guidelines focus on balancing risks (risk of CA-AKI, patient delays, and healthcare costs) as well as significant benefits of timely diagnostic tests with ICM. The vast majority of patients having diagnostic tests and procedures with ICM will not experience a significant or permanent worsening of renal function, dialysis, or increased morbidity.

Arterial Contrast Administration

There is some evidence that the risk of CA-AKI is increased with the administration of intra-arterial ICM compared to the administration of intravenous ICM.[25] For elective diagnostic procedures requiring intraarterial ICM, a similar approach to intravenous ICM is recommended with an acknowledgment that there might be an increased risk. In the setting of therapeutic procedures, the risk to the kidneys must be balanced against the benefits of the proposed treatment and the risks associated with an alternate procedure not requiring intra-arterial ICM, if available. With therapeutic procedures requiring ICM, alternates are rarely available or clinically appropriate, and ICM administration may be necessary, even in high-risk settings (e.g., with eGFR <30 mL/min/1.73 m^2). This decision should be made by the care team in discussion with the patient, or family/alternate decision maker.

Prophylactic Measures

In this section, we discuss the evidence for various pharmaceutical agents and strategies to minimize the risk of CA-AKI.

N-Acetylcysteine

N-acetylcysteine (NAC) is a mucolytic and can act as an antioxidant by regenerating glutathione. Since reactive oxygen species were initially thought to be involved in the pathogenesis of CI-AKI, there was some rationale for trying NAC in this setting. The initial small RCT was encouraging and reported a large benefit in lowering AKI, and given that this molecule is easy to administer, use became widespread.[26] However, subsequent trials showed mixed results. In the last decade, 2 large RCTs that together enrolled more than 7000 patients have settled this issue, with conclusive evidence that NAC use does not protect from the development of CA-AKI.[27,28] Some intriguing recent evidence suggests that NAC may actually have an artifactual effect on creatinine measurement, rather than on the physiology of nephrotoxicity.[29,30] **Thus there is strong evidence against prophylactic use of NAC for CA-AKI.**

Hydration or Volume Expansion

The data on the need for volume expansion, and the type of fluid used are summarised in Table 4. Briefly, there is high quality evidence to support that in those with eGFR >30 mL/min/1.73 m^2 undergoing elective ICM administration, there is little benefit with intravenous (IV) hydration compared to no hydration.[31,32] There is insufficient evidence to support or refute the current widespread practice of hydration (IV or oral) at or below eGFR 30 mL/min/1.73 m,^{2}, compared to no hydration. Additionally, there is low quality evidence that oral hydration may be as effective as IV hydration.[33] **There is a lack of evidence to either support or refute the use of hydration for prophylaxis of CA-AKI in high-risk patients (severe CKD, eGFR ≤30 mL/min/1.73 m^2). As such, the working group makes no recommendation in this regard**

Table 4. Summary of the literature with volume expansion and hydration.

Trial	Study Details	Main Findings	Comments
Solomon et al (1994)	N = 78, undergoing coronary angiography compared *.45% saline alone* vs *Saline + mannitol* vs *Saline + furosemide*	.45% saline superior to other 2 groups (events 3/28 vs 7/25 and 10/25 respectively; *P* = .05)	This was the definitive trial for superiority of volume expansion, but had no control group (without volume expansion)
Mueller et al (2002)	N = 1620, undergoing coronary angioplasty compared *.9% saline* vs *.45% saline + 5% glucose*	.9% saline superior to .45% saline +5% glucose (events 5/685 vs 14/698 respectively, *P* = .04)	Normal saline became standard of care after this study
Merten et al (2004)	N = 119, undergoing any contrast procedure (venous or arterial) compared *sodium bicarbonate (mixed in 5% dextrose)* vs *.9% saline*	Bicarb superior to saline (events 1/60 vs 8/59, *P* = .02)	Volume expansion was delivered over 1 hour pre- and 4 hours post-procedure, which made the protocol popular, and lead to greater use of sodium bicarbonate-based volume expansion
Hiremath et al (2013)	Systematic review of trials comparing oral hydration (salt and/or water) vs intravenous hydration	Six trials (513 patients) relative risk 1.19 (95% CI 0.46, 3.10, *P* = .73)	Study suggests no difference between the oral and intravenous routes of volume expansion
Nijssen et al (AMACING, 2017)	N = 660, receiving contrast (arterial or venous) compared *.9% saline* vs *no prophylaxis*	No difference (events 8/296 in hydrations vs 8/307 in control)	Non-inferiority design, in intermediate risk patients demonstrating safety of no hydration when eGFR >30
Weisbord et al (PRESERVE, 2017)	N = 4993, receiving arterial contrast compared *.9% saline* versus *1.26% sodium bicarbonate*	No difference (events 110/2511 in bicarb vs 116/2482 in saline)	Established that sodium bicarbonate was not superior to saline, reversing the findings of Merten et al, 2004
Timal et al (KOMPAS), 2020	N = 523, receiving venous contrast compared *1.26% sodium bicarbonate* vs *no prophylaxis*	No difference (7/262 in no prophylaxis vs 4/261 in bicarbonate)	Non-inferiority design, in intermediate risk patients, along with Nijssen et al, 2017, establishing the safety of no hydration when eGFR >30

