SPECIAL REPORT

Three Perspectives on the Reduction of Contrast Induced Acute Kidney Injury in Invasive Cardiology

Contrast-Induced Acute Kidney Injury in Interventional Cardiology

Contrast Media Use in Cardiac Procedures: How to Protect Patients and Avoid Renal Complications

Reducing AKI Complications in Patients with Chronic Kidney Disease

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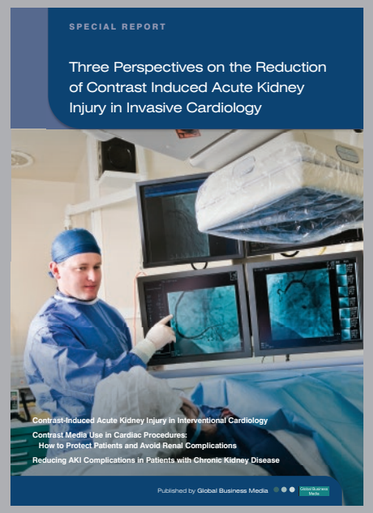

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Foreword

Medical imaging techniques have become important diagnostic and therapeutic tools in the era of significant scientific and technological advances in medicine. Contrast media (CM) is increasingly used for diagnostic and therapeutic purposes in a broad spectrum of areas such as radiology, interventional cardiology, nuclear radiology, vascular surgery, and oncology. Adverse effects of iodinated CM include nausea, vomiting, thyroid dysfunction, and hypersensitivity reactions that can potentially occur and occasionally result in severe complications[1].

Contrast-induced acute kidney injury (CI-AKI) is considered in international cardiology and nephrology guidelines as a possible complication in patients undergoing interventional procedures in the cardiac catheterisation laboratory. In the past, CI-AKI was frequently underestimated and neglected and a mild and transient elevation in serum creatinine (SCr) level was considered a minor clinical problem. However, CI-AKI has been found to be strongly associated with morbidity and mortality with increased hospital stay and healthcare costs[2]. Furthermore, CI-AKI may not always be reversible and may progress to chronic kidney disease (CKD), potentially leading to end-stage kidney disease requiring dialysis[3,4].

As recently suggested, a subclinical form of CI-AKI may occur in a proportion of patients exposed to iodinated CM, which is much higher than that reported using classic SCr diagnostic criteria. Thus, in healthy subjects with intact renal functional reserve, partial renal damage can occur undiagnosed as it is compensated for by the remaining nephrons. The only final effect can be a partial loss of renal mass, with a loss of renal functional reserve (RFR), while baseline glomerular filtration rate and SCr remain unchanged. However, in patients with comorbidities (e.g. CKD and diabetes mellitus) who have a decreased RFR and highly susceptible kidneys, a reduced number of functioning nephrons and an impaired ability to regenerate tubular epithelial cells indicate a higher risk of developing CI-AKI even with exposure to standard volumes of CM, which is normally well tolerated in the general population with preserved functioning renal mass.

This focus reports the perspectives of three European expert groups with particular attention to a multidisciplinary approach. There is consensus that appropriate risk stratification should be performed in every patient undergoing catheterisation procedures. A thorough evaluation of risk factors together with the enforcement of adequate preventive and protective strategies may help to mitigate the risk of CI-AKI, especially in high-risk patients[5].

Federico Ronco and Claudio Ronco
Editors

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Contrast-Induced Acute Kidney Injury in Interventional Cardiology

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Diagnosis and Epidemiology of Contrast-Induced Acute Kidney Injury

The spread of diagnostic and interventional procedures has been accompanied by increased attention to the potential adverse effects of iodinated contrast media (ICM).

Despite the fact that the ICM used currently is more tolerable and safer than those used in the past, contrast-induced acute kidney injury (CI-AKI) is a clinically relevant complication in patients undergoing diagnostic and interventional procedures (especially those in the cardiac catheterisation laboratory). CI-AKI may present with a wide variety of clinical scenarios depending on the severity of the AKI stage and comorbidities, ranging from a transient asymptomatic increase in serum creatinine (SCr) (>0.3 mg/dl within 48 h) to severe kidney dysfunction requiring dialysis.

The epidemiology and incidence of CI-AKI vary widely in the literature. This is attributable to the different criteria of AKI used in reporting and definitions, as well as to the heterogeneity of the studied patient populations and procedures performed in catheterisation laboratories.

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines standardised the definition and staging of AKI for use as diagnostic criteria in clinical trials. So far, these criteria have also been applied to CI-AKI[1]. They recommend the criteria adopted by the Acute Kidney Injury Network (AKIN), which has updated the RIFLE criteria, to define AKI as an increase in SCr > 0.3 mg/dl (26.5 umol/l) or as an increase in SCr > 50% over baseline values within 48 h from ICM administration[2]. However, new AKI biomarkers have been recently proposed to allow for a more accurate and timely diagnosis[3-6].

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines standardised the definition and staging of AKI for use as diagnostic criteria in clinical trials

New ADQI Classification

Functional criteria	Stage	Damage criteria
No change or sCr level increase <0.3 mg/dL and no UO criteria	1S	Biomarker positive
Increase of sCr level by ≥0.3 mg/dL for ≤48 h or ≥150% for ≤7 days and/or UO <0.5 mL/kg/h for >6 h	1A	Biomarker negative
	1B	Biomarker positive
Increase of sCr level by >200% and/or UO <0.5 mL/kg/h for >12 h	2A	Biomarker negative
	2B	Biomarker positive
Increase of sCr level by >300% (≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL) and/or UO <0.3 mL/kg/h for >24 h or anuria for >12 h and/or acute KRT	3A	Biomarker negative
	3B	Biomarker positive

Figure 1 - Proposed new definition of AKI from the Acute Dialysis Quality Initiative (ADQI)13 with permission. (SCr = serum creatinine; UO = urine output; KRT = kidney replacement therapy)

CI-AKI physiopathology is complex and likely multifactorial. Three main mechanisms seem to be responsible:
-Direct cytotoxic effect of ICM on renal tubular cells
-Damage attributable to ROS
-Hemodynamic hypoxia

In particular, early stress and injury biomarkers such as N-GAL or cell cycle arrest biomarkers such as Nephrocheck (product of IGFBP-7 and TIMP-2) have been used to make an early diagnosis of AKI, implement preventive and protective measures[7-10], evaluate subclinical ICM toxicity[11-12], and generate a new AKI classification[13] **(Figure 1)**.

In the near future, this new classification and AKI biomarkers will likely be used as endpoints for research and trials in the field of CI-AKI.

CI-AKI is an important cause of AKI in hospitalised patients (10%), together with ischaemic septic and toxic causes[14]. CI-AKI at any stage correlates with poor middle-and long-term outcomes (mortality and MARCE -major adverse cardiovascular and renal events-) and is associated with a poor outcome in catheterisation laboratories procedures. In particular, it increases the risk of ischaemia recurrence, rate of target vessel revascularisation in percutaneous coronary interventions, and bleeding complications[15-17]. Furthermore, CI-AKI leads to a significant economic burden on hospitals, increasing hospital and ICU length of stay, and management of complications.

The incidence of CI-AKI in patients with cardiovascular disease could be partially overestimated due to concomitant causes or exposures other than ICM[18]. A correct diagnosis of CI-AKI would require ruling out other causes of AKI. Unfortunately, current diagnostic criteria do not allow distinguishing between a causative effect of ICM (CI-AKI) and a simple association (contrast-associated acute kidney injury), where ICM is just one of many other risk modifiers[19]. Finally, the diagnosis of subclinical AKI (stage 1 S) may be completely overlooked unless a careful biomarker-driven evaluation is performed. This new entity in the continuum of AKI should be considered in the future, not only for an accurate molecular diagnosis of AKI but also for epidemiological studies and interventional trials. As a practical example, a recent study[20] analysed CM toxicity and the impact of different CM on subclinical CI-AKI using stress and damage biomarkers as endpoints. Two different ICM protocols displayed comparable results in terms of SCr variation (clinical AKI) but significantly different incidence of biomarker increase (subclinical AKI), suggesting that the criteria to determine safety profiles of ICM should be reassessed.

