Management and recommendations for the prevention of contrast-induced acute kidney injury: state of the art in clinical practice

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ABSTRACT

Contrast-induced acute kidney injury (CI-AKI) is defined as an acute kidney failure following iodine-based contrast medium administration determining relevant health and socio-sanitary implications. Knowledge of pathophysiology, early diagnosis, and prevention in patients at risk are critical points in CI-AKI management. Determination of risk and functional kidney evaluation must precede every iodine-based contrast medium (CM) administration in order to eventually introduce medical prophylaxis. Furthermore, early laboratoristic evaluation after iodine-based CM exposure should be performed for a prompt identification of acute kidney injury. Therefore, clinicians must know and strictly follow valid recommendations to minimize the development of complications.

Introduction

Since its first description in 1954, following intravenous pyelography in a patient with myelomatosis,[1] contrast-induced acute kidney injury (CI-AKI) has always been clinically interesting. Indeed, roughly 80 million contrast-enhanced diagnostic and therapeutic procedures are performed worldwide, making CI-AKI the third cause of acute kidney injury (AKI), after ischemic and drugs-related ones.[2] While overall incidence of CI-AKI is 5.5%,[3] in particular it reaches similar values for contrast-enhanced computed tomography (6.8%) and for elective percutaneous coronary intervention (7.1%), and drops to 3% for peripheral vascular interventional procedures.[4-6]

AKI is defined by a serum creatinine (sCr) increase ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h, known or presumed sCr increase ≥1.5 times within the prior 7 days, or urine output <0.5 mL/kg/h for 6 h. Instead, CI-AKI is characterized by an sCr increase ≥0.5 mg/dL (≥44 μmol/L) or >25% from baseline value within the 48 hours following iodine-based contrast medium (CM) administration.[7] Three severity levels AKI classification based on sCr and urine output could be a useful evaluation tool for CI-AKI as well (Table 1).[7,8]

Short and long-term complications - AKI and chronic kidney disease (CKD) development, need for dialysis, increased mortality, stroke, myocardial infarction and other cardiovascular events - might occur with relevant socio-sanitary implications.[9]

During CI-AKI management, a fundamental step is the determination of estimated glomerular filtration rate (eGFR). Among three main known equations, modification of diet in renal disease (MDRD) and chronic kidney disease epidemiology collaboration (CKD-EPI) showed the highest accuracy since they are affected only by GFR, unlike Cockcroft-Gault estimation that is additionally related to body weight and body mass index.[10] However, eGFR evaluation should be performed with Cockcroft-Gault formula in elderly patients, in those ones on low-protein diet, or with reduced muscle mass since MDRD and CKD-EPI for-

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mulas could result inaccurate assuming a body surface area of 1.73 m^2.[11]

Although its importance is generally overestimated by most clinicians with a role in decision-making,[3] suspension of nephrotoxic drugs, use of new CM - low-osmolar contrast media (LOCM) and iso-osmolar contrast media (IOCM) -, and pharmacological prophylaxis are mandatory, especially for at risk or critically ill patients.

Risk factors and risk scores

Prevalence of chronic diseases is increasing among patients aged >65 years, reaching values of 38% in those admitted to Internal Medicine Department. These closely-related comorbidities, particularly heart-kidney interconnection, introduce the concept of multimorbidity and require a careful risk evaluation for CI-AKI.[12-16]

While pre-existing kidney disease is the major risk factor for CI-AKI, intra-venous (IV) CM administration is not an independent risk factor in patients with a stable baseline eGFR ≥45 mL/min/1.73 m^2 and it infrequently results nephrotoxic for a stable baseline eGFR of 30-44 mL/min/1.73 m^2. Thus, the lowest threshold for CM administration should be 30 mL/min/1.73 m^2,[17] although no correlation between CI-AKI and CM administration has been recently found in patients with sCr ≥4 mg/dL.[4] In particular, eGFR can be considered stable in patients without CKD, underlying comorbidities (*e.g.*, heart failure), or who are not taking nephrotoxic drugs. Furthermore, eGFR should be performed 3 months, 7 days, and 1-2 days before CM administration respectively in patients with stable renal function or outpatients, acutely ill or inpatients, and those ones with AKI.[18]

Along with CKD, other important risk factors should be sought to estimate the risk of CI-AKI and evaluate the needs of preventive therapies administration.

