



Review Article

Contrast-induced Acute Kidney Injury: A Review

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Abstract

Contrast-induced acute kidney injury (CI-AKI) is a transient impairment of renal function which occurs after intravascular administration of iodinated contrast media (CM). Because of the increasing number of procedures requiring CM and the relevant impact on prognosis and costs, CI-AKI has become a subject of interest for researchers and physicians. In the last years many efforts have been made to better understand CI-AKI pathophysiology and to find new measures of prevention and management. This review aims to provide an overview of epidemiology, diagnostic criteria and tools, pathophysiology, clinical implications and prevention measures of CI-AKI.

Keywords: Acute kidney injury; Nephropathy

Background and Epidemiology

Contrast-induced acute kidney injury (CI-AKI) is a transient impairment of renal function which occurs after intravascular administration of iodinated contrast media (CM). CI-AKI negatively affects clinical outcome and in patients undergoing percutaneous coronary intervention (PCI) CI-AKI has been linked with higher short and long-term mortality [1,2]. Furthermore, higher rates of major adverse cardiac events (MACE) and prolongation of hospital stay have also been associated with CI-AKI [3]. Given the increasing number of diagnostic and therapeutic procedures requiring CM and the impact on prognosis and costs, CI-AKI has become a subject of increasing interest for patients and physicians.

In the National Cardiovascular Data Registry Cath-PCI including 985737 patients undergoing elective and urgent PCI the incidence of CI-AKI was 7.1%, being the cases requiring dialysis 0.3% [4]. However, incidence values of CI-AKI widely vary among different studies.

CI-AKI incidence is multifactorial, being dependent on patient-related and contrast-related risk factors.

Among the patient-related factors, the most important is the baseline renal function: the incidence of CI-AKI ranges from 2% in patients with normal renal function to 30-40% in patients with creatinine >2 mg/dl [5-7]. Other important risk factors of CI-AKI are diabetes mellitus and advanced age, even if there is a discussion on whether these factors are independent predictors of CI-AKI or confounders, due to the fact that they are often associated with impaired renal function [7]. Anemia due to periprocedural bleeding may also affect the risk for CI-AKI development, according to the decrease in haemoglobin levels [8]. Moreover, heart failure and hemodynamic instability such as periprocedural hypotension and use of intra-aortic balloon pump have shown to be associated with an increased risk of CI-AKI [3]. CI-AKI

post-hoc analysis of the PRODIGY trial CI-AKI occurred in 12% of patients undergoing PCI during ST-elevation myocardial infarction (STEMI), 9.2% in patients with unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI) and 4.5% in patients undergoing elective PCI (p=0.0005) [9].

Also contrast-related factors, both quantitative and qualitative characteristics of CM administered, may affect the incidence of CI-AKI. Higher volumes of CM associated with increased CI-AKI incidence [10]. The risk of CI-AKI is also dependent on CM osmolality and viscosity: High osmolality and high viscosity are associated with a nephrotoxic potential [11].

A relevant additional problem of CI-AKI epidemiology is the use of non-homogenous definitions in literature [12]. This has important implications in defining actual CI-AKI incidence and impact on clinical outcomes and comparing performance of preventive strategies [13-20].

Definition and diagnosis

The most commonly used definition of CI-AKI in clinical trials is a raise in serum creatinine (SCr) of 0.5 mg/dl or a 25% increase from the baseline value, assessed at 48 h after the procedure. However, there is a considerable number of alternative definitions and cut-off values for SCr used to define CI-AKI.

For example, the Contrast-Induced Nephropathy Consensus Working Panel defines CI-AKI as an absolute increase in SCr concentration of 0.5 mg/dL (44.2 μM/L) or a 25% relative increase in creatinine from baseline [21]. According to the European Society of Urogenital Radiology CI-AKI is defined as an impairment in renal function (an

increase in SCr by >0.5 mg/dL or >25% within 3 days after CM exposition, without an alternative etiology) [22,13]. The Acute Kidney Injury Network definition includes a rise in serum creatinine \geq 0.3 mg/dL with oliguria [22]. More recently, the European Renal Best Practise (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) guidelines has defined CI-AKI as an increase by \geq 50% or by \geq 0.3 mg/dL at 48 h [14].

The Contrast-Induced Nephropathy Consensus Working Panel has recommended using the relative increase in SCr to define CI-AKI [15]. However, it has been shown that an absolute increase of SCr>0.5 mg/dL) is associated with lower incidence but with stronger association with clinical outcome [16,19].

