Update on the renal toxicity of iodinated contrast drugs used in clinical medicine

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Abstract: An important side effect of diagnostic contrast drugs is contrast-induced acute kidney injury (CI-AKI; a sudden decrease in renal function) occurring 48–72 hours after injection of a contrast drug that cannot be attributed to other causes. Its existence has recently been challenged, because of some retrospective studies in which the incidence of AKI was not different between subjects who received a contrast drug and those who did not, even using propensity score matching to prevent selection bias. For some authors, only patients with estimated glomerular filtration rate <30 mL/min/1.73 m² are at significant risk of CI-AKI. Most agree that when renal function is normal, there is no CI-AKI risk. Many experimental studies, however, are in favor of the existence of CI-AKI. Contrast drugs have been shown to cause the following changes: renal vasoconstriction, resulting in a rise in intrarenal resistance (decrease in renal blood flow and glomerular filtration rate and medullary hypoxia); epithelial vacuolization and dilatation and necrosis of proximal tubules; potentiation of angiotensin II effects, reducing nitric oxide (NO) and causing direct constriction of descending vasa recta, leading to formation of reactive oxygen species in isolated descending vasa recta of rats microperfused with a solution of iodixanol; increasing active sodium reabsorption in the thick ascending limbs of Henle's loop (increasing O₂ demand and consequently medullary hypoxia); direct cytotoxic effects on endothelial and tubular epithelial cells (decrease in release of NO in vasa recta); and reducing cell survival, due to decreased activation of Akt and ERK1/2, kinases involved in cell survival/proliferation. Prevention is mainly based on extracellular volume expansion, statins, and *N*-acetylcysteine; conflicting results have been obtained with nebivolol, furosemide, calcium-channel blockers, theophylline, and hemodialysis.

Keywords: renal failure, ARF, acute kidney injury, AKI, contrast media, intracellular signaling

Introduction

Iodinated contrast drugs are used in clinical medicine to visualize internal organs, since one of the properties of iodine is its high-contrast density. This property makes these drugs useful to increase the visibility of the urinary tract (excretory urography or intravenous [IV] pyelography) of vascular structures (angiography) in computed tomography (CT) scans of internal organs; it also allows important therapeutic maneuvers, such as angioplasty and coronary interventions. The use of contrast drugs has been growing in recent years, mainly due to the increase in life span and consequently more frequent diagnostic needs in older patients with more comorbid conditions (eg, long-standing or severe hypertension, long-standing or severe diabetes, and chronic renal failure).

We are aware that all drugs used in clinical practice have some side effects in addition to therapeutic efficacy; only when their efficacy prevails over the side effects are

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we allowed to use them. The same is valid for contrast drugs, the use of which is not therapeutic, but diagnostic: they have some side effects. Unfortunately, we are obliged to use them in many, often severe, clinical conditions to reach a diagnosis. Therefore, to overcome the problem, we must try to reduce their severity by choosing less nephrotoxic contrast drugs and by pretreating and treating patients when using them.

Iodinated contrast drugs

Iodinated contrast drugs have different osmolalities. According to their osmolality, we can divide contrast drugs into three groups: 1) ionic high-osmolar contrast media (HOCM; eg, iohalamate) have an osmolality (1,500–1,800 mOsm/kg) five to eight times plasma osmolality; 2) nonionic low-OCM (LOCM; eg, iohexol) have an osmolality (600–850 mOsm/kg) two to three times plasma osmolality; and 3) nonionic iso-OCM (IOCM; eg, iodixanol) have an osmolality (~290 mOsm/kg) similar to that of plasma.¹ HOCM are more cytotoxic in vitro on proximal tubular cells than LOCM or IOCM. The use of LOCM rather than HOCM reduces nephrotoxicity in patients with renal failure. Therefore, HOCM are used less frequently.^{2,3}

Possible side effects of contrast drugs

Unwanted effects of contrast drugs may vary from mild inconvenience (such as mild itching or cutaneous reactions) to more severe reactions (such as allergic effects, delayed allergic reactions, or anaphylactic reactions) including a life-threatening emergency. For these, we refer to the literature.^{4–6} With the advent of nonionic LOCM in the 1980s, most adverse events became relatively mild and required no medical treatment.

Contrast-induced acute kidney injury

A very important unwanted effect of the use of contrast drugs is acute kidney injury (AKI), ie, a sudden decrease of renal function due to renal damage.⁷ AKI secondary to contrast drugs is called contrast-induced AKI (CI-AKI; or contrast-induced nephropathy [CIN]); it is actually an iatrogenic AKI. This relatively frequent renal complication is due to the following factors.

