European Journal of Radiology 116 (2019) 231–241

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Review

Nephrotoxicity of iodinated contrast media: From pathophysiology to prevention strategies

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ARTICLE INFO

Keywords:
Acute kidney injury
Contrast-induced nephropathy
Iodinated contrast media

ABSTRACT

Iodinated contrast media (ICM) induced acute kidney injury (AKI) accounts for 11% of cases of AKI and is its third most common cause in hospitalized patients. However, the pathophysiological mechanisms are not yet completely understood. The nephrotoxicity of ICM is partly the consequence of a direct cytotoxic effect on renal tubular epithelial and endothelial cells. It is also the consequence of impaired intrarenal hemodynamics, these two mechanisms being closely linked. The rheological properties of ICM, the volume infused, and the route of administration increase the intrinsic toxicity generated by the contrast media used. Furthermore, various clinical situations increase the risk of developing AKI. There is no specific treatment. Hydration is the cornerstone of prevention. Preventive measures have reduced the incidence of AKI over the last ten years. After an overview of the pathophysiology of the renal toxicity of ICM, we review risk factors and scores, diagnosis, and means of prevention in the light of the 2018 European Society of Urogenital Radiology and the 2018 American College of Radiology guidelines and recent studies on the subject. In addition, a side-by-side comparison of the updated and less conservative guidelines from the Radiology community and the more cautionary attitude from the Nephrology community are also presented.

1. Introduction

Iodinated contrast media (ICM) are nephrotoxic and can cause acute kidney injury (AKI) or be responsible for the worsening of chronic kidney disease (CKD). There is no consensus on the definition of iodinated contrast media-induced AKI. In accordance with the European Society of Urogenital Radiology (ESUR), the definition widely used in both interventional and observational studies is an increase in serum creatinine by 44 µmol/L or by a more than 25% increase from baseline, occurring in the 72 h following the injection of ICM, in the absence of another cause for renal failure [1].

ICM-induced AKI is the third most common cause of acute renal failure in hospitalized patients, after renal hypoperfusion and medications [2]. It accounts for 11% of the causes of AKI. The introduction of preventive measures has reduced its incidence over the last 10 years, from 15 to 7% [3]. Its incidence is currently estimated at between 3.3 and 10.5% [4–6], and up to 10–20% or even 50% in high risk patients [7], depending on the definition used. Even if the outcome of AKI is often favorable, it is well known that AKI *per se* is an independent risk factor for CKD [3,8,9], cardiovascular events and mortality [9–11]. Resorting to dialysis remains rare in the general population (< 1%) [3,12], but can reach 7% in case of pre-existing CKD [13]. The increased risk of mortality persists over one to five years, especially in patients on hemodialysis therapy [14].

After an initial section on the pathophysiology of renal ICM toxicity, this review will successively discuss risk factors and scores, diagnosis, and means of prevention in the light of recent guideline updates and recent studies in this field.

Abbreviations: ACR, American College of Radiology; AKI, acute kidney injury; CKD, chronic kidney disease; ERBP, European Renal Best Practice; ESUR, European Society of Urogenital Radiology; GFR, glomerular filtration rate; ICM, iodinated contrast media; KDIGO, Kidney Disease: Improving Global Outcomes; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; NO, nitric oxide; ROS, reactive oxygen species; TAL, thick ascending limb of the loop of Henle

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https://doi.org/10.1016/j.ejrad.2019.03.008
Received 2 January 2019; Received in revised form 9 March 2019; Accepted 12 March 2019

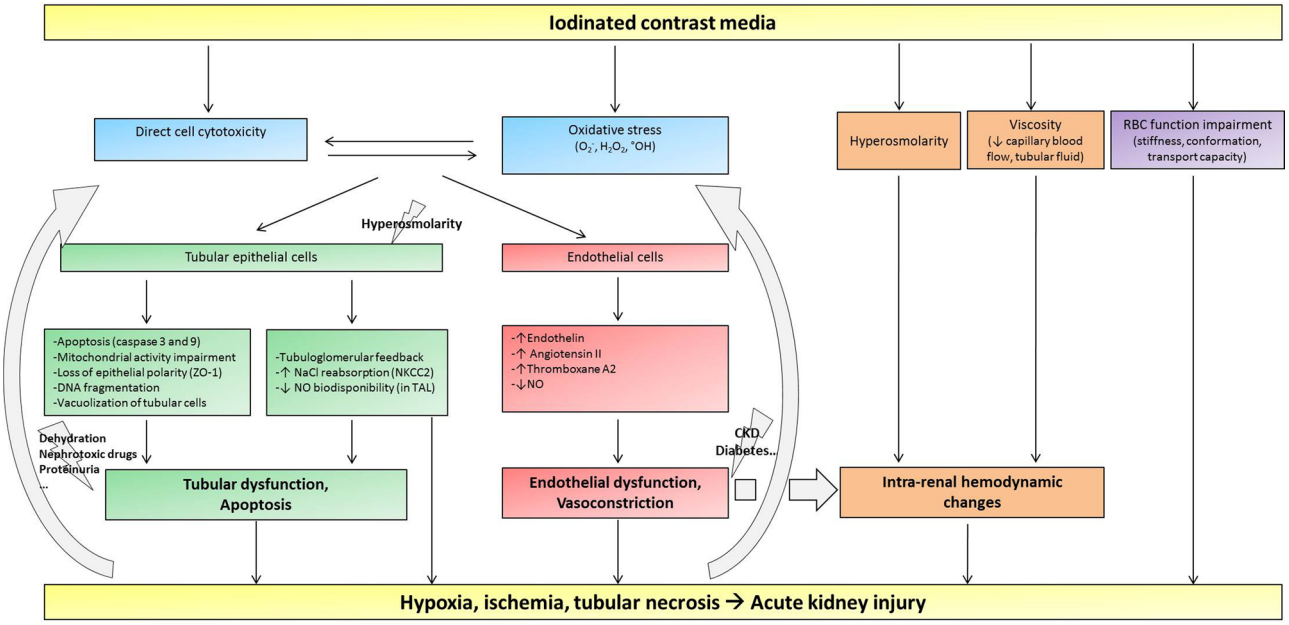

Fig. 1. Pathophysiology of renal damage associated with the administration of iodinated contrast media. ZO-1: Zonula occludens-1, TAL: Thick ascending limb of the loop of Henle, NKCC2: Na-K-Cl cotransporter, NO: nitric oxide, CKD: chronic kidney disease, RBC: red blood cell.

2. Pathophysiology

ICM-induced AKI occurs rapidly after the administration of radiopaque media, with an increase in serum creatinine concentration detectable after 48 h; it reaches a maximum after three to five days, and usually returns to its baseline value around the tenth day (range, one to three weeks) [15,16].

Renal involvement related to ICM consists of tubular injury (Fig. 1). Renal toxicity of ICM is partly the consequence of a direct, intrinsic cytotoxic effect on renal tubular epithelial and endothelial cells. It is also the consequence of an impairment of intrarenal hemodynamics, these two mechanisms being closely linked. High ICM osmolality, viscosity, and volume as well as route of administration (intra-arterial *versus* intravenous) increase the intrinsic toxicity generated by the contrast agent used [16,17].

2.1. Tubular epithelial and endothelial cytotoxicity of ICM

ICM are tri-iodinated benzene derivatives. “Iodine”, in its ionic (I^-), molecular (I_2), or hydrated H_2OI^+ form is an antiseptic agent capable of lysing bacterial walls due to its oxidizing power.

The iodine contained in ICM has a direct toxic effect on human cells, and in particular on renal tubular epithelial cells (vacuolization of tubular cells and osmotic nephrosis) and on endothelial cells. The exact pathophysiological mechanism of this cytotoxicity remains unknown. Several mechanisms may be involved (Fig. 1). ICM could act by directly stimulating the signaling pathways involved in apoptosis *via* an activation of caspases-3 and 9 and the bcl2 pathway [18], and by disrupting mitochondrial activity [19], independently of oxidative and hypoxic stress and of physicochemical properties of ICM [20].

Furthermore, by their strong oxidizing power, ICM stimulate the synthesis of reactive oxygen species (ROS) that are toxic to endothelial and tubular epithelial cells, among others. ROS stimulate the JNK/p38 signaling pathway involved in the activation of apoptosis intrinsic pathway [21]. However, according to Liu et al, the increase in ROS synthesis appears to be more a consequence of direct ICM toxicity on tubular cells than the cause of cellular damage [22]. Thus, ROS would only accentuate the cell damage caused by the administration of ICM.

Finally, hyperosmolality increases the intrinsic toxicity of ICM. *In vitro*, the osmolar power of ICM has been shown to exert a toxic effect on tight junction proteins [23,24], and ICM hypertonicity also induces DNA fragmentation and tubular cell apoptosis [25].

2.2. Impairment of intra-renal hemodynamics

ROS induce an increase in the synthesis of endothelin, angiotensin II, adenosine and thromboxane A2, and a reduction in the synthesis of nitric oxide (NO). The *vasa recta*, peritubular capillaries and glomerular capillaries acquire a “vasoconstriction” phenotype [26], causing endothelial cell dysfunction, which can be accentuated in case of pre-existing endothelial dysfunction (CKD, diabetes). Endothelial cells then become very sensitive to angiotensin II. Furthermore, after ICM injection the increase in ROS synthesis (in particular O_2^-), induces an increase in tubuloglomerular feedback in the distal convoluted tubule, increasing renal hypoperfusion [22]. Superoxide anion (O_2^-) also reduces the bioavailability of NO in the thick ascending limb of the loop of Henle (TAL) [27] and stimulates the reabsorption of NaCl in this tubular segment [28–30]. TALs located in the outer medulla are sensitive to hypoxia, as in the basal state tubular reabsorption of sodium, the initial passage of blood into the cortex, and the *vasa recta*-TAL distance (“physiological” shunt effect) create a situation of relative renal parenchymal hypoxia [31,32]. Consequently, owing to the ICM-induced increase in tubular sodium reabsorption the kidney's oxygen requirement rapidly becomes much higher than oxygen supply, thus worsening the pre-existing state of renal tubular hypoxia.

