

Contrast-induced acute kidney injury: the dark side of cardiac catheterization

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KEY WORDS

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ABSTRACT

The rapidly growing number of percutaneous coronary interventions has led to a considerable improvement in the outcome of patients with acute coronary syndromes, yet concurrently exposing patients to enormous volumes of contrast media with the inherent risk of renal function impairment. The issue of contrast-induced acute kidney injury (CI-AKI) is not only associated with direct sequelae such as prolonged hospital stay, but also with increased risk of chronic kidney disease, recurrent acute coronary syndromes, cerebral ischemia, and increased mortality rate. The ubiquitous application of contrast media warrants active search for reliable risk factors, diagnostic markers, preventive measures, and therapeutic modalities that could be used in the management of CI-AKI. The vast majority of CI-AKI incidents remain undiagnosed due to insufficient efficiency of the serum creatinine level as the marker of acute kidney injury. Recently, several novel renal injury biomarkers have been proposed to facilitate early diagnosis of CI-AKI and better reflect the complex interplay between kidney and cardiac pathology, known as cardio-renal syndrome. This review aimed to summarize the contemporary knowledge on predictors, markers, prevention strategies, and management of CI-AKI.

Introduction Contrast-induced acute kidney injury (CI-AKI), previously known as contrast-induced nephropathy (CIN), represents a specific form of acute renal function impairment triggered by the use of iodinated contrast media (CM). As CI-AKI remains the subtype of acute kidney injury (AKI), it is recommended to use common definitions of AKI, such as the 2012 KDIGO criteria,¹ RIFLE classification (Risk, Injury, Failure, Loss of Function, End-Stage Renal Disease),² AKI Network criteria,³ or the definition by Harjai⁴ (Supplementary material online, *Table S1*).

The rapid development of invasive cardiology triggered a massive increase in CM exposure. Since the implementation of the first CM in the 1950s, CI-AKI has emerged as the third most common subtype of hospital-acquired renal failure (reaching 11% of all cases), after renal hypoperfusion (42%) and postoperative AKI.⁵ Nearly half of all cases of CI-AKI occur after invasive cardiac procedures owing to CM-related nephrotoxicity and frequently present hemodynamic instability.⁵

The exact rate of CI-AKI in the setting of a cardiology department varies depending on

the diagnostic criteria applied, comorbidities, and the type of procedure (coronary angiography [CA]; percutaneous coronary intervention [PCI]). CI-AKI is a challenge mainly for well-developed countries, in which excessive amounts of CM are used on a daily basis. When using the definition of CI-AKI as an increase of serum creatinine concentrations (SCr) by more than 25% relative to baseline and/or by more than 0.5 mg/dl at 48 hours after PCI, the rate of CI-AKI ranged from 3.3% according to the Mayo Clinic PCI registry⁶ to 13.1% as stated by Mehran et al.⁷ In the largest registry by Gurm et al.,⁸ based on 68 573 procedures, the rate of CI-AKI was 2.5%, defined as an absolute elevation in SCr by more than 0.5 mg/dl. Still, when only clinically relevant CI-AKI requiring dialysis was considered, the incidence decreased to a range from 0.8% to 1.7%.⁹

This review sought to summarize the contemporary knowledge on pathophysiology, risk factors, diagnostic markers, and management of CI-AKI, with a special interest in CI-AKI as a result of cardiac catheterization. Accordingly, the Medline and EmBase databases were queried to

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obtain original research articles and review papers using the following key words: contrast-induced acute kidney injury, CI-AKI, contrast-induced nephropathy, CIN, contrast media, risk factors and biomarkers, and cardiac catheterization.

Pathophysiology Double-hit scenario The mechanism underlying CI-AKI is best described by a double-hit scenario, in which harmful effects of CM coincide with the different extent of renal hypoperfusion or venous congestion leading to hemodynamic renal injury. In addition, a considerable number of patients with stable coronary artery disease (CAD) and heart failure suffer from preexisting renal function impairment as a consequence of cardio-renal syndrome type 2, in which chronic cardiac pathology results in chronic kidney disease (CKD). The overview of CI-AKI pathophysiology is presented in **FIGURE 1**.

Contrast media The explanation of CI-AKI pathophysiology is inextricably connected with the physicochemical properties of CM, which are water-soluble tri-iodinated benzene compounds.¹⁰ CM are almost exclusively distributed in the extracellular fluid compartment, minimally protein-bound, and undergo virtually no metabolism. Every available CM is characterized by its distinct osmolality, iodine content, iconicity, and viscosity, which all affect its role in the pathophysiology of CI-AKI. The most widespread classification of CM is based on osmolality,¹¹ which used to be regarded as the key factor modifying its pathogenic impact on the kidney (**FIGURE 1**). Indeed, initial high-osmolar CM (HOCM; 1000–2500 mOsmol/kg H₂O) were ionic monomeric compounds with osmolality up to 8-fold higher than human plasma (**TABLE 1**). The next generations of CM were nonionic compounds with the unchanged iodine content (250–400 mg I/ml solution), but with significantly reduced osmolality, namely, monomeric low-osmolar CM (LOCM; 400–800 mOsmol/kg H₂O) and finally dimeric iso-osmolar CM (IOCM; 290 mOsmol/kg H₂O).