Intravenous or intra-arterial injection of a contrast drug

There is widespread (and long-standing) recognition that the risk of CI-AKI is greater with intra-arterial than IV

administration. This would be due to higher contrast-drug concentration in the intrarenal vessels,⁸ particularly when the intra-arterial injection is suprarenal.⁹ Under these conditions, in fact, there is a very high concentration of contrast drug. Nyman et al¹⁰ totally disagreed, mainly because of a lack of comparative trials on the risk of CI-AKI between intra-arterial and IV procedures. More recent literature provides increasing evidence of very limited/no demonstrable CI-AKI with the IV route.^{11–13}

Main route of excretion by the kidneys

After intravascular injection, the drug is diluted in the bloodstream (this allows the visualization of vessels of liver, spleen, pancreas, and kidneys, etc) and immediately distributed throughout the extracellular fluid. Being poorly bound to serum albumin, the contrast drug is freely filtered by renal glomeruli and excreted by the kidneys.

CI-AKI is defined as any case of AKI occurring 48–72 hours after intravascular injection of a contrast drug that cannot be attributed to other causes. It is more frequent in aged patients,^{14–17} those with diabetes, and in patients with renal insufficiency (<60 mL/min/1.73 m² glomerular filtration rate [GFR]), and is usually nonoliguric and frequently asymptomatic, such that often its diagnosis is missed. It peaks on the third to fifth day, and returns to normality within 10–14 days. It is usually indicated as an increase in serum creatinine by 0.5 mg/dL or greater, or by a decrease to 30–60 mL/min of GFR obtained with special formulas from serum creatinine (estimated GFR [eGFR]).^{5,18–20}

The incidence of CI-AKI in subjects undergoing a radiological examination with an iodinated contrast drug is low (2%) if renal function is normal (eGFR >45 mL/min/1.73 m²).²¹ However, it has been reported that in 10% of patients with renal failure exposed to contrast drugs for coronary angiography, a severe oliguric acute renal failure occurred that led to dialysis or death.²² Recent studies have questioned whether CI-AKI in patients with chronic renal insufficiency really does exist.^{23,24} Another study also concluded that no significant increase in CI-AKI occurs after LOCM administration in critically ill patients.²⁵

There have been many retrospective studies (usually carried out in more than 20,000 and sometimes 50,000 adult patients over a 10-year period) to demonstrate that the incidence of AKI was not different between subjects who had received an iodinated contrast drug and control subjects who had not.^{13,26–29} McDonald et al²⁹ have also demonstrated that the use of contrast drugs was not associated with higher risk

of AKI, dialysis, or death, even in patients usually indicated at high risk of CI-AKI (because of diabetes, congestive heart failure, or chronic renal failure). However, patients with CI-AKI had a higher rate of dialysis or death. In another retrospective study, the same authors divided more than 41,000 patients on the basis of their baseline eGFR into four groups: >90 , $60-80$, $30-50$, and less than $30 \text{ mL/min/1.73 m}^2$. They concluded that there was an increased risk of AKI with the decrease in eGFR; but there was no difference between patients exposed and patients unexposed to contrast drugs, even in those with $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$.³⁰

As such, in the last few years the existence of CI-AKI has been challenged on the basis of the aforementioned retrospective studies demonstrating no effect of contrast drugs on incidence of AKI compared with control patients who had not been treated with contrast drugs. Davenport et al³¹ recently underlined the many drawbacks of these retrospective clinical studies. The main criticism was the creation of the control group of patients not treated with contrast drugs, for whom selection bias was frequent. For instance, it may not be unusual to include in control groups (not treated with contrast drugs) patients who have multiple comorbidities and for this reason had been excluded from the group receiving contrast drugs. To reduce this selection bias, Parsons³² suggested the use of an advanced statistical technique: propensity score matching.

As stated by Davenport et al,³¹ it is surprising that through the propensity score-matching technique they found that contrast drugs represented an independent nephrotoxic risk factor in patients with severe and progressive chronic renal failure,^{26,27} whereas McDonald et al²⁸ had not, despite using the same technique. Davenport et al³¹ recognized that either their studies had a systematic bias favoring inclusion in the contrast-drug group of patients with a tendency to have AKI or in the McDonald et al study the propensity score-matching technique was less effective. The conclusions of the authors of these studies were: according to McDonald et al,²⁸ there is no risk of AKI with contrast drugs; and according to Davenport et al,³¹ only patients with $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ are at significant risk of CI-AKI, while patients with $\text{eGFR} 30-44 \text{ mL/min/1.73 m}^2$ are at borderline risk of AKI. The two groups of authors agreed that when renal function is normal, there is no risk of CI-AKI.

