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INVITED REVIEW ARTICLE

Contrast-induced acute kidney injury

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Abstract
Although major advancements in the field of cardiology have allowed for an increasing number of patients to undergo minimally invasive imaging and interventional procedures, contrast-induced acute kidney injury (CI-AKI) continues to be a dreaded complication among patients receiving intravascular contrast media. CI-AKI is characterized by progressive decline in kidney function within a few days of contrast medium administration. Physiological changes resulting from the direct nephrotoxic effect of contrast media on tubular epithelial cells and release of vasoactive molecules have been implicated in creating a state of increased oxidative stress and subsequent ischemic renal cell injury. Over the last several years, preventive strategies involving intravenous hydration, pharmaceutical agents and renal replacement therapies have resulted in lower rates of CI-AKI. However, due to the evolving paradigm of diagnostic and therapeutic interventions, several unanswered questions remain. This review highlights the epidemiology, pathogenesis and preventive strategies of CI-AKI.

Keywords Contrast · Acute kidney injury · Nephropathy

Introduction

State-of-the-art minimally invasive cardiac interventions have been rapidly gaining popularity over traditional surgical techniques in the last few decades. This has allowed patients to undergo diagnostic and therapeutic procedures with lower rates of complications and faster recovery time. The use of advanced imaging technology is key for these procedures, with the vascular system and other anatomical structures often being visualized by administration of iodinated intravenous contrast. Yet, despite major advances in the field, contrast-induced acute kidney injury (CI-AKI) remains a major complication of these procedures, prolonging hospital stay and resulting in worse short- and long-term outcomes [1].

CI-AKI is characterized by a decline in kidney function within the first 48–72 h following contrast administration, in the absence of alternative etiologies [2, 3]. The very first cases of CI-AKI were reported around the mid-20th century in patients undergoing X-ray imaging of urinary tracts using contrast material [4, 5]. Since then, research has led to the development of novel contrast agents with reduced nephrotoxicity, and improvement in peri-procedural management strategies (Table 1). While recent evidence suggests that the risk of CI-AKI may be overestimated [6, 7], a considerable number of patients are precluded from undergoing less invasive procedures due to concerns regarding CI-AKI [8]. As an example, a large number of studies have shown that patients with chronic kidney disease (CKD) are less likely to undergo angiography or percutaneous revascularization due to apprehensions of worsening kidney function [9–11]. Given the uncertain causal relationship between CI-AKI and adverse outcomes, there is a crucial need to determine the true risk of clinically significant kidney injury and the best clinical practice to prevent it. This paper reviews the epidemiology, underlying pathophysiology and current strategies for the prevention of CI-AKI.

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Table 1 Physicochemical characteristics of common types of contrast agents

Type	Molecular structure	Examples	Iodine concentration (mg/ml)	Osmolality (mOsm/kg H_2O)	Viscosity (mPa s at 37 °C)
High-osmolal contrast medium	Ionic monomer	Diatrizoate	370	1551	10.5
Low-osmolal contrast medium	Ionic dimer	Ioxaglate	320	~600	7.5
	Nonionic monomer	Iopamidol	200–370	413–796	2.0–9.4
Iso-osmolal contrast medium	Nonionic dimer	Iodixanol	270–320	290	6.3–11.8

Characteristics of specific agents are described according to the American College of Radiology's Manual on Contrast Media (version 10.2.2016)

Definition and incidence of CI-AKI in clinical practice

Definition

An increase in creatinine level of ≥ 0.5 mg/dl (44 µmol/l), or ≥ 25% from baseline, within 2–5 days of contrast exposure had been the universal definition of CI-AKI for a long time [3]. More recently, the Kidney Disease Improving Global Outcomes (KDIGO) provided an updated definition, which is currently the most widely used. According to KDIGO, CI-AKI is defined as a creatinine level increase of ≥ 0.3 mg/dl (26.5 µmol/l) above baseline value within 48 h of contrast media exposure, or an increase of at least 1.5 times the baseline value within 7 days [12, 13]. However, it is important to note that although serum creatinine level is associated with moderate sensitivity, its specificity is low as it is directly affected by fluid shifts and administered drugs [14]. In addition to contrast agents, factors such as hypotensive episodes, congestive heart failure and plaque embolization can also contribute to the development of AKI. Since these additional parameters must be taken into consideration along with the contrast medium itself, the term 'contrast-induced' has been recently changed to 'contrast-associated' kidney injury.