Pathophysiological Mechanisms

CI-AKI physiopathology is complex and likely multifactorial, as reported in in-vitro and animal studies. Furthermore, in clinical practice, several confounding factors are present. Nevertheless, three main mechanisms seem to be responsible for AKI in cases of ICM administration[21], as follows:

- Direct cytotoxic effect of ICM on renal tubular cells (apoptosis, membrane protein redistribution, migration of adhesion molecules, reduction in intracellular Ca++, fragmentation of the DNA, intercellular junctional changes, altered mitochondrial function, and abnormal cellular proliferation and adaptive repair)
- Damage attributable to the formation of reactive oxygen species (ROS) (ICM causes a moderate-to-severe hypoxic condition in the tubules of the renal medulla with an increase in oxygen demand and a concomitant decrease in oxygen supply. This results in a pathological increase in the local production of ROS, which affects cellular membranes, nuclear DNA, and mitochondria. The increased level of ROS also leads to a significant vasoconstriction mediated by endothelin-I and angiotensin-II, with a reduction in circulating NO, further aggravating hypoxia.)
- Haemodynamic hypoxia (ICM has a direct biphasic effect on renal vasculature; short-lasting transient vasodilation is followed by a prolonged state of vasoconstriction that significantly reduces arterial flow).

Although all types of ICM have a direct cytotoxic effect on in-vitro cultures of renal tubules (especially high-osmolarity contrast media [HOCM] and low-osmolarity contrast media [LOCM]), the iso-osmolar contrast medium (IOCM) was found to be less toxic in cultured renal tubular cells of the rat[22]. Clinical studies in high-risk patients and selected conditions seem to suggest that IOCM has a a lower toxicity than LOCM, which led to the clinical recommendation of using IOCM in patients at risk[1].

Patient Risk Assessment

The identification of patients at risk for CI-AKI enables the concentration of efforts on preventive and protective strategies and better allocation of human and economic resources. Risk assessment protocols may also contribute to improving the quality of information provided to patients on the risks and benefits associated with planned procedures and the optimisation of post-procedural care. To achieve effective patient risk stratification, clinical conditions and comorbidities such as pre-existing chronic kidney disease (CKD) (CKD with estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2), older age, diabetes, anaemia, and reduced left ventricular ejection fraction (LVEF) should be carefully evaluated. Based on this assessment and the results of a recent consensus conference on CI-AKI in interventional cardiology[23], further evaluation should be performed on potential risk modifiers or exposures[19] such as critical illness at

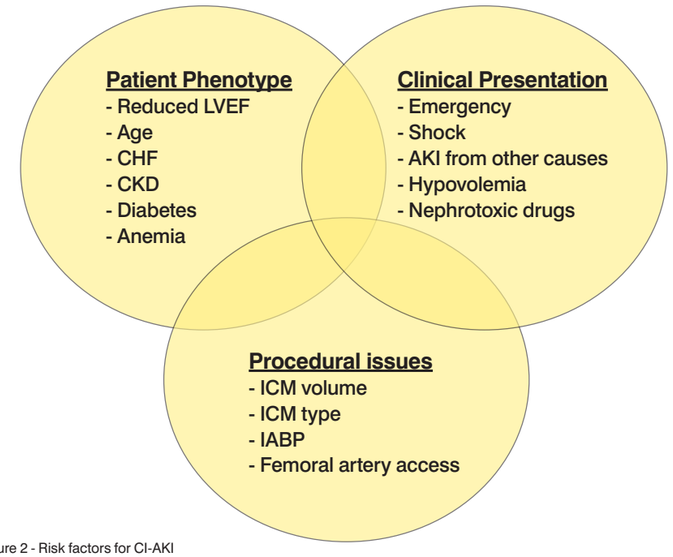

Figure 2 - Risk factors for CI-AKI

presentation (shock, hypovolaemia, dehydration, and oliguria), previously diagnosed AKI/acute and chronic kidney disease, concomitant use of nephrotoxic drugs, urgency/emergency of the procedure, procedure-related issues (use of intra-aortic balloon pump, dose and type of ICM, and site of arterial access) **(Figure 2)**.

Multiple models and scores to predict the risk of CI-AKI have been developed from retrospective studies of patients who underwent coronary interventional procedures[24-29]. The value of such risk scores in daily clinical practice has been questioned, as most of them have not been validated in prospective studies. The presence of multiple risk modifiers or exposures increases the risk of CI-AKI exponentially, and the clinician's judgement is crucial in identifying susceptible patients in addition to any risk model prediction. Furthermore, current evidence shows that sometimes we are unaware of some risk conditions that may be present in our patients. As an example, in a case of CKD, kidney function based on eGFR is commonly evaluated, assuming that the patient's condition is stable. This assumption may not be true because hospitalised patients are subject to different pharmacological treatments and interventions that may cause a change in the actual GFR. Since eGFR is based on SCr and it may take 48 h for SCr to spike in case of a sudden GFR decline, an undiagnosed condition of AKI may be present at the time of the procedure. Furthermore, even in steady-state patients, baseline GFR or eGFR may not reflect real kidney health. Patients may have lost up to 50% of the renal mass in previous pathological events without any significant increase in SCr levels. This condition can only be explained by the kidney glomerular stress test[30-32], which determines the presence and entity of subclinical kidney damage by measuring the renal functional reserve (RFR)[33-35]. Recent studies have demonstrated that a reduction in RFR may represent a risk factor for AKI after elective cardiac surgery[37]. The explanation of these findings resides in an undiagnosed condition of CKD due to partial loss of nephron mass detected only by a reduction in RFR. In these conditions, while we are unaware of the initial CKD condition, patients display a significant increase in AKI risk since they are already on the slippery slope of progressive nephron loss.

Pharmacologic Strategies

Various preprocedural protocols have been proposed to mitigate the risk of CI-AKI. Fluid administration is the most widely employed, safe, and cost-effective approach. The European Society of Cardiology (ESC) guidelines recommend that all patients undergoing coronary angiography receive adequate fluid intake (class I, level of evidence: "C"). In particular, they recommend that all patients with moderate-to-severe CKD (National Kidney Foundation stages 3b and 4) receive 1 mL/kg/h of isotonic saline 12 h before the procedure and continue for 24 h afterwards (0.5 mL/kg/h if LVEF ≤ 35% or NYHA >2) if the expected contrast volume is >100 mL (class IIa, level of evidence C)[38].

Furthermore, several studies have shown that hydration protocols based on patients' haemodynamic parameters (central venous pressure, left ventricular end diastolic pressure, or bioelectrical impedance) are superior to standard protocols. In these studies, the volume of saline

Various preprocedural protocols have been proposed to mitigate the risk of CI-AKI. Fluid administration is the most widely employed, safe, and cost-effective approach

Iodinated-contrast mediums today are mainly non-ionic and have a lower degree of osmolarity (LOCM) than those used in the past (HOCM). Iodixanol is the only iso-osmolar contrast dye available (IOCM)

The volume of ICM represents a modifiable risk factor for CI-AKI and it should be reduced as much as possible

tailored according to the patients' hydration status was greater than that in controls. This indicates that hydration protocols should be personalised as current guideline-driven standards of hydration are probably inadequate to ensure a proper degree of nephroprotection[39-44]. There is some evidence regarding the nephroprotective efficacy of forced diuresis and simultaneous euvolaemic balancing. The Renal Guard System (PLC Medical Systems, Milford, Massachusetts) allows the achievement of a high urine flow rate (≥ 450 ml/h), simultaneously balancing urine output with adequate venous fluid infusion to prevent hypovolaemia. Such a system appears to be more effective than conventional hydration regimens in preventing CI-AKI [45-47].

The antioxidant and vasodilating properties of N-acetylcysteine have introduced the rationale for its application as a pharmacologic pre-treatment method to reduce the incidence of CI-AKI. The results of clinical studies, however, were conflicting[48-50] until the PRESERVE trial finally reported the lack of efficacy of N-acetylcysteine in preventing CI-AKI[51]. In the same trial, pretreatment with sodium bicarbonate did not yield any additional benefit in the prevention of CI-AKI when compared to the administration of N-acetylcysteine, normal saline, or a placebo. In spite of these results, N-acetylcysteine is still widely used due to the absence of side effects and low cost.

The ESC 2018 guidelines recommend administration of high doses of statins (atorvastatin 80 mg; rosuvastatin 20 mg or 40 mg) prior to ICM exposure (recommendation class IIa, evidence level A)[38]. In a meta-analysis of 124 clinical trials and a total of 28,240 patients comparing the ten most evaluated pretreatment strategies, statins were shown to be the only agent effectively able to reduce the risk of CI-AKI[52].