The first observation of CI-AKI following urography made by Alwall et al¹² in 1955 shed light on the dangerous effect of extremely high osmolality of infused agents. High osmolality was deemed to cause direct cytotoxicity towards renal tubular cells via cellular shrinkage secondary to osmotic water drainage. Cytotoxicity was also linked to the phenomenon of photolysis and iodine release from the CM, causing cellular membrane damage.¹⁰ The introduction of LOCM resulted in a considerably decreased rate of CI-AKI; however, further reduction of osmolality to the level of human plasma in the form of IOCM did not confer much of a clinical benefit and, unexpectedly, was even shown to increase the risk of CI-AKI according to 1 report.⁶ In the rat model of CI-AKI, highly viscous IOCM were shown to impede renal blood flow more profoundly than LOCM and even HOCM,¹³ suggesting a pivotal role of viscosity in CI-AKI

development (**FIGURE 1**). A proportional relationship between osmolality and nephrotoxicity was documented exclusively for CM with osmolalities exceeding 800 mOsmol/kg H₂O.¹⁴ It may be conditioned by the exceptional environment of the renal medulla chronically exposed to osmolalities of 400 to 1200 mOsmol/kg H₂O. Conversely, the beneficial effect of reduced osmolality is opposed by increasing viscosity of dimeric compounds. High viscosity of IOCM yields a reduced tubular urine flow and extended exposure of tubular cells to CM, and results in reduced estimated glomerular filtration rate (eGFR). Viscosity exponentially increases while CM become more concentrated due to tubular fluid reabsorption, which may trigger tubular plugging. The subsequent increased tubular pressure translates into increased interstitial pressure and a further reduction of medullary blood flow via the direct compression of the direct vasa recta. Importantly, flow (both tubular and vascular) does not rely on osmolality but on viscosity; therefore, this parameter considerably contributes to the development of CI-AKI. This is precisely reflected by the Poiseuille's law: $R = \eta \cdot l \cdot 8 / \pi \cdot r^4$, where η denotes viscosity coefficient; l , length of the vessel; and r , the diameter of the vessel.

Interestingly, a recent report has emphasized the crucial role of adequate hydration before the use of IOCM (eg, iodixanol). It was postulated by Seelinger et al¹⁵ that LOCM and IOCM share a comparable risk of CI-AKI development in well-hydrated patients, while in subjects with an inadequate hydration status, high viscosity prevails over low osmolality and may paradoxically favor the use of technologically older LOCM.

Renal tubular hypoxia The cornerstone of the CI-AKI pathophysiology is renal tubular hypoxia, which is conditioned by the shifted balance between vasodilative and vasoconstrictive agents (**FIGURE 1**). Inadequate oxygen supply is manifested predominantly in the outer renal medulla. The vulnerability of this zone is conditioned by high oxygen requirement related to urine concentrations achieved by Na⁺K⁺ ATP-ase activity powering sodium reabsorption through the Na⁺K⁺2Cl⁻ cotransporter, located in the thick ascending limb of the Henle loop. Simultaneously, oxygen delivery to the outer medulla is scant because the direct vasa recta are relatively remote to tubular cells and are characterized by increased vascular resistance (great length, small diameter). HOCM were shown to negatively interfere with erythrocyte flexibility hampering renal microcirculation.¹⁶ As a consequence, physiological blood oxygen partial pressure in the outer medulla was reported to be as low as 20 mmHg.¹⁷ The administration of CM also triggers endothelial dysfunction,¹⁸ manifested by reduced nitric oxide¹⁹ and prostaglandin E₂²⁰ availability, as well as increased endothelin and adenosine signaling,²¹ together with the formation of reactive oxygen species²² (**FIGURE 1**). Altogether, this

TABLE 1 Contrast-media classification with examples of substances commonly used in Poland¹⁴

CM	Osmolality, mOsm/kg H ₂ O	Viscosity at 37°C, mPa*s ^a	Example	
			ionic	nonionic
HOCM	1000–2500	2.4	diatrizoate (monomer)	–
LOCM	400–800	7.5 (ionic dimer) 4.5–4.7 (nonionic monomer)	ioxaglate (dimer)	iopromide (monomer) iomeprol (monomer) iopamidol (monomer)
IOCM	290	11.1	–	iodixanol (dimer)

^a for iodine content of approximately 300 mg/ml

Abbreviations: CM, contrast media; HOCM, high-osmolar contrast media; LOCM, low-osmolar contrast media; IOCM, iso-osmolar contrast media