In addition, ICM hyperviscosity further impairs glomerular hemodynamics by inducing a reduction of blood flow in both glomerular and tubular capillaries, and by slowing the flow of tubular fluid, thereby increasing contact time with ICM and their cytotoxicity. In addition, owing to negligible or no tubular reabsorption, ICM concentration rises progressively on its way through the tubular segments, to become highly concentrated in the medullary part of the distal nephron. The tubular concentration process enhances fluid viscosity in an exponential manner [33].

Finally, hypoperfusion of the medulla is further enhanced by changes in red blood cell structure and function including dessicocyte and echinocyte formation, enhanced rigidity, and diminished O_2 transport capacity induced by the ICM itself [34].

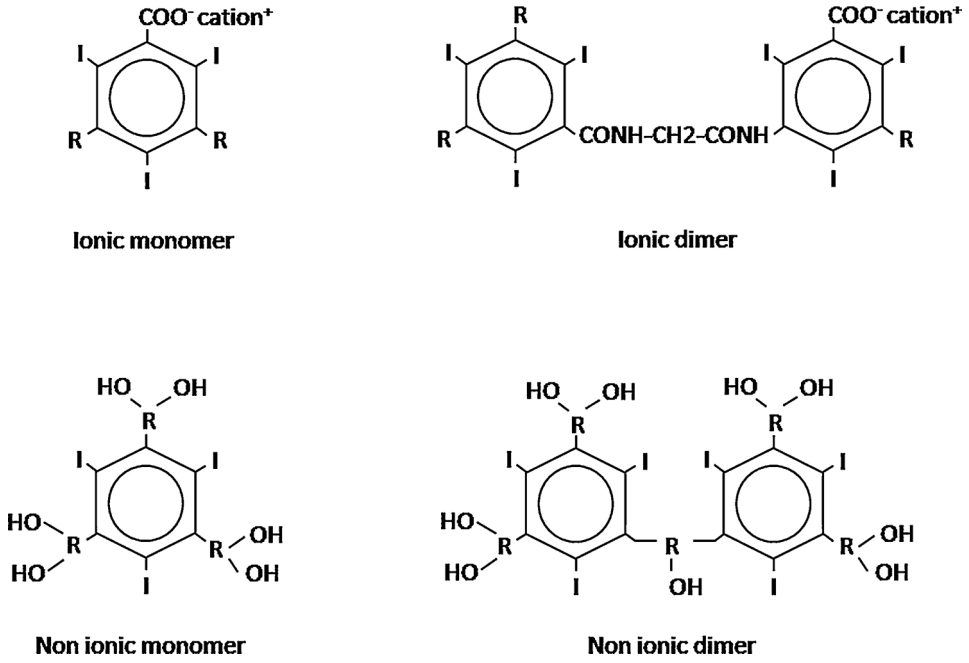

Fig. 2. Iodinated contrast media are tri-iodinated benzene derivatives. Four families of iodinated contrast media: tri-iodinated ionic monomer, tri-iodinated nonionic monomer, hexa-iodinated ionic dimer, hexa-iodinated nonionic dimer. The cation can be a sodium ion or meglumine.

The result is an impairment of intra-renal hemodynamics, hypoxia, ischemia, and eventually tubular cell necrosis, leading to an increased synthesis of pro-inflammatory cytokines and ROS and thus creating a vicious circle. Being very sensitive to hypoxia, the renal medulla with its physiological partial pressure of O_2 of only 10–30 mmHg [35], is the region of the kidney which is most severely affected by the oxidative and ischemic changes induced by ICM.

3. Towards a reduction in the nephrotoxicity of iodinated contrast media

ICM are tri-iodinated benzene derivatives (Fig. 2). Their synthesis consists of the fixation of 3 radiopaque iodine atoms onto hydrosoluble carbon atoms (benzene ring) [24]. As mentioned above, the physical and rheological properties of ICM (osmolality and viscosity) increase their intrinsic cytotoxicity. In the 1950s, the first ICM used were ionic tri-iodinated monomers, that is, combined with a cation (sodium and/or meglumine). In solution, the ICM separates into two particles: the benzene ring and the cation, which doubles their osmolality. To reach a sufficient quantity of iodine for radiological opacification (around 300 mg of iodine/ml), the osmolality of the ICM has to be 5–6 times higher than that of plasma (1,530 to 1,860 mOsmol/kg H_2O), thus considerably increasing their toxicity. From the 1970s, the osmolality of ICM has been reduced either by duplicating the ionic monomer (dimerization), or by substituting the acid function of the benzene ring for an amide function (Fig. 2). In the first case, obtaining a hexa-iodinated ionic dimer enables an increase in the iodine concentration while reducing the osmolality of the ICM. In the second case, as the substitution of the acid function for an amide function (tri-iodinated nonionic monomers) does not require the addition of a cation, the osmolality of the solution is reduced. Modification of the chemical structure of ICM made it possible to reduce their osmolality to 600 mOsmol/kg H_2O. Since 1980, another approach has been developed for obtaining osmolality close to that of plasma (290 mOsmol/kg H_2O), by creating hexa-iodinated nonionic dimers. Four families of ICM are currently marketed: ionic monomers and dimers, and nonionic monomers and dimers (Table 1, Fig. 2) [36]. While low osmolality ICM are associated with a lower risk of AKI than ICM with a higher osmolality [37], the results of studies comparing low osmolality ICM and iso-osmolar ICM remain controversial [38–41].

4. Risk factors for acute kidney injury

The most significant risk factor is pre-existing CKD [42]. There is a strong correlation between the risk of ICM-induced AKI and the degree of kidney disease. Other factors such as diabetes, age, dehydration, proteinuria, or nephrotoxic medication also increase the risk of AKI [42,43] (Table 2). ICM with high osmolality, high viscosity, repeated ICM injection within a short interval (48–72 h) [44], and intra-arterial administration represent further risk factors for AKI. In the case of intra-arterial injection, the ICM dose used is often higher, and its renal intravascular concentration is higher, increasing the risk of AKI [1,42,45]. However, retrospective studies reported a similar risk of AKI in patients who underwent either route of administration [46,47]. The injected volume of ICM is another risk factor that must be taken into account. Although there is no threshold dose, the risk of kidney failure has been shown to double with every 20 ml increase of ICM [17]. According to Laskey et al., an ICM volume to creatinine clearance ratio greater than 3.7 is an independent predictive factor for an increase in serum creatinine following ICM injection, in any population [48]. Furthermore, Nyman et al. showed that a ratio < 1 of iodine quantity (g) / estimated glomerular filtration rate (eGFR, ml/min/1.73m^2 using MDRD equation) was associated with a 3% risk of AKI, as compared to a 25% risk with an iodine quantity / eGFR MDRD ratio ≥ 1 [49]. All these factors potentially combine to increase the risk of AKI.

In the 2018-ESUR guidelines, the traditional non-renal risk factors are now considered as non-specific for post-contrast AKI. In addition, compared to the previous guidelines, intra-arterial route was split in first and second pass renal exposure, *i.e.* when ICM reaches the renal arteries in either undiluted or diluted form. This distinction led to a decrease in GFR threshold as a risk factor for AKI to < 45 ml/min/1.73m^2 before intra-arterial ICM administration with first pass renal exposure, and to < 30 ml/min/1.73m^2 before intravenous injection or intra-arterial injection with second pass renal exposure [42]. However, these new, less conservative recommendations need to be debated and validated (or not) by the Nephrology community.

Can the risk of ICM-induced nephropathy be precisely predicted? In 2004, Merhan et al. developed a risk stratification scoring system for

Table 1
Classification of intravascular iodinated contrast media. According to the *American College of Radiology, Manual on contrast media, version 10.3, 2018* [36].

		International non-proprietary name (mg contrast/ml)	Commercial name	Concentration of iodine (mg/ml)	Osmolality (mOsm/kg H_2O)	Viscosity 37°C (mPa.s)
High osmolality 1000 - 2000 mOsmol/kg H_2O	Tri-iodinated ionic monomers	Diatrizoate 760	MD-76	370	1551	10.5
		Iothalamate 600	Conray	282	1400	4
		Iothalamate 430	Conray 43	202	1000	2
Low osmolality 300 – 800 mOsmol/kg H_2O	Tri-iodinated ionic monomers	Iothalamate 300	Conray 30	141	600	1.5
	Hexa-iodinated ionic dimers	Iodipamide 520	Cholografin	257	664	5.6
		Ioxaglate 589	Hexabrix	320	≈ 600	7.5
	Tri-iodinated nonionic monomers	Iopamidol 755	Isovue 370	370	796	9.4
		Iopamidol 612	Isovue 300	300	616	4.7
		Iopamidol 510	Isovue 250	250	524	3.0
		Iopamidol 408	Isovue 200	200	413	2.0
		Iohexol 755	Omnipaque 350	350	844	10.4
		Iohexol 647	Omnipaque 300	300	672	6.3
		Iohexol 518	Omnipaque 240	240	520	3.4
		Iohexol 388	Omnipaque 180	180	408	2.0
		Iohexol 302	Omnipaque 140	140	322	1.5
		Ioxilan 727	Oxilan 350	350	721	8.1
		Ioxilan 623	Oxilan 300	300	610	5.1
		Ioversol 740	Optiray 350	350	792	9.0
		Ioversol 680	Optiray 320	320	702	5.8
		Ioversol 640	Optiray 300	300	651	5.5
		Ioversol 509	Optiray 240	240	502	3.0
		iopromide	Ultravist 370	370	774	10.0
		iopromide	Ultravist 300	300	607	4.9
		iopromide	Ultravist 240	240	483	2.8
		iopromide	Ultravist 150	150	328	1.5
Iso-osmolality 290 mOsmol/kg H_2O	Hexa-iodinated nonionic dimers	Iodixanol 652	Visipaque 320	320	290	11.8
		Iodixanol 550	Visipaque 270	270	290	6.3

Table 2
Risk factors for nephrotoxicity associated with the administration of iodinated contrast media.