Thomsen and Stacul³³ asked the question: "Have we spent almost 40 years trying to find the way to prevent a disease (CI-AKI) that does not exist and is only the expression of normal fluctuation of a parameter (creatinine) used for its diagnosis, at least in patients with moderately reduced renal

function?"³⁴ However, they added that it is too early to decide that CI-AKI does not exist, at least in patients with severe renal failure.

We should underline that patients having contrast-enhanced CT exams would receive prophylaxis treatment that would decrease the incidence of AKI, whereas in patients not receiving contrast prophylaxis would not be given, thereby increasing the incidence of AKI. Taken together, these differences would tend to minimize the differences between the contrast group of patients and the control group. In retrospective studies suggesting similar incidence of AKI in patients undergoing contrast-enhanced and those taking unenhanced CT exams, a bias may have been created by the prophylaxis carried out in patients receiving the contrast. Prophylaxis, in fact, would decrease the incidence of AKI. In patients who did not receive contrast, prophylaxis was not given, thereby increasing the incidence of AKI. Taken together, these differences would tend to minimize the differences between the contrast group of patients and the control group.

Prospective studies on CI-AKI are difficult to perform in humans for ethical reasons. This is not a problem in experimental animals. Many experimental studies have been in favor of the existence of CI-AKI. Contrast drugs have been shown to be nephrotoxic, regardless of their osmolality, by causing the changes outlined in the following sections.

Renal hemodynamics

The intravascular injection of a contrast drug causes rapid renal vasodilatation followed by long vasoconstriction that results in a rise of intrarenal vascular resistance, with a decrease in renal blood flow (RBF) and a fall in filtration fraction.^{1,35-38} Liu et al³⁹ carried out an experimental study on isolated afferent and efferent glomerular arterioles of mice to figure out the effects of the iodinated contrast drug iodixanol on arteriolar tone of afferent and efferent arterioles.

The arterioles were isolated from mice and perfused with iodixanol (23 mg iodine/mL) for 20 minutes, followed by angiotensin II administration. Arterioles perfused with the vehicle solution without the contrast drug functioned as control. The diameters of the afferent arterioles perfused with iodixanol were significantly reduced from 9.2 to $8.3 \mu\text{m}$, while in control arterioles diameters increased from 8.7 to $9.3 \mu\text{m}$. The inhibition of nitric oxide synthase increased iodixanol-induced constriction. The authors also observed impaired nitric oxide bioavailability and enhanced angiotensin II response following iodixanol perfusion. In efferent arterioles, instead, their basal diameters and response to angiotensin II were not affected by iodixanol. The decrease

in nitric oxide bioavailability and increase in concentration of superoxide explain the increased tone and reactivity in afferent arterioles perfused with iodixanol. The authors concluded that the constricting effect of iodixanol in vitro on the afferent arterioles explains the reduction in RBF and GFR by contrast drugs observed in vivo.

Therefore, hemodynamic changes by contrast drugs are responsible for a decrease in RBF and GFR on one hand, and on the other for medullary hypoxia in a medullary area where O_2 supply is already low (Figure 1). Under normal conditions, nitric oxide (NO), prostaglandins, and adenosine adjust tubular transport of sodium to adapt to this low O_2 supply.⁴⁰ A reduced blood supply due to vasoconstriction, and increasing sodium reabsorption in the descending limb of Henle's loop due to an increased sodium delivery to the distal tubule will alter this mechanism, thereby causing more severe hypoxia (Figure 1).

Adenosine also seems to play an important role in CI-AKI. Normal dogs given iohexol have been shown to have

renal vasodilatation following activation of adenosine A_2 receptors, with an increase in RBF. The injection of iohexol in dogs with reduced renal function activates A_2 and A_1 : A_2 activation is associated with the initial renal vasodilatation, and activation of A_1 causes the subsequent longstanding vasoconstriction⁴¹ (Figure 1). On the basis of this observation, theophylline and aminophylline (adenosine-receptor antagonists) would have protective effects against contrast drugs. Unfortunately, while theophylline does prevent further impairment of renal function by contrast drugs in dogs with renal insufficiency,⁴¹ conflicting results have been obtained in humans: some articles have reported beneficial effects,^{42,43} while others have not.^{44,45}

Tubular epithelial vacuolization and necrosis

Rats and many other laboratory animals tolerate high doses of contrast drugs without any impairment of renal function. Jensen et al⁴⁶ proposed an animal model of CI-AKI in rats for

Figure 1 After intravascular injection, contrast drugs cause immediate and short-term renal vasodilatation.