Non-steroidal anti-inflammatory medications, along with angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, may enhance kidney susceptibility to damage, contributing to the worsening of renal function in cases of ICM exposure. Metformin is potentially associated with an increased risk of lactic acidosis in patients with CKD stage 3 and above due to reduced renal elimination of the molecule. Because of conflicting data, there are no recommendations to temporarily suspend these agents in the general population of patients scheduled for procedures involving the use of ICM.

However, a special concern should arise from a completely nihilistic approach due to the negative results of randomised controlled trials. A negative trial does not mean that in a specific patient or group of patients, the intervention is ineffective. In fact, most trials have a significant number of exclusion criteria, often leading to a trial population that hardly reflects the characteristics of patients encountered in the clinical routine. For this reason, the approach suggested by precision medicine and a personalised approach should be encouraged to manage single patients at risk of AKI.

Non-Pharmacologic Strategies

The volume of ICM represents a modifiable risk factor for CI-AKI and is one of the determinants of Mehran's risk score[24]. It should be reduced as much as possible, particularly in patients with high AKI risk, including those with moderate-to-severe CKD[38]. Different studies aimed at reducing the maximum ICM dose are considered safe to prevent CI-AKI. Cigarroa proposed a formula based on pre-procedure SCr and the patient's body weight (5 mL of ICM/kg of body weight [max 300 mL]/SCr in mg/dL]) to estimate the safe ICM dose[53]. More recently, the ratio of ICM/creatinine-clearance (ClCr) <3.7 has proven to be a cut-off threshold with good sensitivity and specificity in detecting patients at risk of developing CI-AKI[25]. A lower threshold (ICM/ClCr <2.7) has been proposed for patients undergoing transcatheter aortic valve implantation, considering the greater frailty of this patient population[54]. The analysis of data from the National Cardiovascular Data Registry of 1.3 million subjects showed great variability in the volume of ICM utilised by different operators during various procedures. This variability was not related to the complexity of the procedures. Furthermore, there seemed to be no tendency to reduce the volume of ICM in patients at a greater risk of CI-AKI[55]. These findings highlight the need for continuous education for operators involved in diagnostic and interventional procedures, in order to create alertness and awareness of the importance of minimising the volumes of ICM in all conditions and even more in high-risk patients.

The DyeVert device (Osprey Medical Inc., Minnesota, USA) was developed to perform assisted injection of ICM in the coronary arteries **(Figure 3)**. The intent is to reduce any useless volume of ICM administered during the procedure, particularly the backflow of ICM from the coronary ostia in the ascending aorta, while maintaining adequate quality of angiographic images. Various studies have demonstrated the efficacy of this device in reducing the amount of ICM administered while preserving angiographic image quality[56,57]. These findings have been confirmed in a recent randomised study in which the device allowed a significant reduction in ICM volume from 15.5% in the general population to 46% in patients with complex multivessel percutaneous coronary intervention

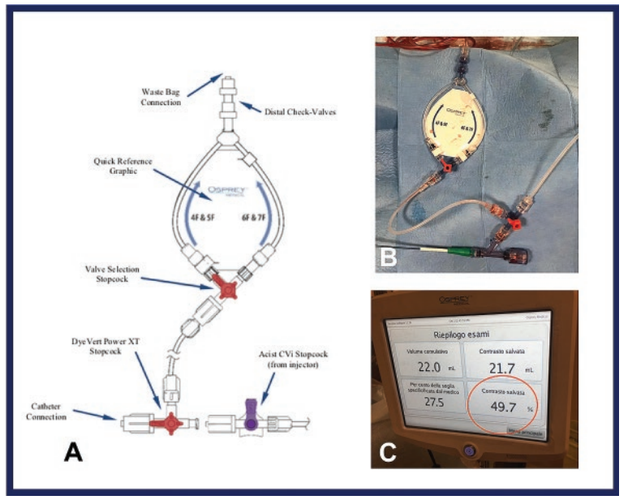

Figure 3 - A: DyeVert Power XT System for automated injectors. B: DyeVert device

(PCI) procedures. Despite the demonstrated reduction in the volume of ICM administered, no significant differences in CI-AKI were observed in this trial (CI-AKI incidence: 27% vs. 26.6%; p = 0.70)[58]. A recent multicentre, single-arm, observational study of 114 patients undergoing coronary angiography, including PCI procedures with the most recent version of this device (DyeVert Plus System), confirmed ICM volume reduction clinically while maintaining image quality. No device-related adverse events have been reported[59]. Briguori et al. found a significant reduction in the ICM dose in patients undergoing coronary interventions for acute coronary syndrome (ACS) using the DyeVert System. Acute kidney injury occurred in 7/90 patients (8%) in the DyeVert group and in 17/90 (19%) patients in the control group (odds ratio = 0.37; 95% confidence interval 0.14-0.95; p =.047), suggesting that the ICM volume reduction obtained by the DyeVert system is an effective strategy to prevent AKI in ACS patients undergoing invasive procedure[60]. While evaluating negative trials, we should focus on the criteria to evaluate kidney toxicity, which are based on clinical parameters and changes in SCr levels. According to our previous observation, biomarker studies should be conducted to refine our evaluation of the efficacy of this device and other methods as preventive/protective strategies for the kidney.

Evidence Regarding Different ICMs

The safety and tolerance of the various ICM agents are a matter of constant debate in the attempt to identify the class of agents (LOCM or IOCM) with lower nephrotoxic effects.

Iodinated-contrast mediums today are mainly non-ionic and have a lower degree of osmolarity (LOCM) than those used in the past (HOCM). Iodixanol is the only IOCM available with osmolarity analogous to that of blood (280–295 mOsm/kg H_2O), while LOCM agents still present an osmolarity double or triple that of blood (521–915 mOsm/kg H_2O).

A number of randomised clinical trials comparing the incidence of CI-AKI in patients exposed to LOCM or IOCM reported a lower incidence of CI-AKI in patients who received IOCM[61-64].

Considering the higher safety gradient in favour of the IOCM, international KDIGO guidelines, and the Italian SIN/SIAARTI guidelines, recommend the use of IOCM in patients at high risk of CI-AKI

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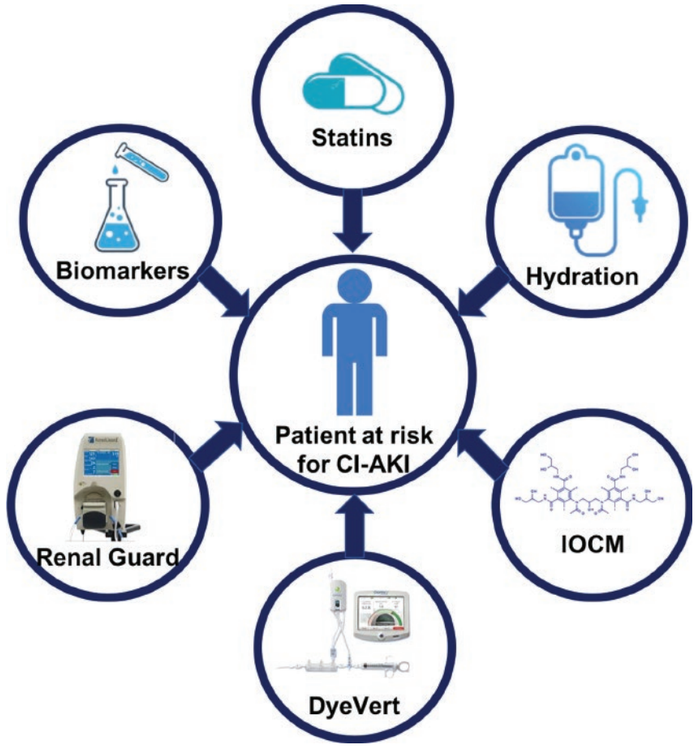

Figure 4 - Strategies to reduce the risk of CI-AKI in interventional cardiology

Several trials, however, found no significant differences in the incidence of CI-AKI between LOCM and IOCM[6571]. No randomised clinical trial has ever found a better safety profile of LOCM vs. IOCM in terms of the incidence of CI-AKI in interventional cardiology. Some meta-analyses comparing the nephrotoxicity of IOCM and LOCM concluded that IOCM has a better safety profile[72,73,] while others reported no significant difference[74-78]. Considering the higher safety gradient in favour of the IOCM, international KDIGO guidelines, and the Italian SIN/SIAARTI guidelines, recommend the use of IOCM in patients at high risk of CI-AKI[79-81]. In the field of cardiology, while the ESC does not make such a recommendation, the GISE qualifies this view, suggesting the use of IOCM in high-risk patients[38,23].