Incidence of CI-AKI

The incidence of CI-AKI, as reported in the literature, varies between 3.3% and 14.5% [15, 16]. In a cohort of 985,737 patients undergoing elective or urgent percutaneous coronary intervention (PCI) from the National Cardiovascular Data Registry (NCDR), the incidence of CI-AKI was estimated to be around 7.1% [17]. However, the numbers are not consistent across studies because of the use of different definitions. As more data are being published, a trend towards a decrease in the incidence of CI-AKI is being observed. Indeed, in a large national study including 33,249 hospitalizations for acute myocardial infarction (AMI) in the United States (US), the overall incidence of AKI decreased by 26% from years 2000 to 2008 [18]. Whether this trend is due to use of different definitions or better management of patients remains unknown. A meta-analysis involving 25,950 patients who underwent an imaging procedure showed no significant difference in the risk of CI-AKI between patients who received contrast vs. those who did not [Relative Risk (RR) 0.79, 95% CI 0.62–1.02, $p = 0.07$] [19]. In a prospective study of patients with CKD undergoing coronary angiography, only 1.2% had an increase of more than 50% in creatinine level, none had more than 100% increase, and none needed dialysis [20].

The underlying pathophysiology

The exact mechanisms by which contrast agents induce kidney injury are not completely understood. Several factors have been suspected to influence renal physiology by causing hemodynamic changes that alter normal kidney function [21, 22] (Fig. 1). Contrast media exert a direct nephrotoxic effect on tubular epithelial cells leading to osmotic nephrosis and decreased O_2 delivery. In addition, these agents induce the release of vasoactive molecules (i.e., endothelin, adenosine) and reduce the availability of vasodilators (prostaglandins and nitric oxide), leading to vasoconstriction and ischemic injury [23]. All these pathophysiological changes result in a state of increased oxidative stress and cell injury. In particular, the renal medulla, with a relatively low partial pressure of oxygen, is highly vulnerable to vascular changes [25]. Additionally, peri-procedural cholesterol embolization during intravascular catheter manipulation may represent another potential indirect contributor to the development of CI-AKI [26].

Associated risk factors

There are several patient- and procedure-related risk factors associated with the development of CI-AKI. They include baseline kidney disease, advanced age, diabetes mellitus, anemia, and patient status on presentation (i.e., cardiogenic