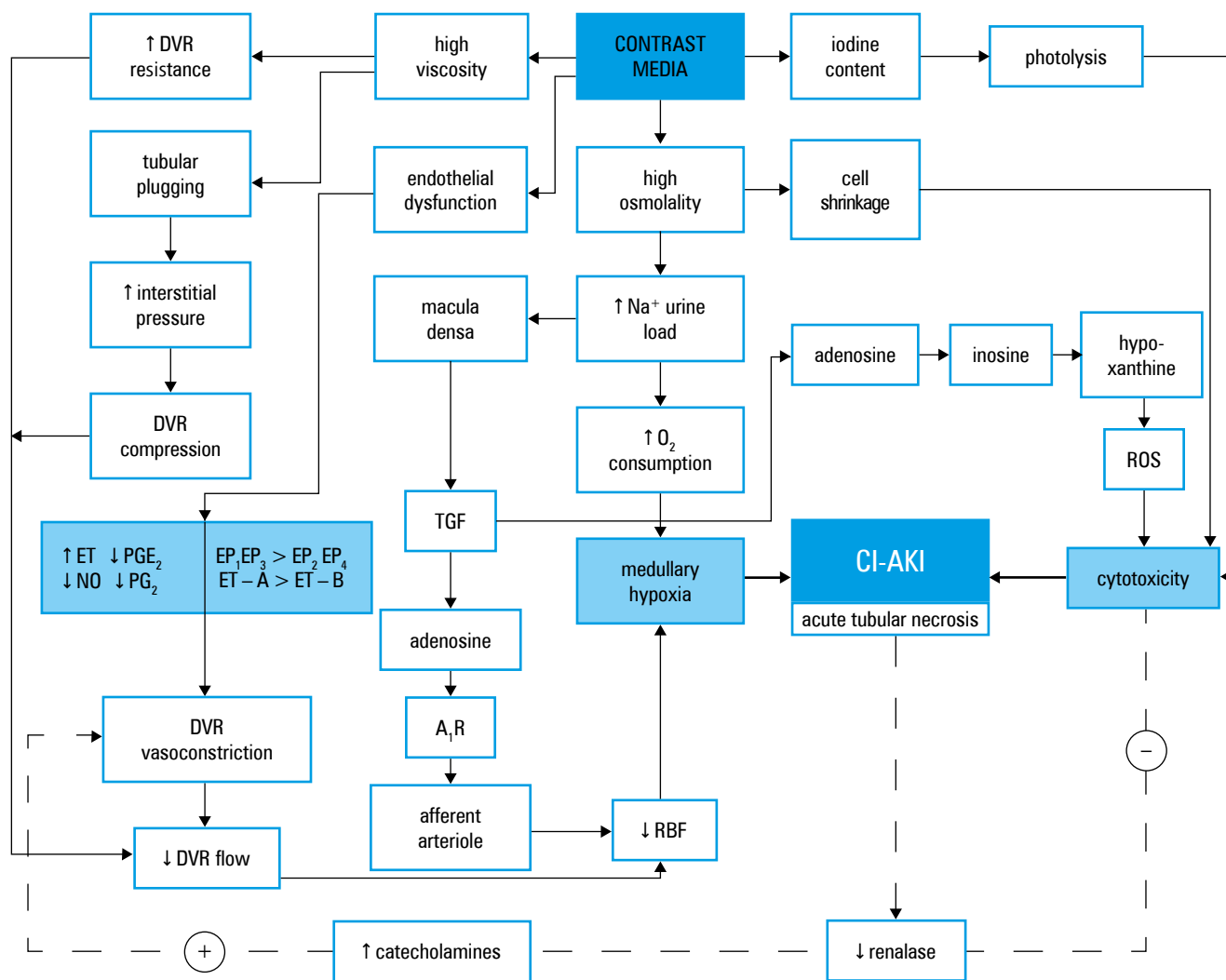


FIGURE 1 Overview of the pathophysiology of contrast-induced acute kidney injury.^{10,13,16-23,53} The sequence of events initiated by contrast-media administration triggers acute tubular necrosis by means of a) tubular medullary hypoxia and b) direct cytotoxicity. The dashed line shows proposed renase involvement in the pathophysiology of CI-AKI based on experimental and animal-based research.

Abbreviations: A₁R, adenosine receptor type 1; CI-AKI, contrast-induced acute kidney injury; DVR, direct vasa recta; EP₁₋₄, prostaglandin E receptor type 1-4; ET, endothelin; ET-A, ET-B, endothelin receptor; NO, nitric oxide; PGE₂, prostaglandin type 2; PGI₂, prostacyclin; RBF, renal blood flow; ROS, reactive oxygen species; TGF, tubuloglomerular feedback

external stimulus interferes with a fragile hemodynamic equilibrium of the outer medulla and causes acute tubular necrosis.

Hyperglycemia Severe hyperglycemia of 30 mmol/l or higher was demonstrated to potentiate

contrast-induced tubular cell apoptosis as reflected by an in-vitro dog kidney model.²³ This fact may be of paramount importance when it comes to periprocedural management, implicating renal benefits of tight glycemic control, contrary to the contemporary lenient approach favoring

glycemic targets of less than 180 to 200 mg/dl in the acute phase of myocardial infarction, which were shown to promote survival.²⁴

Tubuloglomerular feedback Tubuloglomerular feedback (TGF) used to be regarded as the principal mechanism explaining CI-AKI under the label of osmotic diuresis theory. TGF is based on the unique role of the macula densa involved in the local secretion of adenosine in response to elevated concentrations of Na⁺, K⁺, or Cl⁻ in tubular fluid detected via the activity of the Na⁺K⁺2Cl⁻ cotransporter. In turn, adenosine activates A₁ receptors on extraglomerular mesangial cells, resulting in afferent arteriole vasoconstriction and eGFR reduction. This protective mechanism is thought to reduce oxygen consumption in the event of excess natriuresis and osmotic load. It was believed that high osmolality of CM and subsequent increased tubular sodium load were responsible for overstimulation of TGF and severe eGFR reduction. This hypothesis was somewhat undermined by the observation that Na⁺K⁺2Cl⁻ cotransporter inhibitors, such as loop diuretics (eg, furosemide), do not protect against CI-AKI.²⁵ Nonetheless, rolofylline, the selective antagonist of A₁ adenosine receptors, exerted a protective effect on CI-AKI in a nitric-oxide-deficient rat model.²⁶ It is possible that adenosine signaling is engaged in CI-AKI pathogenesis irrespective of TGF.

Osmotic nephrosis In the era of HOCM, CI-AKI was linked to a characteristic histopathological pattern recognized as “osmotic nephrosis”, exemplified by a massive vacuolization of proximal tubular cells.²⁷ This phenomenon can be also found in the setting of any tubular exposure to highly osmolar substances, such as mannitol, and is dependent on the process of pinocytosis. Of note, it is merely an indicator of CM exposure but does not precisely correspond to the degree of renal function impairment.