Most of the risk scores for CI-AKI identified different risk categories - low to very high risk- relying mainly on CKD (eGFR <60 mL/min/1.73 m^2), age >75 years, congestive heart failure (or EF_{LV} <45%), hypotension (systolic blood pressure <80 mmHg or >1 h of inotropic support), intra-aortic balloon pump use, diabetes mellitus, and anemia (hematocrit <39% in men and <36% in women). In particular, Mehran model (Figure 1) shows an important risk of CI-AKI (57.3%) and dialysis (12.6%) for very high risk patients, and a minor one, but not negligible, for the low risk ones (7.5 and 0.04% respectively for CI-AKI and dialysis).[19-33] These scores are validated only for intra-arterial (IA) CM administration, although the past opinion that the risk of CI-AKI (3.44 times) was greater for IA CM than IV administration has been denied by more recent data.[34-38]

Knowledge of risk factors for CI-AKI can suggest clinicians eGFR evaluation when unknown, especially in patients requiring emergency CM administration - normal sCr values in 98% in patients aged >60 years without risk factors.[39] Furthermore, two anamnestic questionnaires showed their effectiveness (sensitivity of 100%) in recognition of patients with an eGFR <45 mL/min/1.73 m^2 (Table 2).[40]

Dipstick testing for urine protein is a possible alternative to sCr or eGFR evaluation.[41] This data has been confirmed by recent studies and introduced into the newest Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[7,42,43]

A further CM exposure should occur 48 h after the first one in patients without risk factors for CI-AKI, and after 72 h in those ones with diabetes mellitus or CKD. Furthermore, if possible, hemodynamic status should be stabilized and sCr levels normalized before CM administration in patients suffering from AKI after the first CM exposition.[44] Lastly, CI-AKI should be distinguished from post-contrast AKI indicating a sudden renal function alteration during the 48 h after

Table 1. Staging of acute kidney injury.

Stage*	sCr	Urine output
1	↑ sCr ≥0.3 mg/dL (≥26.5 μmol/L) *or* ↑ sCr 150-190% from baseline	<0.5 mL/kg/h for 6-12 h
2	↑ sCr 200-290% from baseline	<0.5 mL/kg/h for ≥12 h
3	↑ sCr >300% *or* ↑ SCr ≥4 mg/dL (≥353.6 μmol/L) *or* renal replacement therapy use *or* eGFR <35 mL/min/1.73 m^2 (<18 years)	<0.3 mL/kg/h for ≥24 h *or* anuria for ≥12 h

*Worst criterion for stage assignment has to be used. sCr, serum creatinine; eGFR, estimated glomerular filtration rate. *Modified from Khwaja, 2012.*[7]

A

Risk Factors	OR (95% CI)
CKD	2.89 (2.32–3.59)
CHF	2.68 (2.09–3.44)
Hypotension*	2.36 (1.89–2.95)
Intra-aortic balloon pump	2.05 (1.47–2.87)
Anemia§	2.02 (1.72–2.36)
Age > 75 years	1.90 (1.59–2.27)
Diabetes mellitus	1.73 (1.48–2.02)
CM volume	1.24 (1.01–1.54)

B

Risk Factors	Score
eGFR 40-60 eGFR 20-40 eGFR < 20	2 4 6
Hypotension*	5
IABP	5
CHF	5
Age > 75 years	4
Anemia§	3
Diabetes mellitus	3
CM volume	1 (each 100 ml)

Risk Score	Risk of CI-AKI (%)	Risk of Dialysis (%)
Low (≤ 5)	7.5	0.04
Moderate (6-10)	14	0.12
High (11-16)	26.1	1.09
Very high (≥ 16)	57.3	12.6

Figure 1. Risk factors (A) and risk score (B) for contrast-induced acute kidney injury (CI-AKI) in patients receiving percutaneous coronary intervention. *Systolic blood pressure <80 mmHg or >1 hour of inotropic support; §Hematocrit <39% in men and <36% in women. OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease; CHF, congestive heart failure (New York Heart Association functional classification III/IV and/or history of pulmonary edema); CM, contrast medium; eGFR, estimated glomerular filtration rate; IABP: intra-aortic balloon pump. *Modified from Mehran* et al., *2004.*[19]

CM administration, possibly related to other causes (*e.g.* critically ill patients).[18]

Pathophysiology

CI-AKI pathophysiology is very complex, and so far, only partially understood. What happens *in vivo* after CM administration can only be hypothesized based on the results of animal and laboratory studies.

