

Contrast-induced acute kidney injury: A review of practical points

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Abstract

Contrast-induced acute kidney injury (CI-AKI) is one

of the most common causes of AKI in clinical practice. CI-AKI has been found to be strongly associated with morbidity and mortality of the patients. Furthermore, CI-AKI may not be always reversible and it may be associated with the development of chronic kidney disease. Pathophysiology of CI-AKI is not exactly understood and there is no consensus on the preventive strategies. CI-AKI is an active research area thus clinicians should be updated periodically about this topic. In this review, we aimed to discuss the indications of contrast-enhanced imaging, types of contrast media and their impact on nephrotoxicity, major pathophysiological mechanisms, risk factors and preventive strategies of CI-AKI and alternative non-contrast-enhanced imaging methods.

Key words: Angiography; Nephrotoxicity; Computed tomography; Contrast-induced acute kidney injury; Contrast media; Cholesterol embolization syndrome; Hemodialysis; Contrast nephropathy

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Core tip: The best preventive measure of contrast-induced acute kidney injury is to avoid unnecessary contrast administration which requires a good knowledge of indications and risk factors of contrast-enhanced imaging. Recently, alternative non-contrast-enhanced imaging modalities have been developed which may help us to decrease the frequency of contrast administration. In this review, these alternative modalities are discussed concisely. Type, osmolality, molecular structure and viscosity of contrast media (CM) are important determinants of nephrotoxicity. Major studies and meta-analyses comparing CM in terms of renal safety are also discussed.

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INTRODUCTION

Medical imaging has become an important diagnostic and therapeutic tool in clinical medicine in the era of great technological advances. Contrast media (CM) are increasingly used for better imaging in a broad spectrum of areas such as diagnostic computed tomography (CT) and magnetic resonance imaging (MRI), procedures of interventional radiology and percutaneous transluminal coronary angioplasty (PTCA). There are several adverse effects of CM including nausea, vomiting, thyroid dysfunction and hypersensitivity reactions such as urticaria, laryngeal edema, bronchospasm, hypotension and anaphylactoid shock^[1].

Contrast-induced acute kidney injury (CI-AKI) is one of the most important adverse effects of CM. In the past, CI-AKI was considered to be a mild state with asymptomatic and transient elevations in serum creatinine values however recent studies have demonstrated that both short term and long-term mortality rates have been found to be significantly higher in patients with CI-AKI compared to patients without CI-AKI^[2]. Furthermore, a history of CI-AKI may be associated with development of chronic kidney disease (CKD) and progression to end-stage renal disease (ESRD) in long term^[3,4].

In this review, we aimed to discuss the indications of contrast-enhanced imaging, types of CM and their impact on nephrotoxicity, major pathophysiological mechanism of CI-AKI, risk factors and preventive strategies of CI-AKI and alternative non-contrast-enhanced imaging methods.

DEFINITION OF CM

CM is a chemical substance which is used to improve the image quality of various body parts, to differentiate pathological from healthy tissues and to better delineate vascular structures. CM may be used by the way of oral route, intravascular or also through other luminal organs however absorption and nephrotoxic effects of CM used other than intravascular route may be negligible. In this review, the effects of intravascular administration of CM will be discussed.

DEFINITION OF CI-AKI

Various definitions of CI-AKI have been used in the literature. The most widely used definition is the increase in serum creatinine ≥ 0.5 mg/dL or 25% increase of serum creatinine from the baseline value at 48 h after CM administration. However timing of serum creatinine analysis after CM-enhanced imaging is controversial. Measurement as early as 12 h after the procedure (% change of creatinine from baseline) was found to significantly predict CI-AKI and furthermore it was

associated with the development of renal damage after 30 d^[5]. Serum cystatin C levels have also been evaluated as an early marker of CI-AKI. In the study by Briguori *et al.*^[6] performed on CKD patients undergoing PTCA, increase of cystatin C levels $\geq 10\%$ at 24 h after the procedure was found to reliably predict the patients with high risk of CI-AKI.

EPIDEMIOLOGY OF CI-AKI

Incidence of CI-AKI in patients undergoing elective, non-emergent contrast-enhanced CT has been found to be very low, $< 1\%$ ^[7]. In CKD patients, incidence of CI-AKI after intravenous CM administration was found to be 4%^[8]. However incidence of CI-AKI following contrast-enhanced CT performed in an emergency setting was found to be higher, $> 10\%$ which might reflect the underlying severe clinical status of the patient^[9]. Critically ill patients seem to be much more vulnerable to CI-AKI. In a study performed on critically ill patients without pre-existing renal disease, serum creatinine levels were elevated $\geq 25\%$ from the baseline in 18% of the patients after CM-enhanced CT^[10].

Incidence of CI-AKI in patients undergoing PTCA with normal baseline renal function was reported to be $< 3\%$ ^[11]. However, the incidence of CI-AKI was found to be as high as 40% in CKD patients undergoing PTCA^[12,13].

NEPHROTOXICITY OF MRI CONTRAST AGENTS

Until recently, MRI contrast agents also called gadolinium-based contrast agents (GBCA) have been considered to be safe in terms of nephrotoxicity. However GBCA has also been reported to cause AKI especially at high doses used for angiography in patients with pre-existing CKD and diabetic nephropathy^[14-16]. In an *in vitro* study, cytotoxicity of GBCA was compared to that of iodinated CM in renal tubular cells at angiographic concentrations and GBCA was not less cytotoxic compared with iomeprol^[17]. In another study, urinary interleukin-18 and N-acetyl-glucosaminidase levels were found to increase transiently after administration of GBCA in patients with normal renal function^[18]. These results suggest that GBCA also induces cytotoxicity in renal tubular cells. Another important adverse effect of GBCA is the specific clinical entity called nephrogenic systemic fibrosis (NSF) which occurs especially in patients with CKD. NSF is a potentially mortal complication associated with GBCA. Recently, a relationship between previous gadolinium administrations and high signal intensity in the several parts of the brain has been suggested independent of renal function^[19,20]. Gadolinium concentration in tissue was found to be strongly associated with cumulative gadolinium dose^[21]. Currently, clinical significance of gadolinium deposition in tissues is unclear, further studies are needed to clarify this issue.

In clinical practice, although GBCA are considered to

Table 1 Common indications for contrast media use in medical imaging

Diagnosis and treatment of vascular diseases such as coronary artery disease, pulmonary thromboembolism, arteriovenous malformations, aneurysms, arterial dissections and thrombosis
Diagnosis and staging of neoplastic diseases and mass lesions
Diagnosis of inflammatory and infectious diseases such as multiple sclerosis, meningitis, pancreatitis, diverticulitis

be relatively safer than iodinated CM, risks of AKI, NSF and brain deposition should be kept in mind^[14,16].

CLINICAL ISSUES NECESSITATING CM USE

It is important for clinicians to know the indications of contrast-enhanced imaging to avoid unnecessary contrast administration and its related complications. Common indications of CM use in clinical medicine are presented in Table 1. Accordingly, vascular, neoplastic and inflammatory diseases necessitate contrast-enhanced imaging. However CM is not usually suitable for the imaging of intracranial hemorrhages, cervical trauma, simple bone fractures, interstitial lung diseases and urinary system stones.

TYPES OF IODINATED CM AND THEIR IMPACT ON NEPHROTOXICITY

Type, osmolality, molecular structure and viscosity of CM are important determinants of nephrotoxicity associated with these agents (Table 2). Hyperosmolal CM (HOCM) was shown to more frequently cause CI-AKI compared with low-osmolal CM (LOCM)^[22]. However HOCM are no more used in clinical practice. There are controversial results in studies comparing iso-osmolal CM (IOCM) and LOCM as seen in Table 3. In most of these studies, no difference was found between IOCM and LOCM in terms of renal safety. Meta-analyses comparing IOCM and LCOM are presented in Table 4. In the meta-analysis by Reed *et al*^[23], iodixanol (IOCM) was found to be associated with a reduced risk of CI-AKI compared to iohexol (LOCM) however risk of CI-AKI was not significantly different between iodixanol and other LOCM. In a very recent meta-analysis by Eng *et al*^[24], a modest decrease in the risk of CI-AKI was found with iodixanol (IOCM) when compared to other LOCM however no difference was found between the groups in terms of risk of renal replacement therapy, cardiovascular outcomes or death. Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommended to use LOCM or IOCM instead of HOCM however due to lack of reliable evidence, no recommendation was made about the preference of IOCM or LOCM^[25].

IOCM has lower osmolality compared with LOCM, however since IOCM has dimeric structure, it has higher

viscosity than that of monomeric LOCM. Viscosity rather than osmolality determines the resistance to blood flow, thus IOCM may impair renal medullary blood flow to a greater extent compared to LOCM^[26]. Lack of clear superiority of IOCM over LOCM in terms of renal safety may be caused by higher viscosity of IOCM.

MAJOR PATHOPHYSIOLOGICAL MECHANISMS OF CI-AKI

Exact pathophysiological mechanism of CI-AKI is not known and includes complex cascades of events. Proposed mechanisms of CI-AKI are presented in Table 5. The most important elements of pathophysiological mechanism of CI-AKI seem to be the medullary hypoxia due to CM-induced medullary vasoconstriction^[27-29] and direct renal tubular cytotoxicity^[30-33]. CM-induced vasoconstriction is not exactly understood but it is probably caused by an imbalance between vasoconstrictive (endothelin, adenosine) and vasodilatory mediators (nitric oxide and prostacyclin)^[28,32,34]. The contribution of oxidative stress seems to be an important and complementary event that further exacerbates CI-AKI^[32,35,36].