Risk factors Since the management of CI-AKI is limited to symptomatic treatment, careful risk stratification is crucial for selecting patients requiring more aggressive intravenous hydration and limitation of CM dose. Every catheterization laboratory should develop its own preprocedural risk-adjusted hydration protocol. In case of elective CA, it is indispensable to define patients' pretest probability of CAD and apply noninvasive diagnostic tests²⁸ to select patients ineligible for CA and thus avoid redundant exposure to CM.

Consistently with its multifaceted pathophysiology, CI-AKI has numerous risk factors that can be categorized into modifiable and nonmodifiable subgroups (TABLE 2). A large body of evidence suggests that preexisting CKD and the volume of CM injected are the two most significant predictors of CI-AKI (TABLE 2).

Baseline renal function The Mayo Clinic Registry reported that baseline SCr exceeding 2.0 mg/dl

was associated with a 7-fold higher risk of CI-AKI, and SCr exceeding 3.0 mg/dl—with approximately 13-fold higher risk.⁶ The largest PCI study to date confirmed that patients with CI-AKI had significantly higher preprocedural SCr than subjects without this complication (1.0 and 1.5 mg/dl, respectively; *P* < 0.001).⁸ The CI-AKI Consensus Working Panel proposed a threshold of 1.3 mg/dl for men and 1.0 mg/dl for women (equivalent to an eGFR of 60 ml/min/1.73 m²) as clinically relevant cut-off level.²⁹ Nonetheless, contemporary guidelines on myocardial revascularization by the European Society of Cardiology and European Association for Cardio-Thoracic Surgery (ESC/EACTS) support the eGFR of less than 40 ml/min/1.73 m² as a high-risk threshold.³⁰ A putative explanation is that preexisting chronic kidney disease (CKD) aggravates renal injury because a reduced amount of nephrons needs to excrete the excess CM and compensatory mechanisms maintaining filtration are limited, resulting in an extended exposure time of tubular cells to CM. Taking the pharmacokinetics of iomeprol as an example, it requires 2 hours to eliminate 50% of a given dose of CM, while from 16 to 84 hours are needed in the case of severe CKD.³¹

The gradual reduction of eGFR with age is also responsible for a higher incidence of CI-AKI in patients older than 75 years of age.⁷ Approximately one-third of people older than 60 years of age have an eGFR of less than 60 ml/min/1.73 m²,³² while according to recent data, 9.5% of adults older than 80 years of age have an eGFR of less than 45 ml/min/1.73 m²,³³ which makes elderly patients particularly vulnerable to CM.

Volume of contrast media The role of CM volume is critical for the pathogenesis of CI-AKI; therefore, its use should be limited to the smallest extent required to perform cardiac catheterization. The majority of studies proved that exceeding 100 ml of CM significantly increases the clinical probability of CI-AKI.^{6,34} In the randomized RECOVER trial, the high-risk threshold of CM administered to patients with preexisting CKD was more than 140 ml.³⁵ In line with the 2014 ESC/EACTS guidelines on myocardial revascularization, it is contraindicated to exceed the level of 350 ml or 4 ml/kg.³⁰ Conversely, no safe volume of CM exists and even doses of less than 30 ml were reported to trigger CI-AKI.³⁰

In order to easily reflect the cumulative risk of CI-AKI, Laskey et al³⁶ proposed a volume-to-creatinine clearance ratio (V/CrCl). The ratio exceeding 3.7 accurately predicted the occurrence of CI-AKI (odds ratio [OR], 3.84; *P* < 0.001), defined as an absolute increase of SCr by 0.5 mg/dl within 24 to 48 hours following CM infusion.³⁶ Furthermore, Cigarroa et al³⁷ long ago established a clinically useful algorithm for the prediction of the maximum acceptable CM dose: 5 ml × body weight (kg) / baseline SCr (mg/dl).³⁷

TABLE 2 Risk factors for contrast-induced acute kidney injury risk factors^{7-8,34}

modifiable	Patient-related risk factor		Procedure-related risk factors
	modifiable	nonmodifiable	
hydration status		baseline SCr – CKD	CM volume
glycemia		diabetes	CM type (HO CM, LO CM, IO CM)
blood pressure – hypoperfusion ^a		CI-AKI in anamnesis	CM type preheating and storing
anemia		age > 75 years	CM intra-arterial or intravenous ^b
obesity ^a		female sex	automated CM syringe
nephrotoxic drug use:		LVEF	repeated CM exposure
NSAIDs		CHF	biplane angiography
aminoglycosides		ACS	use of IABP ^b
amphotericin B		previous MI	operator
high dose loop diuretics		previous PCI	
acyclovir, foscarnet		peripheral arterial disease	
		SYNTAX score	
		neutrophil-to-lymphocyte ratio	

a modifiable to certain extent; **b** in case of CA/PCI, CM is administered intra-arterially

Abbreviations: ACS, acute coronary syndrome; CHF, congestive heart failure; CKD, chronic kidney disease; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention; SCr, serum creatinine concentrations; others, see **TABLE 1** and **FIGURE 1**

Types of contrast media As previously stated, the use of HO CM is associated with an increased risk of CI-AKI in comparison with the use of LO CM or IO CM.³⁸ All LO CM confer a comparable risk of CI-AKI; however, there are conflicting data regarding the comparison of LO CM and IO CM. It was implied that LO CM might be superior to IO CM in dehydrated patients,¹³ while some research endorsed the advantage of IO CM over LO CM in patients with preexisting CKD and diabetes.³⁵

Dehydration The maintenance of adequate volume status is the cornerstone of CI-AKI prevention, while dehydration is a major risk factor for CI-AKI, since it directly modifies urinary, tissue, and plasma CM concentrations. The total body water measured by means of a bioimpedance vector analysis immediately before the procedure (a correlate of effective intravascular volume) was shown to accurately predict the occurrence of postprocedural CI-AKI.³⁹