In conclusion, there is a growing interest in defining and safely implementing appropriate preventive strategies to minimise the risk of CI-AKI in patients undergoing diagnostic and interventional procedures **(Figure 4)**. Scientific research, technological innovation, and continuous education of healthcare professionals aim to improve patient safety and procedural outcomes. Finally, efforts should be made to optimise resources and procedures, possibly reducing the economic burden due to CI-AKI on healthcare systems and on patients' clinical history: primum non nocere!

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Contrast Media Use in Cardiac Procedures: How to Protect Patients and Avoid Renal Complications

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Focus on high-risk patients, hydration regimes, choice of contrast media, and measures to reduce the volume of contrast

Contrast-induced acute kidney injury is an important complication that may account for a significant number of cases of hospital-acquired renal failure and relates with adverse effects on prognosis as well as increased health care costs

Abbreviations
CI: contrast-induced
AKI: acute kidney injury
CM: contrast media
CKD: chronic kidney disease
GFR: glomerular filtration rate
PCI: percutaneous coronary intervention

Contrast-induced (CI) acute kidney injury (AKI) is an important complication when using iodinated contrast media (CM) for diagnostic and therapeutic cardiac procedures. It may account for a significant number of cases of hospital-acquired renal failure [1,2] and is associated with adverse effects on prognosis and increased health care costs [3].

CI-AKI has been defined as the occurrence of acute renal impairment within 2-7 days of administration of iodinated CM. According to the 2018 guidelines of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR), a diagnosis of CI-AKI can be established if the serum creatinine level increases by at least 0.3 mg/dL (26.5 μmol/L) or 1.5 times above baseline within 48 to 72 h of intravascular administration of a CM [4].

The complex pathophysiology of CI-AKI involves different mechanisms, such as vasoconstriction, oxidative stress, medullary ischaemia, and the direct toxic effects of CM. The risk of AKI is also influenced by patient- and procedure-related factors. Preexisting chronic kidney disease (CKD) is the strongest patient-related risk factor, with lower levels of kidney function associated with higher degrees of risk [3,5]. Other clinical factors have also been associated with the development of CI-AKI, especially the presence of diabetes mellitus, anaemia, congestive heart failure, and advanced age [6].

The reported incidence of CI-AKI varies widely across the literature, depending on the patient population and baseline risk factors. However, the frequency of CI-AKI has decreased over the past decade[6]. This is due to a greater awareness of the problem, better risk prevention measures, and improved iodinated CM with less renal toxicity. Despite this, many cases of CI-AKI continue to occur because of the ever-increasing number of procedures requiring contrast.

It is well known that almost all patients who receive intravascular CM may have slight and transient changes in renal function, but most of them do not require treatment. However, patients with individual or multiple risk factors have an increased probability of developing CI-AKI, so the pathogenesis of any underlying disease must be considered in combination with individual risk factors.

THREE PERSPECTIVES ON THE REDUCTION OF CONTRAST INDUCED ACUTE KIDNEY INJURY IN INVASIVE CARDIOLOGY

How Can We Identify High-Risk Patients?

An important consideration in evaluating patients before CM administration is that serum creatinine is an inaccurate measure of renal function, especially in elderly and female populations. In these patients, a borderline normal creatinine level may lead clinicians to overestimate renal function. The glomerular filtration rate (GFR) calculated using the Cockroft-Gault formula or the modification of diet in renal disease (MDRD) formula for adults have better accuracy and should be routinely used to estimate creatinine clearance [7].

Many risk factor models have been developed and applied clinically. Mehran et al. developed and validated a comprehensive risk prediction score, including age, haemoglobin, preexisting CKD, contrast volume, need for intra-aortic balloon counterpulsation, and other variables, in order to anticipate the rate of CI-AKI as well as the need for potential renal replacement therapy 8. This tool is not helpful before the procedure because it incorporates variables that can only be known after the case is completed in the cath-lab. The most useful parameters for preprocedural screening are eGFR and the presence of diabetes.

There is additional evidence that the risk of AKI varies with the clinical presentation and type of imaging procedure. For example, patients with ST-segment elevation myocardial infarction who undergo percutaneous coronary intervention (PCI) have a particularly high risk of CI-AKI [9,10].

As there is no specific treatment for CI-AKI, prevention is the key. Before the use of CM, all risk factors should be assessed (Table 1), indications for use of contrast should be confirmed, and risk stratification should be performed [6].

Because there is no specific treatment for CI-AKI, prevention is the key

Non-modifiable and modifiable risk factors for CI-AKI

Non-modifiable	Modifiable
Chronic kidney disease	Hypotension
Congestive heart failure	Anemia
Diabetes mellitus	Nephrotoxic drugs
Age	Type of contrast
Female sex	Contrast volume
Emergency procedure (primary PCI)	Preprocedural dehydration

Table 1

What Hydration Protocols Should Be Used?

At present, perioperative hydration is considered the “gold standard” for prevention of CI-AKI. This can be achieved by increasing the amount of liquid flowing through the renal tubules with an intravenous injection of a crystal solution and by reducing the contact time between the CM and renal tubular epithelial cells.

The most widely recommended procedure is intravenous infusion of normal saline at a rate of 1 mL/kg/h from 12 h before to 12 h after contrast administration. Alternatively, quick infusion protocols in ambulant patients have been used with similar results.

There have been numerous randomised trials, many with small samples, comparing isotonic bicarbonate solutions to intravenous saline for the prevention of CI-AKI, based on the hypothesis that urinary alkalinisation would reduce contrast-induced generation of injurious oxygen free radicals. Even in the largest and highest-quality trials, there have been no differences in the rates of renal outcomes [1,6].

The Prevention of Serious Adverse Events Following Angiography (PRESERVE) study was a double-blind trial that randomly assigned 5177 high-risk patients undergoing non-emergency angiography to receive intravenous isotonic sodium bicarbonate or intravenous isotonic saline, as well as oral acetylcysteine or oral placebo, for the prevention of a primary 90-day composite endpoint comprising death, need for dialysis, or persistent impairment in kidney function [11]. The trial showed no significant difference in the incidence of the primary outcome (4.4% with bicarbonate and 4.7% with saline; odds ratio, 0.93; 95% CI, 0.72 to 1.22; P = 0.62) or in the incidence of CI-AKI, which was a secondary endpoint (9.5% with bicarbonate and 8.3% with saline; odds ratio, 1.16; 95% CI, 0.96 to 1.41; P = 0.13). Exclusion of patients undergoing emergency procedures and the low overall median volume of contrast administered (85 mL) were limitations of this trial, but the investigators concluded that isotonic sodium bicarbonate provides no benefit relative to isotonic saline. Hence, either isotonic crystalloid solution is recommended, with guidance on the volume of fluid according to patient characteristics [3,11].

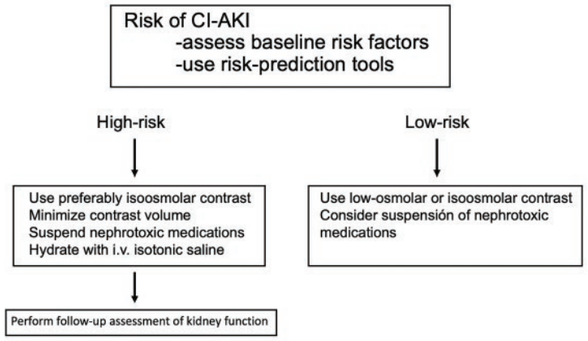

Table 2

Targeted hydration protocols have shown promising results in several studies. Adjusting infusion rates to central venous pressure or left ventricle end-diastolic pressure could result in a decrease in CI-AKI in selected patients [12,13]. In addition, a strategy of controlled hydration with forced diuresis and matched saline infusion using an automated system (RenalGuard) in patients with established CKD was superior to that in the control group [14].

indicated for highest-risk patients [1].