Notes: Vasodilatation is very soon followed by renal vasoconstriction that causes 1) a decrease in renal blood flow (RBF) and glomerular filtration rate (GFR) and 2) vasa recta constriction (favored by increased effects of angiotensin II, adenosine, and endothelin), with consequent medullary hypoxia. Though contrast drugs are rapidly filtered by renal glomeruli and excreted with urine, their high osmolality will cause osmotic diuresis. This is responsible for an increase in sodium delivery to the medullary ascending limb of Henle's loop and consequent increase in sodium reabsorption. However, in this medullary area there is already significant O_2 demand due to the low blood supply. The increased O_2 consumption due to increased sodium reabsorption will cause significant medullary hypoxia with epithelial tubular injury that further decreases the GFR; a contribution to this obstruction is made by proinflammatory cytokines and complement activation that lead to protein precipitation. The latter injury is also due to a direct cytotoxic effect of contrast drugs, because of their high concentration in the tubular lumen due to the reabsorption of tubular fluid in the proximal tubules. The endothelial cells directly damaged by contrast drugs will lead to formation of reactive oxygen species (ROS) that will decrease nitric oxide, thereby contributing to vasa recta constriction and medullary hypoxia. Renal medullary hypoxia itself leads to formation of ROS. The final result will be an important decrease in GFR. Adapted from Andreucci M, Faga T, Pisani A, et al. Pathogenesis of acute renal failure induced by iodinated radiographic contrast media. *Austin J Nephrol Hypertens.* 2014;1(1):1005.³⁶

Abbreviations: All, angiotensin II; NO, nitric oxide; PG, prostaglandin; $ONOO^-$, peroxynitrite anion.

studying the different toxicities of different contrast drugs. Sprague Dawley rats were treated with gentamicin (70 mg/kg body weight [BW]) to cause relatively mild renal damage. Normal rats received physiological saline infusion (control group). One group of the gentamicin-treated rats was then given a single dose of ioversol (6 g/kg BW); a second group of the gentamicin-treated rats was not. Histopathology of the kidneys of untreated rats (control with physiological saline) revealed no histopathological kidney damage. Gentamicin + ioversol rats and gentamicin-only rats had similar incidence and severity of hyaline droplets in the proximal tubular epithelium. Rats treated with gentamicin + ioversol demonstrated an incidence and severity of inflammation greater than the gentamicin group. Vacuolization, dilatation, and necrosis of proximal tubules were observed only in rats treated with gentamicin + ioversol.

Potential of angiotensin II effects, reduction of NO bioavailability and direct constriction of medullary descending vasa recta: formation of reactive oxygen species

Sendeski et al⁴⁷ demonstrated *in vitro* in isolated outer medullary descending vasa recta of rats microperfused with a solution of iodixanol that this contrast drug directly constricted these vessels by 52%, reduced NO, and increased the vasoconstrictor response to angiotensin II. The consequence of this constriction *in vivo* will be severe local hypoxia³⁶ (Figure 1). The same authors demonstrated an important role for reactive oxygen species (ROS) in constricting medullary vasa recta following contrast-drug administration; in fact, the superoxide dismutase mimetic Tempol reduced the vasoconstriction by iodixanol.^{36,47}

It is also known that in normal kidneys, epithelial tubular transport leads to ROS formation, particularly in the medullary thick ascending limb of Henle's loop, where the dense mitochondrial population is the main source for the generation of superoxide anions ($O_2^{\cdot-}$), and hydroxyl radicals ($\cdot OH$) by NAD(P)H-oxidase.^{48,49} The injection of a contrast drug causes an increase in ROS formation and oxidative stress that exerts direct injury to endothelial and epithelial cell membranes in vascular and tubular structures, respectively, which leads to cellular apoptosis and necrosis and increased medullary hypoxia⁴⁹ (Figure 1).

More recently Pisani et al^{49,50} demonstrated that recombinant manganese superoxide dismutase given to rats that were under diatrizoate treatment reduced renal oxidative stress,

thereby preventing reduction in GFR and occurrence of renal histopathological lesions observed after contrast-drug administration. Another vasoconstrictive agent, endothelin, is released by the damaged endothelial cells, thereby contributing to medullary vasoconstriction and consequent hypoxia.⁵¹ Renal medullary hypoxia itself leads to the formation of ROS^{52,53} (Figure 1).

The decrease in NO observed after injection of contrast drugs may also be due to the reaction of NO with ROS, in particular superoxide.^{49,54} This reaction causes the formation of peroxynitrite,⁵⁵ which causes severe damage to endothelial cells. In conclusion, studies in experimental animals and in humans have demonstrated that contrast drugs cause a rise in ROS generation, decrease in NO, potentiation of angiotensin II effects, and direct constriction of medullary descending vasa recta, thereby contributing to the occurrence of CI-AKI⁴⁹ (Figure 1).