Hemodynamic status CI-AKI is frequently accompanied by prerenal component associated with hypoperfusion secondary to acute heart failure, low left ventricular ejection fraction (LVEF), the need for the use of an intra-aortic balloon pump, or renal congestion secondary to congestive heart failure. High central pulse pressure potentiates renal injury via impaired autoregulation of renal blood flow.⁴⁰ In the setting of acute coronary syndrome (ACS), the systemic inflammatory response aggravates renal injury, while excessive administration of CM is often indispensable for procedural success. The need for frequent catheter exchange or intra-aortic balloon pump insertion could result in renal microembolization. Correspondingly, complex coronary anatomy reflected by a high SYNTAX score in subjects presenting with ST-segment elevation myocardial infarction

(STEMI) was linked to CI-AKI burden, presumably due to hemodynamic instability and higher CM requirement.⁴¹

Impaired glucose metabolism Impaired glucose metabolism acts as a permissive factor to CI-AKI owing to diabetic microangiopathy promoting renal tubular hypoxia, as well as the synergy between hyperglycemia and high osmolality of CM.²⁴ Roughly one-third of diabetic patients display Kimmelstiel–Wilson glomerulosclerosis, which is the most frequent cause of end-stage renal disease (ESRD) and an indication for dialysis in developed countries.⁴² Numerous studies underscored the harmful effect of diabetes on kidney function following the use of CM.^{7,43} Interestingly, Rihal et al⁶ demonstrated that the presence of diabetes significantly increased the risk of CI-AKI only in patients with SCr of less than 2.0 mg/dl, while in patients with severe CKD, it did not confer additional risk of renal injury. Both mild (110–140 mg/dl; OR, 1.31) and severe (>200 mg/dl; OR, 2.14) preprocedural hyperglycemia was associated with a higher incidence of CI-AKI in comparison with normoglycemia (<110 mg/dl), but exclusively in subjects without the previous diagnosis of diabetes.⁴⁴

Predictive scales In 2004, Mehran et al⁷ formulated a transparent and clinically relevant risk classification for CI-AKI (Supplementary material online, *Table S2*). Notwithstanding its simplicity and utility, this statistical model neglected some other very important risk factors, which were further included in a subsequent risk prediction algorithm developed by Gurm et al.⁸ The latter score, derived from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium registry, incorporates a wide range of clinical variables and is available as an easily accessible online

computational tool with an excellent area under the curve of 0.85 for CI-AKI risk prediction.⁸

Biomarkers To date, no AKI marker has achieved the diagnostic power sufficient for an early and definite diagnosis of CI-AKI. In particular, the use of SCr as an early disease marker is limited. Following renal injury, SCr accumulates in bloodstream no sooner than 24 to 48 hours, and it may take even up to 5 days, while in the setting of a cardiology department, the majority of patients are discharged within 2 days after CM administration.⁴⁵ SCr depends on numerous factors including age, sex, total muscle mass, diet, or hydration status. Since the relationship between SCr and eGFR is exponential, SCr initially remains intact following renal injury, despite a rapid decrease in actual GFR.⁴⁶ In turn, notable day-to-day variability of SCr was demonstrated in patients who did not receive CM during hospitalization, as more than half of 32 161 patients experienced a relative increase in SCr of at least 25%.⁴⁷

Thus, the idea of so called renal troponin has driven the search for an ideal biomarker, which could facilitate the early initiation of treatment such as intravenous hydration or renal replacement therapy (RRT). To date, several markers have been proposed, such as cystatin C,⁴⁸ neutrophil gelatinase-associated lipocalin,⁴⁹ liver fatty acid-binding protein,⁵⁰ kidney injury molecule 1,⁵¹ or interleukin 18.⁵² Catecholamine-metabolizing enzyme known as renalase is particularly promising because a rapid postprocedural decrease in its urinary levels could reflect not only real-time renal injury but also the actual renal function loss (FIGURE 1).⁵³ Time will show whether any of these markers will be incorporated into daily clinical practice.

Prevention and management Risk assessment So far, no pharmacological agent proved fully effective in reducing the risk of CI-AKI (TABLE 3). Thus, an adequate preparation for cardiac catheterization and estimation of CI-AKI risk are of paramount importance (class IIa, level C).³⁰ This includes the use of electronic alertness systems, which are capable of selecting patients at high risk of CI-AKI merely on the basis of data included in a patient's electronic history, allowing for the timely incorporation of a preventive strategy.⁵⁴

Drug review The easiest and least expensive precaution is cessation of all potentially nephrotoxic drugs in all high-risk patients, including nonsteroidal anti-inflammatory drugs, cyclosporine A, and aminoglycosides at least 48 hours before the injection of CM. The current clinical data on the role of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the pathophysiology of CI-AKI^{55,56} are conflicting; however, it is reasonable to consider withholding these agents in patients with severe CKD at a very high risk of CI-AKI.