However, the main mechanism is hypoxic medullary damage, caused by hemodynamic alterations, production of reactive oxygen species (ROS) and free radicals, direct CM toxicity on tubular cells.[45]

Following CM administration, a biphasic response is characterized by a brief initial increase (vasodilation) and a following longer lasting reduction (vasoconstriction) in renal blood flow.[46] Several mediators including adenosine, dopamine, nitric oxide, atrial natriuretic peptide and prostaglandins among vasodilators, and vasopressin, angiotensin II, endothelium among vasoconstrictors play a key role in this mechanism. In addition, the different renal distribution of the receptors is the basis of the different regional renal response to these molecules.[45,47]

As well as these latter causes, increased blood viscosity, distortion and aggregation of red blood cells[48] and probably the formation of atherogenic microembolism during IA CM administration participate in medullary ischemia onset.[46]

The role of ROS - superoxide, hydrogen peroxide, hydroxyl radical - in renal physiology is to regulate cell signaling, regional microcirculation and cellular transport. In response to medullary hypoxia, ROS production increases and, once the cellular elimination capacity is reached, the *ischemia-reperfusion injury* occurs. Renal impairment during CI-AKI was lower in patients treated with molecules reducing ROS production (allopurinol) or concentration (superoxide dismutase and magnesium ions).[45,47]

Finally, CM causes direct kidney cells damage. CM is water-soluble; it can be filtered without causing glomerular damage (it does not cause hematuria) and is reabsorbed by renal proximal tubular cells causing swelling, vacuolization and apoptosis. The secondary intra-renal CM stasis, contributes to damage worsening.[46] Generally, in healthy subjects, this mechanism causes only a transient and asymptomatic worsening of renal function lasting 8-10 days. In patients where diabetes mellitus or CKD caused a decrease in nephrons number, function and regenerative capacity, each CM administration results in loss of functional units, which are replaced by fibrosis. Further mechanisms underlying direct CM damage include redistribution of membrane proteins, alteration of intercellular junctions, DNA fragmentation, mitochondrial function alterations, apoptosis, extracellular Ca^{2+} reduction, reduced cell proliferation.[45,49]

Markers for early diagnosis

CI-AKI diagnosis is still based on sCr modification.[7] Among markers, those indicating a change in renal function and those ones indicating a kidney injury are listed. Subclinical CI-AKI, a new category of patients identified from this classification, is characterized by positive kidney damage and negative renal function markers as well as by an increased risk for complications.[50] However, further scientific evidence will be necessary to validate new markers within clinical practice.

Creatinine

Cr is the most commonly used test to determine renal function, despite its several limitations. Among these, dependence on muscle mass (therefore on age, sex, race and body weight), elimination also through tubular secretion (impaired by the administration of certain drugs), altered metabolism for hypercatabolic status and overload volume dilution due to AKI, indirect and late reflection of kidney function can be mentioned.[51] In fact, sCr reaches its peak level and return to baseline values respectively within 2-5 days and 1-3 weeks after CM administration. sCr distribution in total body water is responsible for such phenomenon.[50]

Table 2. Questionnaires for detection of chronic kidney disease (presence of ≥1 risk factors).

Questionnaire*	Risk factors for chronic kidney disease
A	Diabetes mellitus Urological/nephrological disease Cardiovascular disease Arterial hypertension
B	Diabetes mellitus Urological/nephrological disease Age >75 years Heart failure

*Questionnaire A or B have to be used for the recognition of patients with an estimated glomerular filtration rate <45 mL/min.