In patients with very high-risk profiles (eGFR <30 ml/min/1.73 m^2 with diabetes, heart failure, or urgent PCI for acute coronary syndrome), there is no absolutely safe limit of contrast dose. Therefore, the most reasonable approach is to maximise the benefit-to-risk balance of the procedure by performing revascularisation, followed by close monitoring and management of CI-AKI (Table 2).

Some studies suggest the selection of the least-toxic iodinated contrast agent in the highest-risk patients. Low-osmolar contrast agents are reasonable for moderate-risk patients and isoosmolar contrast is indicated for the highest-risk patients

Contrast-sparing strategies in cardiac interventions

- Use 5-French catheters for diagnostic and therapeutic coronary interventions
- Avoid acquiring new diagnostic images if previous angiograms are available
- Limit the volumen of contrast per injection
- Avoid test injections unless necessary
- Allow for elimination of contrast from guiding catheter by backbleeding or aspirating before entering equipment
- Use stent-enhancement techniques (ClearStent, StentBoost)
- Use increased acquisition rates (15 or 25 frames/sec) to improve image quality and to evaluate final result
- Use additional guidewires to create a roadmap of the target vessel and its side branches, or use dedicated software
- Extensive use of intravascular ultrasound, non-contrast optical coherence tomography, and coronary physiology testing

Table 3

Choice of CM

The European Society of Cardiology (ESC) 2018 guidelines on myocardial revascularisation, as well as the ESUR CM guidelines, recommends the use of low- or iso-osmolar contrast agents instead of high-osmolar contrast agents because they reduce the risk of CI-AKI [4,15].

Several meta-analyses and clinical studies have shown a trend but no definitive evidence that iso-osmolar CM is associated with a significantly lower rate of CI-AKI than low-osmolar CM [6]. However, some studies have suggested the selection of the least toxic iodinated contrast agent in the highest-risk patients. Low-osmolar contrast agents are reasonable for moderate-risk patients, and iso-osmolar contrast is

Measures to Reduce the Volume of CM

Several studies have shown that contrast dose is directly related to the risk of CI-AKI 2, 6,8. Therefore, calculating the maximum acceptable contrast dose seems to be a potentially effective measure to reduce the development of CI-AKI in most patients. The ESC guidelines suggest using a contrast volume <4 mL/kg or a total contrast volume/GFR <3.7, especially in patients with some degree of CKD 15.

Some studies comparing the use of manual injections and automated contrast injection devices have shown a reduction in the volume of contrast administered when using injectors 16.

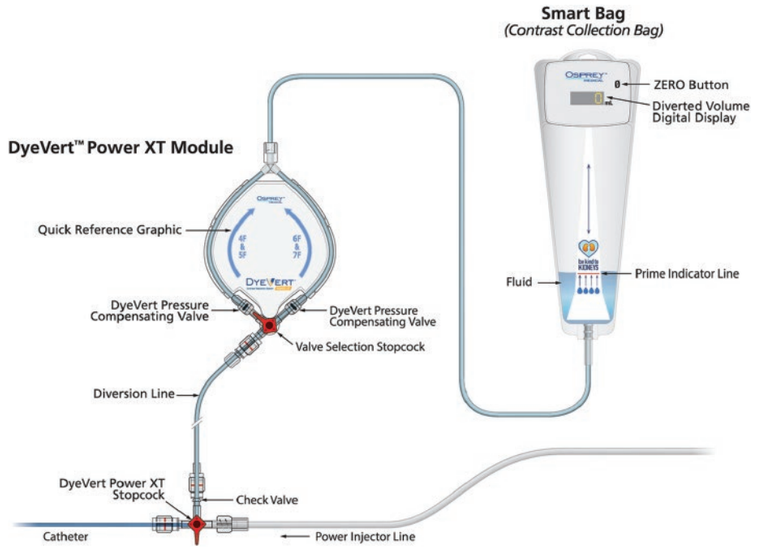

Figure 1 - DyeVert-Power-XT

These devices allow the use of smaller French catheters (5F) while maintaining the quality of the images, thus reducing the volume of CM. The use of these injectors has significantly increased in recent years. Other factors that can help reduce the volume of contrast include radial access, the use of intravascular imaging (IVUS or non-contrast OCT), physiological evaluation (fractional flow reserve and instantaneous wave free ratio), stent enhancement techniques (StentBoost, ClearStent), and increased acquisition rates (15 or 25 frames/s) to improve image quality and reduce the number of angiograms (Table 3). Avoiding left ventriculography and aortography are additional strategies commonly used to reduce the overall contrast dose.

Dedicated devices have been developed to reduce the overall contrast volume. The DyeVert system (Osprey Medical, Minneapolis) is a device that allows diversion of excess contrast during injection. The fraction of CM that does not contribute to coronary opacification but gets refluxed into the aortic root is diverted into a reservoir chamber (Figure 1).

DyeVert was initially developed for manual injection (DyeVert EZ plus), while a more recent version designed for power injection (DyeVert Power XT) is available. This was further evaluated to demonstrate that it effectively spares CM volume for the patient without reducing the image quality for the physician or increasing the risk for adverse events 17, 18. When used in conjunction with the ACIST system, the DyeVert Power XT reduced the amount of CM by 34% to 40%. This device could be an excellent alternative to decrease the incidence of CI-AKI or to avoid staged procedures in the growing number of complex procedures (multivessel and chronic total occlusion PCI, transcatheter aortic valve implantation, and left atrial appendage closure) that interventional cardiologists perform.

In conclusion, although guideline-recommended preventive measures are effective, CI-AKI remains a frequent complication of CM use during coronary angiography and cardiac interventions. Patients with CKD are at a high risk of CI-AKI and exposed to a significant burden of morbidity and mortality and therefore are linked to increased length of hospital stay and health care costs. New and creative procedural strategies, such as implementation of contrast-sparing protocols, may reduce the risk of CI-AKI in patients undergoing complex cardiac procedures and improve the outcomes of this population.

New and creative procedural strategies, like implementing contrast-sparing protocols, may reduce the risk for CI-AKI in patients undergoing complex cardiac procedures and improve the outcomes of this population

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Reducing AKI Complications in Patients with Chronic Kidney Disease

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Definitions and Diagnostic Criteria

Contrast-induced acute kidney injury (CI-AKI) consists of an acute decline in renal function following iodinated contrast media (ICM) exposure. Three pathophysiological mechanisms contribute to acute tubular injury: direct cytotoxic damage to ICM, oxygen radical-mediated injury, and ischaemic damage due to haemodynamic impairment.[1,2]

Over the years, owing to the increasing number of diagnostic and interventional procedures requiring ICM administration, greater efforts to prevent and diagnose CI-AKI have been pursued.

Various diagnostic criteria based on contrast-induced renal impairment have been proposed to define CI-AKI.

Kidney Disease: Improving Global Outcomes (KDIGO) proposes the following:

- serum creatinine (SCr) increase of ≥ 0.3 mg/dL (26.5 μmol/L) within 48 h of ICM exposure
- ≥ 50% relative increase from baseline within 7 days or urinary volume < 0.5 ml/kg/h in 6 h;[3]

The Italian Society of Interventional Cardiology/Italian Society of Nephrology (SICI-GISE/SIN) Consensus panel suggests the following:

- An SCr increase of ≥ 0.3 mg/dL (26.5 μmol/L) or ≥ 50% relative increase from baseline within 48 h of ICM exposure.[4]

Epidemiology and Clinical Implications

Depending on the adopted diagnostic criteria, the incidence of CI-AKI following percutaneous coronary intervention (PCI) is 3.3-10.2%5 (10.5-18.3 % in patients with STEMI 6) and is associated with a poor short-term and long-term prognosis.[7,8,9]

Azzalini et al.[10] investigated the incidence of CI-AKI in 2660 patients undergoing complex or non-complex PCIs. They defined CI-AKI as an increase in post-PCI creatinine of ≥0.3 mg/dl or ≥50% from baseline. Complex PCI was defined as the presence of one or more of the following characteristics: three vessels treated, three or more stents implanted, two-stent bifurcation intervention, total stent length > 60 mm, PCI of chronic total occlusions (CTOs), saphenous vein grafts, or left main coronary artery; protected PCI; and use of rotational/laser atherectomy. This retrospective study showed no significant difference in the incidence of CI-AKI between complex and non-complex PCIs (12.1% vs. 11.5%, p = 0.63), even though complex PCI patients received a higher mean contrast volume (284 ± 137 vs. 189 ± 90 mL, p < 0.001).