In normal physiological state, renal medullary blood flow and oxygen tension are relatively lower than those of the renal cortex. Furthermore, thick ascending limb located in the outer part of the renal medulla has a high-rate of ion transport with increased oxygen consumption exacerbating the relative hypoxia of the renal medulla. The most susceptible part of the nephron to hypoxia is well-known to be the renal medulla. CM is shown to decrease the oxygen tension of the renal medulla and simultaneously CM - induced osmotic diuresis causes increased sodium delivery to thick ascending limb leading to increased oxygen demand^[27,37].

CM is known to cause direct mesangial and tubular cell toxicity. Proposed mechanisms of CM-induced cytotoxicity include oxidative stress, cellular energy failure, impaired cellular calcium homeostasis and increased apoptosis^[33,38-40]. In the study by Peer *et al*^[33], iodinated CM at different concentrations was found to induce apoptosis in both mesangial and tubular cells. The relationship between hypoxia, oxidative stress and direct cytotoxicity is not well-understood in the context of CI-AKI. Previously, a mismatch between the metabolic demands and the perfusion of renal medulla, in another words "relative hypoxia" was suggested to cause increased oxidative stress leading to further cytotoxicity^[36]. However, recently, in the study by Liu *et al*^[32], CM-induced direct cytotoxicity has been shown to cause increased oxidative stress even in the absence of hypoxia. Oxidative stress seemed to be a consequence not a cause of renal tubular injury. Furthermore, in this study CM was found to increase tubuloglomerular feedback which might contribute to disturbances of renal perfusion and filtration^[32]. It may suggested that direct cytotoxicity of CM may be the primary event that pull the trigger rather than hypoxia, hypoperfusion or oxidative stress in the pathophysiological mechanism of CI-AKI.

Table 2 Types, osmolalities and molecular structures of iodinated-contrast media

Osmolality	High osmolal (> 1400 mosm/kg)	Low osmolal (500-850 mosm/kg)	Iso-osmolal (290 mosm/kg)
Molecular structure	Ionic/monomer	Ionic/dimer	Non-ionic/monomer
Name of molecule	Diatrizoate (Hypaque)	Ioxaglate (Hexabrix)	Iohexol (Omnipaque) Iopamidol (Isovue) Ioversol (Optiray) Iopromide (Ultravist) Iopentol (Imagopaque) Iomeprol (Iomeron)

Table 3 Major studies comparing low-osmolal and iso-osmolal contrast media in terms of renal safety

Ref.	Baseline renal functions/patient population	Procedure/administration route	Compared drugs	Aim of the study/primary end points	Results
Feldkamp <i>et al</i> ^[94]	Normal GFR	PTCA (intra-arterial)	Iodixanol (IOCM) vs Iopromide (LOCM)	≥ 25% increase in SCr at 48 h	No difference
Hardiek <i>et al</i> ^[95]	Normal GFR, diabetic patients	PTCA (intra-arterial)	Iodixanol (IOCM) vs Iopamidol (LOCM)	≥ 25% increase in SCr days 1, 3 and 7	No difference
Aspelin <i>et al</i> ^[96] (NEPHRIC)	CKD, diabetic patients	PTCA (intra-arterial)	Iodixanol (IOCM) vs Iohexol (LOCM)	Peak increase in SCr day 0-3	Iso-osmolal safer than low-osmolal CM
Jo <i>et al</i> ^[97] (RECOVER)	CKD	PTCA (intra-arterial)	Iodixanol (IOCM) vs Ioxaglate (LOCM)	Increase in SCr ≥ 25% or ≥ 0.5 mg/dL within 2 d	Iso-osmolal safer than low-osmolal CM
Solomon <i>et al</i> ^[98] (CARE)	CKD	PTCA (intra-arterial)	Iodixanol (IOCM) vs Iopamidol (LOCM)	Increase in SCr > 0.5 mg/dL at 45-120 h	No difference
Rudnick <i>et al</i> ^[99] (VALOR)	CKD	PTCA (intra-arterial)	Iodixanol (IOCM) vs Ioversol (LOCM)	Increase in SCr > 0.5 mg/dL within 72 h	No difference
Barrett <i>et al</i> ^[8] (IMPACT)	CKD	CT (intravenous)	Iodixanol (IOCM) vs Iopamidol (LOCM)	Increase in SCr > 0.5 mg/dL or ≥ 25% at 48-72 h	No difference
Kuhn <i>et al</i> ^[100] (PREDICT)	CKD	CT (intravenous)	Iodixanol (IOCM) vs Iopamidol (LOCM)	Increase in SCr > 0.5 mg/dL within 48-72 h	No difference
Thomsen <i>et al</i> ^[101] (ACTIVE)	CKD	CT (intravenous)	Iodixanol (IOCM) vs Iomeprol (LOCM)	Increase in SCr > 0.5 mg/dL at 48-72 h	Low-osmolal safer than iso-osmolal CM
Nguyen <i>et al</i> ^[102]	CKD	CT (intravenous)	Iodixanol (IOCM) vs Iopromide (LOCM)	Peak rise in SCr days 1-3	Iso-osmolal safer than low-osmolal CM
Wessely <i>et al</i> ^[103]	CKD	PTCA (intra-arterial)	Iodixanol (IOCM) vs Iomeprol (LOCM)	Peak increase in SCr	No difference

CM: Contrast media; CKD: Chronic kidney disease; LOCM: Low-osmolal contrast media; CT: Computed tomography; PTCA: Percutaneous transluminal coronary angioplasty.

CM - induced increase in blood and renal tubular viscosity may lead to resistance to blood flow and further exacerbate the medullary hypoxia^[41]. Another important mechanism may be the mitochondrial dysfunction, especially ionic CM was found to impair the mitochondrial functions and membrane potentials in proximal tubular cells^[42].

RISK FACTORS FOR CI-AKI

Patients who are scheduled to have a contrast-enhanced diagnostic or interventional procedure should be evaluated for risk factors of CI-AKI (Table 6). Most important risk factors for CI-AKI are pre-existing CKD (GFR < 60 mL/min per 1.73 m²) and diabetes mellitus which may have additive effects on each other. In a study performed on patients undergoing contrast-enhanced CT, incidence of CI-AKI was found to be higher in diabetic CKD patients compared with non-diabetic CKD patients^[43].

Impacts of the type of imaging procedure and administration route of CM on CI-AKI

Type of the contrast-enhanced procedure seems to be an important determinant of CI-AKI. As aforementioned in this review, risk of CI-AKI with invasive PTCA seems to be higher compared to that of contrast-enhanced CT. This difference of the risk of CI-AKI between the two procedures may be caused by two reasons: (1) clinical status and comorbidities of the patients; and (2) administration route of the CM. Patients undergoing PTCA usually have significant ischemic heart disease and advanced atherosclerosis. During PTCA, significant hypotension may occur leading to ischemic nephropathy in addition to CI-AKI. Another important adverse event that may occur with invasive angiographic procedures is the cholesterol embolization syndrome (CES) which is sometimes hard to differentiate from CI-AKI. Administration route of the CM may also be important in the occurrence of CI-AKI. For contrast enhanced CT, CM is given intravenously, however

Table 4 Meta-analyses comparing iso-osmolal and low-osmolal contrast media in terms of renal safety

Metaanalyses	Baseline renal functions	Procedure/administration route	Compared drugs	Results
McCullough <i>et al</i> ^[104] (16 trials)	Both normal GFR and CKD	PTCA (intra-arterial)	Iodixanol (IOCM) <i>vs</i> various LOCM	Iodixanol safer than LOCM, <i>e.p.</i> in patients with CKD or CKD + diabetes mellitus
Reed <i>et al</i> ^[23] (16 trials)	Both normal GFR and CKD	PTCA + CT (intra-arterial + intravenous)	Iodixanol (IOCM) <i>vs</i> various LOCM	Overall, no difference. However, iodixanol safer than ioxaglate and iohexol
Heinrich <i>et al</i> ^[48] (25 trials)	Both normal GFR and CKD	PTCA + IV urography + CT (intra-arterial + intravenous)	Iodixanol (IOCM) <i>vs</i> various LOCM	Overall, no difference. However, iodixanol safer than iohexol in CKD patients when CM used <i>via</i> intra-arterial route
From <i>et al</i> ^[105] (36 trials)	Both normal GFR and CKD	PTCA + CT (intra-arterial + intravenous)	Iodixanol (IOCM) <i>vs</i> various LOCM	Overall, no difference.
Eng <i>et al</i> ^[24] (29 trials)	Both normal GFR and CKD	PTCA + IV urography + CT (intra-arterial + intravenous)	Iodixanol (IOCM) <i>vs</i> various LOCM	Iodixanol safer than iohexol Iodixanol slightly safer than LOCM but the lower risk did not exceed a minimally important clinical difference

CM: Contrast media; CKD: Chronic kidney disease; LOCM: Low-osmolal contrast media; CT: Computed tomography; PTCA: Percutaneous transluminal coronary angioplasty.