Cystatin C

A new and functional marker of reduced renal function is cystatin C (sCyC), a 12-amino acid non-glycosylated protein, member of the family of cysteine proteinase inhibitor. Synthesized at a constant rate from all nucleated cells, it is filtered by the glomerulus and completely reabsorbed and degraded, but not secreted by renal tubules.[52] In addition, extracellular volume distribution of sCyC explains its faster positivization compared to sCr during altered kidney function. Despite previous evidence, sCyC is partly related to gender, age, race/ethnicity, uric acid and blood urea nitrogen.[53]

Other factors affecting its blood levels include thyroid function, smoke, immunosuppressive drugs (*e.g.* glucocorticoids) and C-reactive protein levels.[54]

Several studies confirmed the ability of sCyC to detect AKI earlier (24-48 h) and better than sCr (sensitivity values of 98% and 80% for sCyC and sCr respectively) and its diagnostic and prognostic relevance regarding CI-AKI.[52,55-57]

Furthermore, a CI-AKI risk classification, stratified patients into no risk, potential- and high-risk groups based on none, one and all positivity of sCr (≥0.3 mg/dL and/or 50% from baseline) and sCyC increase (≥15% from baseline).[57]

KIM-1

KIM-1 is a 100-KDa type I trans-membrane glycoprotein, member of the TIM family of immunoglobulin superfamily molecules.[52] Since its discovery in 2002,[58] it has proved to be a good AKI and early and prognostic CI-AKI marker.[52,59-67]

However, KIM-1 may be affected by the use of nephrotoxic drugs (cisplatin, ring spore element, gentamicin, cadmium), inflammation, fiber lesions, persistent proteinuria.[52]

NGAL

Defined since its discovery as *kidney troponine*,[68] the NGAL is one of the most studied AKI markers. NGAL is a 25-KDa protein covalently bound to gelatinase by neutrophils that performs bacteriostatic functions, stimulates cell differentiation towards an epithelial phenotype and repairs cell damage.

During AKI, while serum NGAL levels derive from renal, hepatic and pulmonary production and from its accumulation due to the lower glomerular filtration,[68] urinary NGAL derives from altered reabsorption or the *de novo* increased production following tubular damage.[68,69] Albeit with some limitations (CKD, chronic hypertension, systemic infections, inflammatory conditions, neoplasms for serum NGAL, and anuria, glomerulonephritis for urinary NGAL)[68,69] this marker seems to maintain its diagnostic role in CI-AKI.[70-78]

Other markers

Among other markers, N-acetyl-β-glucosaminidase,[67,79,80] liver fatty acid binding protein,[51,81,82] interleukin-18,[51,83-86] midkine,[87] netrins, cell cycle arrest markers (insulin-like growth factor-binding protein 7 and the tissue inhibitor of met-alloproteinases-2), a and p-glutathione S-transferase, gamma-glutamyl transpeptidase, β2-microglobulin, retinol-binding protein, microRNA molecules are listed.[51]

Prevention

After having evaluated the correct indication for CM administration and excluded the use of a less invasive procedure (especially for eGFR <30 mL/min), clinicians should apply preventive measures in patients at risk for CI-AKI (Figure 2).

Type and volume of contrast medium

Given the known ability of the old high-osmolar contrast media to induce CI-AKI, the choice of CM type is essential (Table 3). As long as most recent LOCM and IOCM are concerned, an unexpected result has emerged: despite lower IOCM then LOCM osmolarity, the risk of CI-AKI, renal replacement therapy, cardiovascular outcomes or death result only modestly decreased. This phenomenon can be linked

Table 3. Types of contrast medium.

Osmolality*	Iso-osmolar (290-320 mOsm/kg)	Low-osmolar (500-695 mOsm/kg)		High-osmolar (1500-1860 mOsm/kg)
Molecular structure	Non-ionic	Ionic	Non-ionic	Ionic
Name of molecules	Iodixanol Iotrolan	Ioxaglate	Iobitridol Iohexol Iomeprol Iopamidol Iopromide Ioversol	Diatrizoate Iothalamate Ioxitalamate

*Concentration of 300-320 mg of iodine/mm. *Modified from Heinrich* et al., *2009.*[89]

in part to the higher IOCM viscosity.[88-91] Since there are not enough data demonstrating which one should be preferred, last KDIGO guidelines recommend the use of both LOCM and IOCM.[7]

Another risk factor for CI-AKI is CM volume. Small amounts of CM (about 30 mL) may cause kidney damage in patients at high risk of CI-AKI; in particular, administration ≤100 mL of CM is suggested in patients with eGFR<60 mL/min/1.73 m^2. Furthermore, a threshold of 5 mL/kg of CM normalized to sCr has been proposed in patients with CKD and a high CM volume to eGFR ratio and grams of iodine to eGFR ratio have been associated with increased risk of CI-AKI.[9,44,92-94]