The incidence of CI-AKI was less frequent following CTO-PCIs than that following non-CTO-PCIs.[11] However, preexisting chronic kidney disease (CKD) plays a pivotal role in the development of CI-AKI after CTO-PCI and is associated with lower technical and procedural success rates.[12]

Contrast-induced acute kidney injury is relatively common in patients undergoing transcatheter aortic valve implantation (TAVI), with an incidence rate of 22%, and it is associated with a poor early and late prognosis.[13] However, the incidence of CI-AKI after TAVI is lower than that after surgical aortic valve replacement.[14]

In patients undergoing left atrial appendage closure, CI-AKI has an incidence of 9% considering the SICI-GISE/SIN diagnostic criteria and is associated with increased mortality (22%) compared to patients without CI-AKI (9.8%).[15]

Spieker et al.[16] investigated the incidence of AKI in patients undergoing percutaneous mitral valve repair (PMVR): of over 206 subjects, 38 (18%) suffered AKI after PMVR, which was associated with increased 1-month mortality and 1-year all-cause mortality.

Tonchev et al.[17] obtained similar results with their retrospective analysis of data from 163 patients who underwent PMVR. The incidence of AKI was 29%, and in those who did not recover from AKI, it was associated with increased 1-year mortality.

Over the years, owing to the increasing number of diagnostic and interventional procedures requiring ICM administration, greater efforts to prevent and diagnose CI-AKI have been pursued

Procedure	CI-AKI / AKI incidence
PCIs	3,3-10,2%[5]
PCIs in STEMI patients	10,5-18,3%[6]
Complex PCIs	12.1%[10]
CTO-PCIs	9.4%[11]
TAVI	22%[13]
LAAC	9%[15]
PMVR	18%[16,17]

Table 1 – CI-AKI incidence in percutaneous cardiovascular interventions.
PCI: percutaneous coronary intervention. STEMI: ST-elevated myocardial infarction. CTO: chronic total occlusions. TAVI: trans-catheter aortic valve implantation. LAAC: left atrial appendage closure. PMVR: percutaneous mitral valve repair.

CI-AKI is associated with a worse short-term and long-term prognosis. Primary PCI, TAVI are the procedures carrying the greatest risk of CI-AKI development

Renal impairment due to ICM administration is linked to a higher probability of dialysis and hospitalisation requirement, resulting in increased public health expenditure.

CI-AKI may favour the development of CKD or, in most cases, to a transient impairment of renal function, after which complete restoration to original condition occurs. In patients with preexisting CKD (GFR ≤60 ml/min/1.73 m^2), persistence of renal function impairment is associated with worse prognosis than in patients who develop transient CI-AKI.[18]

In a retrospective study of 14,782 patients, James et al. showed that CI-AKI has a significant impact on long-term prognosis and mortality, development of CKD, and the rate of hospitalisation due to cardiovascular or renal events.[19]

Primary PCI, TAVI, carry the greatest risk of CI-AKI development. These results may depend on the intrinsic characteristics of the patients undergoing these procedures. TAVI and is performed in most cases, in a relatively older population with comorbidities that predispose to CI-AKI such as CKD, heart failure, and diabetes.

In patients undergoing emergency PCI due to STEMI, the higher incidence of CI-AKI may be due to haemodynamic instability.[20]

Risk Patient Stratification

Many risk assessment strategies have been proposed to predict the risk of developing CI-AKI. The Mehran risk score[21] was based on risk factors such as intra-aortic balloon pump, CHF, age >75 years, anaemia, diabetes, contrast media volume, SCr > 1.5 mg/dL or GFR <60 ml/min/1.73 m2 to predict CI-AKI occurrence according to the presence of these conditions (**Table 2**); Gurm et al.[22] developed a risk score with 15 variables that has to be calculated using a smart device or a computer; Capodanno et al.[23] proved the validity of the ACEF (age, serum creatinine, left ventricular ejection fraction) score, and the SICI-GISE/SIN Consensus Panel suggested considering patients at risk of CI-AKI with preexisting renal insufficiency (GFR ≤60 ml/min/1.73 m^2), diabetes, anaemia, age ≥75 years, heart failure, reduced ejection fraction, and haemodynamic instability.[4]

Risk factors	Score
Hypotension (SBP < 80 mmHg)	5
Intra-aortic balloon pump	5
Congestive heart failure (NYHA III/IV)	5
Age > 75 years	4
Anemia (Ht < 39% in men; < 36% in women)	3
Diabetes	3
Volume of injected contrast media	1 for each 100 mL
SCr > 1,5 mg/dL OR eGFR < 60 ml/min/1,73 m^2	4 - 2 if eGFR 40-60 ml/min/1,73 m^2 - 4 if eGFR 20-40 ml/min/1,73 m^2 - 6 if eGFR < 20 ml/min/1,73 m^2

	Risk score	Risk of CI-AKI	Risk of dialysis
Low	≤ 5	7,5 %	0,04 %
Moderate	6 - 10	14 %	0,12 %
High	11- 15	26,1 %	1,09 %
Very high	≥ 15	57,3 %	12,6 %

Table 2 – Mehran risk score.[21]
SBP: systolic blood pressure. NYHA: New York Heart Association functional classification. Ht: hematocrit. eGFR: estimated Glomerular Filtration Rate

THREE PERSPECTIVES ON THE REDUCTION OF CONTRAST INDUCED ACUTE KIDNEY INJURY IN INVASIVE CARDIOLOGY

Preventive Strategies for CI-AKI

Although haemodialysis and haemofiltration can remove ICM[24], prophylactic haemodialysis has not been shown to prevent CI-AKI or to improve renal outcome, morbidity, and mortality[25,26] and is not recommended by the current guidelines (KDIGO3, European Renal Best Practice[27], or European Society of Urogenital Radiology[28,29]). The key to deal with CI-AKI-related complications is the prevention of CI-AKI.

CI-AKI can be prevented by administration of drugs such as statins, that can reduce the incidence of CI-AKI, and by the suspension of nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), or medications that could be linked to an increased risk of developing CI-AKI.

Many authors have investigated the effects of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) on CI-AKI incidence, but the studies carried out are heterogeneous regarding the population studied, molecules investigated, and CI-AKI definitions used. According to Kalyesubula et al.[30], it is safer to withhold the therapy with ACEi or ARBs prior to angiography, given the lack of convincing renal benefit associated with continuing these medications and the presence of real possibility of harm.

Temporary discontinuation of ACEi or ARB therapy 24 h before the procedure and until the stabilisation of the renal function is recommended by the SICI-GISE/SIN Consensus panel in patients at high risk of CI-AKI.[4] In addition, the panel suggested the initiation of high-dose statin therapy before the procedure,[4] in accordance with European Society of Cardiology (ESC) /EACTS Guidelines on myocardial revascularisation.[31]

Fluid therapy is pivotal in preventing CI-AKI. For patients with moderate-to-severe renal insufficiency, ESC Guidelines recommend (IC) administration of 1 ml/kg/h of isotonic saline solution, during the 12 h preceding ICM exposure and through the subsequent 24 h, becoming 0.5 ml/kg/h in those with left ventricular ejection fraction <35% (IIa C).[31] The SICI-GISE/SIN Consensus panel suggests the same protocol in patients at risk for CI-AKI.[4]

There is no evidence supporting the use of N-acetylcysteine or bicarbonates to prevent CI-AKI.[32,33]

The Renal-Guard® system exploits "controlled forced diuresis" and is based on a technique in which a furosemide-induced increase in urinary output is immediately compensated by intravenous infusion of 0.9% NaCl to avoid dehydration. This system adjusts fluid input on urinary output, aiming to maintain adequate hydration and avoid fluid overload that could lead to pulmonary oedema.

Our centre investigated the Renal-Guard® system efficacy in 112 patients undergoing TAVI.[34] In this study, the patients were randomly assigned to either RenalGuard® or standard hydration regimen. The results showed a reduced AKI incidence in the RenalGuard® group compared with the control group (n= 4, 5.4% vs. n= 13, 25.2%; relative risk: 0.21 [95% confidence interval [CI]: 0.06, 0.71]; p= 0.014); no cases of pulmonary oedema were reported.

A meta-analysis by Putzu et al.[35] included four trials, with a total population of 698 patients undergoing PCI and TAVI. The results of this meta-analysis showed a reduced incidence of CI-AKI in the Renal-Guard group (27 of 348 [7.76%] patients) compared with the control group (75 of 350 [21.43%] patients) with a p-value < 0.00001.