Patient related risk factors
Preexisting chronic kidney disease
Diabetes mellitus
Old age
Dehydration / hypovolemia: sepsis, diuretic treatment, low cardiac output…
Hemodynamic instability
Proteinuria
Myeloma
Anemia
Low serum albumin concentration (< 35 g/L)
Iodinated contrast media related risk factors
Intra-arterial injection
High osmolality
High viscosity
Injected volume > 100 ml
Multiple injections, short time between injections (< 72 h)
Nephrotoxic drugs
Non steroid anti-inflammatory drugs
Aminoglycoside antibiotics
Calcineurin inhibitors…

Table 3
Mehran risk score. SBP: systolic blood pressure. *NYHA: New York Heart Association functional classification, and/or history of pulmonary edema. Ht: hematocrit, eGFR: estimated Glomerular Filtration Rate. According to *Mehran et al. J Am Coll Cardiol, 2004* [50].

Risk factors	Score
Hypotension (SBP < 80 mmHg)	5
Intra-aortic balloon pump	5
Congestive heart failure (NYHA III or IV)*	5
Age > 75 years	4
Anemia (Ht< 39% in man ; < 36% in woman)	3
Diabetes	3
Volume of injected contrast media	1 for each 100 mL
Serum creatinine concentration> 1.5 mg/dL OR eGFR < 60 mL/min/1.73m²	4 2 if eGFR = 40-60 4 if eGFR = 20-40 6 if eGFR < 20

	Risk score	Risk of contrast induced nephropathy	Risk of dialysis
Low	≤ 5	7.5 %	0.04 %
Moderate	6 – 10	14%	0.12 %
High	11 – 15	26.1%	1.09 %
Very high	≥ 16	57.3%	12.6 %

intra-arterial injections of ICM, based on 8 variables (Table 3) [50]. According to this study, if the score is ≤5, the incidence of nephropathy is 7.5%, that of dialysis 0.04%, and that of and mortality at one year 1.9% after intra-arterial injection of ICM. On the other hand, for a score greater than 16, estimated risks are 57.3%, 12.6% and 31.2% respectively. However, the score does not take into account the existence of proteinuria, use of nephrotoxic medications, presence or absence of prior hydration, or serum creatinine 48 h later. Prediction models using statistical tools such as a propensity score, also appear to be unable to predict the risk of ICM-induced nephropathy, and sometimes lead to unexpected findings [51,52]. Out of the 12 scores and prediction models studied by Silver et al., none appeared to be able to precisely evaluate or predict the risk of ICM-induced nephropathy in the context of coronary angiography [53]. In addition, no risk prediction scores are available for CT-scan. Nevertheless, all patients receiving ICM should be evaluated for the risk of AKI. According to the 2018-American College of Radiology (ACR) guidelines, patients with one of the following risk factors, age > 60 years, history of renal disease (dialysis, kidney transplant, single kidney, renal cancer, renal surgery), history of hypertension requiring medical therapy, history of diabetes mellitus, and metformin treatment, do require a baseline serum creatinine determination before ICM injection [36].

5. Diagnosis

"ICM-induced AKI" should be distinguished from "post contrast-induced AKI" [36,42]. The term "ICM-induced" should be used to describe only AKI caused by the ICM *per se*, thus being a causal diagnosis. Conversely, the term "post contrast-induced" should be used for deteriorations of kidney function following ICM injection, without evidence of direct renal toxicity. It can be induced by many other causes, for instance hemodynamic instability or cholesterol embolism. However, causal diagnosis of AKI is sometimes misinterpreted and wrongly attributed to the ICM. ICM-induced AKI occurs rapidly after administration of the radiopaque media, resulting in acute tubular necrosis. Currently, there is no consensus on the definition of ICM-induced AKI. The definition generally used is an increase in serum creatinine concentration by 44 µmol/l (0.5 mg/dl) or by more than 25% compared to baseline, within 72 h following the ICM injection, in the absence of other identified AKI causes [1]. The recently updated ESUR guidelines recommend using the Kidney Disease Improving Global Outcomes (KDIGO) defined stage 1 classification of AKI: an increase in serum creatinine ≥ 26.5 µmol/l (0.3 mg/dl), or ≥ 1.5–1.9 times baseline [54], within 48–72 h following ICM administration [42]. Use of serum creatinine as a diagnostic marker has certain limitations [55]. Serum creatinine reflects GFR impairment but is not a marker for renal "injury" (in the way that troponin is a marker for cardiomyocytes injury). Furthermore, serum creatinine concentration increases late and remains insensitive, especially when renal function is normal at baseline (the creatinine/GFR relationship is an inverse hyperbolic curve). Other biomarkers such as cystatin-C, neutrophil gelatinase-associated lipocalin (NGAL) or kidney injury molecule-1 (KIM-1), which are early markers for renal tubular dysfunction, appear to be more sensitive and specific in establishing the diagnosis of AKI [56,57]. Cystatin-C would be a more sensitive biomarker than creatinine for detecting rapid variations in GFR [58,59], enabling an earlier diagnosis of AKI [56,60]. It would also be a predictive marker for the occurrence of serious adverse events in patients with CKD after ICM injection [56,61]. In addition, an increase in KIM-1 and NGAL levels are respectively associated with proximal [56,62], and distal tubular damage [63]. Finally, as impairment of intra-renal hemodynamics and hypoxia are pivotal element in pathophysiology, functional imaging techniques (such as blood oxygen level-dependent magnetic resonance imaging, BOLD-MRI) develop as diagnostic tools to assess renal hemodynamics and oxygenation [64]. These different approaches are not yet routinely used.

6. Treatment and prevention

There is no specific treatment for ICM-induced acute tubular necrosis. Symptomatic treatment is based on the maintenance or restoration of a correct state of hydration and discontinuation of nephrotoxic drugs. Even if hemodialysis and hemofiltration can remove ICM [65], prophylactic hemodialysis has not been shown to be beneficial either on the incidence of AKI, on renal outcome, or on morbidity and mortality [66,67], and is not recommended by KDIGO [54], European Renal Best Practice (ERBP) [68], or ESUR guidelines [69,70]. However, it could have a place in case of volume overload or hyperkalemia, that are refractory to medical treatment.

The best approach to limit ICM-induced renal toxicity is still prevention. It is based on discontinuing nephrotoxic drugs (NSAIDs…) 48 h before the examination, maintaining sufficient hydration (stopping diuretics 48 h before), removal of conditions causing an increase in plasma osmolality (hyperglycemia, intravenous immunoglobulin), screening for at-risk patients, and finally, avoiding ICM injection if possible, or considering an alternative imaging method such as MRI or ultrasound, especially when renal function is impaired (Table 4). If ICM injection cannot be avoided, ICM with low osmolality and low viscosity should be preferentially used (Table 1). However, the "ideal" ICM remains to be determined, as the lower the osmolality of ICM, the higher is its viscosity [17]. Finally, the volume of ICM administered should be as low as possible. It should not exceed three times the value of GFR, in milliliters (using ICM 350 mg iodine/ml) [42].

6.1. Hydration

Hydration is the cornerstone of preventive treatment [71]. Hydration enables a reduction in the tubular concentration of ICM and its viscosity, a less marked stimulation of the renin-angiotensin-aldosterone system, inhibition of antidiuretic hormone synthesis, and minimization of the reduction of NO and prostacyclin synthesis [72], thus reducing kidney hypoperfusion and medullary hypoxia. Diuretics should be stopped 48 h before the examination. Recommended methods of hydration vary. In the majority of cases, oral intake of water and NaCl for 48 h is sufficient. However, in at-risk patients, oral hydration should be reinforced and supplemented with intravenous administration of NaCl (Table 4). Oral water intake, by suppressing vasopressin release, leads to a rapid increase in diuresis and provides rapid short-term renal protection. Conversely, the renal response to intravenous administration of isotonic saline is delayed – as saline loading suppresses the renin-angiotensin-aldosterone system – but offers long-lasting renal protection. Intravenous NaCl 0.9% or sodium bicarbonate 1.4% can be used and must be started hours before exposure to ICM. In addition to its effect on volemia, sodium bicarbonate reduces ROS synthesis [73]. However, the results of studies comparing sodium bicarbonate with NaCl remain controversial [74]. In 2013, Weisbord et al. examined the 17 clinical trials and 12 meta-analyses on the subject. The small number of people included, the heterogeneity of inclusion criteria and hydration protocols, the use of surrogate primary endpoints, the absence of long-term follow-up, as well as study heterogeneity and publication bias did not enable a firm conclusion to be drawn regarding a potential superiority of bicarbonate *versus* NaCl [74].