In order to reduce the CM volume necessary for a proper execution of the exam, newer CT modalities have been introduced.[91]

Pharmacotherapy

Despite the great scientific efforts, only a few therapeutic strategies have shown a significant efficacy in preventing CI-AKI occurrence (Table 4; Figure 2). However, PRESERVE trial group found no benefit of IV sodium bicarbonate ($NaHCO_3$) over 0.9% normal saline (NaCl) or of oral N-acetyl cysteine (NAC) over placebo for the prevention of death, need for dialysis, persistent decline in renal function at 90 days, or CI-AKI in patients undergoing angiography.[95]

Moreover, most of the results relate to IA CM administration and future studies will be needed to confirm the pharmacological efficacy of these therapies with IV CM administration.

Nephrotoxic drugs suspension

Since polypharmacy reached a prevalence of more than 50% in Internal Medicine patients aged >65 years[96] and is often associated with inappropriate prescriptions,[14-16] suspension of all non-essential nephrotoxic drugs from 24 h before to 48 h after CM administration is a considerably important practice. Among these non-steroidal anti-inflammatory (naproxen, ibuprofen, diclofenac, celecoxib), high doses of loop diuretics, antibiotics (aminoglycosides), antifungals (amphotericin B), antivirals (acyclovir, tenofovir, foscarnet), immunomodulatory (cyclosporin A), antineoplastic (cisplatin, ifosfamide, mitomycin) drugs are listed.[7,48]

Although most clinicians prefer to suspend angiotensin converting enzyme inhibitor and angiotensin receptor blockers prior to CM administration, results of the most recent studies are conflicting.[97-100] In view of longer lasting effects of these drugs on hemodynamic renal system, their 24-h suspension should not provide significant benefit in reducing the occurrence of CI-AKI.[91]

Metformin suspension

Metformin, a first-line oral hypoglycemic agent in diabetes mellitus management, is not a nephrotoxic drug, and yet presents renal elimination. Furthermore,