Ideal Contrast Media Agent

Initially, high osmolarity ionic-based ICM and high-osmolar contrast media were available, but they were poorly tolerated by patients and caused frequent adverse reactions. Currently, low-osmolar contrast media (LOCM) and iso-osmolar contrast media (IOCM) are used in clinical practice. Iodixanol is the only currently available IOCM in the market.

Many authors have investigated the difference between LOCM and IOCM in terms of CI-AKI incidence, and several meta-analyses have been published on this topic. Aspelin et al.[36], in a multicentre, double-blind, prospective, randomised study, compared peak SCr increase in diabetic patients with CKD after the administration of iodixanol or LOCM (iohexol), with a significantly lower incidence in the first group (0.13 mg/dl vs. 0.55 mg/dl; p= 0.001).

The RECOVER study showed a lower incidence of CI-AKI in patients with GFR ≤60 mL/min randomised to the IOCM group than in those randomised to the LOCM (ioxaglate) group (7.9 vs. 17%, P = 0.021).37 Song et al. obtained similar results comparing iodixanol and iohexol in 220 patients with reduced left ventricular systolic function undergoing coronary angiography, with or without angioplasty (CI-AKI incidence: 12.7% in the iodixanol group vs. 29.1% in the iohexol group; P = 0.041).[38]

The ICON study, in which Mehran et al. compared median peak increase of SCr in patients with renal impairment randomised to receive IOCM or LOCM (ioxaglate), showed a trend in favor of IOCM without statistically significant differences between the two groups (0.09 mg/dl vs. 0.15 mg/dl; p= 0.07).[39] The results of this study may have been affected by the small sample size and low statistical power.

In the VALOR study, the authors investigated the incidence of CI-AKI in 300 patients undergoing coronary angiography using IOCM or ioversol

CI-AKI can be prevented by administration of drugs such as statins and by the suspension of nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), or medications that could be linked to an increased risk of developing CI-AKI. Fluid therapy is pivotal in preventing CI-AKI

SICI-GISE/SIN Consensus panel suggested to use IOCM in high-risk patients as a result of its "trend" of increased safety compared to LOCM

(LOCM). It did not show any significant difference in CI-AKI incidence (21.8% in the iodixanol group and 23.8% in the ioversol group; P = 0.78) and in SCr mean peak percentage change (MPPC), although in diabetic subjects MPPC was significantly lower in the iodixanol group (12.9% vs. 22.4% with ioversol; P = 0.01).[40]

In the CARE study, Solomon et al.[41] compared the incidence of CI-AKI in patients with CKD undergoing coronary angiography or PCI, randomised to iodixanol or iopamidol. No significant difference in CI-AKI was observed between the two groups (6.7% iodixanol vs. 4.4% iopamidol; P = 0.39).

The risk of CI-AKI may depend on the contrast administration route. Dong et al.[42] investigated the incidence of CI-AKI in patients undergoing intra-arterial or intravenous administration of LOCM versus IOCM. This meta-analysis showed a significantly decreased risk of CI-AKI after intra-arterial administration of IOCM compared to LOCM (risk ratio [RR] = 0.68; 95% CI, 0.50-0.92; Z=2.47; p=0.01). No difference in the incidence of CI-AKI was found in patients undergoing intravenous administration of IOCM or LOCM. McCullough et al.[43] compared the association between intra-arterial (IA) and intravenous (IV) administration of IOCM or LOCM and CI-AKI, defined as an increase in serum creatinine (SCr) ≥ 0.5 mg/dL or ≥ 25% from baseline. After IA administration, the incidence of CI-AKI was significantly lower in the IOCM group (RR 0.462; 95% CI: 0.272–0.786, p = 0.004) ≥ 0.5 mg/dl definition. No statistically significant difference was found between IOCM and LOCM in the IA group using (SCr) ≥ 25% definition, although the incidence of CI-AKI was lower after IOCM administration. In the IV group, there was no significant difference in the incidence of CI-AKI using either definition.

According to these findings, iodixanol should be preferred over LOCM in IA cardiovascular procedures.

There is no strong evidence in support of using IOCM over LOCM in the general population, but in patients at high risk of CI-AKI, such as those with CKD, diabetes, or heart failure, IOCM showed better results. The SICI-GISE/SIN Consensus Panel suggested the use of IOCM in high-risk patients as a result of its "trend" of increased safety compared to LOCM.[4]

Volume Reduction

ICM volume has been reported to be a modifiable risk factor for CI-AKI and represents one of the variables of the Mehran risk score.[21] Many authors have demonstrated that it is not the ICM volume that determines the increased risk for CI-AKI, but its adjustment for patient's weight and SCr level.

Laskey et al.[44], in a study with a population of 3179 patients, showed that ICM/CrCl (creatinine clearance) volume ratio <3.7 is a sensitive and specific cutoff for identifying patients at risk for CI-AKI.

Gurm et al.[45] showed that an ICM dose based on CrCl with a planned ICM volume restricted to 2 × CrCl and not exceeding 3 × CrCl might be valuable in reducing the risk of CI-AKI.

The ESC guidelines on myocardial revascularisation and the SICI-GISE/SIN Consensus Panel recommend minimising ICM administration in patients with moderate to severe CKD.[31,4]

There are various additional measures that can be adopted in order to minimise ICM volume: using 5-6 Fr catheters without "side holes", limiting dye injections during fluoroscopic angiography, reducing injected dye volume to the necessary minimum to ensure correct vessel visualisation, removing the dye with the "back bleeding", and using stored images, intravascular ultrasound (IVUS) and functional stenosis evaluation.[20]

The dynamic coronary roadmap (DCR) system can be used to reduce the administration of ICM during percutaneous coronary intervention. Yabe et al.[46] compared the volume of contrast media during PCIs with or without DCR and reported a significant difference in ICM volume (118.8 ± 49.7 mL vs. 152.1 ± 73.0 mL, P = 0.006) between the two groups. The ongoing multi-centre, prospective, unblinded, stratified 1:1 randomised controlled trial "Dynamic Coronary Roadmap for Contrast Reduction (DCR4Contrast)" aims to assess whether using a dynamic coronary roadmap reduces the total iodinated contrast volume related to PCI compared to the control group without dynamic coronary roadmap; its results are expected by October 2021.

The automated contrast injector system (ACIST) has been proven to reduce injected ICM volume compared to manual injections although there is no evidence of its effect on the incidence of CI-AKI.[47,48]

Various devices have been designed to optimise the amount of dye administered to the patient using an automated contrast injector system during angiographic procedures.

Duffy et al.[49] tested the CINCOR contrast removal system (Osprey Medical, St. Paul, MN, USA), which is a dedicated tool for the removal of contrast medium from the coronary sinus. In this study, the physicians obtained adequate cannulation of the coronary sinus in 31 of the 41 patients studied, removing approximately 32.3% of the administered ICM. Further studies are needed to assess the clinical impact of removing contrast medium from the coronary sinus.

Mehran et al.[50] assessed the efficacy of the AVERT Contrast Modulation System (AVERT)

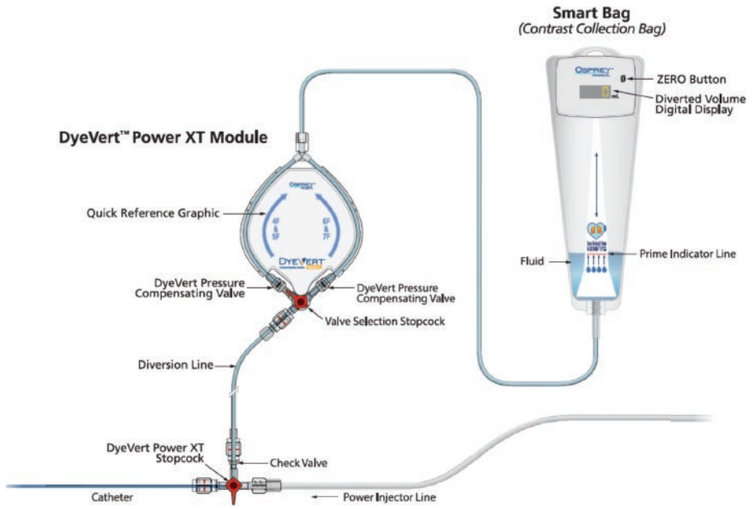

Figure 1 - DyeVert™ Power XT, compatible with automatic injectors.