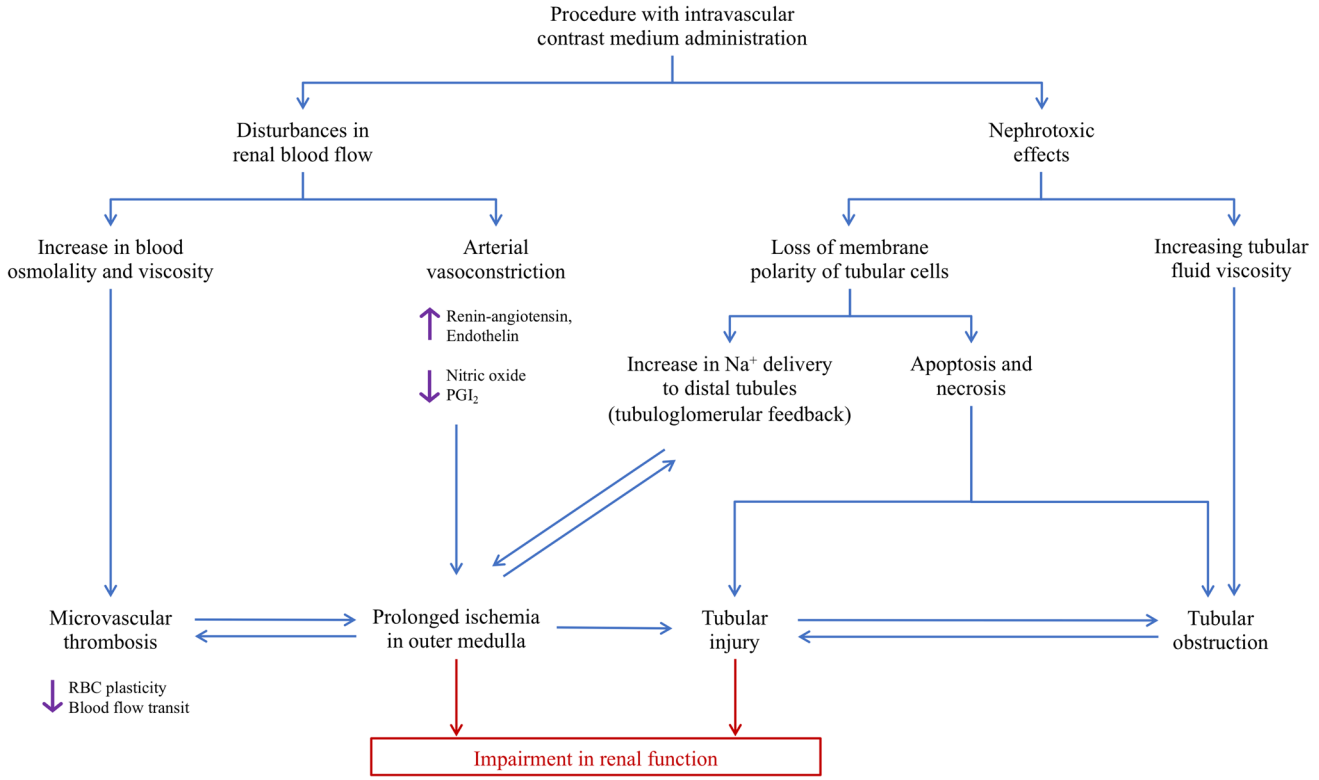

Fig. 1 Proposed mechanisms of contrast-induced acute kidney injury. *PGI_2* prostaglandin I_2, *RBC* red blood cell Adapted from Mehran et al. [14]

shock, congestive heart failure, acute coronary syndrome, ST-segment elevation, etc.) [23, 24, 27, 28]. Advanced CKD, with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73 m^2, is the strongest patient-related risk factor contributing up to a threefold increase in risk of CI-AKI [17]. Indeed, the lower the renal function the higher the risk of kidney injury [29]. Due to a high prevalence of kidney disease among diabetic patients, diabetes mellitus had also been considered a strong predictor of CI-AKI for a long time. However, the Iohexol Cooperative Study (1995), a randomized trial involving 1196 patients, showed that diabetes was not independently associated with the risk of developing CI-AKI but increased susceptibility of patients with underlying kidney disease [30].

Risk assessment for CI-AKI prior to an intervention is of utmost importance as it helps direct peri-procedural management of patients, leading to shorter hospital stay and better outcomes. Multiple risk scores that take both patient and procedural characteristics into account have been developed and validated using large population data (Mehran Risk Score [27], NCDR Cath-PCI registry AKI prediction model [17], and the Blue Cross Blue Shield of Michigan Cardiovascular Collaborative model [31]). However, these risk-prediction models also rely on variables such as total amount of contrast volume, use of mechanical circulatory support, etc., which can only be roughly estimated prior to the completion of the procedure. As such, their usefulness in clinical practice remains limited.