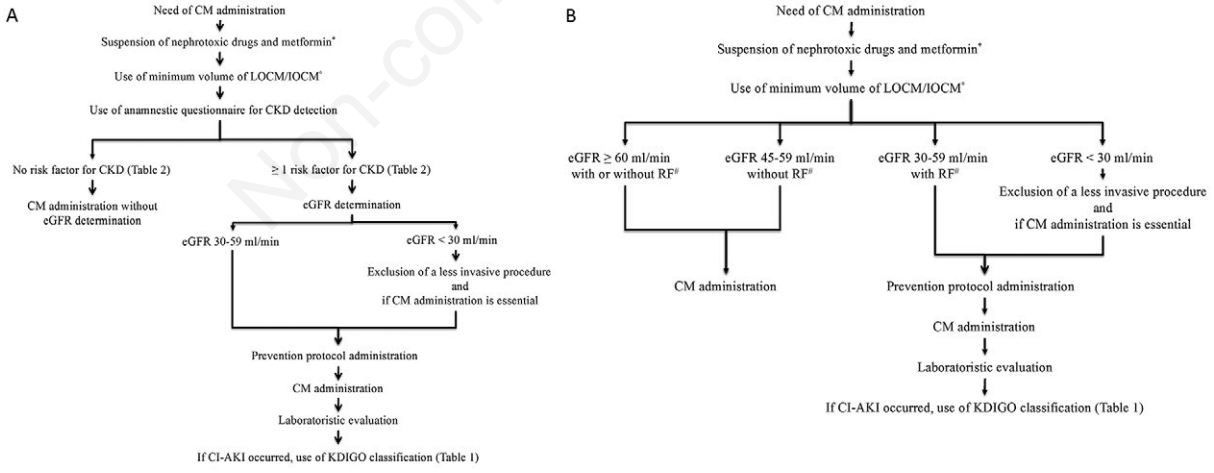

Figure 2. Recommendations for the management of contrast medium (CM) administration. A) patient without known estimated glomerular filtration rate (eGFR) or requiring emergency CM administration; B) patient with known eGFR. If possible, wait for hemodynamic status stabilization, acute kidney injury (AKI) restoration, 48 and 72 h for second CM administration respectively in patients without and with risk factor for CI-AKI. *In patient with AKI or eGFR <60 mL/min suspend metformin 48 h before CM administration and reintroduce it once the risk of CI-AKI has been averted; °5 mL/kg of CM normalized to serum creatinine; #age >75 years, congestive heart failure (or EF_{LV} <45%), hypotension (systolic blood pressure <80 mmHg or >1 h of inotropic support), intra-aortic balloon pump use, diabetes mellitus, and anemia (hematocrit <39% in men and <36% in women). LOCM, low-osmolar contrast media; IOCM, iso-osmolar contrast media; CKD, chronic kidney disease.

CM administration does not represent an independent risk factor for complications of metformin therapy, but their combined assumption could be dangerous in case of CI-AKI. Following its accumulation in CKD, it may cause lactic acidosis, and 8% of these cases are related to CI-AKI.[17,91]

It is therefore essential, in patients with AKI or severe CKD (eGFR <60 mL/min/1.73 m^2), to suspend this treatment roughly 48 h before CM administration and to reintroduce it once the risk of CI-AKI has been averted.[17,101]

Hydration

Hydration is the main preventive therapeutic intervention. In low-risk patients or outpatients who have to undergo elective procedures, oral hydration may be used, while in moderate/high risk patients or inpatients, IV hydration with isotonic crystalloids should be preferred -especially NaCl.[48,102-105]

Several studies have demonstrated its clinical efficacy despite the different protocols used.[106-108]

Two recent studies have also shown that, in patients with CKD (eGFR between 30 and 60 mL/min/1.73 m^2) no prophylaxis is non-inferior to hydration in CI-AKI prevention.[108,109] To confirm this hypothesis, further data will be needed.

Sodium bicarbonate

The mechanism underlying the efficacy of $NaHCO_3$ in preventing CI-AKI is based on Haber-Weiss reaction inhibition, which causes ROS formation in an acidic environment similar to that of the renal medulla. Alkalizing the renal parenchyma, $NaHCO_3$ reduces ROS production due to toxic and ischemic CM damage.[110]

So far, its effectiveness in preventing CI-AKI has not yet been proved, unlike the known risk of hypervolemia in heart failure and CKD.[91] In fact, while some studies showed its superiority to NaCl, others highlighted its inferiority and even its ineffectiveness.[95,110-120] For this reason too, a standard dosage of $NaHCO_3$ for CI-AKI prevention has not yet been established.[110-115,117-119]

However, a recent trial involving roughly 5000 patients, have demonstrated $NaHCO_3$ inefficacy over NaCl in CI-AKI prevention or death, need for dialysis, and persistent decline in kidney function during the 90-days follow-up.[95]

N-acetyl cysteine

NAC is a thiol-containing cell-membrane-permeable antioxidant decreasing typical CI-AKI damage by oxidative stress reduction, stimulation of nitric oxide-dependent renal vasodilation, and inhibition of renal cells apoptosis.[121]

In spite of contrasting data,[95,121-134] NAC is still generally used, given its low side effects probability and costs of oral administration. While the latest KDIGO guidelines recommend the use of NAC along with the administration of IV crystalloids in patients at risk of CI-AKI, a recent large trial showed no benefit of NAC over placebo on primary outcomes (CI-AKI or death, need for dialysis, and persistent decline in kidney function at 90-day follow-up).[7,95]

Statins

Among the mechanisms proposed to explain the protective role of statins in CM damage, inhibition of contrast uptake in renal tubular cells, mesangial cell

Table 4. Main therapeutic schemes for prevention of contrast-induced acute kidney injury.