In 2017, the Dutch monocentric open-label randomized trial AMACING, conducted between 2014 and 2016, showed that the absence of prophylaxis was non-inferior to intravenous hydration with NaCl (the absolute difference in incidence was -0.1% (one-sided 95% confidence interval: [-2.25;2.06]; one-tailed p = 0.471), in preventing the risk of occurrence of contrast-induced nephropathy, among 660 ambulatory patients with CKD stage 3 [75]. However, these results should be interpreted with caution. First, they may not apply to hospitalized patients or patients referred for an emergent procedure. Second, it is well known that the current definition of CKD is very sensitive, but poorly specific, resulting in inclusion of a broad range of CKD severity (from renal senescence to "true" renal disease, *i.e.* from a relative low-risk to a very high-risk profile). In this study patients' mean age was 72 years and mean baseline serum creatinine 118 µmol/l, suggesting that renal "senescence" was the primary driver of CKD diagnosis and may not reflect "true" intrinsic renal disease. Third, the mean administered volume of ICM was lower (90.5 ml) than three times the mean baseline GFR of 47 ml/min/1.73m^2, and only < 16% of patients were referred for an interventional procedure. Finally, the observed event rate in these intermediate-risk patients was lower (2.6–2.7%) than that previously reported in the literature.

Very recently, the large prospective PRESERVE trial randomly assigned 5177 patients at risk for renal complications (median eGFR, 50 ml/min/1.73m^2) to receive intravenous NaCl or sodium bicarbonate solution, and oral N-acetylcysteine or placebo, in a 2 × 2 factorial design [76]. In this well conducted and sufficiently powered clinical trial using a relevant primary outcome of major adverse kidney events (MAKE), *i.e.* a composite end-point including death, dialysis or a persistent decline in GFR at 90 days, there was no benefit of sodium bicarbonate over NaCl or of N-acetylcysteine over placebo. However, this study included low to moderate-risk patients (according to Mehran score), and whether this result would extend to high-risk patients, the use of higher doses of ICM (*i.e.* complex intervention procedures), or intravenous ICM administration remains unclear.

Table 4
Comparison of European Society of Urogenital Radiology (ESUR), American College of radiology (ACR), European renal Best Practice (ERBP) and Kidney Disease Improving Global Outcomes (KDIGO) guidelines. AKI: acute kidney injury; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ICM: iodinated contrast media; i.a: intra-arterial route; i.v: intra-venous route.

	European Society of Urogenital Radiology 2018	American College of Radiology 2018	European Renal Best Practice 2012	Kidney Disease Improving Global Outcomes 2012
Screening				
	Either in all patients, or in patients who have a history of renal disease (eGFR < 60 ml/min/1.73m2), kidney surgery, proteinuria, hypertension, hyperuricemia or diabetes mellitus.	Age > 60, history of renal disease (dialysis, kidney transplant, single kidney, renal cancer, renal surgery), history of hypertension requiring medical therapy, history of diabetes mellitus, metformin.	Patients have to be stratified for risk of AKI according to their susceptibilities, especially preexisting proteinuria and CKD.	Assess the risk for CI-AKI (in particular, screen for pre-existing impairment of kidney function) in all patients.
Patient-related risk factor				
Renal risk factors	- eGFR < 45 ml/min/1.73m2 before i.a. ICM administration with 1st pass renal exposure or in ICU patients. - eGFR < 30 ml/min/1.73m2 before i.v. ICM or i.a. ICM administration with 2nd pass renal exposure. - Known or suspected acute renal failure	eGFR < 30 ml / min/1.73m2 seems to be the threshold with the greatest level of evidence.	Precautions to reduce the risk should be implemented in patients with a baseline eGFR < 60 ml/min/1.73m^2. This threshold could probably be < 45 ml/min/1.73m^2).	Precautions to reduce the risk should be implemented in patients with a baseline eGFR < 60 ml/min/1.73m^2. This threshold could probably be < 45 ml/min/1.73m^2).
Non-renal risk factors	Non-renal risk factors are risk factors for the presence of CKD or AKI, and are not specific for post-contrast AKI	Multiple other non-renal risk factors have not been rigorously confirmed.	- Diabetes - Dehydration - Nephrotoxic medications	- Diabetes - Hypertension - Congestive heart failure - Advanced age - Volume depletion - Hemodynamic instability - Nephrotoxic medications
Prevention strategies				
Nephrotoxic medications	There is insufficient evidence to recommend withholding nephrotoxic drugs before CM administration. Stop metformine if eGFR < 30 ml/min/1.73m^2 or all patients receiving i.a. ICM with 1st renal pass exposure or patient with AKI.	Stop metfomine in patients with AKI or severe CKD (eGFR < 30), or are undergoing i.a. catheter studies that might result in emboli to the renal arteries.	Nephrotoxic medications would have to be stopped for days or even weeks, and not only hours, before ICM administration.	Nephrotoxic medication should preferably be stopped.
Preventive i.v. hydration	For i.v. and i.a. ICM administration with 2nd pass renal exposure: - i.v. sodium bicarbonate 1.4%: 3 ml/kg/h for 1 h before ICM - or i.v. saline 0.9%: 1 ml/kg/h for 3-4 h before and 4-6 h after ICM. For i.a. ICM administration with 1st renal exposure: - i.v. sodium bicarbonate 1.4% : 3 ml/kg/h for 1 h before and 1 ml/kg/h for 4-6 h after ICM - or i.v. saline 0.9%: 1 ml/kg/h for 3-4 h before and 4-6 h after ICM.	One possible protocol would be 0.9% saline at 100 ml/h, beginning 6-12 h before and continuing 4-12 h after.	i.v. volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions, in patients at risk.	i.v. volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions in patients at risk. ≥ 1.0-1.5 ml/kg/h of i.v. fluid has to be injected for 3-12 h before and 6-12 h after ICM exposure, in order to achieve a urine flow rate of at least 150 ml/h.
Other pharmacological preventions strategies	No other pharmacological prophylaxis (N-acetylcysteine, statins…) are recommended.	There is insufficient evidence of N-acetylcysteine efficacy to recommend its use.	Use oral N-acetylcysteine only in patients who receive appropriate fluid and salt loading.	Use oral N-acetylcysteine together with i.v. isotonic crystalloids, in patients at risk.
Iodinated contrast-media	Consider an alternative imaging method not using ICM.			
	Osmolarity: use low or iso-osmolar ICM.	**Osmolarity:** use low or iso-osmolar ICM.	–	**Osmolarity:** use either iso-osmolar or low-osmolar ICM, in patients at risk.

(*continued on next page*)

Table 4 (*continued*)

	European Society of Urogenital Radiology 2018	American College of Radiology 2018	European Renal Best Practice 2012	Kidney Disease Improving Global Outcomes 2012
Dose: use the lowest dose of ICM consistent with a diagnostic result. - For i.v. ICM administration, there is insufficient evidence that CM dose is a risk factor. - For i.a. ICM administration with 1st pass renal exposure keep either the ratio ICM dose (in gram iodine) / absolute eGFR (in ml/min) < 1.1 or the ratio ICM volume (in ml)/eGFR (in ml/min/1.73 m2) < 3.0 (ICM of 350 mg iodine/ml). **Repeated injections:** repeated ICM injections in a short period (48-72 h) should be avoided	**Dose:** use the lowest possible dose of ICM (there is insufficient evidence to recommend a specific threshold of ICM volume). **Repeated injections:** there is insufficient evidence to specifically endorse the decision to withhold a repeat ICM injection until > 24 h have passed since the prior injection.	–	**Dose:** use the lowest possible dose of ICM, in patients at risk. **Repeated injections:** should be delayed for 48 h in patients without risk factors and for 72 h in those with diabetes mellitus or pre-existing CKD. If acute renal dysfunction develops after ICM administration, repeated exposure should preferably be delayed until the serum creatinine level has returned to baseline levels.	–

The ESUR guidelines recommend for both intravenous and intra-arterial ICM administration with second pass renal exposure, an intravenous hydration with NaCl 0.9% at 1.0 ml/kg/h for 3–4 h before the injection and continuing for 4–6 h after the procedure, or the intravenous administration of sodium bicarbonate 1.4% (154mEq/L), 3 mg/kg/h starting 1 h before the injection of ICM (followed by 1 mg/kg/h for 4–6 h after intra-arterial ICM administration with first pass renal exposure) [69,70]. The KDIGO guidelines suggest ≥1-1.5 ml/kg/h infusion of crystalloid 3–12 h before and 6–12 h after ICM exposure, in order to achieve a urine ouput > 150 ml/h [54].

6.2. N-acetylcysteine

N-acetylcysteine is an antioxidant and vasodilator that potentiates the effects of NO. However, the results of studies on the efficacy of N-acetylcysteine in the prevention of ICM-related renal toxicity remain controversial. According to Liu et al., one of the pathophysiological hypotheses that could explain why the administration of antioxidant molecules is ineffective in the prevention of ICM-induced renal toxicity, is that ICM exert a direct toxicity on tubular cells, resulting in hypoxic and oxidative stress, and not the reverse [22]. Since the first randomized study conducted by Tepel et al. in 2000 [77], 37 studies and around 20 meta-analyses have been published on the subject. In total, only 15 of the 38 studies suggest that N-acetylcysteine is effective in the prevention of ICM-related renal toxicity [74]. However, the small numbers of people studied, the heterogeneity of the populations, the use of small change in serum creatinine as the primary endpoint, and the absence of long-term follow-up, do not enable conclusions to be drawn on the efficacy of N-acetylcysteine in this indication. These contradictory results were the reason for carrying out numerous meta-analyses. However, they also were unable to reach generally accepted conclusions, mainly due to methodological limitations [74]. In fact, these meta-analyses were even used as an example for a methodological critique of this type of study [78]. Nevertheless, due to the complete safety of the molecule, the KDIGO and the ERBP working group guidelines suggest the use of N-acetylcysteine *per os* together with intravenous fluid loading [54,68], in contrast to the 2011 recommendations of the American College of Cardiology / American Heart Association / Society for Cardiovascular Angiography and Intervention [79] and the 2018 guidelines of the ESUR [69,70]. It is worth noting that the recently published well powered prospective randomized PRESERVE trial showed no benefit of N-acetylcysteine over placebo [76].