Table 5 Proposed pathophysiological mechanisms of contrast-induced acute kidney injury

Medullary vasoconstriction and hypoxia ^[27-29]
Direct cytotoxicity to renal tubular cells ^[30-33]
Release of vasoconstrictive mediators: Endothelin, adenosine, angiotensin II, vasopressin ^[28]
Reduction of vasodilatory mediators: Nitric oxide, prostacyclin ^[28,32,34]
Increased oxidative stress ^[32,35,36]
Impairment of tubulo-glomerular feedback ^[32]
Increased blood and renal tubular viscosity ^[41]
Impairment of mitochondrial function and mitochondrial membrane potential ^[42]

in PTCA, CM is given intra-arterially. Risk of CI-AKI has been found to be higher with intra-arterial CM compared to intravenous CM administration especially when CM is used suprarenally^[44,45]. With suprarenal intra-arterial administration of CM, peak CM concentration within the kidney was found to be higher^[46]. In the meta-analysis by Dong *et al*^[47], risk of CI-AKI with intra-arterial iodixanol was found to be significantly lower when compared with intra-arterial LOCM. However no difference was found between IOCM and LOCM in terms of renal safety when CM was used intravenously. Similarly, in another meta-analysis by Heinrich *et al*^[48], iodixanol was found to be safer than iohexol in CKD patients undergoing a procedure with intra-arterial CM administration. Iodixanol (IOCM) may be suggested to be a better choice for patients in the interventional cardiology setting^[47].

Volume of CM

Lower doses of CM (definitions of low dose are variable: < 30-125 mL) were found to be less nephrotoxic^[49,50]. In a study by Manske *et al*^[49], low dose of CM was defined as < 5 mL/kg per serum creatinine. Recently, newer CT modalities have been developed using low tube voltage and low CM volume to reduce radiation exposure and the risk of CI-AKI without sacrificing image quality^[51-53]. However it should be kept in mind that even very low doses of CM may lead to CI-AKI in patients with high

Table 6 Patient-related and contrast media-related risk factors for contrast-induced acute kidney injury

Patient-related risk factors
Pre-existing CKD
Diabetes mellitus and diabetic nephropathy
Older age
Simultaneous use of nephrotoxic drugs
Multiple myeloma
States of reduced kidney perfusion
Dehydration
Congestive heart failure
Hemodynamic instability
Contrast-media related risk factors
High volume of CM
Use of hyperosmolal CM
Multiple exposure to CM in short-term
Intra-arterial administration

CKD: Chronic kidney disease; CM: Contrast media.

risk factors.

RISK SCORING FOR CI-AKI

Several risk scoring systems have been developed to predict the CI-AKI. In the study by Mehran *et al*^[54], CI-AKI was defined as an increase $\geq 25\%$ and/or ≥ 0.5 mg/dL in serum creatinine at 48 h after PCI and they proposed a CI-AKI risk stratification score based on 8 readily available variables including (1) patient-related features such as age > 75 years, diabetes mellitus, chronic congestive heart failure (CHF), acute pulmonary edema, hypotension, anemia, and CKD; (2) procedure-related features such as the use of IABP or increasing volumes of CM. Integer scores of these risk factors were determined as: Hypotension, 5; IABP, 5; CHF, 5; age > 75 years, 4; anemia, 3; diabetes mellitus, 3; each 100 mL of CM, 1; serum creatinine > 1.5 mg/dL, 4; eGFR = 40-60 mL/min per 1.73 m², 2; eGFR = 20-40 mL/min per 1.73 m², 4; eGFR < 20 mL/min per 1.73 m², 6. These scores are summed up and total risk score is obtained. For example, if total risk score is ≤ 5 , risk of CI-AKI is 7.5% and risk of

Table 7 Strategies to reduce the risk of contrast-induced acute kidney injury

Assess the risk of CI-AKI
Assess the need of contrast-enhancement, avoid unnecessary contrast administration
Avoid concomitant use of other nephrotoxic drugs
Hydrate the patient with isotonic saline and/or sodium bicarbonate before and after the procedure
N-acetyl-cysteine 1200 mg orally twice daily
Prefer iso-osmolal or hypo-osmolal CM
Use minimum amount of CM
Check renal functions within 1 wk of the procedure

CI-AKI: Contrast-induced acute kidney injury; CM: Contrast media.

dialysis is 0.04%. However risk of CI-AKI is 57% and risk of dialysis is approximately 13% with a total risk score of ≥ 16 . In conclusion, in this study, increasing total risk score was found to exponentially predict increased risk of CI-AKI. Another simple risk scoring for CI-AKI in patients undergoing PTCI is composed of age, creatinine and ejection fraction (ACEF score) which has been found to be an independent and useful predictor of CI-AKI defined as a rise in serum creatinine ≥ 0.5 mg/dL^[55,56].

TREATMENT OF CI-AKI

There is no specific treatment for CI-AKI. There is no evidence that any of the preventive strategies are helpful once the CI-AKI develops. Similar to the management of other types of AKI, stabilization of hemodynamic parameters and maintenance of normal fluid and electrolyte balance is crucial. Thus, prevention may be the only treatment modality for CI-AKI.

PREVENTION OF CI-AKI

Preventive strategies of CI-AKI are presented in Table 7. First things first, to prevent CI-AKI, avoid unnecessary contrast administration which requires good communication between the clinician and the radiologist. Clinicians should be informed about the medical imaging techniques alternative to contrast-enhanced medical imaging. If contrast use is inevitable, every patient should be evaluated for the risk factors for CI-AKI. Re-evaluation of concomitant use of other nephrotoxic drugs is of the utmost importance. Non-steroid anti-inflammatory drugs and nephrotoxic antibiotics such as aminoglycosides, colistin and antifungals such as amphotericin B should not be used if clinically possible.

Intravenous hydration

Various strategies and drugs have been tried to prevent CI-AKI in the literature (Table 8), however intravascular hydration seems to be the best preventive measure against CI-AKI^[57-59].

In a prospective randomized study, hydration with isotonic (0.9% saline) and half-isotonic (0.45% sodium chloride plus 5% glucose) solutions were compared in

Table 8 Experimental drugs and procedures to prevent contrast-induced acute kidney injury

Drugs
Hydration with isotonic saline ^[57-59]
N-acetyl-cysteine ^[69,106-110]
Sodium bicarbonate ^[58,68,108,109,111]
Theophylline ^[112-114]
Mannitol ^[115]
Furosemide ^[115-117]
Ascorbic acid (vitamin C) ^[118]
Tocopherol (vitamin E) ^[119]
Statins ^[120-124]
Mesna ^[125]
Dopamine ^[126]
Fenoldopam (dopamin agonist) ^[127]
Calcium channel blockers (verapamil, diltiazem) ^[128]
Adenosine ^[129]
Endothelin receptor antagonists ^[130]
Atrial natriuretic peptide ^[131]
Iloprost (PGI ₂ analogue) ^[132]
Misoprostol (PGE ₁ analogue) ^[133]
Trimetazidine ^[134]
Erythropoetin ^[135,136]
Nebivolol ^[137]
Sodium citrate ^[138]
Procedures
Remote ischemic preconditioning ^[72,73]
Prophylactic hemodialysis/hemofiltration/hemodiafiltration ^[71,139,140]

terms of efficiency in prevention of CI-AKI in patients undergoing coronary angioplasty. Hydration was performed before, during and after the procedure and total amount of hydration was approximately 2000 mL. In this study, isotonic hydration was found to be superior to half-isotonic hydration in the prevention of CI-AKI^[57]. In a study performed on patients undergoing non-emergency cardiac catheterization, saline hydration starting from 12 h before the procedure was compared to unrestricted oral fluid intake^[59]. Patients in the first group received normal saline for 24 h (at a rate of 1 mL/kg per hour). Intravenous saline hydration was found to decrease the both incidence and severity of CI-AKI. In contrast, in a very recent prospective, randomized, non-inferiority study performed on CKD patients (eGFR: 30-59 mL/min per 1.73 m²) undergoing an elective procedure with CM, patients were randomly assigned to receive intravenous 0.9% NaCl or no prophylaxis^[60]. No prophylaxis group was found to be non-inferior to prophylaxis group and furthermore it was found to be cost-effective. However, despite the results of this study, we still strongly recommend hydration especially in patients with high risk of CI-AKI. Hypervolemia should be avoided during hydration of the patients. Monitorization of left ventricular end diastolic pressure was found to be a useful and effective way of guiding fluid replacement in a randomized controlled trial^[61]. Further studies are needed to prove the efficacy of hydration in prevention of CI-AKI.

Sodium bicarbonate

There is controversy about the efficacy of sodium bicarbonate to prevent CI-AKI, several studies found

sodium bicarbonate as protective against CI-AKI^[62,63] while others found no beneficial effect^[64-66]. In a meta-analysis, sodium bicarbonate was found to be protective against CI-AKI but with a borderline significance^[63]. In another 2 meta-analyses, no difference was found between bicarbonate and saline in terms of prevention from CI-AKI^[67,68].

There is no standard dose of sodium bicarbonate for the prevention of CI-AKI. In a study, bicarbonate solution was prepared by adding 154 mL of 1000 mEq/L sodium bicarbonate to 846 mL of 5% dextrose in H₂O^[62]. In this study, hydration with sodium bicarbonate before contrast exposure is more effective than hydration with sodium chloride for prophylaxis of CI-AKI. In another study, bicarbonate solution was prepared with 75 mL of 8.4% sodium bicarbonate added to 1 L of isotonic saline^[65]. In this study, no difference was found between sodium bicarbonate plus saline group and hydration with only saline group in terms of prevention from CI-AKI. Since sodium bicarbonate contains high amount of sodium, risk of hypervolemia should be taken into consideration especially in patients with congestive heart failure and CKD and dose of the bicarbonate should be individualized.