The raise of SCr during CI-AKI typically occurs within 1-3 days after CM administration, peaking within 3-5 days [22]. Therefore, it is recommended to follow SCr values at not less than 24 h or more than 72 h following contrast exposure [15].

At present SCr, that is used to measure the glomerular filtration rate (GFR), represents the main tool to evaluate renal function and eventually an indicator of AKI.

Nevertheless, the use of SCr change to define CI-AKI carries important limitations. First of all, SCr is not a direct marker of tubular epithelial cells or glomerular endothelial cells damage. As a consequence, in response to renal function impairment the increase of SCr values is linked to the reduction in its clearance and it takes several days to take place [23,24]. Furthermore, SCr depends not only on renal function, but also on the production rate and on distribution volume [23].

Additionally, there are some disadvantages using either absolute or percentage increases of SCr as a diagnostic criterion [24,25]. Using relative increases over baseline can lead to a delayed diagnosis in patients with chronic kidney disease (CKD) [24]. On the other hand, SCr is not highly sensitive in patients with low baseline levels, using an absolute definition [25].

Moreover, a post-hoc analysis of PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia study (PRODIGY trial) showed a dose-effect relationship between the threshold of percentage increase of SCr used to define CI-AKI and the impact on clinical events, both in stable and in unstable patients [26]. Those findings called into question the most used cut-off value of \geq 25% for CI-AKI, which may be an insufficient relative increase to impact clinical outcome (Figure 1).

In general, all these inconveniences put the need for novel biomarkers to improve AKI early diagnosis and help management. Neutrophil gelatinase-associated lipocalin (NGAL) is a member of the lipocalin family, readily excreted and detected in urine. It is accumulated in the human kidney cortical tubules, blood, and urine after nephrotoxic and ischemic injuries, representing an early, sensitive biomarker for AKI. In particular, NGAL levels have a sensitivity of 77.8% (95% confidence interval [CI] 62.8%-88.0%) and a specificity of 96.3% (95% CI 74.4%-99.6%) with a median cut-off NGAL value of 100 ng/ml (95% CI, 80-100 ng/ml)

[27]. A recent study conducted in patients with acute heart failure showed that peak NGAL was a better predictor than first NGAL for worsening of renal function, while first NGAL was more predictive than peak NGAL for adverse in-hospital outcomes [28]. Importantly, neither were superior to creatinine for the prediction of worsening renal function [28].

Clinical Impact of Increasing Δ SCr cut-offs in overall PRODIGY population

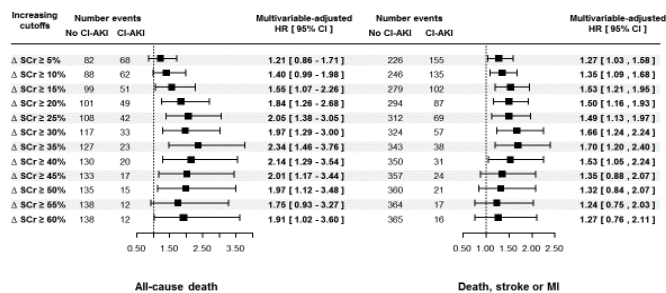


Figure 1: The threshold of percentage increase of serum creatinine (SCr) used to define contrast-induced acute kidney injury (CI-AKI) has a dose-effect relationship with clinical events.

Cystatin C (CysC) is a serum protein produced steadily by all types of nucleated cells in the body, filtered out of the blood by the kidneys. Thanks to its low molecular mass, it is freely filtered by the glomerular membrane and its blood concentration correlates with the GFR. Importantly, the levels of CysC are independent of weight and height, muscle mass, age and gender and measurements can be interpreted from a single random sample. When compared with GFR calculated by SCr, GFR calculated by measurement of CysC showed an improvement of 0.23 (95% CI 0.18-0.28) for death and 0.10 (95% CI 0.00-0.21) for progression to end-stage renal disease (ESRD) [29]. For these reasons, CysC is cleared for use by the U.S. Food and Drug Administration.

Another biomarker of CI-AKI recently proposed is the urine levels of IL-18. In a recent meta-analysis published in 2013, IL-18 was found to have a sensitivity of 58% (95% CI 52%-64%) and specificity of 75% (95% CI 70 %-80%) [30]. Of note, predictive value of urinary IL-18 did not differ significantly across the various time points of measurement.