6.3. Statins

In addition to inhibiting Hydroxy-Methyl-Glutaryl Coenzyme A reductase, statins have “pleiotropic” properties including antioxidant, anti-inflammatory, anti-thrombotic properties [80], and an anti-apoptotic effect. Furthermore, statins are able to decrease the vasoconstriction response to angiotensin II and to reduce the synthesis of endothelin, thereby preventing renal hypoperfusion and medullary hypoxia [81,82]. Despite certain methodological biases, several meta-analyses appear to confirm these observations (Table 5) [83–97]. A protective effect of statins was found in the general population [98–100] and particularly among people with renal impairment [57,97], especially if they had diabetes [97,101] and were “statin-naive”. Although study results remain controversial [102–106], a high dose, or “loading dose” of statin appears to be more effective than a low dose in the prevention of ICM-induced nephrotoxicity, regardless of the type of statin studied (atorvastatin, simvastatin or rosuvastatin). However, the populations studied, the type of statin, dosage, rate of administration and associated hydration protocols were heterogeneous. In most cases, serum creatinine was measured only early on (48–72 h), with no long term follow-up. The “target population”, optimal agent, dosage and rate of administration are still to be determined. Statins are neither recommended by the 2018 guidelines of the ESUR [69,70], nor

Table 5
Meta-analysis of randomized controlled studies on the use of statins in the prevention of iodinated contrast media-induced renal toxicity, following angiography.* Only randomized studies evaluated by this meta-analysis have been included in the table.

Author, journal	Publication year	Studies (n)	Patients (n)	Intervention	Pooled Risk Ratio or Odds Ratio [CI 95%] ; p	Statistical model	Heterogeneity: I^2	Publication bias: funnel plot, Egger's or Begg's tests
Zhang L, et al Int J Clin Pract. [103]	2011	4	751	Statin *versus* no statin	0.76 [0.44–1.29] p = 0.30	Random-effects model	I^2 = 0%	– Egger's test:p = 0.17
Pappy R, et al Int J Cardiol*. [104]	2011	3	770	Statin *versus* hydration and/or placebo	0.76 [0.41–1.41] p = 0.39	Der Simonian and Laird random-effects model	I^2 = 0%	– –
Zhang BC, et al, Can J Cardiol. [82]	2011	8	1423	High-dose statin *versus* low-dose or placebo	0.51 [0.34–0.77] p = 0.001	Fixed-effects model	I^2 = 0%	Yes (asymmetric) Begg's test: p = 0.764
Zhou Y, et al Clin Nephrol. [83]	2011	5	1009	High-dose statin *versus* low-dose or placebo	0.53 [0.32–0.87] p = 0.01	Mantel-Haenszel fixed-effects model	I^2 = 19%	Yes (asymmetric) Egger's test: p = 0.27
Takagi H, et al Int J Cardiol. [91]	2011	7	1251	Statin (atorvastatin) *versus* low-dose or placebo or other statin	0.56 [0.33–0.95] p = 0.03	Fixed-effects model	I^2 = 0%	Yes (but not shown) Egger's test: p = 0.29
Zhang T, et al Am J nephrol. [105]	2011	6	1194	High-dose statin *versus* low-dose or placebo	0.70 [0.48–1.02] p = 0.06	Fixed-effects model	I^2 = 38%	– –
Li Y, et al PLoS One. [84]	2012	7	1399	High-dose statin *versus* low-dose or placebo	0.51 [0.34–0.76] p = 0.001	Fixed-effects model	I^2 = 0%	Yes (asymmetric) –
Giacoppo D, et al Am J Cardiol. [85]	2014	8	4984	Statin *versus* no statin	0.54 [0.38–0.78] p = 0.001	Der Simonian and Laird random-effect model	I^2 = 42%	Yes (asymmetric) Egger's test: p = 0.218
Ukaigwe A, et al Am J Cardiol. [87]	2014	12	5564	High-dose statin *versus* low-dose or placebo	0.43 [0.33–0.55] p < 0.001	Random-effects model	I^2 = 19%	Yes –
Lee JM, et al Plos One. [86]	2014	13	5825	High-dose statin *versus* low-dose or placebo	0.45 [0.35–0.57] p < 0.001	Der Simonian and Laird random-effects model	I^2 = 8.2%	Yes Egger's test: p = 0.13 Begg's test: p = 0.62
Marenzi G, et al Int J Cardiol. [88]	2015	9	5212	High-dose statin *versus* low-dose or placebo	0.50 [0.39–0.64] p < 0.001	Mantel-Haenszel fixed-effects model	I^2 = 1%	Yes Egger's test: p = 0.51
Liu YH, et al J CardiovascPharmacolTher. [90]	2015	9	5143	Statin *versus* placebo	0.47 [0.37–0.60] p < 0.0001	Fixed-effects model	I^2 = 28%	Yes Egger's test: p = 0.352
Wu H, et al J Clin Pharmacol. [89]	2015	14	1689	High-dose statin *versus*low-dose	0.41 [0.29–0.56] p < 0.05	Fixed-effects model	I^2 = 0%	– Egger's test: p = 0.27 Begg's test: p = 0.88

by the ACR [36], and nor by KDIGO [54]. In contrast, the European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines suggest that "the implementation of high-dose statin before diagnostic catheterization should be considered as an additional preventive measure in patients without contraindications" [107].

6.4. Other pharmacological agents

Many other pharmacological agents have been studied, including ascorbic acid, calcium channel blockers, furosemide, prostaglandin analogs, endothelin agonists, adenosine antagonists, L-arginine, hypertonic mannitol, dopamine, and theophylline [108–110]. None of these treatments seem to be effective in the prevention of ICM-induced renal toxicity.

6.5. Ischemic preconditioning

Ischemic preconditioning is a non-pharmacological, non-invasive technique, first described in 1986 in dogs [111] and then in 1993 in humans [112]. This method consists of creating short sequences of ischemia/reperfusion, some time before the occurrence of prolonged ischemia, in order to "prepare" the cells against the risk of later ischemic damage. This technique relies on a ubiquitous endogenous cytoprotection mechanism, which is highly conserved across species [112]. Depriving cells of oxygen and nutrients induces on the one hand, stimulation of anaerobic glycolysis, and on the other, inhibition of oxidative phosphorylation [113]. After reperfusion, cell metabolism being slowed down, the massive intake of oxygen causes an "oxidative burst". Cell damage is caused by the release of a large quantity of ROS and pro-inflammatory cytokines. In response to ischemia, the cells slow down their metabolic activity and activate a number of cytoprotective mechanisms [113], which are often overwhelmed if the ischemia is prolonged, leading to cell death, resulting in acute tubular necrosis.

Ischemic preconditioning can be performed using a blood pressure cuff before administration of the ICM. The cuff is inflated for 5 min (ischemia), then deflated for 5 min (reperfusion), 4 cycles in a row. While studies on the efficacy of ischemic preconditioning seem to show cardiovascular [112,114] and renal [115,116] benefit before cardiac surgery, studies conducted on the prevention of ICM-induced AKI are few, have involved less people, and their results remain controversial [117,118].

6.6. RenalGuard® system

In 1999, Stevens et al. showed that the administration of a single dose of diuretic combined with hydration adapted to the volume of diuresis, limited the risk of ICM-induced nephropathy, and that urinary output greater than or equal to 150 ml/h was associated with a reduction in renal medullary toxicity related to the administration of ICM [119]. The principle of the Renal-Guard® system or "controlled forced diuresis" is based on a technique in which a furosemide-induced increase in urinary output is immediately compensated by intravenous infusion of 0.9% NaCl in order to avoid dehydration. The aim is to combine a potentially beneficial effect of furosemide with the maintenance of normal hydration. Furosemide, which inhibits the tubular Na-K-2Cl co-transporter is thought to limit epithelial ATP consumption and hence renal medullary hypoxia. This system requires a perfect adequacy between furosemide's diuretic effect and NaCl infusion rate. If the achieved increase in urinary volume is greater than its compensation by 0.9% NaCl the risk of AKI is increased. Conversely, if the infusion rate is greater than urinary output, there is a risk of fluid overload an eventually even pulmonary edema, as reported in some studies [120].

A recent meta-analysis has shown that the RenalGuard® system reduced the incidence of ICM-induced AKI in high-risk patients undergoing percutaneous coronary intervention or transcatheter aortic valve replacement [121]. While the results of this technique are interesting [120,122] studies remain few in number and small in size, were not always randomized, and were mainly conducted in highly selected populations. Furthermore, to our knowledge, the effectiveness of this system has only been assessed with intra-arterial ICM administration. Its usefulness needs to be explored with intravenous ICM use as well. Finally, the device is invasive, probably expensive, and the therapeutic protocol should be refined to prevent hypovolemia and AKI risk.