N-acetylcysteine

N-acetylcysteine (NAC) did not decrease the risk of CI-AKI in patients undergoing PTCA in a large randomized trial^[69]. There are several meta-analyses about the efficacy of NAC against CI-AKI with both non-significant^[70] and significant results^[67]. Although the strength of the evidence is low, NAC is a well tolerated, inexpensive drug and it has a relatively good profile of adverse effects. Thus, in 2012, KDIGO suggested NAC for patients with high risk of CI-AKI^[25]. There is no consensus on the dose of the NAC however it is usually used at a dose of 600-1200 mg orally twice daily.

Prophylactic hemodialysis/hemofiltration

Prophylactic hemodialysis (HD) and hemofiltration (HF) were not found to be protective against CI-AKI. In the meta-analysis including 8 studies of HD and 3 studies of HF, no beneficial effects of these treatment modalities was found against CI-AKI^[71]. Furthermore, HD was found to increase the risk of CI-AKI. Thus prophylactic renal replacement treatments are not recommended.

Remote ischemic preconditioning

Remote ischemic preconditioning (RIP) is an interesting procedure that has been evaluated as a potential protective mechanism of CI-AKI. RIP depends on a hypothesis that a transient ischemia of an organ may protect against an ischemic injury of another distant organ. Mostly, RIP has been induced by arm ischemia performed by inflation of blood pressure cuffs. In preliminary studies, RIP has been found to decrease the risk of CI-AKI^[72,73]. However further randomized clinical trials are needed before a recommendation can be made.

Should we stop ACEI/ARB treatments before the contrast-enhanced imaging?

Some clinicians may prefer to stop angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) before the contrast administration because ACEI/ARB are considered to increase the risk of CI-AKI. Supporting these concerns, in a retrospective study, use of ACEI/ARBs during PTCA was found to be independently associated with increased risk of CI-AKI^[74]. However in a prospective randomized trial, discontinuation of ACEI/ARB treatments 24 h before PTCA did not influence the incidence of CI-AKI in patients with CKD^[75]. We think that, cessation of ACEI/ARB treatments for only 1 d before the procedure might not be adequate because renal hemodynamic effects of these drugs might last longer. In a very recent meta-analysis, ACEI use was not found to have a significant effect on the CI-AKI in patients undergoing PTCA^[76]. In summary, there is not enough evidence to recommend withholding or continuing ACEI/ARB treatments before contrast-enhanced imaging.

Should we stop metformin treatment before the contrast-enhanced imaging?

Metformin is not a nephrotoxic drug however it is excreted by the kidney. Metformin is known to cause severe lactic acidosis in patients with renal impairment. About 8% of cases reporting metformin induced lactic acidosis were found to be associated with CI-AKI^[77]. Cessation of metformin at least 48 h before the contrast administration is a common but controversial clinical practice^[78]. According to other researchers, the risk of metformin induced lactic acidosis is extremely low in patients with normal renal function thus discontinuation of metformin is considered unnecessary in non-uremic patients^[79]. We think that it will be appropriate to discontinue metformin especially in CKD patients who are planned to have a contrast-enhanced procedure.

ALTERNATIVE NON-CONTRAST ENHANCED IMAGING TECHNIQUES

In the era of rapidly evolving technology, new non-contrast-enhanced imaging modalities have been developed (Table 9). Most of these modalities are MRI-based techniques. Knowledge of these new techniques may be beneficial for the renal health of the patients needing contrast-enhanced imaging and interventions. Preference of these imaging modalities may be discussed between the clinician and radiologist.

CONTRAST USE IN END-STAGE RENAL DISEASE

There are two concerns about the use of iodinated CM in patients with ESRD; risk of loss of residual renal function (RRF) and CM-induced hypervolemia.

Table 9 Alternative non-contrast enhanced imaging techniques

Name of the technique	Clinical indications	Notes
TOF MR angiography	Cerebral aneurysm Stroke Atherosclerotic carotid disease Arteriovenous malformation Peripheral artery disease (less frequently)	No contrast agent is required
ECG-gated fast spin echo MR angiography	Peripheral artery disease Thoraco-abdominal aortic aneurysm	No contrast agent is required. Higher image quality compared to TOF MR angiography in peripheral arterial imaging
SSFP MR imaging	Coronary artery disease Myocardial viability and function Pericardial diseases Renal artery stenosis Congenital heart diseases	No contrast agent is required
Arterial spin labeling with/without SSFP	Native and transplanted renal renal artery stenosis Renal perfusion Cerebral blood flow Characterization of masses	No contrast agent is required. Evaluation of organ perfusion When combined with SSFP, it can be used as an angiographic imaging
Phase contrast MR imaging	Imaging of major thoraco-abdominal vascular structures Congenital heart disease Renal artery stenosis	No contrast agent is required. Quantification of blood flow and velocity
Carbon-dioxide angiography	Peripheral artery disease (mostly infra-diaphragmatic)	No contrast agent is required. Non-allergenic, non-nephrotoxic, inexpensive. Neurotoxic, risk of air trapping and distal ischemia

TOF: Time-of-flight; MR: Magnetic resonance; ECG: Electrocardiography; SSFP: Steady-state free precession.

RRF is associated with better outcome and survival in patients with ESRD^[80]. Thus it should be preserved by avoiding unnecessary use of CM and nephrotoxic drugs. HD treatment after iodinated CM exposure was not shown to preserve RRF in patients with ESRD^[81].

Another concern about the contrast administration is the hypervolemia that may be induced by the CM. Sometimes clinicians may prefer to perform HD immediately after contrast enhanced imaging. However as reported by Hamani *et al*^[82], new non-ionic LOCM does not seem to increase serum osmolality, arterial blood pressure and it does not cause hypervolemia. Thus immediate HD may not be warranted to prevent hypervolemia in stable chronic HD patients.

GBCA should be better avoided in ESRD patients because of the risk of potentially mortal complication: NSF which is a systemic fibrosing disease that occurs due to exposure to GBCA especially in patients with GFR < 30 mL/min^[83]. If it is inevitable to use GBCA in ESRD patients, immediate HD after the imaging procedure should be considered because GBCA has been shown to be effectively removed by HD^[84]. However no proof exists that HD after GBCA exposure reduces the risk of NSF.

In HD patients without urine output (no RRF), if contrast-enhanced imaging is required, CT is clearly preferred over MRI to avoid the risk of NSF.

without CI-AKI^[85-87]. However there are few studies about the long-term renal prognosis of patients who developed CI-AKI. In a prospective study performed on patients with symptomatic peripheral artery disease undergoing PTCA, patients with CI-AKI were found to be at increased risk of long-term loss of renal function, cardiovascular events, and death^[88]. In this study, one year after the procedure, decline in eGFR was significantly higher in patients with CI-AKI compared with patients without CI-AKI (12.4 mL/min vs 6.2 mL/min). In another observational study on CKD patients undergoing PTCA, persistent renal dysfunction was defined as the decrease of creatinine clearance \geq 25% of baseline values at 3 mo^[3]. In this study, overall incidence of CI-AKI was found to be 12%, and persistent renal dysfunction was found in 18.6% of CI-AKI patients. Similarly, in another study performed on patients undergoing PTCA, continuous deterioration of kidney function (CDKF) was defined as > 25% increase in serum creatinine or serum creatinine > 0.5 mg/dL above baseline at 6 to 8 mo after PTCA^[4]. In this study CDFK was found in 16% of the study population and this group of patients was found to have significantly higher 5-year mortality rate. In a large study performed to find the incidence of CKD onset after PTCA, incidence of new-onset CKD within 6 mo of the procedure was found to be 0.9%^[89]. Furthermore, in this study trans-radial access site was found to be associated with less CKD than the femoral approach.

PROGNOSIS OF CI-AKI

Short and long term mortalities of patients with CI-AKI have been shown to be higher compared with patients

CES

The most important alternative diagnosis of AKI after

contrast-enhanced imaging especially PTCA is the CES which is rarer than CI-AKI however long-term renal survival is significantly worse than CI-AKI^[90]. CES manifests later than CI-AKI, usually 1-2 wk after the procedure. Dislodgement of cholesterol crystals from the atherosclerotic plaques leads to embolization of the small peripheral arterioles causing a multisystemic disease with allergic-immunological features including eosinophilia, hypocomplementemia, livedo reticularis, distal gangrenes with palpable pulses (blue-toe syndrome) and pathognomonic Hollenhorst plaques on ophthalmologic examination^[91]. Renal biopsy reveals empty clefts within the obliterated lumens of the arterioles^[90]. Differentiation of CI-AKI and CES is important because these two diseases may have different types of treatment modalities. Once developed, CI-AKI necessitates only supportive measures. However since CES is a type of allergic-immunological disease, anti-inflammatory treatments such as corticosteroids and cyclophosphamide may be considered^[92,93]. But there is no proof of efficacy of these anti-inflammatory treatments on CES.