A number of risk scores have been developed and validated for CI-AKI, to identify patients at high risk and accordingly affect clinical decision making [17,18,31,32]. Importantly, the general applicability of each score deeply depends on the clinical setting of the study from which a score derives. For example, among patients with STEMI it has been recently elaborated the first risk score that allow to predict the development of CI-AKI, before primary PCI [33].

A recently published review sought to assess the performance and clinical usefulness of 12 risk scores for CI-AKI published from 2004 to 2015 [34]. Although the majority

of these risk scores achieves an adequate accuracy, their usability in clinical practice is extremely limited, due to the lack of external validation in multicenter studies, an unclear association between the stratification to a risk category and clinical decision making and the lack of easy-to-use electronic risk calculators [34].

Pathophysiology

The pathophysiology of CI-AKI is multifactorial and it is based on a combination of mechanisms, including direct cytotoxic effects, auto-, para- and endocrine factors. Of note, these factors act on pre-existing individual risk profile and hydration status (Figure 2).

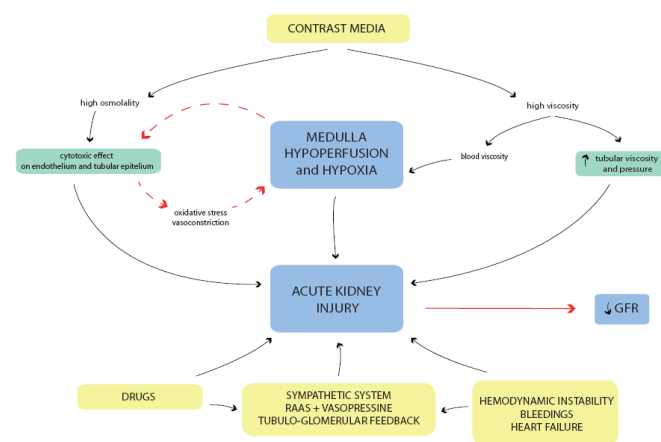


Figure 2: Contrast induced-acute kidney injury (CI-AKI) pathophysiology based on a combination of mechanisms including direct cytotoxic effect, auto, para and endocrine factors. Renal medullary hypoxia plays a central role in the pathophysiology of CI-AKI [15-17,39,40]. In particular, medullary hypoperfusion magnifies contrast media (CM) cytotoxicity initiating a vicious circle between direct CM toxic effect and renal damage (GFR: Glomerular Filtration Rate).

Iodinated CM exert cytotoxic effect *in vitro* and *in vivo* on epithelial tubular cells [35,36]. The extent of this direct cytotoxic damage is related to the duration of the exposure of these cells to the CM [22]. It was shown that CM can reduce cell proliferation and reversibly alter mitochondrial function in a porcine tubule cell line [37]. This effect was linked to CM ionicity, molecular structure and osmolality. In particular, low-osmolar (LO) CM affect mitochondrial function to a lesser extent compared to iso-osmolar (IO) and high-osmolar (HO)CM [37]. Moreover, HOCM are associated with an increased concentration of adenosine as compared with LOCM. Adenosine is connected to the generation of reactive oxygen species (ROS) promoting oxidative stress and renal vasoconstriction [38,39]. CM in the renal medulla can affect the fragile balance between vasodilatory and vasoconstrictive factors and result in medullary hypoperfusion, mainly caused by constricting descending vasa recta (DVR) [40]. CM exert a vasoconstrictor effect also in

the renal cortex, inducing pre-glomerular vasoconstriction and a consequent reduction in GFR [36]. High osmolality amplifies the intrinsic cytotoxicity and the hypoxic effect of CM, compared to lower osmolality. As a result, HOCM are associated with high nephrotoxicity [35,41].

On the other hand, the introduction of IOCM was associated with an increase in viscosity as compared to HOCM. High viscosity significantly slows tubular flow, increases tubular pressure and intrarenal retention time of CM [42].

Furthermore, high viscosity is associated with elevated interstitial and vascular pressures [42], accordingly reducing medullary blood flow and favoring hypoperfusion.

Through the alteration of renal tubulo- and haemo-dynamic, high viscosity of CM may eventually play an important role in the pathophysiology of the CI-AKI.

CM exert their damaging effects mostly by inducing renal hypoperfusion [35,43], holding renal medullary hypoxia a key position in the pathophysiology of CI-AKI.