7. Conclusion

ICM-induced nephropathy is the third most common cause of AKI. It is the result of direct intrinsic toxicity of ICM for renal tubular epithelial and endothelial cells, the impairment of renal hemodynamics, and/or ICM administration modalities; all these mechanisms being very closely linked. There is no specific diagnostic biomarker or treatment. Preventive measures are therefore essential for limiting iatrogenic AKI. The risk-benefit ratio should be assessed before each examination using ICM. If the injection of ICM is necessary the volume, osmolality and viscosity of the ICM should be as low as possible. Nephrotoxic treatments should be discontinued and salt and water intake be sufficient. Correcting volume depletion remains the cornerstone of prevention. The use of antioxidants such as statins or N-acetylcysteine may complement preventive measures, but should never replace a correct hydration status. Predicting the risk of ICM-induced AKI or persistent loss of kidney function following ICM injection remains very difficult. Current AKI definitions lump together heterogeneous phenotypes but in future, development of "biomarker signatures" and functional imaging techniques may help distinguish "hemodynamic AKI" from AKI related "tissue injury", and thus identify different phenotypes of patients for a better understanding of the pathophysiology and the development of new therapeutic approaches.

Disclosure

The authors have no conflict of interest to declare.

Support / funding

None.

Author contributions

All authors researched the data, wrote the draft and made critical revision of the manuscript for important intellectual content.

Conflict of interest

The authors have no conflict of interest to declare.

References

[1] F. Stacul, A.J. van der Molen, P. Reimer, et al., Contrast media safety committee of European Society of Urogenital Radiology (ESUR). Contrast induced nephropathy: updated ESUR contrast media safety committee guidelines, Eur. Radiol. 21 (2011) 2527–2541.
[2] K. Nash, A. Hafeez, S. Hou, Hospital-acquired renal insufficiency, Am. J. Kidney Dis. 39 (2002) 930–936.
[3] P.A. McCullough, Contrast-induced acute kidney injury, J. Am. Coll. Cardiol. 51 (2008) 1419–1428.
[4] R. Jabara, R.R. Gadesam, L.K. Pendyala, et al., Impact of the definition utilized on the rate of contrast-induced nephropathy in percutaneous coronary intervention, Am. J. Cardiol. 103 (2009) 1657–1662.
[5] A.M. Mitchell, A.E. Jones, J.A. Tumlin, J.A. Kline, Incidence of contrast-induced nephropathy after contrast-enhanced computed tomography in the outpatient setting, Clin. J. Am. Soc. Nephrol. 5 (2010) 4–9.
[6] E. Wilhelm-Leen, M.E. Montez-Rath, G. Chertow, Estimating the risk of radiocontrast-associated nephropathy, J. Am. Soc. Nephrol. 28 (2017) 653–659.
[7] P.A. McCullough, A. Adam, C.R. Becker, et al., CIN Consensus Working Panel. Risk prediction of contrast-induced nephropathy, Am. J. Cardiol. 98 (2006) 27–36.
[8] S.G. Coca, S. Singanamala, C.R. Parikh, Chronic kidney disease after acute kidney

injury: a systematic review and meta-analysis, Kidney Int. 81 (2012) 442–448.
[9] O. Rewa, S.M. Bagshaw, Acute kidney injury-epidemiology, outcomes and economics, Nat. Rev. Nephrol. 10 (2014) 193–207.
[10] E.M. Levy, C.M. Viscoli, R.I. Horwitz, The effect of acute renal failure on mortality. A cohort analysis, JAMA. 275 (1996) 1489–1494.
[11] C.S. Rihal, S.C. Textor, D.E. Grill, et al., Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention, Circulation 105 (2002) 2259–2264.
[12] R. Solomon, H.L. Dauerman, Contrast-induced acute kidney injury, Circulation 122 (2010) 2451–2455.
[13] L. Gruberg, G.S. Mintz, R. Mehran, et al., The prognostic implications of further renal function deterioration within 48h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency, J. Am. Coll. Cardiol. 36 (2000) 1542–1548.
[14] P.A. McCullough, R. Wolyn, L.L. Rocher, R.N. Levin, W.W. O'Neill, Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality, Am. J. Med. 103 (1997) 368–375.
[15] P.A. McCullough, Epidemiology of contrast induced nephropathy, Rev. Cardiovasc. Med. 4 (2003) 53–59.
[16] P.B. Persson, M. Tepel, Contrast medium-induced nephropathy: the pathophysiology, Kidney Int. 69 (2006) S8–S10.
[17] E. Seeliger, M. Sendeski, C.S. Rihal, P.B. Persson, Contrast-induced kidney injury: mechanisms, risk factors, and prevention, Eur. Heart J. 33 (2012) 2007–2015.
[18] G. Romano, C. Briguori, C. Quintavalle, et al., Contrast agents and renal cell apoptosis, Eur. Heart J. 29 (2008) 2569–2576.
[19] K. Hardiek, R.E. Katholi, V. Ramkumar, C. Deitrick, Proximal tubule cell response to radiographic contrast media, Am. J. Physiol. Renal Physiol. 280 (2001) F61–F70.
[20] M.M. Sendeski, Pathophysiology of renal tissue damage by iodinated contrast media, Clin. Exp. Pharmacol. Physiol. 38 (2011) 292–299.
[21] C. Quintavalle, M. Brenca, F. De Micco, et al., In vivo and in vitro assessment of pathways involved in contrast media-induced renal cells apoptosis, Cell Death Dis. 2 (2011) e155.
[22] Z.Z. Liu, K. Schmerbach, Y. Lu, et al., Iodinated contrast media cause direct tubular cell damage, leading to oxidative stress, low nitric oxide, and impairment of tubuloglomerular feedback, Am. J. Physiol. Renal Physiol. 306 (2014) F864–72.
[23] C.S. Schick, C. Haller, Comparative cytotoxicity of ionic and non-ionic radiocontrast agents on MDCK cell monolayers in vitro, Nephrol. Dial. Transplant. 14 (1999) 342–347.
[24] C. Christiansen, X-Ray contrast media: an overview, Toxicology 209 (2005) 185–187.
[25] I. Hizóh, J. Sträter, C.S. Schick, W. Kübler, C. Haller, Radiocontrast-induced DNA fragmentation of renal tubular cells in vitro: role of hypertonicity, Nephrol. Dial. Transplant. 13 (1998) 911–918.
[26] M.M. Sendeski, A.B. Persson, Z.Z. Liu, et al., Iodinated contrast media cause endothelial damage leading to vasoconstriction of human and rat vasa recta, Am. J. Physiol. Renal Physiol. 303 (2012) F1592–8.
[27] P.A. Ortiz, J.L. Garvin, Interaction of O2 and NO in the thick ascending limb, Hypertension. 39 (2002) 591–596.
[28] P.A. Ortiz, J.L. Garvin, Superoxide stimulates NaCl absorption by the thick ascending limb, Am. J. Physiol. Renal Physiol. 283 (2002) 957–962.
[29] R. Juncos, J.L. Garvin, Superoxide enhances Na-K-2Cl co-transporter activity in the thick ascending limb, Am. J. Physiol. Renal Physiol. 288 (2005) 982–987.
[30] G.B. Silva, P.A. Ortiz, N.J. Hong, J.L. Garvin, Superoxide stimulates NaCl absorption in the thick ascending limb via activation of protein kinase C, Hypertension 48 (2006) 467–472.
[31] S.N. Heyman, S. Rosen, C. Rosenberger, Renal parenchymal hypoxia, hypoxia adaptation, and the pathogenesis of radiocontrast nephropathy, Clin. J. Am. Soc. Nephrol. 3 (2008) 288–296.
[32] S.N. Heyman, S. Rosen, M. Khamaisi, J.M. Idée, C. Rosenberger, Reactive oxygen species and the pathogenesis of radiocontrast-induced nephropathy, Invest. Radiol. 45 (2010) 188–195.
[33] G. Jost, P. Lengsfeld, D.C. Lenhard, H. Pietsch, J. Hütter, M.A. Sieber, Viscosity of iodinated contrast agents during renal excretion, Eur. J. Radiol. 80 (2011) 373–377.