Impact of CI-AKI on outcomes

Studies have shown a direct association between incidence of CI-AKI and worse short- and long-term outcomes. However, these findings could either be due to compromised kidney function at baseline or after contrast agent use [15, 32, 33]. Indeed, the odds of decline in kidney function 3 months after PCI were more than fourfold in patients with mild CKD at baseline [Odds ratio (OR) 4.7, 95% CI 3.9–5.7] and more than 17-fold in those with moderate to severe CKD at baseline (OR 17.3, 95% CI 12.0–24.9) [34]. Nonetheless, this study and many others establish associations but do not clarify whether CI-AKI is a potential marker of kidney injury or a mediator of the injury itself. For example, Lassnigg et al. [35] showed that both increases and decreases in creatinine level after surgical intervention were associated with poorer outcomes. Hence, fluctuations in creatinine level (increase or decrease) may simply reflect the instability of the patient's hemodynamic status that translates into worse short- and long-term outcomes.

Strategies to prevent CI-AKI

The focal points of research addressing the prevention of CI-AKI are the following: use of intravenous fluids, pharmacological agents and renal replacement therapies (Fig. 2).

Hydration

Hydration initiated prior to and continued until after the completion of the contrast-based procedure is the single most important periprocedural strategy to prevent kidney injury. However, recent data questioning its role has resulted in uncertainty around the optimal approach to hydration. The Maastricht Contrast-Induced Nephropathy Guideline (AMACING) trial, a non-inferiority trial, randomized 660 patients with moderate CKD (eGFR of 30–59 ml/min/1.73 m^2) undergoing contrast-based procedures to either receive normal saline peri-procedurally or no fluids at all. There was no significant difference in the incidence of CI-AKI between the two groups (2.7% in the hydration group vs. 2.6% in the no-hydration group, 95% CI −2.25 to 2.06, $p=0.47$) [36]. It is important to consider, however, that this trial only enrolled 660 out of 1300 patients originally planned and had low rates of intra-arterial (48%) and interventional procedures (16%) overall. Similarly, in the recently published Kompas trial involving 523 patients with stage 3 CKD undergoing elective contrast-enhanced computed tomography, there was no significant difference in the incidence of CI-AKI between patients receiving no prehydration (2.7%) and those receiving prophylactic prehydration with sodium bicarbonate (1.5%) (RR 1.7, 95% CI 0.5–5.9, $p=0.36$) [37]. However, it would be premature to conclude that administration of intravenous fluids does not prevent CI-AKI based solely on the results of these studies due to their limited sample size and inclusion of only moderate CKD patients undergoing low-risk procedures.

The optimal choice of fluid to be administered also remains a topic of debate. Normal saline use is currently the most cost-effective option, with an efficacy that is comparable to other solutions such as bicarbonate and half-normal saline [23]. Most of the evidence in support of periprocedural intravascular volume expansion has been based on small observational studies rather than large randomized clinical trials (RCT). A small RCT consisting of 53 patients