and institutions may choose practices best suited to their local environments.

The working group recognizes that organizing IV hydration may be logistically challenging in some patients. Thus, if volume expansion is being considered, either oral or IV hydration may be utilized in these patients for CA-AKI prophylaxis, acknowledging the low certainty of the benefit of this approach. For choice of IV hydration, bicarbonate-based fluid does not provide any added benefit to the use of normal saline for volume repletion around contrast administration. .9% saline is easier to procure and administer, so would be the preferable option, though bicarbonate-based fluids may be used as being equivalent if local factors, protocols, or convenience support this. Some members of the working group endorsed a strategy of hydration and volume expansion more strongly for high-risk patients receiving IA ICM. However, there is insufficient evidence to support the benefits and the working group felt this was best left to judgement of the practitioner.

Contrast Dose

Higher doses and repeat dosing of contrast have been associated with a higher risk of CA-AKI.[34,35] However, confounding by indication may contribute to the observed incidence. For example, technically complicated procedures in high-risk patients may receive higher contrast doses, particularly for some cardiac interventions. Extrapolating this to routine clinical doses in lower risk clinical scenarios is likely to result in suboptimal scans with little or no safety benefit. Reduced dosing of IV contrast administration for CT examinations is discouraged because it will lower parenchymal enhancement and deviate from established high quality protocols. The working group recommend using the appropriate IV dose for high quality CT imaging in all patients. For IA interventions a pragmatic approach is recommended using the necessary dose to achieve the diagnostic and therapeutic results but judiciously reducing dose when adjunctive imaging and doses are low yield or can be

delayed (such as ventriculography after cardiac catheterization).[36]

The physico-chemical characteristics of the contrast media also have a role to play in its nephrotoxicity. Until a few decades ago, ionic and high osmolar contrast media were used, with osmolality greater than 1200 mOsm/L. Since then, non-ionic and low-osmolar (osmolality typically ~600 mOsm/L) as well as iso-osmolar contrast media have been developed, and these are the only agents now used globally. There is convincing evidence from a meta-analysis with data from 31 RCTs that there is lower risk of CA-AKI (relative risk [RR] .61, 95% .48 – .77) with low-osmolar compared to high-osmolar contrast media.[37]

With respect to low vs iso-osmolar contrast media, the literature is mixed. A small initial RCT showed a large benefit in favour of iso-osmolar contrast, but subsequent RCTs and meta-analyses have conflicting and heterogenous results.[38] As an example, moderate statistical heterogeneity was reported in this meta-analysis of 25 RCTs with an overall RR of .75 (95% CI 0.44 – 1.26).[39] The authors resolved the heterogeneity by grouping low-osmolar contrast into iohexol (RR for iodixanol versus iohexol .45, 95% CI 0.26 – .76) and all other low-osmolar contrast (RR .97, 95% CI 0.72 – 1.32). Another 2017 systematic review included 10 RCTs, and demonstrates no added benefit with using iso-osmolar contrast media compared to low-osmolar (RR .72, 95% CI 0.50 – 1.04).[40] Any possible observed benefit was attenuated further when the analysis was restricted to large RCTs with sample size more than 250, as a surrogate for trial quality (RR .93, 95% CI 0.66 -1.30). Thus, overall, there is little difference for AKI events between iso-osmolar and low-osmolar contrast in a high-risk setting, and hence a negligible difference in low-risk setting (venous contrast) for clinically meaningful outcomes. **Hence the choice of contrast media between low- and iso-osmolar should be made based on other considerations (e.g., cost, availability).**