[34] P. Aspelin, F. Stacul, H.S. Thomsen, S.K. Morcos, A.J. van der Molen, Members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR). Effects of iodinated contrast media on blood and endothelium, Eur. Radiol. 16 (2006) 1041–1049.
[35] M. Brezis, S. Rosen, Hypoxia of the renal medulla -its implications for disease, N. Engl. J. Med. 332 (1995) 647–655.
[36] American College of Radiology Committee on Drugs and Contrast Media, ACR Manual on Contrast Media, Version 10.3, (2018) https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf.
[37] B.J. Barrett, E.J. Carlisle, Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media, Radiology 188 (1993) 171–178.
[38] P. Liss, P.B. Persson, P. Hansell, B. Lagerqvist, Renal failure in 57 925 patients undergoing coronary procedures using iso-osmolar or low-osmolar contrast media, Kidney Int. 70 (2006) 1811–1817.
[39] P.A. McCullough, M.E. Bertrand, J.A. Brinker, F. Stacul, A meta-analysis of the renal safety of isosmolar iodixanol compared with low-osmolar contrast media, J. Am. Coll. Cardiol. 48 (2006) 692–699.
[40] M. Reed, P. Meier, U.U. Tamhane, K.B. Welch, M. Moscucci, H.S. Gurm, The relative renal safety of iodixanol compared with low-osmolar contrast media: a meta-analysis of randomized controlled trials, JACC Cardiovasc. Interv. 2 (2009) 645–654.
[41] J. Eng, R.F. Wilson, R.M. Subramaniam, et al., Comparative effect of contrast media type on the incidence of contrast-induced nephropathy: a systematic review and meta-analysis, Ann. Intern. Med. 164 (2016) 417–424.
[42] A.J. van der Molen, P. Reimer, I.A. Dekkers, et al., Post-contrast acute kidney injury - Part 1: Definition, clinical features, incidence, role of contrast medium and risk factors: Recommendations for updated ESUR Contrast Medium Safety Committee guidelines, Eur. Radiol. 28 (2018) 2845–2855.
[43] O. Toprak, Risk markers for contrast-induced nephropathy, Am. J. Med. Sci. 334 (2007) 283–290.
[44] C.E. Balemans, L.J. Reichert, B.I. van Schelven, J.A. van den Brand, J.F. Wetzels, Epidemiology of contrast material-induced nephropathy in the era of hydration, Radiology 263 (2012) 706–713.
[45] R. Solomon, Contrast-induced acute kidney injury: is there a risk after intravenous contrast? Clin. J. Am. Soc. Nephrol. 3 (2008) 1242–1243.
[46] J. Kooiman, P.A. Le Haen, G. Gezgin, et al., Contrast-induced acute kidney injury and clinical outcomes after intra-arterial and intravenous contrast administration: risk comparison adjusted for patient characteristics by design, Am. Heart J. 165 (2013) 793–799.
[47] J.S. McDonald, C.B. Leake, R.J. McDonald, et al., Acute Kidney injury after intravenous versus intra-arterial contrast material administration in a paired cohort, Invest. Radiol. 51 (2016) 804–809.
[48] W.K. Laskey, C. Jenkins, F. Selzer, et al., NHLBI Dynamic Registry Investigators. Volume-to-creatinine clearance ratio: a pharmacokinetically based risk factor for prediction of early creatinine increase after percutaneous coronary intervention, J. Am. Coll. Cardiol. 50 (2007) 584–590.
[49] U. Nyman, J. Bjork, P. Aspelin, G. Marenzi, Contrast medium dose-to-GFR ratio: a measure of systemic exposure to predict contrast-induced nephropathy after percutaneous coronary intervention, Acta radiol. 49 (2008) 658–667.
[50] R. Mehran, E.D. Aymong, E. Nikolsky, et al., A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation, J. Am. Coll. Cardiol. 44 (2004) 1393–1399.
[51] J.S. McDonald, R.J. McDonald, J. Comin, et al., Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis, Radiology 267 (2013) 119–128.
[52] J.S. McDonald, R.J. McDonald, R.E. Carter, R.W. Katzberg, D.F. Kallmes, E.E. Williamson, Risk of intravenous contrast material-mediated acute kidney injury: a propensity score-matched study stratified by baseline-estimated glomerular filtration rate, Radiology 271 (2014) 65–73.
[53] S.A. Silver, P.M. Shah, G.M. Chertow, S. Harel, R. Wald, Z. Harel, Risk prediction models for contrast induced nephropathy: systematic review, BMJ 351 (2015) h4395.
[54] Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, KDIGO clinical practice guideline for acute kidney injury, Kidney Int. Suppl. 2 (2012) 1–138.
[55] H.S. Thomsen, S.K. Morcos, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). In which patients should serum creatinine be measured before iodinated contrast medium administration? Eur. Radiol. 15 (2005) 749–754.
[56] C. Briguori, G. Visconti, N.V. Rivera, et al., Cystatin C and contrast-induced acute kidney injury, Circulation 121 (2010) 2117–2122.
[57] C. Quintavalle, D. Fiore, Micco F. De, et al., Impact of a high loading dose of atorvastatin on contrast-induced acute kidney injury, Circulation 126 (2012) 3008–3016.
[58] D.J. Newman, H. Thakkar, R.G. Edwards, et al., Serum cystatin C measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine, Kidney Int. 47 (1995) 312–318.
[59] V.R. Dharnidharka, C. Kwon, G. Stevens, Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis, Am. J. Kidney Dis. 40 (2002) 221–226.
[60] H. Rickli, K. Benou, P. Ammann, et al., Time course of serial cystatin C levels in comparison with serum creatinine after application of radiocontrast media, Clin. Nephrol. 61 (2004) 98–102.
[61] R.J. Solomon, R. Mehran, M.K. Natarajan, et al., Contrast-induced nephropathy and long-term adverse events: cause and effect? Clin. J. Am. Soc. Nephrol. 4 (2009) 1162–1169.
[62] A.I. Lim, S.C. Tang, K.N. Lai, J.C. Leung, Kidney injury molecule-1: more than just an injury marker of tubular epithelial cells? J. Cell. Physiol. 228 (2013) 917–924.
[63] E. Singer, L. Markó, N. Paragas, et al., Neutrophil gelatinase-associated lipocalin: pathophysiology and clinical applications, Acta Physiol. (Oxf.) 207 (2013) 663–672.
[64] L.P. Li, J. Lu, Y. Zhou, et al., Evaluation of intrarenal oxygenation in iodinated contrast-induced acute kidney injury-susceptible rats by blood oxygen level-dependent magnetic resonance imaging, Invest. Radiol. 49 (2014) 403–410.
[65] G. Deray, Dialysis and iodinated contrast media, Kidney Int. Suppl. 100 (2006) S25–9.
[66] T. Lehnert, E. Keller, K. Gondolf, T. Schäffner, H. Pavenstädt, P. Schollmeyer, Effect of haemodialysis after contrast medium administration in patients with renal insufficiency, Nephrol. Dial. Transplant. 13 (1998) 358–362.
[67] B. Vogt, P. Ferrari, C. Schönholzer, et al., Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful, Am. J. Med. 111 (2001) 692–698.
[68] The ad-hoc working group of ERBP, A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy, Nephrol. Dial. Transplant. 27 (2012) 4263–4272.
[69] A.J. van der Molen, P. Reimer, I.A. Dekkers, et al., Post-contrast acute kidney injury. Part 2: risk stratification, role of hydration and other prophylactic measures, patients taking metformin and chronic dialysis patients: recommendations for updated ESUR Contrast Medium Safety Committee guidelines, Eur. Radiol. 28 (2018) 2856–2869.
[70] European Society of Urogenital Radiology, Contrast-Media Guidelines 10.0, (2018) http://www.esur.org/esur-guidelines/.
[71] S.D. Weisbord, P.M. Palevsky, Prevention of contrast-induced nephropathy with