Renal active sodium transport

Active sodium reabsorption occurs in S_3 segments of proximal renal tubules of the outer medulla and in the medullary thick ascending limbs of Henle's loop, in a medullary area where O_2 delivery is poor even in normal conditions, due to the long distance from vasa recta, while O_2 demand is high due to active sodium reabsorption. After intravascular injection, the contrast drug is filtered by the glomeruli in Bowman's capsule and then excreted with urine. Its high osmolality will create osmotic diuresis. The latter increases the delivery of sodium to Henle's loop, causing a rise in sodium reabsorption and consequently in O_2 consumption. The result will be more severe medullary hypoxia³⁶ (Figure 1).

Direct renal tubular cytotoxic effects

Iodinated contrast drugs have direct cytotoxic effects on endothelial cells and tubular epithelial cells that have been attributed to the free iodine in the solution of the contrast drug.⁵⁴ The damage to endothelial cells has been studied by scanning electron microscopy that allowed visualization of cell shrinkage, fenestration of the endothelial layer, and formation of microvilli (blebbing) on the cell membrane, nuclear protrusion, and cellular apoptosis.² Damaged and apoptotic endothelial cells reduce the release of NO in the medullary vasa recta.^{54,56,57}

Damage to epithelial tubular cells by contrast drugs is severe, because of the high concentration of these drugs in the tubular fluid due to important water reabsorption in the proximal tubules. Studies *in vitro* in isolated tubular segments of rat kidney and cultured cells have demonstrated a

disruption of cell integrity and apoptosis following treatment with contrast drugs.^{3,58,59} Heinrich et al³ studied the cytotoxic effects of different contrast drugs on renal tubular cells in vitro. They concluded that iomeprol (LOCM) and iodixanol (IOCM) were not different at equal iodine concentrations in their toxicity on renal proximal tubular epithelial cells in vitro.⁶⁰

Intracellular signaling pathways involved in cell survival and death

Important results have been obtained by in vitro studies on primary human tubular cells and on HK2 cells exposed to contrast drugs.⁶¹ Andreucci et al⁶² demonstrated reduced cell survival due to decreased activation of Akt and ERK1/2, which are kinases that are known to be involved in cell survival/proliferation; this was alleviated by transfecting the HK2 cells with a constitutively active form of Akt. Even a white grape (*Vitis vinifera*) juice extract may alleviate toxicity on human renal proximal tubular (HK2) cells treated with a contrast drug, through modulation of signaling molecules.⁶³ The same authors have given evidence that in human renal tubular cells, contrast drugs affect the activation/deactivation of: transcription factors like FoxO3a and STAT3, which control the genes that are involved in apoptosis and cell proliferation; and other molecules known to be modulated by oxidative stresses, with some differences having been noted between low-osmolar and iso-osmolar contrast drugs.^{64–69} Experimental animal studies performed in vivo and in vitro have suggested that iodinated contrast drugs can induce caspase-mediated apoptosis of tubular epithelial cells.⁵⁷ Activation of shock proteins and concurrent inhibition of cytoprotective enzymes and prostaglandins may also cause contrast drug-induced apoptosis.^{70,71}

Pathogenesis of CI-AKI

On the basis of what has been demonstrated (and reported herein) by clinical studies in humans, but mainly by experimental studies in vivo and in vitro, the complex mechanisms by which contrast drugs cause AKI are summarized in Figure 1.⁷²

Prevention of CI-AKI

Discontinuation of other nephrotoxic drugs

Nephrotoxic drugs, such as aminoglycosides, vancomycin, amphotericin B, metformin, and nonsteroidal anti-inflammatory drugs, should be discontinued in patients receiving contrast drugs. It should be noted that metformin (an

oral antihyperglycemic drug for treating type 2 diabetes) stimulates intestinal production of lactic acid, is excreted unchanged by the kidneys, is retained in AKI, and may cause severe lactic acidosis that can be fatal. It has to be discontinued 12 hours before the contrast drug and not resumed until at least 36 hours after the procedure.⁷³ With regard to angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs), according to many authors, patients with chronic renal failure under treatment with ACEIs or ARBs are at high risk of CI-AKI,^{74–80} particularly those of advanced age.⁸¹ According to KDIGO (Kidney Disease – Improving Global Outcomes) guidelines for the Acute Kidney Injury Work Group, there is insufficient evidence in favor of discontinuation of these drugs in patients undergoing injection of contrast drugs.⁸²

Choice of contrast drug

The first measure for prevention is the correct choice of contrast drug: a preference for IOCM has been suggested, since clinical studies have proven that the nephrotoxicity of iodixanol is lower than that of LOCM;⁸³ the lowest possible dose has to be used, and repetitive injection of the drug within the same procedure needs to be avoided. We should mention, however, that multiple meta-analyses of randomized clinical trials have failed to demonstrate differences between IOCM and LOCM.^{60,84} However, it has been pointed out that the relative renal safety of the low-osmolar iodixanol may vary with the different type of low-osmolar contrast agent, with a reduction in CI-AKI observed compared with iohexol/ioxaglate, but no difference noted when compared with iopromide/iopamidol/ioversol.⁸⁴