Of note, renal hypoxic insult is worsened by the activation of sympathetic system and the hormonal response [44]. In AKI, the activation of the sympathetic system, the increased renin-angiotensin-aldosterone activity and the activation of tubular-glomerular feedback lead to a relevant renal vasoconstriction. Simultaneously, arginine vasopressin is released and contributes to water retention [44]. Additionally, drugs seem to contribute to AKI in about 20% of patients, especially in critically ill patients [45]. Frequently prescribed drugs such as non-steroidal anti-inflammatory drugs, antibiotics like β -lactam antibiotics, aminoglycosides or sulphonamides, angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers may contribute to AKI.

Clinical implications

CI-AKI has been associated with adverse short- and long-term outcomes including mortality and cardiovascular events, worsening of renal function and prolongation of hospital stay [1,26,46].

The association of CI-AKI with mortality varies significantly among studies published over the years. Results are influenced by study design and data analysis so that patient selection criteria, CI-AKI definition and adjustment for confounders may affect the values.

The association of CI-AKI and mortality in patients undergoing PCI is deeply influenced by the clinical, elective or emergent, setting. CI-AKI was found to be less frequent and less associated with mortality and other adverse outcomes in stable patients when compared to acute coronary syndrome (ACS) [7,26]. In particular, among patients with ACS, those presenting with STEMI have been shown to exhibit a more complicated course compared to NSTEMI patients [47].

Crimi et al. found that the adjusted prognostic impact of CI-AKI on the composite endpoint (death, stroke, myocardial infarction) was worse in patients with stable

coronary artery disease than in patients with ACS (p for multivariable-adjusted interaction=0.048) [26] (Figure 3).

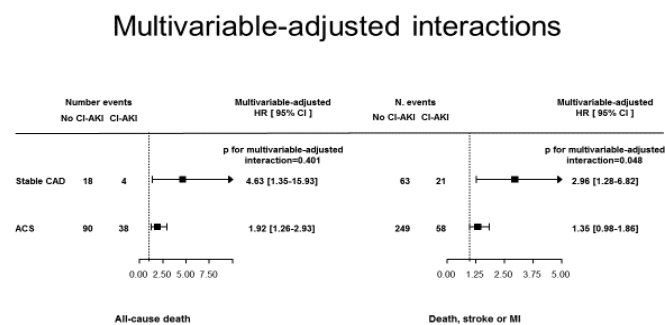


Figure 3: The impact of contrast induced acute kidney injury (CI-AKI) on the composite endpoint (death, stroke, myocardial infarction) is worse in patients with stable coronary artery disease (CAD) than in patients with acute coronary syndromes (ACS).

A meta-analysis published in 2013 confirmed the association between CI-AKI and an increased risk of mortality (pooled adjusted risk ratio 2.39; 95% CI 1.98-2.90; I²=88.3%) and of cardiovascular events (pooled adjusted risk ratio 1.98 95% CI 1.52-2.59) in patients undergoing coronary angiography [1]. However, the association between CI-AKI and mortality was strongly confounded by baseline clinical characteristics that simultaneously predispose to both kidney injury and mortality [1].

Of note, CKD is an independent predictor for the development of CI-AKI, but it is also associated with higher mortality [2,3]. In particular, the progression to CKD strongly affects prognosis and mortality. For example, its frequency post-PCI varies from <1% in the general population 48 to 7% in patients with CKD [49].

A recently published study including patients with ACS undergoing PCI reported higher rate of CI-AKI post-PCI and also higher 5 year mortality rates in patients with persistently impaired renal function (defined as a >0.5 mg/dl or >25% increase of SCr levels 6-8 months after PCI) compared to the group who had no persistent of renal function (25% vs. 9.4%, p=0.0006) [46]. CI-AKI was an independent predictor for the development of persistent impairment of renal function (40% in patients with CI-AKI vs. 11% in the control group) [46].

Prevention and management

The increasing use of CM in clinical practice and the consequent increasing risk of CI-AKI, with its relevant clinical implications, put the need preventive measures and potential treatment of CI-AKI.

First of all, following “primum non nocere”, it should be used the minimum amount of contrast needed, avoiding HOCM for their high nephrotoxicity [50]. All non essential-nephrotoxic medications should to be stopped for 24 hours prior and for 48 hours following the procedure [50].