volume expansion, Clin. J. Am. Soc. Nephrol. 3 (2008) 273–280.
[72] F. Stacul, A. Adam, C.R. Becker, et al., CIN Consensus Working Panel. Strategies to reduce the risk of contrast-induced nephropathy, Am. J. Cardiol. 98 (2006) 59K–77K.
[73] G.J. Merten, W.P. Burgess, L.V. Gray, et al., Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial, JAMA 291 (2004) 2328–2334.
[74] S.D. Weisbord, M. Gallagher, J. Kaufman, et al., Prevention of contrast-induced AKI: a review of published trials and the design of the prevention of serious adverse events following angiography (PRESERVE) trial, Clin. J. Am. Soc. Nephrol. 8 (2013) 1618–1631.
[75] E.C. Nijssen, R.J. Rennenberg, P.J. Nelemans, et al., Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial, Lancet 389 (2017) 1312–1322.
[76] S.D. Weisbord, M. Gallagher, H. Jneid, et al., PRESERVE trial group. Outcomes after angiography with sodium bicarbonate and acetylcysteine, N. Engl. J. Med. 378 (2018) 603–614.
[77] M. Tepel, M. van der Giet, C. Schwarzfeld, U. Laufer, D. Liermann, W. Zidek, Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine, N. Engl. J. Med. 343 (2000) 180–184.
[78] P.T. Vaitkus, C. Brar, N-acetylcysteine in the prevention of contrast-induced nephropathy: publication bias perpetuated by meta-analyses, Am. Heart J. 153 (2007) 275–280.
[79] G.N. Levine, E.R. Bates, J.C. Blankenship, et al., ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College Of Cardiology Foundation/American heart association task force on practice guidelines and the society for cardiovascular angiography and interventions, Circulation 124 (2011) (2011) e574–651.
[80] E. Profumo, B. Buttari, L. Saso, R. Rigano, Pleiotropic effects of statins in atherosclerotic disease: focus on the antioxidant activity of atorvastatin, Curr. Top. Med. Chem. 14 (2014) 2542–2551.
[81] P.O. Bonetti, L.O. Lerman, C. Napoli, A. Lerman, Statin effects beyond lipid lowering – are they clinically relevant? Eur. Heart J. 24 (2003) 225–248.
[82] A.S. Wierzbicki, R. Poston, A. Ferro, The lipid and non-lipid effects of statins, Pharmacol. Ther. 99 (2003) 95–112.
[83] B.C. Zhang, W.M. Li, Y.W. Xu, High-dose statin pretreatment for the prevention of contrast-induced nephropathy: a meta-analysis, Can. J. Cardiol. 27 (2011) 851–858.
[84] Y. Zhou, W.J. Yuan, N. Zhu, L. Wang, Short-term, high-dose statins in the prevention of contrast-induced nephropathy: a systematic review and meta-analysis, Clin. Nephrol. 76 (2011) 475–483.
[85] Y. Li, Y. Liu, L. Fu, C. Mei, B. Dai, Efficacy of short-term high-dose statin in preventing contrast-induced nephropathy: a meta-analysis of seven randomized controlled trials, PLoS One 7 (2012) e34450.
[86] D. Giacoppo, D. Capodanno, P. Capranzano, P. Aruta, C. Tamburino, Meta-analysis of randomized controlled trials of pre-procedural statin administration for reducing contrast-induced acute kidney injury in patients undergoing coronary catheterization, Am. J. Cardiol. 114 (2014) 541–548.
[87] J.M. Lee, J. Park, K.H. Jeon, et al., Efficacy of short-term high-dose statin pretreatment in prevention of contrast-induced acute kidney injury: updated study-level meta-analysis of 13 randomized controlled trials, PLoS One 9 (2014) e111397.
[88] A. Ukaigwe, P. Karmacharya, M. Mahmood, et al., Meta-analysis on efficacy of statins for prevention of contrast-induced acute kidney injury in patients undergoing coronary angiography, Am. J. Cardiol. 114 (2014) 1295–1302.
[89] G. Marenzi, N. Cosentino, J.P. Werba, C.C. Tedesco, F. Veglia, A.L. Bartorelli, A meta-analysis of randomized controlled trials on statins for the prevention of contrast-induced acute kidney injury in patients with and without acute coronary syndromes, Int. J. Cardiol. 183 (2015) 47–53.
[90] H. Wu, D. Li, M. Fang, H. Han, H. Wang, Meta-analysis of short-term high versus low doses of atorvastatin preventing contrast-induced acute kidney injury in patients undergoing coronary angiography/percutaneous coronary intervention, J. Clin. Pharmacol. 55 (2015) 123–131.
[91] Y.H. Liu, Y. Liu, C.Y. Duan, et al., Statins for the prevention of contrast-induced nephropathy after coronary angiography / percutaneous interventions: a meta-analysis of randomized controlled trials, J. Cardiovasc. Pharmacol. Ther. 20 (2015) 181–192.
[92] H. Takagi, T. Umemoto, A meta-analysis of randomized trials for effects of periprocedural atorvastatin on contrast-induced nephropathy, Int. J. Cardiol. 153 (2011) 323–325.
[93] Y. Yang, Y.X. Wu, Y.Z. Hu, Rosuvastatin treatment for preventing contrast-induced acute kidney injury after cardiac catheterization: a meta-analysis of randomized controlled trials, Medicine (Baltimore) 94 (2015) e1226.
[94] W. Cheungpasitporn, C. Thongprayoon, W. Kittanamongkolchai, et al., Periprocedural effects of statins on the incidence of contrast-induced acute kidney injury: a systematic review and meta-analysis of randomized controlled trials, Ren. Fail. 37 (2015) 664–671.
[95] N. Wang, P. Qian, T.D. Yan, K. Phan, Periprocedural effects of statins on the incidence of contrast-induced acute kidney injury: a systematic review and trial sequential analysis, Int. J. Cardiol. 206 (2016) 143–152.
[96] T. Zografos, E. Oikonomou, G. Siasos, et al., High-dose statin therapy is effective at preventing the development of contrast-induced nephropathy in patients undergoing percutaneous coronary intervention for acute coronary syndromes: a meta-analysis, J. Am. Coll. Cardiol. 67 (13) (2016) p173 Supplement (abstract).
[97] M. Liang, S. Yang, N. Fu, Efficacy of short-term moderate or high-dose rosuvastatin in preventing contrast-induced nephropathy: a meta-analysis of 15 randomized controlled trials, Medicine (Baltimore) 96 (2017) e7384.
[98] J. Xinwei, F. Xianghua, Z. Jing, et al., Comparison of usefulness of simvastatin 20 mg versus 80 mg in preventing contrast-induced nephropathy in patients with acute coronary syndrome undergoing percutaneous coronary intervention, Am. J. Cardiol. 104 (2009) 519–524.
[99] G. Patti, E. Ricottini, A. Nusca, et al., Short-term, high-dose atorvastatin pretreatment to prevent contrast-induced nephropathy in patients with acute coronary syndromes undergoing percutaneous coronary intervention (from the ARMYDA-CIN [Atorvastatin for Reduction of Myocardial Damage during Angioplasty–contrast-Induced Nephropathy] Trial, Am. J. Cardiol. 108 (2011) 1–7.
[100] M. Leoncini, A. Toso, M. Maioli, F. Tropeano, S. Villani, F. Bellandi, Early high-dose rosuvastatin for contrast-induced nephropathy prevention in acute coronary syndrome: results from the PRATO-ACS Study (Protective Effect of Rosuvastatin and Antiplatelet Therapy on contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome), J. Am. Coll. Cardiol. 63 (2014) 71–79.
[101] Y. Han, G. Zhu, L. Han, et al., Short-term rosuvastatin therapy for prevention of contrast-induced acute kidney injury in patients with diabetes and chronic kidney disease, J. Am. Coll. Cardiol. 63 (2014) 62–70.
[102] S.H. Jo, B.K. Koo, J.S. Park, et al., Prevention of radiocontrast medium-induced nephropathy using short-term high-dose simvastatin in patients with renal insufficiency undergoing coronary angiography (PROMISS) trial - a randomized controlled study, Am. Heart J. 155 (499) (2008) e1–8.
[103] A. Toso, M. Maioli, M. Leoncini, et al., Usefulness of atorvastatin (80 mg) in prevention of contrast-induced nephropathy in patients with chronic renal disease, Am. J. Cardiol. 105 (2010) 288–292.
[104] L. Zhang, L. Zhang, Y. Lu, et al., Efficacy of statin pretreatment for the prevention of contrast-induced nephropathy: a meta-analysis of randomised controlled trials, Int. J. Clin. Pract. 65 (2011) 624–630.
[105] R. Pappy, S. Stavrakis, T.A. Hennebry, M.S. Abu-Fadel, Effect of statin therapy on contrast-induced nephropathy after coronary angiography: a meta-analysis, Int. J. Cardiol. 151 (2011) 348–353.
[106] T. Zhang, L.H. Shen, L.H. Hu, B. He, Statins for the prevention of contrast-induced nephropathy: a systematic review and meta-analysis, Am. J. Nephrol. 33 (2011) 344–351.
[107] Authors/Task Force members, ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the european society of cardiology (ESC) and the european association for cardio-thoracic surgery (EACTS) developed with the special contribution of the european association of percutaneous cardiovascular interventions (EAPCI), Eur. Heart J. 35 (2014) (2014) 2541–2619.
[108] R. Solomon, C. Werner, D. Mann, J. D'Elia, P. Silva, Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents, N. Engl. J. Med. 331 (1994) 1416–1420.
[109] B. Dussol, S. Morange, A. Loundoun, P. Auquier, Y. Berland, A randomized trial of saline hydration to prevent contrast nephropathy in chronic renal failure patients, Nephrol. Dial. Transplant. 21 (2006) 2120–2126.
[110] S.R. Majumdar, C.M. Kjellstrand, W.J. Tymchak, M. Hervas-Malo, D.A. Taylor, K.K. Teo, Forced euvolemic diuresis with mannitol and furosemide for prevention of contrast-induced nephropathy in patients with CKD undergoing coronary angiography: a randomized controlled trial, Am. J. Kidney Dis. 54 (2009) 602–609.
[111] C.E. Murry, R.B. Jennings, K.A. Reimer, Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium, Circulation 74 (1986) 1124–1136.
[112] R.K. Kharbanda, T.T. Nielsen, A.N. Redington, Translation of remote ischaemic preconditioning into clinical practice, Lancet 374 (2009) 1557–1565.
[113] J.M. Weinberg, The cell biology of ischemic renal injury, Kidney Int. 39 (1991) 476–500.
[114] S.R. Walsh, T.Y. Tang, P. Kullar, D.P. Jenkins, D.P. Dutka, M.E. Gaunt, Ischaemic preconditioning during cardiac surgery: systematic review and meta-analysis of perioperative outcomes in randomized clinical trials, Eur. J. Cardiothorac. Surg. 34 (2008) 985–994.
[115] A. Zarbock, J.A. Kellum, Remote ischemic preconditioning and protection of the kidney – a novel therapeutic option, Crit. Care Med. 44 (2016) 607–616.
[116] A. Zarbock, J.A. Kellum, H. Van Aken, et al., Long-term effects of remote ischemic preconditioning on kidney function in high-risk cardiac surgery patients: follow-up results from the renal RIP trial, Anesthesiology 126 (2017) 787–798.
[117] F. Er, A.M. Nia, H. Dopp, et al., Ischemic preconditioning for prevention of contrast medium-induced nephropathy: randomized pilot Ren Pro Trial (Renal Protection Trial), Circulation 126 (2012) 296–303.
[118] T.P. Menting, T.B. Sterenborg, Y. de Waal, et al., Remote ischemic preconditioning to reduce contrast-induced nephropathy: a randomized controlled trial, Eur. J. Vasc. Endovasc. Surg. 50 (2015) 527–532.
[119] M.A. Stevens, P.A. McCullough, K.J. Tobin, et al., A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the P.R.I.N.C.E. Study. Prevention of Radiocontrast induced Nephropathy Clinical Evaluation, J. Am. Coll. Cardiol. 33 (1999) 403–411.
[120] C. Briguori, G. Visconti, A. Focaccio, et al., REMEDIAL II investigators. Renal insufficiency after contrast media administration trial II (REMEDIALII): renal guard system in high-risk patients for contrast-induced acute kidney injury, Circulation 124 (2011) 1260–1269.
[121] A. Putzu, M. BoscoloBerto, A. Belletti, et al., Prevention of contrast-induced acute kidney injury by furosemide with matched hydration in patients undergoing interventional procedures: a systematic review and meta-analysis of randomized trials, JACC Cardiovasc. Interv. 10 (2017) 355–363.
[122] G. Marenzi, C. Ferrari, I. Marana, et al., Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (induced diuresis with matched hydration compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial, JACC Cardiovasc. Interv. 5 (2012) 90–97.