REFERENCES

- Bottinor W**, Polkampally P, Jovin I. Adverse reactions to iodinated contrast media. *Int J Angiol* 2013; **22**: 149-154 [PMID: 24436602 DOI: 10.1055/s-0033-1348885]
- Rudnick M**, Feldman H. Contrast-induced nephropathy: what are the true clinical consequences? *Clin J Am Soc Nephrol* 2008; **3**: 263-272 [PMID: 18178787 DOI: 10.2215/CJN.03690907]
- Maioli M**, Toso A, Leoncini M, Gallopin M, Musilli N, Bellandi F. Persistent renal damage after contrast-induced acute kidney injury: incidence, evolution, risk factors, and prognosis. *Circulation* 2012; **125**: 3099-3107 [PMID: 22592896 DOI: 10.1161/CIRCULATIONAHA.111.085290]
- Nemoto N**, Iwasaki M, Nakanishi M, Araki T, Utsunomiya M, Hori M, Ikeda N, Makino K, Itaya H, Iijima R, Hara H, Takagi T, Joki N, Sugi K, Nakamura M. Impact of continuous deterioration of kidney function 6 to 8 months after percutaneous coronary intervention for acute coronary syndrome. *Am J Cardiol* 2014; **113**: 1647-1651 [PMID: 24656479 DOI: 10.1016/j.amjcard.2014.02.019]
- Ribichini F**, Graziani M, Gambaro G, Pasoli P, Pighi M, Pesarini G, Abaterusso C, Yabarek T, Brunelleschi S, Rizzotti P, Lupo A, Vassanelli C. Early creatinine shifts predict contrast-induced nephropathy and persistent renal damage after angiography. *Am J Med* 2010; **123**: 755-763 [PMID: 20670731 DOI: 10.1016/j.amjmed.2010.02.026]
- Briguori C**, Visconti G, Rivera NV, Focaccio A, Golia B, Giannone R, Castaldo D, De Micco F, Ricciardelli B, Colombo A. Cystatin C and contrast-induced acute kidney injury. *Circulation* 2010; **121**: 2117-2122 [PMID: 20439784 DOI: 10.1161/CIRCULATIONAHA.109.919639]
- Weisbord SD**, Mor MK, Resnick AL, Hartwig KC, Palevsky PM, Fine MJ. Incidence and outcomes of contrast-induced AKI following computed tomography. *Clin J Am Soc Nephrol* 2008; **3**: 1274-1281 [PMID: 18463172 DOI: 10.2215/CJN.01260308]
- Barrett BJ**, Katzberg RW, Thomsen HS, Chen N, Sahani D, Soulez G, Heiken JP, Lepanto L, Ni ZH, Ni ZH, Nelson R. Contrast-induced nephropathy in patients with chronic kidney disease undergoing computed tomography: a double-blind comparison of iodixanol and iopamidol. *Invest Radiol* 2006; **41**: 815-821 [PMID: 17035872 DOI: 10.1097/01.rli.0000242807.01818.24]
- Mitchell AM**, Jones AE, Tumlin JA, Kline JA. Incidence of contrast-induced nephropathy after contrast-enhanced computed tomography in the outpatient setting. *Clin J Am Soc Nephrol* 2010; **5**: 4-9 [PMID: 19965528 DOI: 10.2215/CJN.05200709]
- Polena S**, Yang S, Alam R, Gricius J, Gupta JR, Badalova N, Chuang P, Gintautas J, Conetta R. Nephropathy in critically ill patients without preexisting renal disease. *Proc West Pharmacol Soc* 2005; **48**: 134-135 [PMID: 16416679]
- Rihal CS**, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN, Holmes DR. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002; **105**: 2259-2264 [PMID: 12010907]
- Chong E**, Shen L, Poh KK, Tan HC. Risk scoring system for prediction of contrast-induced nephropathy in patients with pre-existing renal impairment undergoing percutaneous coronary intervention. *Singapore Med J* 2012; **53**: 164-169 [PMID: 22434288]
- Marenzi G**, Lauri G, Assanelli E, Campodonico J, De Metrio M, Marana I, Grazi M, Veglia F, Bartorelli AL. Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 2004; **44**: 1780-1785 [PMID: 15519007 DOI: 10.1016/j.jacc.2004.07.043]
- Penfield JG**, Reilly RF. What nephrologists need to know about gadolinium. *Nat Clin Pract Nephrol* 2007; **3**: 654-668 [PMID: 18033225 DOI: 10.1038/ncpneph0660]
- Fujisaki K**, Ono-Fujisaki A, Kura-Nakamura N, Komune N, Hirakawa N, Tsuruya K, Komune S, Iida M. Rapid deterioration of renal insufficiency after magnetic resonance imaging with gadolinium-based contrast agent. *Clin Nephrol* 2011; **75**: 251-254 [PMID: 21329636]
- Perazella MA**. Current status of gadolinium toxicity in patients with kidney disease. *Clin J Am Soc Nephrol* 2009; **4**: 461-469 [PMID: 19201920 DOI: 10.2215/CJN.06011108]
- Heinrich MC**, Kuhlmann MK, Kohlbacher S, Scheer M, Grgic A, Heckmann MB, Uder M. Cytotoxicity of iodinated and gadolinium-based contrast agents in renal tubular cells at angiographic concentrations: in vitro study. *Radiology* 2007; **242**: 425-434 [PMID: 17179401 DOI: 10.1148/radiol.2422060245]
- Mawad H**, Laurin LP, Naud JF, Leblond FA, Henley N, Vallée M, Pichette V, Leblanc M. Changes in Urinary and Serum Levels of Novel Biomarkers after Administration of Gadolinium-based Contrast Agents. *Biomark Insights* 2016; **11**: 91-94 [PMID: 27398022 DOI: 10.4137/BMIS39199]
- Kanda T**, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology* 2014; **270**: 834-841 [PMID: 24475844 DOI: 10.1148/radiol.13131669]
- Olchowy C**, Cebulski K, Łasecki M, Chaber R, Olchowy A, Kałwak K, Zaleska-Dorobisz U. The presence of the gadolinium-based contrast agent depositions in the brain and symptoms of gadolinium neurotoxicity - A systematic review. *PLoS One* 2017; **12**: e0171704 [PMID: 28187173 DOI: 10.1371/journal.pone.0171704]
- McDonald RJ**, McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, Williamson EE, Eckel LJ. Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging. *Radiology* 2015; **275**: 772-782 [PMID: 25742194 DOI: 10.1148/radiol.15150025]
- Lautin EM**, Freeman NJ, Schoenfeld AH, Bakal CW, Haramati N, Friedman AC, Lautin JL, Braha S, Kadish EG. Radiocontrast-associated renal dysfunction: a comparison of lower-osmolality and conventional high-osmolality contrast media. *AJR Am J Roentgenol* 1991; **157**: 59-65 [PMID: 2048540 DOI: 10.2214/ajr.157.1.2048540]
- Reed M**, Meier P, Tamhane UU, Welch KB, Moseucci M, Gurm HS. The relative renal safety of iodixanol compared with low-osmolar contrast media: a meta-analysis of randomized controlled trials. *JACC Cardiovasc Interv* 2009; **2**: 645-654 [PMID: 19628188 DOI: 10.1016/j.jcin.2009.05.002]