Dialysis

Renal replacement therapy (RRT) in the form of hemodialysis or hemofiltration has been tried as a prophylactic strategy, which is paradoxical since the reason to prevent CA-AKI is to avoid dialysis and related morbidity. Physiologically, intravenously injected ICM reaches the kidney within a few cardiac cycles, and subsequent extracorporeal removal of circulating contrast would be unlikely to have any beneficial effect. RRT also lowers serum creatinine, hence leading to a spurious reported benefit in outcomes when measured as a change in serum creatinine in some trials.[41] A 2006 systematic review,[42] and another larger subsequent trial[43] reported no benefit with RRT in AKI after contrast, as expected. The RRT procedure itself is associated with complications associated with catheter placement and hemodynamic instability, and increased healthcare resource utilization. **There is no role for prophylactic RRT in the setting of contrast administration.**

Statins

Statins have been trialed in preventing CA-AKI, mostly in the setting of coronary angiography and percutaneous coronary interventions. There is no clear mechanism by which statins should provide renoprotection, apart from their pleiotropic roles.[44] Most, if not all, RCTs with statins are in the setting of coronary angiography, and it may be argued that these patients with pre-existing cardiovascular disease should be on a statin anyways for cardiovascular protection. Patients at elevated risk of AKI after contrast, specifically those with eGFR ≤30 mL/min/1.73 m,[2], are also at higher cardiovascular risk.[45] Thus, though the mechanism and evidence for AKI prevention in this setting for statins is not strong, there is no signal for harm as well, and the working group acknowledges that statins may be used for cardiovascular prevention in this population. However, **the use of statins for the sole purpose of prophylaxis for CA-AKI is not recommended.**

Other Agents

Several other pharmaceutical agents have been tried for prevention of PC-AKI, including theophylline,[46] prostaglandin E1,[47] nicorandil,[48] ascorbic acid,[49] allopurinol,[50] alpha-tocopherol,[51] fenoldopam, natriuretic peptides,[44] and trimetazidine.[52] Though some of these trials report a small benefit, these trials are small, and with unclear benefit in clinical outcomes, like the initial NAC trials. Unless large RCTs demonstrate any clinical benefit, **there is no role to use these agents for CA-AKI prophylaxis in the contrast setting.**

Drug Interactions With Contrast: Metformin, RAS Inhibitors, Diuretics

Metformin is not a risk factor for developing CA-AKI and the injection of ICM is not contraindicated in patients receiving it. However, serious complications (metformin-associated lactic acidosis (MALA)) may rarely occur in patients taking metformin who subsequently develop CA-AKI. For this reason, metformin has often been held in patients undergoing studies with intravascular ICM. Whether this should be done at the time of, or 48 hours before, contrast injection and whether metformin must be held in all patients or only those with underlying kidney disease is controversial. The monogram for Glucophage (metformin) (Merck Sante Corporation, Lyon, France) in the Compendium of Pharmaceuticals and Specialities[53] recommends that metformin be discontinued at the time of, or prior to, any planned contrast exposure and be

withheld for 48 hours afterwards, only being reinstituted after kidney function has been confirmed to be stable. In general, this guidance has gradually been superseded by less restrictive recommendations as evidence has accumulated that, independent of kidney function, the overall risk of MALA precipitated by metformin accumulation due to CA-AKI is exceptionally low in the absence of other concurrent acute medical conditions such as sepsis and/or AKI.

In this context, the ACR Manual on Contrast Media[5] now recommends that, in patients with eGFR >30 and without evidence of AKI, metformin need not be stopped prior to ICM administration and there is no need for testing to evaluate kidney function afterwards. Similarly, the European Society of Urogenital Radiology which had also previously endorsed a more conservative approach[54] now recommends continuing metformin at the time of contrast injection in patients with a baseline eGFR >30 mL/min/1.73 m2 (except patients with AKI or those receiving intra-arterial contrast with first-pass kidney exposure).[55] In our opinion, this less restrictive approach regarding metformin is warranted. Since the risk to patients is extremely low,[56] we consider it unnecessary to hold metformin or to recheck kidney function in patients with normal to moderately-impaired baseline kidney function. **For patients with AKI or an eGFR ≤ 30 mL/min/1.73 m^2, it remains appropriate to stop metformin at the time of, or prior to, ICM injection.** For these patients, ongoing use of metformin carries a higher risk of MALA irrespective of ICM administration. Therefore radiologists/radiology departments should advise these patients to withhold metformin, and only restart the medication after discussion with the requesting physician (or a physician knowledgeable about their diabetes management plan).