Intravenous volume expansion

Prevention is undoubtedly based on IV extracellular volume (ECV) expansion.^{5,83,85} This is obtained by IV infusion of 0.9% saline at an infusion rate of 1 mL/kg BW/hour that should begin 6–12 hours before the injection of the contrast drug and continue for up to 12–24 hours after the injection.⁸⁶ In patients undergoing cardiac catheterization, assessment of their volume status and left ventricular end-diastolic pressure-guided fluid administration has been shown to be useful in preventing CI-AKI without problems of excessive ECV expansion.⁸⁵

ECV expansion by IV infusion of saline has usually been considered more protective against CI-AKI than oral hydration.^{87,88} Trivedi et al⁸⁸ demonstrated in patients undergoing cardiac catheterization that the occurrence of CI-AKI 24 hours following contrast-drug injection was reduced in those

undergoing ECV expansion with IV normal saline than in those allowed only unrestricted oral fluid.

Surprisingly, a systematic review and meta-analysis of six randomized controlled trials involving 512 patients undergoing a contrast-enhanced procedure over 10 years, carried out by Hiremath et al⁸⁹ to compare oral versus IV ECV expansion demonstrated that oral hydration may be as effective as IV ECV expansion for CI-AKI. The rationale for IV saline infusion is based on the inhibition of reabsorption in the proximal tubules that is caused by ECV expansion, thereby increasing urine output; this will decrease the contact time of the contrast drug with the epithelial cells of the descending limb of Henle's loop, thereby reducing the toxic effects of the drug on these tubular cells.^{90,91} However, simple oral hydration through the inhibition of ADH will decrease water reabsorption in the collecting ducts, ie, distally to Henle's loop; and thus the protective effect on the epithelium of Henle's loop cannot take place.

Some authors have found better results with the use of sodium bicarbonate rather than sodium chloride.^{92–101} A procedure would be administration of a bolus of 3 mL/kg BW/hour for 1 hour of a solution of sodium bicarbonate 154 mEq/L before the injection of contrast drug, followed by 1 mL/kg/hour for 6 hours.⁹⁴ However, other authors have disagreed, since they did not find any better benefit with sodium bicarbonate.^{102–105}

The rationale for using sodium bicarbonate rather than sodium chloride is a further beneficial effect, in addition to ECV expansion: the increased urinary excretion of bicarbonate would decrease urine acidification, thereby reducing the production and increasing the neutralization of ROS.^{92,96,97,106,107} Attention should be paid when proceeding to ECV expansion that urine output is appropriate and the cardiovascular conditions allow it.⁸⁶ European Renal Best Practice¹⁰⁸ “recommends volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions, rather than no volume expansion, in patients at increased risk for CIN”. There is controversy on the usefulness of many therapeutic procedures to prevent CI-AKI: statins, *N*-acetylcysteine (NAC), furosemide, nebivolol, calcium channel blockers, theophylline, and hemodialysis.^{24,109,110}

Statins

Promising results have been obtained with the use of statins (HMG-CoA reductase inhibitors). Several clinical trials have demonstrated that statins protect patients undergoing coronary angiography against CI-AKI.^{87,111,112} Singh et al¹¹² have recently conducted a meta-analysis involving nine randomized controlled trials with 5,143 patients, 2,559 of

whom received statins and 2,584 placebo, all undergoing contrast-drug injection. All patients received standard ECV expansion, and in four studies NAC was added. Of the nine studies, six had patients with GFR <60 mL/min/1.73 m² and two excluded patients with GFR <70 mL/min/1.73 m². Results showed that statin pretreatment induced a significant reduction in risk of CI-AKI, demonstrating a protective effect of statins against CI-AKI in patients with normal renal function and in patients with impaired renal function (there was no significant difference in the degree of beneficial effect of statins on CI-AKI prevention between the two groups), and in patients cotreated with NAC. The authors concluded that statins (irrespective of the type of statin: simvastatin 40 mg, atorvastatin 80 mg, rosuvastatin 10 or 40 mg) have to be used to protect against CI-AKI in patients undergoing diagnostic or interventional procedures involving contrast drugs independently of the type of contrast drug used. Patti et al¹¹³ demonstrated that a short-term high dose of atorvastatin (80 mg, 12 hours before intervention followed by a further 40 mg preprocedure dose) decreased the incidence of CI-AKI in patients undergoing percutaneous coronary interventions.