- 24 **Eng J**, Wilson RF, Subramaniam RM, Zhang A, Suarez-Cuervo C, Turban S, Choi MJ, Sherrod C, Hutfless S, Iyoha EE, Bass EB. Comparative Effect of Contrast Media Type on the Incidence of Contrast-Induced Nephropathy: A Systematic Review and Meta-analysis. *Ann Intern Med* 2016; **164**: 417-424 [PMID: 26830055 DOI: 10.7326/M15-1402]
- 25 **KDIGO**. Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl* 2012; **2**: 8 [DOI: 10.1038/kisup.2012.1]
- 26 **Persson PB**, Hansell P, Liss P. Pathophysiology of contrast medium-induced nephropathy. *Kidney Int* 2005; **68**: 14-22 [PMID: 15954892 DOI: 10.1111/j.1523-1755.2005.00377.x]
- 27 **Heyman SN**, Brezis M, Epstein FH, Spokes K, Silva P, Rosen S. Early renal medullary hypoxic injury from radiocontrast and indomethacin. *Kidney Int* 1991; **40**: 632-642 [PMID: 1745012]
- 28 **Sendeski M**, Patzak A, Pallone TL, Cao C, Persson AE, Persson PB. Iodixanol, constriction of medullary descending vasa recta, and risk for contrast medium-induced nephropathy. *Radiology* 2009; **251**: 697-704 [PMID: 19366904 DOI: 10.1148/radiol.2513081732]
- 29 **Liss P**, Nygren A, Erikson U, Ulfendahl HR. Injection of low and iso-osmolar contrast medium decreases oxygen tension in the renal medulla. *Kidney Int* 1998; **53**: 698-702 [PMID: 9507216 DOI: 10.1046/j.1523-1755.1998.00811.x]
- 30 **Naziroğlu M**, Yoldaş N, Uzgur EN, Kayan M. Role of contrast media on oxidative stress, Ca(2+) signaling and apoptosis in kidney. *J Membr Biol* 2013; **246**: 91-100 [PMID: 23132012 DOI: 10.1007/s00232-012-9512-9]
- 31 **Quintavalle C**, Brenca M, De Micco F, Fiore D, Romano S, Romano MF, Apone F, Bianco A, Zabatta MA, Troncone G, Briguori C, Condorelli G. In vivo and in vitro assessment of pathways involved in contrast media-induced renal cells apoptosis. *Cell Death Dis* 2011; **2**: e155 [PMID: 21562587 DOI: 10.1038/cddis.2011.38]
- 32 **Liu ZZ**, Schmerbach K, Lu Y, Perlewitz A, Nikitina T, Cantow K, Seeliger E, Persson PB, Patzak A, Liu R, Sendeski MM. 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* 2014; **306**: F864-F872 [PMID: 24431205 DOI: 10.1152/ajprenal.00302.2013]
- 33 **Peer A**, Averbukh Z, Berman S, Modai D, Averbukh M, Weissgarten J. Contrast media augmented apoptosis of cultured renal mesangial, tubular, epithelial, endothelial, and hepatic cells. *Invest Radiol* 2003; **38**: 177-182 [PMID: 12595799 DOI: 10.1097/01.RLI.0000054529.61167.84]
- 34 **Ribeiro L**, de Assunção e Silva F, Kurihara RS, Schor N, Mieko E, Higa S. Evaluation of the nitric oxide production in rat renal artery smooth muscle cells culture exposed to radiocontrast agents. *Kidney Int* 2004; **65**: 589-596 [PMID: 14717929 DOI: 10.1111/j.1523-1755.2004.00408.x]
- 35 **Bakris GL**, Lass N, Gaber AO, Jones JD, Burnett JC. Radiocontrast medium-induced declines in renal function: a role for oxygen free radicals. *Am J Physiol* 1990; **258**: F115-F120 [PMID: 2301588]
- 36 **Heyman SN**, Rosen S, Khamaisi M, Idée JM, Rosenberger C. Reactive oxygen species and the pathogenesis of radiocontrast-induced nephropathy. *Invest Radiol* 2010; **45**: 188-195 [PMID: 20195159 DOI: 10.1097/RLI.0b013e3181d2eed8]
- 37 **Cronin RE**. Contrast-induced nephropathy: pathogenesis and prevention. *Pediatr Nephrol* 2010; **25**: 191-204 [PMID: 19444480 DOI: 10.1007/s00467-009-1204-z]
- 38 **Itoh Y**, Yano T, Sendo T, Sueyasu M, Hirano K, Kanaide H, Oishi R. Involvement of de novo ceramide synthesis in radiocontrast-induced renal tubular cell injury. *Kidney Int* 2006; **69**: 288-297 [PMID: 16408118 DOI: 10.1038/sj.ki.5000057]
- 39 **Schick CS**, Haller C. Comparative cytotoxicity of ionic and non-ionic radiocontrast agents on MDCK cell monolayers in vitro. *Nephrol Dial Transplant* 1999; **14**: 342-347 [PMID: 10069186]
- 40 **Haller C**, Hizoh I. The cytotoxicity of iodinated radiocontrast agents on renal cells in vitro. *Invest Radiol* 2004; **39**: 149-154 [PMID: 15076007]
- 41 **Zhang Y**, Wang J, Yang X, Wang X, Zhang J, Fang J, Jiang X. The serial effect of iodinated contrast media on renal hemodynamics and oxygenation as evaluated by ASL and BOLD MRI. *Contrast Media Mol Imaging* 2012; **7**: 418-425 [PMID: 22649048 DOI: 10.1002/cmim.1468]
- 42 **Hardiek K**, Katholi RE, Ramkumar V, Deitrick C. Proximal tubule cell response to radiographic contrast media. *Am J Physiol Renal Physiol* 2001; **280**: F61-F70 [PMID: 11133515]
- 43 **Parfrey PS**, Griffiths SM, Barrett BJ, Paul MD, Genge M, Withers J, Farid N, McManamon PJ. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. *N Engl J Med* 1989; **320**: 143-149 [PMID: 2643041 DOI: 10.1056/NEJM198901193200303]
- 44 **Moore RD**, Steinberg EP, Powe NR, Brinker JA, Fishman EK, Graziano S, Gopalan R. Nephrotoxicity of high-osmolality versus low-osmolality contrast media: randomized clinical trial. *Radiology* 1992; **182**: 649-655 [PMID: 1535876 DOI: 10.1148/radiology.182.3.1535876]
- 45 **Li J**, Solomon RJ. Creatinine increases after intravenous contrast administration: incidence and impact. *Invest Radiol* 2010; **45**: 471-476 [PMID: 20498612 DOI: 10.1097/RLI.0b013e3181dc3b67]
- 46 **Gleeson TG**, Bulugahapitiya S. Contrast-induced nephropathy. *AJR Am J Roentgenol* 2004; **183**: 1673-1689 [PMID: 15547209 DOI: 10.2214/ajr.183.6.01831673]
- 47 **Dong M**, Jiao Z, Liu T, Guo F, Li G. Effect of administration route on the renal safety of contrast agents: a meta-analysis of randomized controlled trials. *J Nephrol* 2012; **25**: 290-301 [PMID: 22252847 DOI: 10.5301/jn.5000067]
- 48 **Heinrich MC**, Häberle L, Müller V, Bautz W, Uder M. Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low-osmolar contrast media: meta-analysis of randomized controlled trials. *Radiology* 2009; **250**: 68-86 [PMID: 19092091 DOI: 10.1148/radiol.2501080833]
- 49 **Manske CL**, Sprafka JM, Strony JT, Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. *Am J Med* 1990; **89**: 615-620 [PMID: 2239981]
- 50 **Cigarroa RG**, Lange RA, Williams RH, Hillis LD. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. *Am J Med* 1989; **86**: 649-652 [PMID: 2729314]
- 51 **Zhang LJ**, Qi L, Wang J, Tang CX, Zhou CS, Ji XM, Spearman JV, De Cecco CN, Meinel FG, Schoepf UJ, Lu GM. Feasibility of prospectively ECG-triggered high-pitch coronary CT angiography with 30 mL iodinated contrast agent at 70 kVp: initial experience. *Eur Radiol* 2014; **24**: 1537-1546 [PMID: 24737530 DOI: 10.1007/s00330-014-3157-2]
- 52 **Chen CM**, Chu SY, Hsu MY, Liao YL, Tsai HY. Low-tube-voltage (80 kVp) CT aortography using 320-row volume CT with adaptive iterative reconstruction: lower contrast medium and radiation dose. *Eur Radiol* 2014; **24**: 460-468 [PMID: 24081645 DOI: 10.1007/s00330-013-3027-3]
- 53 **Szucs-Farkas Z**, Schaller C, Bensler S, Patak MA, Vock P, Schindera ST. Detection of pulmonary emboli with CT angiography at reduced radiation exposure and contrast material volume: comparison of 80 kVp and 120 kVp protocols in a matched cohort. *Invest Radiol* 2009; **44**: 793-799 [PMID: 19884825 DOI: 10.1097/RLI.0b013e3181bfe230]
- 54 **Mehran R**, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004; **44**: 1393-1399 [PMID: 15464318 DOI: 10.1016/j.jacc.2004.06.068]
- 55 **Ranucci M**, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. *Circulation* 2009; **119**: 3053-3061 [PMID: 19506110 DOI: 10.1161/CIRCULATIONAHA.108.842393]
- 56 **Capodanno D**, Ministeri M, Dipasqua F, Dalessandro V, Cumbo S, Gargiulo G, Tamburino C. Risk prediction of contrast-induced nephropathy by ACEF score in patients undergoing coronary catheterization. *J Cardiovasc Med (Hagerstown)* 2016; **17**: 524-529 [PMID: 25304032 DOI: 10.2459/JCM.0000000000000215]