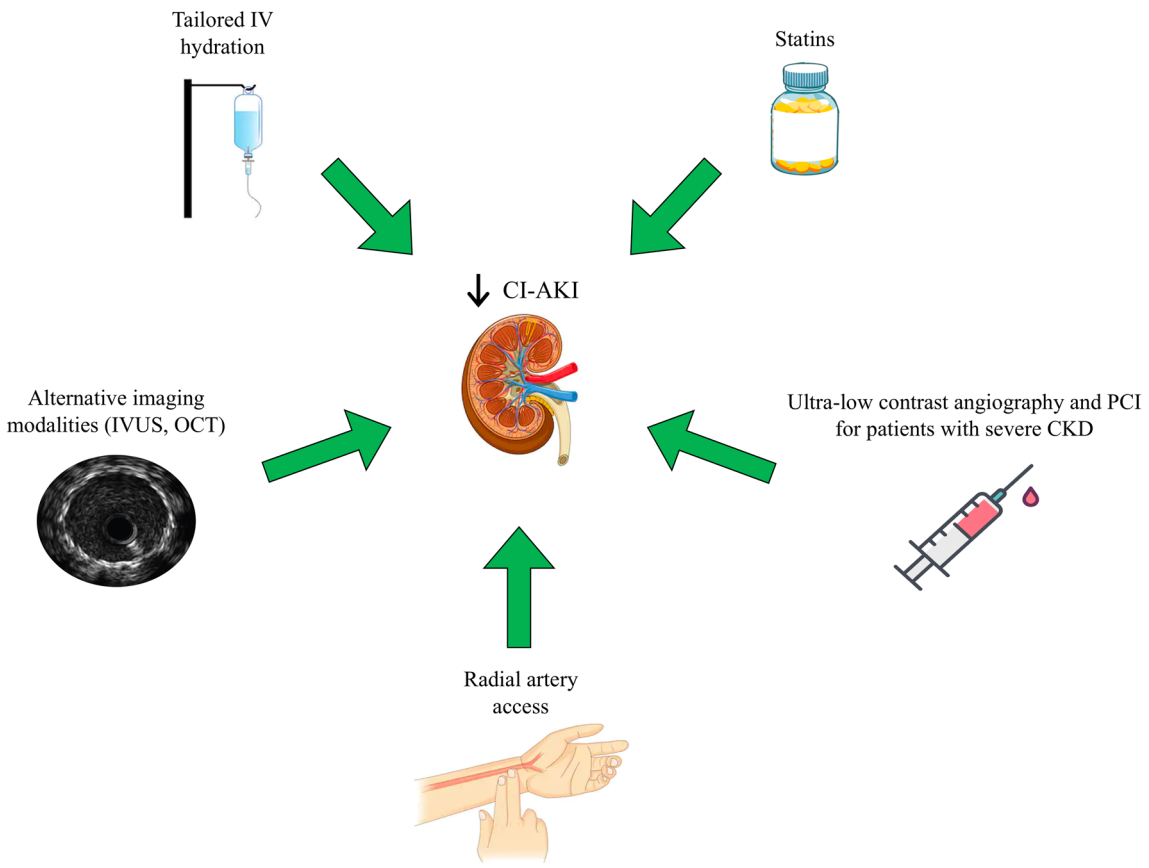

Fig. 2 Main preventive strategies for contrast-induced acute kidney injury. *CI-AKI* contrast-induced acute kidney injury, *CKD* chronic kidney disease, *IV* intravenous, *IVUS* intravascular ultrasound, *OCT* optical coherence tomography, *PCI* percutaneous coronary intervention

undergoing angiography randomized to either intravenous normal saline or unlimited oral fluid intake was stopped prematurely because of a significantly lower incidence of CI-AKI in the intravenous saline group (3.7% vs. 34.6%, $p=0.005$) [38]. Similarly, a lower incidence of CI-AKI was seen in patients who received normal saline as compared to patients with half-normal saline (0.7% vs. 2.0%, $p=0.04$) [39].