Metformin itself does not affect the risk of CI-AKI. Nevertheless, in the event of CI-AKI, metformin can trigger lethal lactic acidosis. No scientific evidence supports routine discontinuation of metformin in all diabetic patients referred for CA, except for diabetic patients with preexisting CKD.⁵⁷ Instead, SCr should be evaluated for 2 to 3 consecutive days following the procedure, and metformin should be suspended when renal function deteriorates.³⁰

Contrast media precautions Merely 2 preventive strategies significantly modified the prevalence of CI-AKI: CM dose modification and adequate hydration. The preferable use of IOCM over LOCM and HOCM (class IIa, level A), CM prewarming to 37°C, and CM volume reduction to less than 350 ml or less than 4 ml/kg body weight (or CM volume-GFR ratio <3.7) all play a pivotal role in the prevention of CI-AKI (class I, level A).³⁰ Automated contrast injectors have proved effective in reducing CM volume approximately by 45 ml per case, which translated into a reduced risk of CI-AKI (OR, 0.85; $P < 0.001$).⁵⁸ Biplane angiography facilitates further reduction in CM dose (25 vs 47 ml; $P < 0.0001$) and results in a lower prevalence of CI-AKI (7.8% vs 26.8%; $P = 0.0007$) and dialysis requirement ($P = 0.02$).⁵⁹ Additionally, an experimental contrast removal device placed in the coronary sinus during CA prevented a postprocedural increase in SCr, without causing any device-related complications.⁶⁰

Hydration The deleterious effect of CM can be somewhat reduced by adequate hydration leading to CM dilution,³⁹ both in renal tubules and intrarenal arteries. Due to excessive viscosity, the use of IOCM, in particular, should always be preceded by sufficient volume expansion.¹³ Current European guidelines endorse the strategy of intravenous hydration with isotonic saline in all patients with moderate-to-severe CKD, especially those with an eGFR of less than 40 ml/min/1.73 m², starting 12 hours before to 24 hours after the procedure (class I, level A).^{30,61} The oral route of hydration was shown to be as effective as the intravenous one in the prevention of CI-AKI.⁶² Yet, blind hydration can trigger pulmonary edema, especially in patients with low LVEF. Thus, a "one size fits all" approach seems outdated, and, nowadays, there is growing experimental evidence to support the concept that volume expansion should be adjusted to the current hydration status.^{63,64} The fundamental results of the POSEIDON trial showed that intraprocedural intravenous hydration guided by left ventricular end-diastolic pressure (LVEDP) measured immediately before the use of CM is superior to the standard hydration protocol (rate of CI-AKI, 6.7% vs 16.3%; $P = 0.005$).⁶³ Patients in whom LVEDP was 18 mmHg or lower received a more aggressive hydration than patients randomized to the control group.⁶³ Of note, all study participants regardless of the assigned group received an intravenous bolus of

TABLE 3 Prevention of contrast-induced acute kidney injury^{53,57-61,64,68,72-74,90-96}

Results	Pharmacological prevention	Nonpharmacological prevention
effective	IV hydration tailored to fluid status nephrotoxic drug discontinuation HMG inhibitors (statins)	contrast media volume limitation, prewarming, use of iso-osmolar contrast media automated contrast injectors biplane angiography
promising preliminary human studies	N-acetylcysteine (NAC) ^a bicarbonate (NaHCO ₃) ^a theophylline ^a ascorbic acid sildenafil iloprost citrate trimetazidine allopurinol atrial natriuretic peptide	remote ischemic preconditioning oxygenation coronary sinus contrast removal systems
promising preliminary animal studies	renalase cardiotrophin 1	
no significant clinical benefit	dopamine fenoldopam	

a conflicting results of studies suggest mild benefit or neutral effect on the risk of contrast-induced acute kidney injury

saline (3 ml/kg) before the procedure, suggesting that intra- and postprocedural hydration is at least equally as important as the preprocedural volume status.⁶³

Forced diuresis with volume expansion Noteworthy, urinary CM levels can be further decreased by forced diuresis due to furosemide-mediated inhibition of the Na⁺K⁺2Cl⁻ cotransporter in the ascending limb of the Henle loop. Although the use of furosemide alone augmented the risk of CI-AKI (OR, 3.27),⁶⁵ adding matched volume expansion to furosemide in high-risk patients undergoing PCI led to the reduction in the rate of CI-AKI (class IIb, level A).³⁰ Current European guidelines are based on the results of the randomized MYTHOS trial, which proposed a preprocedural intravenous bolus of 250 ml of saline over 30 minutes (150 ml in case of low LVEF) with a subsequent intravenous furosemide bolus (0.25–0.5 mg/kg) and further diuresis-tailored hydration during the procedure and 4 hours afterwards.⁶⁶ The procedure was started providing that the urine output exceeded 300 ml/h.⁶⁶ The above approach caused a marked reduction in the CI-AKI rate (RR = 0.29, *P* = 0.023).⁶⁶ This concept was further explored in the REMEDIAL-II trial evaluating the effectiveness of the RenalGuard System,⁶⁴ a closed-loop system adapting furosemide infusion to the current urine output. Clinical application of this system in high-risk patients led to a decrease in the rates of CI-AKI and in-hospital adverse events, significantly limiting cystatin C elevation, as well as in the rate of in-hospital dialysis.⁶⁴

Statins The significance of statins has long been known to extend far beyond their hypolipemic action, with pleiotropic anti-inflammatory and antithrombotic properties. Recently, it has

been shown that patients derive a notable benefit from pretreatment with high-dose statin given 24 hours before radiographic contrast procedures. This was documented both in statin-naïve patients with ACS⁶⁷ and in subjects with stable CAD.⁶⁸ The beneficial effect was observed for atorvastatin at a dose of 80 mg,⁶⁸ rosuvastatin at a dose of 40 or 20 mg,⁶⁷ and simvastatin at a dose of 80 mg.⁶⁹ The efficacy of statins was summarized by a recent meta-analysis comprising 7 randomized controlled trials (RCTs) incorporating 1399 patients, which revealed a favorable effect of statin on the rate of CI-AKI (relative risk [RR], 0.51, *P* = 0.001), yet with no effect on the rate of dialysis requirement.⁷⁰ The effect of statins might be less profound in patients with baseline renal function impairment (eGFR <40 ml/min/1.73 m²).⁷¹ As observed by Quintavalle et al,⁶⁸ atorvastatin induced cell viability via reduction of proapoptotic caspase-3, JNK, and p53 activation, at the same time promoting survival signals mediated by the Akt and ERK pathways.⁶⁸ These data lend support to the current recommendations of the European Society of Cardiology (ESC),³⁰ suggesting the consideration of preprocedural adjuvant loading dose of statin (class IIa, level A).