(Osprey Medical, MN), showing a contrast media volume (CMV) reduction of 15.5% in the general population, which rose to 46% in patients undergoing complex three-vessel PCIs. Despite these results in CMV reduction, no significant differences in CI-AKI incidence were observed with AVERT in this trial.

DyeVert System

DyeVert Power XT (Figure 1) consists of a diversion line and two catheter size-dependent (4-5 Fr and 6-7 Fr) diversion valves that respond to the contrast injection pressure and modulate the amount of contrast diverted and collected in the contrast collection bag. This device works with automatic injectors, reduces CMV, and minimises the backflow of excess dye during injections, which exposes the kidneys to the first passage effect of undiluted ICM.

Amoroso et al.[51] evaluated the novel DyeVert Power XT system in a multicentre, post-market, retrospective study involving 26 patients undergoing coronary angiography or angioplasty. The mean CMV delivered was 87.9 ± 51.5 mL (range 30.6–211.9 mL), and mean MCV saving was 34.4 ± 6.2% (range 24.1–47.0%) per procedure. Physicians characterised the image quality as acceptable in 25 cases (96%).

Briguori et al.[52] demonstrated the efficacy of DyeVert in a single-centre retrospective study involving 451 patients with acute coronary syndrome who underwent urgent or immediate coronary angiography or angioplasty in 112 procedures supported by the DyeVert system. The authors assessed the difference in CMV administration and CI-AKI incidence between the two groups. CMV was higher in the control group than in the DyeVert group, with a mean percentage CMV reduction of 38 ± 13% in the DyeVert group. CI-AKI occurred in 17/90 (19%) patients in the control group and in 7/90 patients (8%) in the DyeVert group (odds ratio = 0.37; 95% CI: 0.14–0.95; p =.047).

Osprey Medical also developed the DyeVert Plus EZ (Figure 2) that allows modulation of CM during manual injection. This system is still based on the diversion of part of the injected CM through a secondary fluid pathway controlled by a pressure compensating valve. The aforementioned compensating valve provides variable resistance to CM manual injection and uniform flow suppression, which results in adequate image quality and decreased aortic reflux. This system can be used with 4–6 French diagnostic catheters and 5–7 French guide catheters. DyeVert Plus EZ can be particularly useful to CTO operators, in fact during CTO-PCIs, double injections to visualise collateral vessels are needed and these procedures are associated with high contrast volume administration.

Tajti et al.[53] evaluated the feasibility and efficacy of the DyeVert Plus EZ during PCIs of chronic total occlusions. In this study, the DyeVert system was used in 39 of 134 CTO-PCIs, and the MCV administered was 200 mL (interquartile range, 153–256 mL) in the DyeVert group and 250 mL (interquartile range, 170–303 mL) in the control group (p= 0.04).

In a multicentre, single-arm, observational study by Gurm et al.[54], the authors investigated CMV saving using DyeVert Plus in 114 patients undergoing coronary angiography with or without

DyeVert Power XT reduces CMV and minimizes the backflow of exceeding dye during injections, that exposes kidneys to first passage effect of undiluted ICM

There is no specific treatment for CI-AKI, and the symptomatic treatment is based on the maintenance or restoration of a correct state of hydration and discontinuation of nephrotoxic drugs

PCI. The mean CMV attempted was 112 ± 85 mL (range 22–681 mL) and mean CMV administered was 67 ± 51 mL (range 12–403 mL), resulting in an overall CMV savings of 40.1 ± 8.8% (95% CI 38.4–41.8; P < 0.0001) per procedure.

Reduction of AKI Complications

There is no specific treatment for CI-AKI, and the symptomatic treatment is based on the maintenance or restoration of a correct state of hydration and discontinuation of nephrotoxic drugs. Furthermore, to prevent CI-AKI complications, it is mandatory to suspend medications that could be harmful in patients with kidney failure.

Metformin is frequently used as an antidiabetic therapy. It is not metabolised, but it is cleared from the body by tubular secretion and excreted unchanged in the urine. In patients with kidney failure, it can accumulate, leading to lactic acidosis.

The ESC/EACTS Guidelines on myocardial revascularisation suggest stopping antidiabetic treatment with metformin in patients with CKD before coronary angiography and checking renal function after the procedure in patients who have taken metformin, withholding it if renal function deteriorates.[31]

The SICI-GISE/SIN Consensus Panel does not recommend withholding metformin in patients with GFR > 30 ml/min/1.73 m^2; on the other hand, it recommends stopping metformin in patients with GFR ≤ 30 ml/min/1.73 m^2, independent of the procedure.[4]

Limitations and Future Perspectives

Although several studies have been conducted on this topic, there is no universally recognised protocol for CI-AKI prevention.

In recent years, many devices have been proposed to assist physicians in preventing CI-AKI by reducing MCV administration, the principal modifiable risk factor. Several retrospective studies have proven the efficacy of these devices, but prospective randomised clinical trials are needed to confirm the efficacy of these devices in reducing the occurrence of CI-AKI in patients undergoing cardiovascular interventions. Meanwhile, in order to reduce the incidence of CI-AKI, it would be desirable to adopt a predetermined protocol for patients at high risk of CI-AKI and encourage the use of IOCM and dedicated devices according to the available evidence.

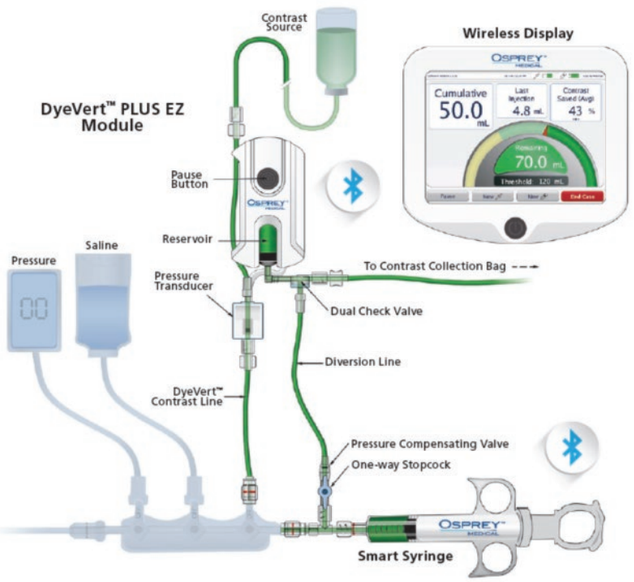

Figure 2 - DyeVert™ Plus EZ, compatible with manual injectors.

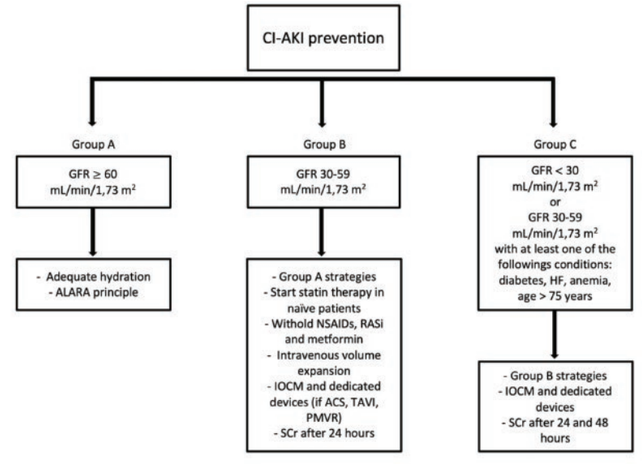

Figure 3 – Algorithm for the prevention of contrast-induced acute kidney injury.
CI-AKI: contrast induced acute kindey injury. GFR: glomerular filtration rate. SCr: serum creatinine. CMV: contrast media volume. ALARA: as low as reasonably achievable. NSAIDs: nonsteroidal anti-inflammatory drugs. RASi: renin-angiotensin system inhibitors. IOCM: iso-osmolar contrast media. ACS: acute coronary syndromes. TAVI: transcatheter aortic valve implantation. PMVR: percutaneous mitral valve repair. HF: heart failure.

Aiming to reduce the incidence of CI-AKI, it would be desirable to adopt a predetermined protocol for patients at high risk of CI-AKI and to encourage the usage of iso-osmolar contrast media and dedicated devices according to the available evidence

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