The ideal volume and rate of fluid administration for the prevention of CI-AKI is controversial, especially in patients with compromised cardiac function. These parameters should be individualized and account for physiological characteristics such as left ventricular end-diastolic pressure, central venous pressure, and body hydration status [40–42]. The Prevention of Contrast Renal Injury with Different Hydration Strategies (POSEIDON) trial aimed at investigating a new sliding scale hydration protocol based on left ventricular end diastolic pressure (LVEDP) [40]. The study included 396 patients with CKD randomized in a 1:1 fashion to either LVEDP-based hydration or standard hydration. In the LVEDP-based hydration group, the fluid administration rate was adjusted as follows: 5 ml/kg/h for LVEDP < 13 mmHg, 3 ml/kg/h for 13–18 mmHg, and 1.5 ml/kg/h for > 18 mmHg. The standard hydration group received fluid at a rate of 1.5 ml/kg/h. Intravenous fluid was administered before contrast exposure and was continued until 4 h after the procedure. The outcome of interest was CI-AKI, defined as an increase of more than 25% or 0.5 mg/dl in serum creatinine concentration up to 4 days after use of contrast medium. The primary outcome was seen in 6.7% of the LVEDP-based hydration group compared to 16.3% of the standard hydration group (RR 0.41, 95% CI 0.22–0.79; $p=0.005$). Another study that used right atrial pressure instead of LVEDP found similar results, in favor of pressure-guided hydration [41]. Although the use of pressure-guided hydration seems favorable across these studies, patients with heart failure or hypertension (hemodynamic states of increased cardiac filling pressures at baseline) may benefit from smaller volumes of intravenous fluid and sodium loads. More sophisticated systems have also emerged recently, such as the RenalGuard, which is based on urine flow rate (UFR)-guided hydration infusion for the prevention of CI-AKI. The Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II) showed that UFR-guided hydration with saline and *N*-acetylcysteine controlled by the RenalGuard System and furosemide was superior to standard hydration with sodium bicarbonate solution and N-acetylcysteine in preventing CI-AKI among high-risk patients undergoing coronary and/or peripheral angiography/angioplasty [43]. Similar results were observed in the more recent REMEDIAL III trial, which showed superiority of UFR-guided hydration over an LVEDP-guided hydration protocol for the composite endpoint of CI-AKI and/or acute pulmonary edema in high-risk patients undergoing angiography or PCI [44]. Nonetheless, further data from clinical trials as well as real-world patient cohorts is needed to better guide practice recommendations on this approach.

Another potential strategy to prevent CI-AKI involves alkalization of urine to reduce contrast-induced generation of oxygen free radicals that cause oxidative damage to tubular cells. Several trials and subsequent meta-analyses compared the intravenous administration of isotonic sodium bicarbonate to isotonic sodium chloride for the prevention of CI-AKI [45–47]. These studies showed conflicting and inconclusive results, which led to the design of the Prevention of Serious Adverse Events Following Angiography (PRESERVE) double-blind randomized trial [48]. Using a 2-by-2 factorial design, this trial randomly assigned 5117 high-risk patients undergoing angiographic procedures to receive: 1.26% sodium bicarbonate vs. intravenous 0.9% sodium chloride and 5 days of oral *N*-acetylcysteine vs. oral placebo. Study fluids were given pre-angiography at 1–3 cc/kg/h over 2–12 h, intra-angiography at 1–1.5 cc/kg/h, and post angiography at 1–3 cc/kg/h over 2–12 h. *N*-acetylcysteine was given as 1200 mg twice daily for 5 days, starting 1 h before angiography. The incidence of CI-AKI was 9.5% in the sodium bicarbonate group and 8.3% in the sodium chloride group (OR 1.16, 95% CI 0.96–1.41; $p=0.13$). Similarly, the incidence of CI-AKI in the *N*-acetylcysteine group was 9.1% and 8.7% in the placebo group (OR 1.06, 95% CI 0.87–1.28; $p=0.58$). Despite limitations related to the exclusion of patients undergoing emergency procedures and use of low overall median volume of contrast material, the PRESERVE trial was a large and adequately powered randomized controlled trial that conclusively showed no benefit of sodium bicarbonate and/or *N*-acetylcysteine over placebo among patients at risk for renal complications who undergo angiography [49, 50]. In line with these findings, the European Society of Cardiology (ESC) guidelines on myocardial revascularization recommend the administration of intravenous normal saline at a rate of 1–1.5 ml/kg/h for 12 h before and 24 h after the intervention [51].