Interestingly, data from a recently published trial, combined with reports from CKD trials, suggest that intensive renin-angiotensin system (RAS) inhibition appears to have deleterious effects in the setting of hospitalization and probably in the setting of cardiac catheterization and PCI [51,52]. The Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker and Contrast Induced Nephropathy in Patients Receiving Cardiac Catheterization (CAPTAIN) trial randomized 208 patients with CKD to continue or hold RAS inhibitor 24 h before coronary angiography [53]. At 48-96 hours, CI-AKI occurred in 10.9% of RAS inhibitor-held compared to 18.4% of RAS inhibitors-continued patients (hazard ratio [HR]: 0.59; 95% CI 0.30-1.19; p=0.16). Of note, the composite endpoint of death, MI, ischemic stroke, congestive heart failure, rehospitalization for cardiovascular cause or need for dialysis periprocedural occurred majorly in patients who continued RAS inhibitors (3.9% vs. 0% in the RAS inhibitor-held group, HR: 0.11; 95% CI 0.01-2.96; p=0.06) [53]. RAS inhibitors have a chronic beneficial effect on kidney by reducing intraglomerular pressure. However, in the setting of acute illness or after administration of iodinated CM, this mechanism may be harmful, due to the inhibition of tubule-glomerular feedback and of the ability in maintaining glomerular filtration and forward flow of urine through the proximal tubules.

Pharmacological and non-pharmacological preventive strategies have been proposed (Figure 4). Among pharmacological strategies, even if small randomized trials and meta-analyses showed benefit with specific agents such as N-acetylcysteine, ascorbic acid, aminophylline, trimetazidine or fenoldopam, in large randomized clinical trials every agent tested to date has failed to prevent or treat CI-AKI [54,56].

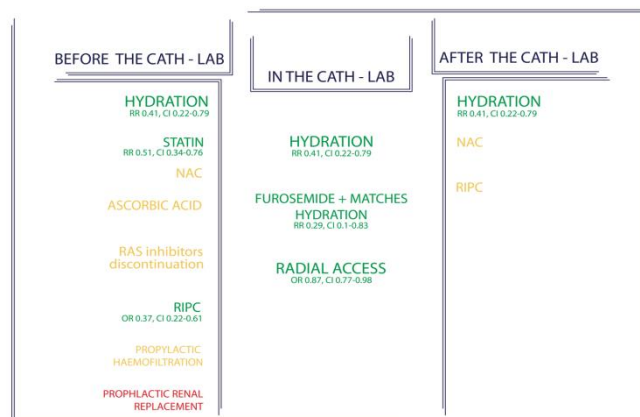


Figure 4: Contrast induced-acute kidney injury (CI-AKI) treatments that may be performed before the catheterization laboratory, in the catheterization laboratory and after the catheterization laboratory. The green therapies showed to be effective in reducing CI-AKI; the yellow one effect is still controversial; the red treatments are not effective (NAC: N-Acetylcysteine; RAS: Renine-Angiotensin System; RIPC: Remote Ischemic Conditioning).

The most widely studied pharmacological strategy for prophylaxis of CI-AKI is N-acetylcysteine (NAC). NAC has direct vasodilating effects on kidney

vessels, contributing to improved renal hemodynamics [57]. It also attenuates endothelial dysfunction and it has anti-oxidant power. However, its efficacy in prevention of CI-AKI is still debated, being the results of different meta-analysis controversial [58,59].

High-dose statins before catheterization have been demonstrated to reduce the incidence of CI-AKI [55]. Statins may be nephro-protective via several mechanisms, including inhibition of uptake of contrast into renal tubular cells, attenuation of endothelial dysfunction and oxidative stress, antiinflammation, antiproliferation of mesangial cells, and protection of podocytes. The Protective effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome (PRATO-ACS) trial demonstrated that statin group had a significantly lower rate of CI-AKI as compared to the no-statin group (6.7% vs. 15.1%; adjusted odds ratio [OR]: 0.38; 95% CI 0.20-0.71; $p=0.003$) [60]. Moreover, there was a decrease in 30-day composite death, dialysis, MI, stroke, or persistent renal damage in the statin group (3.6% vs. 7.9%, respectively; $p=0.036$), and a trend toward a decrease in death or MI at 6 months (3.6% vs. 7.2%, respectively; $p=0.07$) [60]. In patients with diabetes and CKD who were undergoing coronary or peripheral angiography, with or without intervention, rosuvastatin was effective in reducing the incidence of CI-AKI (2.3% vs. 3.9%; $p=0.01$) [61].