Prevention of contrast-induced acute kidney injury: past experience and future perspectives The extensive scientific data from RCTs did not show any clinical benefit of using N-acetylcysteine and sodium bicarbonate^{72,73} or implementing dopamine or selective D₁ receptor-agonist (fenoldopam) in the prevention of CI-AKI.⁷⁴ Therefore, their use is not supported by the current ESC guidelines.³⁰ Although several other substances have been proposed as potential preventive agents in patients with CI-AKI (TABLE 3), the evidence for their benefit remains scarce.

Remote ischemic preconditioning (RIPC) is based on the concept that transient cycles of nonlethal ischemia and reperfusion of one organ prevent another organ from extensive damage following a subsequent episode of lethal ischemia and reperfusion. Notwithstanding the undisclosed underlying mechanism, it involves repeated transient episodes of 5-minute arm cuff inflation and 5-minute deflation immediately before the procedure. Surprisingly, RIPC initially proved effective in reducing the rate of CI-AKI in patients undergoing elective CA⁷⁵ or PCI in the setting of STEMI.⁷⁶ Preliminary data concerning the use of RIPC in CI-AKI are promising but merit verification in high-volume randomized studies.

As renal tubular hypoxia constitutes the ultimate endpoint of all CI-AKI pathogenic pathways, the idea of surplus oxygenation seems noteworthy. Unexpectedly, patients referred for elective CA/PCI who received surplus oxygenation via the nasal cannula suffered from CI-AKI notably less frequently than patients kept on room air.⁷⁷ Still, this preventive strategy requires further research.

Renal replacement therapy Single hemodialysis (HD) session cannot remove the whole load of CM stored in the extravascular compartment. First, CM diffuse into the extracellular fluid and rapidly achieve equilibrium with the intravascular compartment. In patients with normal renal function, the excretion via glomerular filtration leads to a rapid drop in CM concentrations in blood and rediffusion of CM from the extracellular volume to intravascular compartment. In patients with severe CKD, there is a prolonged retention of CM.³¹ Although the mean reduction of CM during HD slightly exceeds 80% of the total iodine content at 4 hours,⁷⁸ circulating CM levels increase significantly directly after HD, suggesting a rebound phenomenon.⁷⁹ Second, CM are classified as middle-sized molecules, and low-flux HD membranes perform suboptimally in the elimination of CM, as opposed to high-flux hemofiltration membranes.

In the largest study to date, Vogt et al⁸⁰ demonstrated that prophylactic HD in 133 patients with CKD was associated with an insignificantly higher demand for repeated HD ($P = 0.12$) and greater variations in SCr with no clinical benefit concerning in-hospital adverse events. Conversely, a meta-analysis comprising 1010 patients indicated a possible harmful effect of prophylactic HD (RR, 1.61) on the risk of CI-AKI (elevation of SCr by >0.5 mg/dl) and a neutral effect on permanent RRT requirement or progression to ESRD.⁸¹ The explanation of these paradoxical findings may be the possibility of real-time renal injury during the procedure, which cannot be prevented by postprocedural dialysis, as well as the harmful effect of HD itself due to variations in blood pressure. Also, SCr is an insensitive AKI marker in patients on RRT since it is eliminated from bloodstream during the procedure itself. Given the above rationale, prophylactic HD

is contraindicated in high-risk patients receiving CM (class III, level B).^{1,30}

The limitations of HD are somewhat overcome by continuous extracorporeal blood purification techniques such as continuous venovenous hemofiltration (CVVH). Marenzi et al⁸² reported that CVVH had an advantage over saline hydration in the reduction of the rate of CI-AKI (5% vs 50% respectively, $P < 0.001$), the need for repeated RRT (3% vs 25%), the rate of in-hospital complications, and the rates of in-hospital (2% vs 14%, $P = 0.02$) and 1-year mortality (10% vs. 30%, $P = 0.01$).⁸² Current guidelines state that prophylactic CVVH may be considered in subjects with severe CKD exposed to CM (Class IIb, level A).³⁰ More recently, Choi et al⁸³ revealed that hemofiltration performed simultaneously with CA resulted in an improved outcome in comparison with the hemofiltration strategy performed 6 hours before and 24 hours after the procedure.

Chronic kidney disease and cardiac interventions

Preexisting renal function impairment remains a clinical challenge because it is the key risk factor for CI-AKI. This is of particular importance because the rate of coronary incidents in CKD far exceeds that observed in healthy individuals.⁴⁵ The general preventive strategy resembles the usual approach applied in normal population. All the potential nephrotoxic drugs should be withheld and the volume of CM minimized, while adequate hydration is a prerequisite for long-term net procedural success. Despite the above data, CVVH should be reserved merely for patients with CKD at an extremely high risk of CI-AKI.¹ Prophylactic HD is contraindicated.¹ In the event of postprocedural worsening of renal function, the indications for RRT are common with other etiologies of ACI.