Drug	Administration route	Dosage	Administration time
NaCl (154 mEq/L)*	IV	1-3 mL/kg/h 1-3 mL/kg/h	1-12 h before 2-12 h after
150 mmol of $NaHCO_3$ per liter°	IV	1-3 mL/kg/h 1-3 mL/kg/h	1-2 h before 2-12 h after
NAC	Oral	600-1200 mg twice daily	12-24 h before 12-48 h after
Statin	Oral	Rosuvastatin 40 mg Rosuvastatin 20 mg	1 day before 2 days after
		Rosuvastatin 10-20 mg	1-2 days before 2-7 days after
		Atorvastatin 40-80 mg	12-72 h before 2-5 days after
		Atorvastatin 40-80 mg	2-24 h before

NaCl, 0.9% normal saline; IV, intra-venous; $NaHCO_3$, sodium bicarbonate; NAC, N-acetyl cysteine. *Oral hydration (neutral water) has to be used at the same dosage as IV hydration in low-risk patients or outpatients and dosage of hydration should be modulated on patient hemodynamic status. °Risk of hypervolemia has to be considered in heart failure and CKD ($NaHCO_3$ contains high sodium amounts).

proliferation, inflammation, endothelial dysfunction, oxidative stress reduction, and podocytes protection are listed.[46]

Indeed, short-term high dose statin therapy has reduced the risk of CI-AKI, especially for patients who received IA CM.[135-152] Furthermore, from animal test results, both atorvastatin and rosuvastatin have been shown capable of reducing CI-AKI occurrence, unlike simvastatin.[153]

Other drugs

Although additional data will be needed to confirm their effectiveness, many other drugs have been proposed and designed to reduce CI-AKI occurrence in patients at risk.

Among these theophylline,[154-157] ascorbic acid (vitamin C),[158,159] tocopherol (vitamin E),[160-163] sodium 2-mercaptoethanesulfonate (MESNA),[164] atrial natriuretic peptide,[165] iloprost (PGI_2 analogue),[166,167] trimetazidine,[168-171] nicorandil,[172,173] Na/K citrate,[174] nebivolol,[175,176] erythropoietin,[177,178] are listed.

Combined therapy

Attempting to propose prevention protocols, numerous studies evaluated the efficacy of combined therapy in reducing CI-AKI occurrence.

Despite contrasting results,[95,179-189] two strategies have to be considered of clinical interest: NAC with IV hydration (NaCl) and NAC with IV hydration (NaCl) and statin respectively in patients who will receive IV and IA CM.[190-193] To date, no preventive combined therapies are recommended over NaCl alone.

Prophylactic hemodialysis/hemofiltration

Prophylactic intermittent hemodialysis or hemofiltration are not recommended for CM removal in patients at increased risk of CI-AKI. However, life-threatening alterations during AKI (severe hyperkaliemia, severe acidosis, pulmonary edema, and uremic complications) represent indication for renal replacement therapy.[7]

Although a single session of intermittent hemodialysis can eliminate 60-90% of bloodstream CM, several studies have shown no ability to reduce CI-AKI occurrence.[7,194,195] Hemodialysis has also been shown responsible for an increased risk of CI-AKI.[91]

Remote ischemic preconditioning

Remote ischemic preconditioning (RIPC) is a short, harmless and temporary suspension of blood flow to a tissue or organ, administered before a longer and lasting ischemia caused in a distant tissue or organ. The mechanisms behind this phenomenon are the activation of various kinase cascades reducing cell death, stimulation of antioxidant processes, and reduction of free radical production.

RIPC is generally performed by generating an arm ischemia for 5 min (reaching a pressure of about 50 mmHg above the patient's systolic blood pressure), followed by a 5-min reperfusion; this process is repeated 4 times. The time between RIPC and exam is generally 45 min.[196]

Although further evidence is needed to establish its effectiveness, numerous studies have confirmed RIPC ability to reduce CI-AKI occurrence.[196-201]

Conclusions and recommendations

In conclusion, CI-AKI represents a considerable clinical problem requiring a careful approach and intensive assessment. We recommend two managements for prevention of CI-AKI, both based on knowledge of eGFR and on presence of risk factors (Figure 2). The first step is to suspend nephrotoxic drugs and metformin (if indicated), use minimum volume of LOCM/IOCM, and wait for hemodynamic status restabilization (if possible). In patients with unknown eGFR, its evaluation should be performed before CM administration if patients have ≥1 risk factor for CI-AKI. Furthermore, preventive hydration (NaCl) should be administered to patients with eGFR <60 mL/min and presence of risk factors for CI-AKI and those with eGFR <30 mL/min, if CM administration is essential. Strict adherence to the examined protocols may reduce CI-AKI occurrence and major adverse events development, improve patients' outcomes and decrease length of stay and health care costs. Future researches will be needed to validate the most appropriate prophylactic scheme for the clinical practice.

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