Hydration plays a pivotal role in prevention of CI-AKI, being the most effective measure to prevent and treat CI-AKI. It preserves renal perfusion and suppresses renine-angiotensin-aldosterone system, the tubule-glomerular feedback and vasopressin, supporting high urine flow rates and lowering CM concentration in tubular fluids. In ambulant stable patients, oral route may be as effective as the intravenous one; conversely in hospitalized patients intravenous hydration has been demonstrated superior in clinical trials [62]. Solomon and colleagues were the first to show in a randomized trial that 45% saline administration at a rate of 1 mL/kg per hour for 12 hours before and after the procedure was more effective than a combination of 0.45% saline with mannitol or furosemide (10.7% vs. 28.0% vs. 40.0%, respectively; $P=0.02$ for comparison with the saline group alone) [63].

Numerous randomized trials compared isotonic bicarbonate solutions to intravenous saline, finding no differences in the rates of renal outcomes [64,65]. Either isotonic crystalloid solution is recommended, with some guidance on the quantity of fluid according to patient factors. The current European guidelines recommend hydration with sodium chloride 0.9% at 1-1.5 ml/kg/h for 12 hours before the procedure and up to 24 hours after the procedure [50]. These recommendations are too general and often do not fit with the heterogeneity of patients presenting during clinical practice. Interestingly, Brar et al. proposed a patient-specific approach for patients undergoing cardiac catheterization: The Prevention of Contrast Renal Injury with Different Hydration Strategies (POSEIDON) trial showed that a strategy of measurement of left ventricular end-diastolic pressure

(LVEDP) and expanding plasma volume was associated with more intensive fluid administration during and after the procedure and with a reduction in CI-AKI compared with the control group (6.7% vs. 16.3% relative risk [RR] 0.41, 95% CI 0.22-0.79; $p=0.005$) [66].

Use of loop diuretics is associated to higher rate of CI-AKI in patients with CKD undergoing PCI [67]. However, it has been shown that volume contraction imposed by furosemide is effective in preventing CI-AKI when counterbalanced by volume supplementation [68,69]. In fact, the Renalguard device adjusts the rate of intravenous saline infusion to match the urine output, providing either volume expansion and valid diuresis. Elevation of urine output to >150 ml/h before and during the procedure significantly reduced the incidence of CI-AKI in patients with chronic kidney disease [69] and in high-risk patients [68,70]. In particular, a recently published study suggested that an intraprocedural urine flow rate of ≥ 450 ml/h is the best threshold for an optimal CI-AKI prevention [71].

In the pathophysiology of CI-AKI medullary vasoconstriction may cause ischemic/reperfusion injury. Remote ischemic conditioning (RIC), including remote ischemic pre-conditioning and remote ischemic post-conditioning has shown to reduce ischemic/reperfusion injury in several organs and clinical settings [72]. A recent meta-analysis showed that remote ischemic conditioning reduced the incidence of CI-AKI compared to the control group (OR 0.52, 95% CI 0.34-0.77, $p=0.001$) [73]. Thus, despite the mechanisms underlying RIC are not completely cleared, it represents an intriguing intervention for reducing ischemic/reperfusion injury and improving clinical outcomes.

Importantly, it has been recently shown that radial access may be beneficial in reducing the risk of CI-AKI in patients with acute coronary syndromes undergoing PCI as compared with femoral access [74]. AKI was reduced in the radial access group (15.4% in the radial access group vs. 17.4% in the femoral access group; OR 0.87, 95% CI 0.77-0.98; $p=0.018$) [74]. Despite these results require future confirmation, they are of clinical relevance and mainly linked to the reduction in access related bleeding events; thus trans-radial approach to perform invasive procedures should be counted among the preventing measures that reduce the risk of CI-AKI.

Conclusion

CI-AKI remains a concern for patients undergoing diagnostic and therapeutic procedures which require iodinated contrast administration. A general consensus is warranted for a correct definition and, consequently, a more precise definition of incidence and prognostic implication of CI-AKI. Better biomarkers are also required to achieve the diagnosis earlier and more accurately.

To date, the best strategy to prevent CI-AKI is to expand intravascular volume, to support high urine flow rates and to limit CM concentration in tubular fluids. Although no adjunctive therapy has been conclusively demonstrated to

reduce CI-AKI incidence, preventive administration of statins and discontinuation of RAS inhibitors \geq 24 hours before contrast exposure, showed to be effective in renal protection. Further research is needed in the development of new prophylactic and therapeutic strategies.

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