- 57 **Mueller C**, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, Marsch S, Roskamm H. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med* 2002; **162**: 329-336 [PMID: 11822926]
- 58 **Klima T**, Christ A, Marana I, Kalbermatter S, Uthoff H, Burri E, Hartwiger S, Schindler C, Breidhardt T, Marenzi G, Mueller C. Sodium chloride vs. sodium bicarbonate for the prevention of contrast medium-induced nephropathy: a randomized controlled trial. *Eur Heart J* 2012; **33**: 2071-2079 [PMID: 22267245 DOI: 10.1093/eurheartj/ehr501]
- 59 **Trivedi HS**, Moore H, Nasr S, Aggarwal K, Agrawal A, Goel P, Hewett J. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. *Nephron Clin Pract* 2003; **93**: C29-C34 [PMID: 12411756]
- 60 **Nijssen EC**, Renneberg RJ, Nelemans PJ, Essers BA, Janssen MM, Vermeeren MA, Ommen VV, Wildberger JE. 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* 2017; **389**: 1312-1322 [PMID: 28233565 DOI: 10.1016/S0140-6736(17)30057-0]
- 61 **Brar SS**, Aharonian V, Mansukhani P, Moore N, Shen AY, Jorgensen M, Dua A, Short L, Kane K. Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. *Lancet* 2014; **383**: 1814-1823 [PMID: 24856027 DOI: 10.1016/S0140-6736(14)60689-9]
- 62 **Merten GJ**, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, Bersin RM, Van Moore A, Simonton CA, Rittase RA, Norton HJ, Kennedy TP. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA* 2004; **291**: 2328-2334 [PMID: 15150204 DOI: 10.1001/jama.291.19.2328]
- 63 **Hoste EA**, De Waele JJ, Gevaert SA, Uchino S, Kellum JA. Sodium bicarbonate for prevention of contrast-induced acute kidney injury: a systematic review and meta-analysis. *Nephrol Dial Transplant* 2010; **25**: 747-758 [PMID: 19703838 DOI: 10.1093/ndt/gfp389]
- 64 **Brar SS**, Shen AY, Jorgensen MB, Kotlewski A, Aharonian VJ, Desai N, Ree M, Shah AI, Burchette RJ. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. *JAMA* 2008; **300**: 1038-1046 [PMID: 18768415 DOI: 10.1001/jama.300.9.1038]
- 65 **Vasheghani-Farahani A**, Sadigh G, Kassaian SE, Khatami SM, Fotouhi A, Razavi SA, Mansournia MA, Yamini-Sharif A, Amirzadegan A, Salarifar M, Sadeghian S, Davoodi G, Borumand MA, Esfehiani FA, Darabian S. Sodium bicarbonate plus isotonic saline versus saline for prevention of contrast-induced nephropathy in patients undergoing coronary angiography: a randomized controlled trial. *Am J Kidney Dis* 2009; **54**: 610-618 [PMID: 19619921 DOI: 10.1053/j.ajkd.2009.05.016]
- 66 **Solomon R**, Gordon P, Manoukian SV, Abbott JD, Kereiakes DJ, Jeremias A, Kim M, Dauerman HL; BOSS Trial Investigators. Randomized Trial of Bicarbonate or Saline Study for the Prevention of Contrast-Induced Nephropathy in Patients with CKD. *Clin J Am Soc Nephrol* 2015; **10**: 1519-1524 [PMID: 26185263 DOI: 10.2215/CJN.05370514]
- 67 **Subramaniam RM**, Suarez-Cuervo C, Wilson RF, Turban S, Zhang A, Sherrod C, Aboagye J, Eng J, Choi MJ, Hutfless S, Bass EB. Effectiveness of Prevention Strategies for Contrast-Induced Nephropathy: A Systematic Review and Meta-analysis. *Ann Intern Med* 2016; **164**: 406-416 [PMID: 26830221 DOI: 10.7326/M15-1456]
- 68 **Brar SS**, Hiremath S, Dangas G, Mehran R, Brar SK, Leon MB. Sodium bicarbonate for the prevention of contrast induced-acute kidney injury: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2009; **4**: 1584-1592 [PMID: 19713291 DOI: 10.2215/CJN.03120509]
- 69 **ACT Investigators**. Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized Acetylcysteine for Contrast-induced nephropathy Trial (ACT). *Circulation* 2011; **124**: 1250-1259 [PMID: 21859972 DOI: 10.1161/CIRCULATIONAHA.111.038943]
- 70 **Zagler A**, Azadpour M, Mercado C, Hennekens CH. N-acetylcysteine and contrast-induced nephropathy: a meta-analysis of 13 randomized trials. *Am Heart J* 2006; **151**: 140-145 [PMID: 16368307 DOI: 10.1016/j.ahj.2005.01.055]
- 71 **Cruz DN**, Goh CY, Marenzi G, Corradi V, Ronco C, Perazella MA. Renal replacement therapies for prevention of radiocontrast-induced nephropathy: a systematic review. *Am J Med* 2012; **125**: 66-78.e3 [PMID: 22195531 DOI: 10.1016/j.amjmed.2011.06.029]
- 72 **Igarashi G**, Iino K, Watanabe H, Ito H. Remote ischemic preconditioning alleviates contrast-induced acute kidney injury in patients with moderate chronic kidney disease. *Circ J* 2013; **77**: 3037-3044 [PMID: 23986081]
- 73 **Er F**, Nia AM, Dopp H, Hellmich M, Dahlem KM, Caglayan E, Kubacki T, Benzing T, Erdmann E, Burst V, Gassanov N. Ischemic preconditioning for prevention of contrast medium-induced nephropathy: randomized pilot RenPro Trial (Renal Protection Trial). *Circulation* 2012; **126**: 296-303 [PMID: 22735306 DOI: 10.1161/CIRCULATIONAHA.112.096370]
- 74 **Rim MY**, Ro H, Kang WC, Kim AJ, Park H, Chang JH, Lee HH, Chung W, Jung JY. The effect of renin-angiotensin-aldosterone system blockade on contrast-induced acute kidney injury: a propensity-matched study. *Am J Kidney Dis* 2012; **60**: 576-582 [PMID: 22658321 DOI: 10.1053/j.ajkd.2012.04.017]
- 75 **Rosenstock JL**, Bruno R, Kim JK, Lubarsky L, Schaller R, Panagopoulos G, DeVita MV, Michelis MF. The effect of withdrawal of ACE inhibitors or angiotensin receptor blockers prior to coronary angiography on the incidence of contrast-induced nephropathy. *Int Urol Nephrol* 2008; **40**: 749-755 [PMID: 18438718 DOI: 10.1007/s11255-008-9368-1]
- 76 **Zhou S**, Wu C, Song Q, Yang X, Wei Z. Effect of Angiotensin-Converting Enzyme Inhibitors in Contrast-Induced Nephropathy: A Meta-Analysis. *Nephron* 2016; **133**: 1-14 [PMID: 27198155 DOI: 10.1159/000445167]
- 77 **Sirtori CR**, Pasik C. Re-evaluation of a biguanide, metformin: mechanism of action and tolerability. *Pharmacol Res* 1994; **30**: 187-228 [PMID: 7862618]
- 78 **Thomsen HS**, Morcos SK. Contrast media and metformin: guidelines to diminish the risk of lactic acidosis in non-insulin-dependent diabetics after administration of contrast media. ESUR Contrast Media Safety Committee. *Eur Radiol* 1999; **9**: 738-740 [PMID: 10354898]
- 79 **Owen RJ**, Hiremath S, Myers A, Fraser-Hill M, Barrett BJ. Canadian Association of Radiologists consensus guidelines for the prevention of contrast-induced nephropathy: update 2012. *Can Assoc Radiol J* 2014; **65**: 96-105 [PMID: 24559602 DOI: 10.1016/j.carj.2012.11.002]
- 80 **Shemin D**, Bostom AG, Laliberty P, Dworkin LD. Residual renal function and mortality risk in hemodialysis patients. *Am J Kidney Dis* 2001; **38**: 85-90 [PMID: 11431186 DOI: 10.1053/ajkd.2001.25198]
- 81 **Rodby RA**. Preventing complications of radiographic contrast media: is there a role for dialysis? *Semin Dial* 2007; **20**: 19-23 [PMID: 17244114 DOI: 10.1111/j.1525-139X.2007.00233.x]
- 82 **Hamani A**, Petitclerc T, Jacobs C, Deraf G. Is dialysis indicated immediately after administration of iodinated contrast agents in patients on haemodialysis? *Nephrol Dial Transplant* 1998; **13**: 1051-1052 [PMID: 9568886]
- 83 **Kuo PH**, Kanal E, Abu-Alfa AK, Cowper SE. Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis. *Radiology* 2007; **242**: 647-649 [PMID: 17213364 DOI: 10.1148/radiol.2423061640]
- 84 **Saitoh T**, Hayasaka K, Tanaka Y, Kuno T, Nagura Y. Dialyzability of gadodiamide in hemodialysis patients. *Radiat Med* 2006; **24**: 445-451 [PMID: 16958426 DOI: 10.1007/s11604-006-0055-9]