What is the mechanism(s) of the protective effects of statins against the nephrotoxicity of contrast drugs? We have mentioned that contrast drugs directly constrict medullary descending vasa recta by 52%, reduce NO, and increase vasoconstrictor response to angiotensin II, and that endothelin, released by the damaged endothelial cells, contributes to medullary vasoconstriction and consequent hypoxia. According to Bonetti et al,¹¹⁴ statins decrease the vasoconstricting response to angiotensin and the synthesis of endothelin, thereby preventing renal hypoperfusion and medullary hypoxia. We have also mentioned that contrast drugs increase the incidence and severity of inflammation, with formation of ROS and proinflammatory cytokines, and complement activation. This leads proteins to precipitate, thereby causing tubular obstruction.¹¹⁵ Statins have antioxidant and anti-inflammatory properties and reduce endothelin secretion; these may be the mechanisms for CI-AKI prevention by statins.^{116,117}

Dashti-Khavidaki et al¹¹¹ published a review of all studies performed in vitro and in vivo evaluating the use of statins to prevent the nephrotoxicity of contrast drugs. They concluded that 1) chronic users of statins are less prone to CI-AKI compared with statin nonusers, 2) high doses of statins reduced the incidence of CI-AKI in statin nonusers, 3) the renoprotective effect of statins occurs in patients with normal kidney function or with mildly reduced renal function, and 4) the renoprotective effect of statins is not observed in patients with moderate-to-severe renal dysfunction.

In addition to their well known cholesterol-lowering activity, statins have pleiotropic effects: antioxidative, anti-inflammatory, and antithrombotic.^{118,119} They have been shown to have nephroprotective effects, eg, it has been demonstrated that they reduce ischemic–reperfusion renal injury in laboratory animals because of their antioxidant and anti-inflammatory activity.¹²⁰

N-acetylcysteine

The most widely used drug to prevent CI-AKI is NAC. As we have seen, an important role for ROS has been implicated in the nephrotoxicity caused by contrast drugs. Therefore, it has been suggested that antioxidants could be useful in preventing CI-AKI.⁸⁷ NAC would have a double-protective effect: in addition to its free radical-scavenger property, it may also increase the vasodilating effect of nitric oxide.^{48,121}

Brown et al¹²² conducted a meta-analysis to evaluate NAC in combination with sodium bicarbonate (NaHCO_3) for the prevention of CI-AKI. They concluded that combination prophylaxis with NAC and NaHCO_3 reduced the occurrence of CI-AKI. According to Chousterman et al,¹²³ however, the incidence of CI-AKI does not seem to be influenced by NAC, except if small changes in creatinine only are considered. Also, Alioglu et al¹²⁴ studied 113 patients (49 patients in an NAC group and 64 patients in a control group) with normal-to-subnormal GFR undergoing cardiovascular procedures. Patients in the NAC group received 600 mg NAC twice a day (on the day before and on the day of the cardiovascular procedure). They concluded that oral NAC administration did not reduce the incidence of cystatin C-based CI-AKI or serum creatinine-based CI-AKI in patients undergoing cardiovascular procedures.

A meta-analysis performed by Gonzales et al¹²⁵ did not support the efficacy of NAC to prevent CIN, and showed that those trials supporting a beneficial effect of NAC were due to an effect on serum creatinine independent of true changes in GFR. Many other meta-analyses have been published since 2003 with conflicting results.⁸⁷ An experimental study on human embryonic kidney cells demonstrated that contrast drugs (ionic HOCM ioxithalamate, nonionic LOCM iopromide, and IOCM iodixanol) caused a reduction in cell viability at 24 hours; pretreatment with NAC improved cell survival.¹²⁶ NAC may be given as an oral dose of 600 mg twice daily (day before and day of the procedure) or an IV dose of 150 mg/kg half an hour before the procedure or 50 mg/kg administered for 4 hours.¹²⁷

Furosemide

The use of the diuretic furosemide has been suggested for protecting the kidney against contrast drugs, based on its effects in reducing active tubular reabsorption (thereby reducing

O_2 consumption and medullary hypoxia) and in increasing urine output (thereby decreasing the contact time of contrast drugs with the tubular epithelium and consequently reducing epithelial damage). To prevent salt depletion, adequate fluid replacement is necessary. Marenzi et al¹²⁸ suggested delivery of IV fluid at an amount exactly matched to the volume of urine produced by the patient under the effect of furosemide. This procedure is performed easily by RenalGuard®, a special device that would guide the physician in achieving high urine output without hypovolemia.¹²⁹ With the help of RenalGuard®, in fact, physicians can deliver IV fluid at an amount exactly matched to the volume of urine produced by the patient under the effect of furosemide.