HMG-CoA reductase inhibitor trials

Statins have well-established anti-inflammatory and antioxidant properties [52, 53]. Based on these favorable cellular mechanisms, statins have been evaluated in several studies for the prevention of kidney injury after contrast material exposure. The Prevention of Radiocontrast Medium-Induced Nephropathy Using Short-Term High-Dose Simvastatin in Patients with Renal Insufficiency Undergoing Coronary Angiography (PROMISS) trial showed no protective effect of simvastatin over placebo in preventing creatinine level elevation in the first 48 h after exposure to contrast material for CKD patients [54]. In contrast, 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 showed that high-dose rosuvastatin (40 mg loading dose followed by a maintenance dose of 20 mg per day) significantly reduced the risk of CI-AKI in statin-naïve patients presenting with non-ST-elevation acute coronary syndrome (NSTE-ACS) compared to those who did not receive statin treatment [55]. The incidence of CI-AKI was 3.6% in the rosuvastatin group and 8.7% in the control group when the KDIGO definition was used, and 6.7% vs. 15.1%, respectively, when the old CI-AKI definition was used (an increase in creatinine level of at least 0.5 mg/dl within 72 h of contrast use) [55]. While some additional studies, mainly clinical trials and meta-analyses, showed a benefit of pre-procedural use of statins in the prevention of CI-AKI [56, 57], others did not show any protective effects, mainly due to study design limitations [58, 59]. Therefore, there remains a need for further evidence in support of the prophylactic use of statins to prevent CI-AKI occurrence in patients undergoing contrast-based procedures.

Alternative imaging modalities

Newer intravascular imaging techniques can help visualize coronary lesions using much lesser contrast (or no contrast at all) than traditional angiographic techniques. Intravascular ultrasound (IVUS) is a contemporary imaging modality that was evaluated in two successive clinical trials: the Minimizing Contrast Utilization with IVUS Guidance in Coronary Angioplasty (MOZART) trial [60] and the Minimizing Contrast Utilization with IVUS Guidance in Coronary Angioplasty to Avoid Acute Nephropathy (MOZART II, NCT02743156) trial. In the first trial, 83 patients were randomized to either IVUS-guided PCI or angiography-guided PCI. In the IVUS group, only 20 ml (interquartile range 12.5–30 ml) of contrast medium was used compared to 64.5 ml (interquartile range 42.8–97 ml) in the angiography group ($p < 0.001$) [60]. However, possibly due to a lack of power related to the small sample size, there was no difference in the incidence of CI-AKI between the two groups. The subsequent MOZART II was designed with sufficient statistical power to detect differences in the incidence of CI-AKI and thereby overcome the limitations of the first trial. This study is currently ongoing and is expected to provide further clarity on the role of IVUS in decreasing the risk of CI-AKI.

Access site and risk of CI-AKI

Although controversial, performing PCI via radial rather than femoral access has been shown to have a lower rate of major bleeding [61, 62]. This finding is important in the context of CI-AKI, because major bleeding can cause hemodynamic instability, which may affect renal perfusion leading to compromised kidney function and subsequent kidney injury. In a meta-analysis of 6 observational studies (a total of 26,185 patients) comparing the incidence of CI-AKI by vascular access site for PCI, radial approach was associated with a lower incidence of CI-AKI (OR 0.51, 95% CI 0.39–0.67; $p < 0.0001$) [63]. Similarly, the Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX (MATRIX-Access) trial showed superiority of radial access in decreasing the risk of CI-AKI (15.4% in radial group vs. 17.4% in femoral group; OR 0.87, 95% CI 0.77–0.98; $p = 0.02$) [26].