Renin-angiotensin system (RAS) inhibitors such as ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are commonly prescribed blood pressure medications that exert an effect on intraglomerular hemodynamics. In doing so, ACEi/ARBs might theoretically trigger or worsen AKI in the context of ICM exposure. A recent systematic review and meta-analysis analyzed the effect of holding ACEi/ARBs prior to coronary angiography.[57] This meta-analysis reported that discontinuation of ACEi/ARB did not decrease AKI risk (RR 1.48, 95% CI 0.84, 2.60]).[14] **As such, the current evidence suggests that there is no meaningful benefit of discontinuing ACEi/ARB prior to contrast injection**.

Although diuretic use has been previously shown to be a risk-factor for CA-AKI,[14] the extent to which this is a causative relationship is unknown. Volume depletion in patients who are 'over-diuresed' could theoretically contribute to a higher likelihood of, and more severe, CA-AKI. Yet there are also obvious risks to holding diuretics in patients who require them to maintain euvolemia. Diuretic discontinuation can precipitate fluid overload which, in addition to presenting a risk for pulmonary edema and other negative outcomes, may itself be detrimental to kidney function.[58] **Currently, there is insufficient evidence to support routinely holding diuretics prior to contrast injection and the theoretical foundation for doing so is considered weak.**

Post Contrast Administration Considerations

Follow up

CA-AKI is diagnosed based on serum creatinine measurement after ICM administration. Typically, CA-AKI is defined by an elevation of creatinine of 26 μmol or higher. However, these are clinical research definitions of AKI, and do not necessarily meet any threshold for symptoms, or necessitate management change. Routine measurement of creatinine in this setting is logistically difficult to arrange, and will provoke unnecessary anxiety for patients, and extra healthcare resource utilization with no clear benefit. Hence routine measurement of creatinine should be reserved for those with extremely high risk of CA-AKI. **A follow-up serum creatinine measurement is therefore recommended 48 to 72 hours only after intra-arterial ICM administration in patients with eGFR ≤ 30 mL/min/1.73 m^2. For the remainder of patients, the risk of AKI is considered sufficiently low that routine testing is not warranted.** However, other at-risk patients should be instructed to seek medical attention should they develop increased shortness-of-breath or peripheral edema and/or note a marked decline in urine output in the days following the procedure, which can trigger testing for kidney function.

Management of CA-AKI

As discussed above, there is no role for routine extracorporeal removal of ICM with dialysis. If CA-AKI occurs we suggest that clinical evaluation and management of AKI due to CA-AKI be undertaken according to the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for AKI[21] and taking account of the Canadian Society of Nephrology (CSN) commentary on those guidelines.[59]

Summary of Recommendations

Risk Stratification Statements

These screening guidelines focus on balancing risks (risk of CA-AKI, patient delays, and healthcare costs) as well as significant benefits of timely contrast enhanced diagnostic imaging.

1. For **stable outpatients** without a current (3- 6 months depending on institutional preference) eGFR on file, and those without a provided history of CKD on the requisition, we recommend a simple screening questionnaire to detect those who may have AKI or severe CKD:

"Do you have kidney problems or a kidney transplant?"

"Have you seen, or are you waiting to see a kidney specialist or urologist (kidney surgeon)?"

a. When the patient or substitute decision maker (SDM) answers ***YES*** to the either question they should have

blood work drawn for a **current eGFR before protocoling** the study with ICM.

b. If the patient (or SDM) answers ***NO*** then an indicated ICM examination can **proceed** without a current eGFR value.

2. We recommend a current eGFR (within 7 days for inpatients, or upon presentation for ER patients), however this should not delay emergent imaging examination.
   a. **Emergent presentation.** When the patient is in an emergent presentation (such as suspected acute stroke, pulmonary embolism, acute aortic syndrome, bowel ischemia or perforation, and other conditions) an indicated contrast enhanced imaging study should proceed without delay. **Do not delay for eGFR and do not withhold contrast that is necessary for an accurate diagnosis of the emergent pathology.**
   b. Use of intravenous or intra-arterial contrast in the setting of pre-existing AKI should consider the trade-off of overall risk of worsening AKI with contrast against the benefit of improved diagnostic capability and therapeutic intervention.