Nebivolol

A β_1 -adrenergic receptor antagonist, nebivolol (5 mg/day for 1 week or 5 mg every 24 hours for 4 days) has been proven in patients with renal dysfunction undergoing coronary angiography to protect against CI-AKI, possibly acting via its antioxidant properties and NO-mediated vasodilating action.^{130–134}

Calcium-channel blockers

Calcium-channel blockers have been suggested to have protective effects against CI-AKI. The rationale is based on the fact that while in normal subjects, the Na^+ – Ca^{2+} exchanger pumps Ca^{2+} outside the renal tubular epithelial cells to keep intracellular Ca^{2+} low, under the effect of contrast drugs the Na^+ – Ca^{2+} exchanger can reversibly extrude Na^+ for Ca^{2+} influx, thereby leading to intracellular Ca^{2+} overload, which is considered a key factor in ischemic cell injury and in CI-AKI.^{135–137} (Figure 1). Conflicting results have been obtained with calcium-channel blockers. Some authors have found a protective effect,^{138–140} while others have not.^{140–142}

Theophylline and aminophylline

After contrast-drug injection, there is an increase in urinary adenosine. Therefore, the adenosine antagonists theophylline and aminophylline were expected to have protective effects against contrast drugs. However, results have been conflicting: some articles were in favor,^{42,43,143,144} others not.^{44,45}

Hemodialysis

It has been demonstrated that in patients with chronic renal failure, different types of hemodialysis may remove contrast drugs from the blood, and that high-flux hemodialysis and hemodiafiltration do it more effectively than low-flux hemodialysis or hemofiltration.¹⁴⁵ However, prophylactic hemodialysis in patients with reduced renal function does not

diminish the incidence of CI-AKI.^{109,146,147} European Renal Best Practice¹⁰⁸ does “not recommend using prophylactic intermittent hemodialysis or hemofiltration for the purpose of prevention of CI-AKI”.

Risk-estimation equations to predict risk of CI-AKI

Risk assessment of CI-AKI before percutaneous coronary intervention is important, since it would allow prophylactic measures.¹⁴⁸ Undoubtedly, many risk factors for CI-AKI have been identified. These include diabetes, renal function impairment (particularly in diabetic patients), salt depletion and dehydration, congestive heart failure, age ≥ 70 years, and concurrent use of nephrotoxic drugs.^{5,109} However, the cumulative risk of their combination is unknown. That is why Mehran et al¹⁴⁹ developed a risk score for CI-AKI after percutaneous coronary intervention.

Many tools to predict the risk of CI-AKI have been reported in the literature. No consensus, however, exists on the best and most effective ones.¹⁵⁰ After reviewing the literature on the scoring tools used to predict the risk of CI-AKI, Raingruber et al¹⁵¹ selected the Mehran risk-scoring tool, which they judged the most comprehensive, reliable, and well tested. Mehran et al¹⁴⁹ compared 4,989 patients with a control group of 2,786 patients. Multivariate logistic regression was used to identify independent predictors of CI-AKI with $P < 0.0001$. Factors used to determine the risk score were hypotension (< 80 mmHg, requiring inotropic support with medications), use of an intra-aortic balloon pump, congestive heart failure, history of pulmonary edema, chronic kidney disease, diabetes mellitus, age > 75 years, anemia, and volume of contrast medium. These variables were assigned a weighted integer; the sum of the integers was a total risk score for each patient.

Bartholomew et al¹⁵² studied 20,479 patients who had undergone percutaneous coronary intervention. Their weighted-score variables were: creatinine clearance ≤ 60 mL/min (two scores), urgent percutaneous coronary intervention (two scores), intra-aortic balloon-pump use (two scores), diabetes mellitus (one score), congestive heart failure (one score), hypertension (one score), peripheral vascular disease (one score), and volume of contrast medium ≥ 260 mL (one score). The incidence of CI-AKI after percutaneous coronary intervention increased with each unit increase in score ($P < 0.0001$). With a score ≤ 1 , there was no CI-AKI after percutaneous coronary intervention. About 26% of patients with scores ≥ 9 developed CI-AKI after percutaneous coronary intervention ($P < 0.0001$).

Maioli et al¹⁵³ developed a simplified scoring system to predict CI-AKI before elective coronary angiography

and percutaneous coronary intervention. Their weighted-score variables were: age ≥ 73 years (one score), diabetes mellitus (two scores), left ventricular ejection fraction $\leq 45\%$ (two scores), baseline serum creatinine ≥ 1.5 mg/dL (two scores), baseline creatinine clearance ≤ 44 mL/min (two scores), posthydration serum creatinine $\geq$ prehydration serum creatinine (two scores), and one procedure effected within the past 72 hours (three scores). A kidney-failure-risk equation (eight variables) is available on the website https://www.qxmd.com/calculate/calculator_125/kidney-failure-risk-equation-8-variable.

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Disclosure

The authors report no conflicts of interest in this work.

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