Hemodynamic support devices

High-risk PCI (i.e., cardiogenic shock, congestive heart failure, hypotension, etc.) predisposes patients to an increased risk of CI-AKI [17]. Short-term use of left ventricular assist devices that maintain hemodynamic stability and protect end-organ function have been proposed to reduce the incidence of CI-AKI in these patients [64, 65]. Devices such as extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP), Tandem Heart™ percutaneous ventricular assist device, Percutaneous Heart Pump™ (PHP) and Impella® are currently available and may serve this purpose. Of these, the Impella device has gained recent popularity and is the only approved transvalvular microaxial pump in the United States and Europe [66]. The Impella 2.5 and Impella CP devices are made of a catheter-mounted axial flow miniature pump capable of pumping up to 4 l of blood per minute from the left ventricle to the aortic root. They also contain a single cannula facilitating blood in/out flow across the aortic valve [67]. After the approval of the device by the United States Food and Drug Administration (FDA) in 2008, multiple registries (PROTECT I, USpella and cVAD), randomized controlled trials (PROTECT II, IMPRESS, IMPRESS in Severe Shock) and other studies emerged to assess the efficacy of the Impella device in providing hemodynamic support for high-risk PCI procedures, cardiogenic shock, decompensated heart failure, etc. [68–70]. Since a long time, the IABP has been the most widely used LVAD in patients undergoing PCI. However, Dangas et al. [71] showed superiority of the Impella device over IABP using data from PROTECT II trial, with lower rates of adverse events at 90 day post-PCI in high-risk patients. Given the absence of randomized trials other than PROTECT II in the area of elective supported PCI with Impella, there remains some uncertainty regarding the full potential of Impella to reduce adverse events in high-risk patients. Flaherty et al. [72] retrospectively analyzed the incidence of AKI after PCI in patients with

reduced left ventricular ejection fraction with or without hemodynamic support using Impella. The study sample included 230 patients with an ejection fraction of less than 35% regardless of baseline kidney function (2 groups of 115 patients each, with and without an Impella device). Only 5.2% of the patients with Impella had AKI within 72 h of procedure compared to 27.8% in patients without Impella support ($p < 0.001$). Interestingly, the analysis of patients with impaired kidney function (defined as GFR < 60 l/min/1.73 m [2]) showed that the incidence of AKI was significantly greater in unsupported CKD patients than supported ones ($p < 0.05$) [72]. However, findings from a much larger propensity-matched study on patients who underwent PCI for acute myocardial infarction complicated by cardiogenic shock showed that use of Impella compared to IABP was associated with higher risk of in-hospital major bleeding and death [73]. Ultimately, the paucity of data currently available mandates further research to identify which subsets of patients undergoing high-risk procedures may or may not benefit from the concomitant use of mechanical circulatory support.

Conclusions

Tremendous advances have been made towards understanding the underlying pathophysiology of CI-AKI and its associated risk factors. Nonetheless, CI-AKI remains a major complication in contrast-based diagnostic procedures and interventions. The true incidence of kidney injury is unclear and is probably overestimated in the literature due to reliance on definitions of CI-AKI that are affected by transient and non-specific increases in creatinine level. Additional research is needed to determine the real impact of contrast agents on kidney function, especially for patients with underlying kidney disease in whom, in fact, angiographic procedures are now underused. In addition, large randomized trials are needed to establish optimal peri-procedural management strategies that improve outcomes in all patients undergoing contrast-based interventions.

Compliance with ethical standards

Conflict of interest Dr. Mehran reports receiving consulting fees from Abbott Vascular, Boston Scientific, Medscape/WebMD, Siemens Medical Solutions, Phillips/Volcano/Spectranetics, Roviant Sciences, Sanofi Italy, Bracco Group, Janssen, and AstraZeneca, grant support, paid to her institution, from Bayer, CSL Behring, DSI, Medtronic, Novartis Pharmaceuticals, OrbusNeich, Osprey Medical, PLC/RenalGuard, and Abbott Vascular, grant support and advisory board fees, paid to her institution, from BMS, fees for serving on a data and safety monitoring board from Watermark Research Funding, advisory fees and lecture fees from Medintelligence (Janssen), and lecture fees from Bayer. All other authors report no conflicts of interest.

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