The maximum acceptable CM dose should be tailored according to the initial creatinine concentration and eGFR. Based on the formula of Cigarroa et al³⁷ and the advised volume-to-creatinine clearance ratio (<3.7) by Laskey et al,³⁶ we calculated a maximal reasonable volume of contrast for an average individual with a weight of 65 kg depending on the baseline renal function (TABLE 4).

End-stage renal disease and cardiac interventions

The effect of iodinated CM on residual renal function in patients with ESRD maintained on RRT is another intriguing clinical dilemma. This problem is particularly important since the current evidence suggests that the use of CM does not trigger the reduction of residual diuresis at 6-month follow-up.⁸⁴ Guidelines do not support performing HD before the next routinely scheduled session in patients maintained on a routine HD schedule of 3 sessions per week and exposed to CM dose. It was demonstrated that this subset of patients does not exhibit surplus in-hospital adverse events following the administration of CM.^{85,86} Under the condition of IOCM use and CM dose limitation, patients with ESRD should

TABLE 4 Maximum acceptable amount of contrast media depending on baseline renal function^{36,37}

Baseline eGFR, ml/min/1.73 m ²	Corresponding SCr according to MDRD ^a , mg/dl	CM volume, ml	
		algorithm by Cigarroa ^{37b}	algorithm by Laskey et al ^{36c}
90	0.9	360	330
60	1.25	260	220
45	1.65	195	165
30	2.3	140	110
15	4.25	75	55

a eGFR based on the MDRD formula for non-African-American male (weight, 65 kg); approximated

b values calculated for an average person with a weight of 65 kg

c recommended volume of contrast-to-creatinine clearance ratio <3.7

Abbreviations: eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; others, see TABLE 1

not undergo preterm and emergent postangiography dialysis.¹

Prognosis Even a slight increase in SCr by more than 0.3 mg/dl within 48 hours after CM administration had a significant impact on the risk of major adverse events in 1-year follow-up (composite endpoint of death, myocardial infarction, stroke, ESRD requiring dialysis; OR, 3.2; $P = 0.02$).⁸⁷ Episode of CI-AKI exerted an even greater effect on future cardiovascular events in patients with ACS and CI-AKI superimposed on preexisting CKD.⁸⁸ In turn, CI-AKI often leads to CKD development in about 18.6% of subjects with CI-AKI.⁸⁷ The Mayo Clinic PCI registry indicated that CI-AKI conferred nearly as great a risk of in-hospital mortality (OR, 10.8; $P < 0.0001$) as preprocedural shock did (OR, 12.1) and emphasized the relationship between CI-AKI and both 1- and 5-year mortality rate following PCI regardless of CAD severity.⁶ In the narrow clinical setting of STEMI, the HORIZONS-AMI substudy revealed a devastating effect of CI-AKI on both 30-day and 3-year mortality rate and the rate of composite endpoint of major bleeding and adverse cardiovascular events.⁸⁹ Subjects with CI-AKI had significantly higher mortality rate at 30 days (8.0% vs 0.9%, $P < 0.0001$) and at 3 years (16.2% vs 4.5%, $P < 0.0001$),⁸⁹ which underlines the extreme importance of renal function deterioration in the setting of a cardiology department.

Conclusions Worsening of renal function following cardiac catheterization represents a major clinical challenge on account of higher morbidity and mortality, far exceeding renal outcome compromise. Patients referred to a catheterization laboratory should be carefully interviewed to elucidate all potential risk factors of CI-AKI. CM volume limitation and tailored volume expansion still remain fundamental measures of CI-AKI prevention. Future renal function indices should reflect not only the extent of kidney

injury, but also the magnitude of combined cardiorenal pathology.

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Ostra nefropatia kontrastowa – ciemna strona kardiologii inwazyjnej

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SŁOWA KLUCZOWE

biomarkery,
cewnikowanie serca,
czynniki ryzyka, ostra
nefropatia
kontrastowa, ostre
uszkodzenie nerek
po podaży kontrastu

STRESZCZENIE

Gwałtownie rosnąca liczba przezskórnych interwencji wieńcowych doprowadziła do znaczącej poprawy rokowania u pacjentów z ostrymi zespołami wieńcowymi, jednocześnie narażając pacjentów na duże ilości środków cieniujących, których użycie nierozdzielnie wiąże się z uszkodzeniem czynności nerek. Zagadnienie ostrego uszkodzenia nerek po podaży kontrastu (*contrast-induced acute kidney injury* – CI-AKI) łączy się nie tylko z bezpośrednimi następstwami w postaci wydłużonego czasu hospitalizacji, ale także ze zwiększonym ryzykiem rozwoju przewlekłej choroby nerek, ponownymi ostrymi zespołami wieńcowymi, wystąpieniem udaru niedokrwinnego mózgu oraz większym ryzykiem zgonu. Wszechobecne zastosowanie środków kontrastowych wymaga podjęcia działań w kierunku znalezienia wiarygodnych czynników ryzyka, markerów diagnostycznych i środków zapobiegania przydatnych w leczeniu CI-AKI. Zdecydowana większość przypadków CI-AKI pozostaje nierozpoznana w związku z niedoskonałością stężenia kreatyniny w surowicy jako markera ostrego uszkodzenia nerek. W ostatnim czasie zaproponowano kilka nowych markerów, umożliwiających wczesne wykrycie CI-AKI oraz lepsze zrozumienie złożonej zależności pomiędzy układem sercowo-naczyniowym a nerkami, znanej jako zespół sercowo-nerkowy. Celem niniejszego artykułu poglądowego jest podsumowanie dotychczasowej wiedzy na temat patofizjologii, czynników ryzyka, markerów, środków prewencji i leczenia ostrej nefropatii kontrastowej.

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