3. For **non-emergent presentation** of stable outpatients, inpatients, and emergency patients when eGFR is available.
   a. If **eGFR >30 mL/min/1.73 m^2** and no signs and symptoms of AKI, then **proceed** with an indicated contrast imaging study. If **eGFR ≤30 mL/min/1.73 m^2**, or suspected AKI we recommend an **individual patient decision** involving the caring team, or patient/patient decision-maker to explain and balance the risks of CA-AKI against the risks and uncertainties of delayed or suboptimal imaging.
   b. Imaging with ICM can be performed in patients on peritoneal or hemodialysis regardless of residual urine output and no change in dialysis schedule is required.

Choice of Contrast

4. We do not recommend preferential use of iso-osmolar ICM for reducing risk of CA-AKI; those decisions should be made based on other factors (e.g., cost and availability).
5. We discourage reduced dosing of IV contrast administration for CT examinations since that lowers parenchymal enhancement and recommend using the appropriate IV dose for high quality CT imaging in all patients.
6. We recommend a pragmatic approach to ICM dosing for IA interventions using the necessary dose to achieve the diagnostic and therapeutic results but judiciously reducing dose when adjunctive imaging and doses are low yield or can be delayed.
7. We do not recommend restricting repeat contrast doses in lower risk patients (eGFR >30, no AKI, IV route) or withholding repeat doses for emergency or inpatients who have life-threatening, or acute presentation of illness. We do recommend avoiding repeated contrast exposures within 48 hours for elective procedures if the patients at higher risk of CA-AKI (eGFR ≤30, AKI, intraarterial ICM administration). However, in the face of life-threatening illness, repeat dosing of ICM may be necessary and justified to establish a confident diagnosis and treatment plan.

Prophylaxis of CA-AKI

8. We do not recommend oral or intravenous hydration for patients with eGFR >30 mL/min/1.73m2, receiving intravenous or intra-arterial ICM.
9. For patients with eGFR ≤30 mL/min/1.73m2, receiving intravenous ICM, there is a lack of evidence on benefit of volume expansion. Hence the working group makes no recommendation in this regard; institutions may choose practices best suited to their local environments.
10. For patients with eGFR ≤30 mL/min/1.73m2, receiving intra-arterial ICM, some members of the working group endorsed a strategy of hydration and volume expansion using either intravenous hydration (with .9% saline or 1.26% sodium bicarbonate) or oral salt and water. Since there is insufficient evidence in this patient group the working group felt the use of hydration or not, and the route of hydration was best left to judgement of the practitioner.
11. We do not recommend preferential use of iso-osmolar ICM for reducing risk of CA-AKI. We recommend decisions about low-osmolar or iso-osmolar ICM be made based on other factors (e.g., cost and availability).
12. We do not recommend any form of post ICM administration renal replacement therapy, either dialysis or continuous renal replacement therapy for reduction of the risk of CA-AKI.
13. We do not recommend N-acetylcysteine use for the prophylaxis of CA-AKI.
14. We do not recommend initiating statins specifically for prevention of CA-AKI.
15. We do not recommend use of other pharmacological agents which have been described in the literature, including theophylline, prostaglandin E1, nicorandil, ascorbic acid, allopurinol, alpha-tocopherol, fenoldopam, natriuretic peptides, and trimetazidine.

Medication Considerations

16. We do not recommend stopping metformin before contrast injection, and/or re-testing kidney function afterwards, for patients with eGFR >30 mL/min/1.73 m2.
17. We recommend that in patients with eGFR ≤30 mL/min/1.73m2 or AKI, metformin

should be held at the time of, or prior to, ICM administration. Metformin should not be restarted for at least 48 hours and only then if kidney function remains stable (<25% increase compared with baseline creatinine) and the ongoing use of metformin has been re-assessed by the patient's clinical team.

18. We do not recommend routinely discontinuing renin angiotensin system inhibitors (ACEi and ARBs) prior to, or after, ICM administration.
19. We do not recommend routinely discontinuing diuretics prior to, or after, ICM administration.

Post ICM Administration Statements

20. We recommend a follow-up serum creatinine measurement 48 to 72 hours after intra-arterial ICM injection in all patients with eGFR ≤30 mL/min/1.73m2. For the remainder of patients, the risk of AKI is extremely low, and routine testing is not warranted. However, any at-risk patient should be instructed to seek medical attention and kidney function testing if they develop increased shortness-of-breath, peripheral edema, or note a marked decline in urine output in the days following the imaging test.
21. We recommend that clinical evaluation and management of AKI due to CA-AKI be undertaken according to the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for AKI and taking account of the Canadian Society of Nephrology (CSN) commentary on those guidelines.

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