- 85 **Kim JH**, Yang JH, Choi SH, Song YB, Hahn JY, Choi JH, Lee SH, Gwon HC. Predictors of outcomes of contrast-induced acute kidney injury after percutaneous coronary intervention in patients with chronic kidney disease. *Am J Cardiol* 2014; **114**: 1830-1835 [PMID: 25438909 DOI: 10.1016/j.amjcard.2014.09.022]
- 86 **Weisbord SD**, Chen H, Stone RA, Kip KE, Fine MJ, Saul MI, Palevsky PM. Associations of increases in serum creatinine with mortality and length of hospital stay after coronary angiography. *J Am Soc Nephrol* 2006; **17**: 2871-2877 [PMID: 16928802 DOI: 10.1681/ASN.2006030301]
- 87 **McCullough PA**, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med* 1997; **103**: 368-375 [PMID: 9375704]
- 88 **Sigterman TA**, Krasznai AG, Snoeijs MG, Heijboer R, Schurink GW, Bouwman LH. Contrast Induced Nephropathy and Long-term Renal Decline After Percutaneous Transluminal Angioplasty for Symptomatic Peripheral Arterial Disease. *Eur J Vasc Endovasc Surg* 2016; **51**: 386-393 [PMID: 26460289 DOI: 10.1016/j.ejvs.2015.08.023]
- 89 **Vuurmans T**, Byrne J, Fretz E, Janssen C, Hilton JD, Klinke WP, Djurdjev O, Levin A. Chronic kidney injury in patients after cardiac catheterisation or percutaneous coronary intervention: a comparison of radial and femoral approaches (from the British Columbia Cardiac and Renal Registries). *Heart* 2010; **96**: 1538-1542 [PMID: 20668106 DOI: 10.1136/hrt.2009.192294]
- 90 **Kronzon I**, Saric M. Cholesterol embolization syndrome. *Circulation* 2010; **122**: 631-641 [PMID: 20697039 DOI: 10.1161/CIRCULATIONAHA.109.886465]
- 91 **Dizman N**, Aydın Bahat K, Özkanlı Ş, Özkök A. Cholesterol embolization syndrome: A report of two cases. *Türk Kardiyol Dern Ars* 2016; **44**: 251-255 [PMID: 27138317 DOI: 10.5543/tkda.2015.94587]
- 92 **Yücel AE**, Kart-Köseoglu H, Demirhan B, Ozdemir FN. Cholesterol crystal embolization mimicking vasculitis: success with corticosteroid and cyclophosphamide therapy in two cases. *Rheumatol Int* 2006; **26**: 454-460 [PMID: 16025335 DOI: 10.1007/s00296-005-0012-4]
- 93 **Dizman N**, Aydın Bahat K, Özkanlı Ş, Özkök A. Authors' reply. *Türk Kardiyol Dern Ars* 2016; **44**: 538 [PMID: 27665347]
- 94 **Feldkamp T**, Baumgart D, Elsner M, Herget-Rosenthal S, Pietruck F, Erbel R, Philipp T, Kribben A. Nephrotoxicity of iso-osmolar versus low-osmolar contrast media is equal in low risk patients. *Clin Nephrol* 2006; **66**: 322-330 [PMID: 17140161]
- 95 **Hardiek KJ**, Katholi RE, Robbs RS, Katholi CE. Renal effects of contrast media in diabetic patients undergoing diagnostic or interventional coronary angiography. *J Diabetes Complications* 2008; **22**: 171-177 [PMID: 18413220 DOI: 10.1016/j.jdiacomp.2006.11.002]
- 96 **Aspelin P**, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med* 2003; **348**: 491-499 [PMID: 12571256 DOI: 10.1056/NEJMoa021833]
- 97 **Jo SH**, Youn TJ, Koo BK, Park JS, Kang HJ, Cho YS, Chung WY, Joo GW, Chae IH, Choi DJ, Oh BH, Lee MM, Park YB, Kim HS. Renal toxicity evaluation and comparison between visipaque (iodixanol) and hexabrix (ioxaglate) in patients with renal insufficiency undergoing coronary angiography: the RECOVER study: a randomized controlled trial. *J Am Coll Cardiol* 2006; **48**: 924-930 [PMID: 16949481 DOI: 10.1016/j.jacc.2006.06.047]
- 98 **Solomon RJ**, Natarajan MK, Doucet S, Sharma SK, Staniloae CS, Katholi RE, Gelormini JL, Labinaz M, Moreyra AE; Investigators of the CARE Study. Cardiac Angiography in Renally Impaired Patients (CARE) study: a randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease. *Circulation* 2007; **115**: 3189-3196 [PMID: 17562951 DOI: 10.1161/CIRCULATIONAHA.106.671644]
- 99 **Rudnick MR**, Davidson C, Laskey W, Stafford JL, Sherwin PF; VALOR Trial Investigators. Nephrotoxicity of iodixanol versus ioversol in patients with chronic kidney disease: the Visipaque Angiography/Interventions with Laboratory Outcomes in Renal Insufficiency (VALOR) Trial. *Am Heart J* 2008; **156**: 776-782 [PMID: 18946896]
- 100 **Kuhn MJ**, Chen N, Sahani DV, Reimer D, van Beek EJ, Heiken JP, So GJ. The PREDICT study: a randomized double-blind comparison of contrast-induced nephropathy after low- or isoosmolar contrast agent exposure. *AJR Am J Roentgenol* 2008; **191**: 151-157 [PMID: 18562739 DOI: 10.2214/AJR.07.3370]
- 101 **Thomsen HS**, Morcos SK, Erley CM, Grazioli L, Bonomo L, Ni Z, Romano L; Investigators in the Abdominal Computed Tomography: IOMERON 400 Versus VISIPAQUE 320 Enhancement (ACTIVE) Study. The ACTIVE Trial: comparison of the effects on renal function of iomeprol-400 and iodixanol-320 in patients with chronic kidney disease undergoing abdominal computed tomography. *Invest Radiol* 2008; **43**: 170-178 [PMID: 18301313 DOI: 10.1097/RLI.0b013e31815f3172]
- 102 **Nguyen SA**, Suranyi P, Ravenel JG, Randall PK, Romano PB, Strom KA, Costello P, Schoepf UJ. Iso-osmolality versus low-osmolality iodinated contrast medium at intravenous contrast-enhanced CT: effect on kidney function. *Radiology* 2008; **248**: 97-105 [PMID: 18483232 DOI: 10.1148/radiol.2481071484]
- 103 **Wessely R**, Koppa T, Bradaric C, Vorpahl M, Braun S, Schulz S, Mehili J, Schömig A, Kastrati A; Contrast Media and Nephrotoxicity Following Coronary Revascularization by Angioplasty Trial Investigators. Choice of contrast medium in patients with impaired renal function undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv* 2009; **2**: 430-437 [PMID: 20031753 DOI: 10.1161/CIRCINTERVENTIONS.109.874933]
- 104 **McCullough PA**, Bertrand ME, Brinker JA, Stacul F. A meta-analysis of the renal safety of isosmolar iodixanol compared with low-osmolar contrast media. *J Am Coll Cardiol* 2006; **48**: 692-699 [PMID: 16904536 DOI: 10.1016/j.jacc.2006.02.073]
- 105 **From AM**, Al Badarin FJ, McDonald FS, Bartholmai BJ, Cha SS, Rihal CS. Iodixanol versus low-osmolar contrast media for prevention of contrast induced nephropathy: meta-analysis of randomized, controlled trials. *Circ Cardiovasc Interv* 2010; **3**: 351-358 [PMID: 20647563 DOI: 10.1161/CIRCINTERVENTIONS.109.917070]
- 106 **Fishbane S**. N-acetylcysteine in the prevention of contrast-induced nephropathy. *Clin J Am Soc Nephrol* 2008; **3**: 281-287 [PMID: 18003766 DOI: 10.2215/CJN.02590607]
- 107 **Thiele H**, Hildebrand L, Schirdewahn C, Eitel I, Adams V, Fuernau G, Erbs S, Linke A, Diederich KW, Nowak M, Desch S, Guterlet M, Schuler G. Impact of high-dose N-acetylcysteine versus placebo on contrast-induced nephropathy and myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. The LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate Percutaneous Coronary Intervention Acute Myocardial Infarction N-ACC) Trial. *J Am Coll Cardiol* 2010; **55**: 2201-2209 [PMID: 20466200 DOI: 10.1016/j.jacc.2009.08.091]
- 108 **Thayssen P**, Lassen JF, Jensen SE, Hansen KN, Hansen HS, Christiansen EH, Junker A, Ravkilde J, Thuesen L, Veien KT, Jensen LO. Prevention of contrast-induced nephropathy with N-acetylcysteine or sodium bicarbonate in patients with ST-segment-myocardial infarction: a prospective, randomized, open-labeled trial. *Circ Cardiovasc Interv* 2014; **7**: 216-224 [PMID: 24714489 DOI: 10.1161/CIRCINTERVENTIONS.113.000653]
- 109 **Recio-Mayoral A**, Chaparro M, Prado B, Cózar R, Méndez I, Banerjee D, Kaski JC, Cubero J, Cruz JM. The reno-protective effect of hydration with sodium bicarbonate plus N-acetylcysteine in patients undergoing emergency percutaneous coronary intervention: the RENO Study. *J Am Coll Cardiol* 2007; **49**: 1283-1288 [PMID: 17394959 DOI: 10.1016/j.jacc.2006.11.034]
- 110 **Teipel M**, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med* 2000; **343**: 180-184 [PMID: 10900277 DOI: 10.1056/NEJM200007203430304]
- 111 **Zhang B**, Liang L, Chen W, Liang C, Zhang S. The efficacy of

- sodium bicarbonate in preventing contrast-induced nephropathy in patients with pre-existing renal insufficiency: a meta-analysis. *BMJ Open* 2015; **5**: e006989 [PMID: 25783425 DOI: 10.1136/bmjopen-2014-006989]
- 112 **Huber W**, Jeschke B, Page M, Weiss W, Salmhofer H, Schweigart U, Ilgmann K, Reichenberger J, Neu B, Classen M. Reduced incidence of radiocontrast-induced nephropathy in ICU patients under theophylline prophylaxis: a prospective comparison to series of patients at similar risk. *Intensive Care Med* 2001; **27**: 1200-1209 [PMID: 11534569]
- 113 **Dai B**, Liu Y, Fu L, Li Y, Zhang J, Mei C. Effect of theophylline on prevention of contrast-induced acute kidney injury: a meta-analysis of randomized controlled trials. *Am J Kidney Dis* 2012; **60**: 360-370 [PMID: 22516682 DOI: 10.1053/j.ajkd.2012.02.332]
- 114 **Katholi RE**, Taylor GJ, McCann WP, Woods WT, Womack KA, McCoy CD, Katholi CR, Moses HW, Mishkel GJ, Lucore CL. Nephrotoxicity from contrast media: attenuation with theophylline. *Radiology* 1995; **195**: 17-22 [PMID: 7892462 DOI: 10.1148/radiology.195.1.7892462]
- 115 **Solomon R**, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide on acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 1994; **331**: 1416-1420 [PMID: 7969280 DOI: 10.1056/NEJM199411243312104]
- 116 **Marenzi G**, Ferrari C, Marana I, Assanelli E, De Metrio M, Teruzzi G, Veglia F, Fabbicocchi F, Montorsi P, Bartorelli 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* 2012; **5**: 90-97 [PMID: 22230154 DOI: 10.1016/j.jcin.2011.08.017]
- 117 **Weinstein JM**, Heyman S, Brezis M. Potential deleterious effect of furosemide in radiocontrast nephropathy. *Nephron* 1992; **62**: 413-415 [PMID: 1300436]
- 118 **Spargias K**, Alexopoulos E, Kyrzopoulos S, Iokovis P, Greenwood DC, Manginas A, Voudris V, Pavlides G, Buller CE, Kremastinos D, Cokkinos DV. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation* 2004; **110**: 2837-2842 [PMID: 15492300 DOI: 10.1161/01.CIR.0000146396.19081.73]
- 119 **Tasanarong A**, Vohakiat A, Hutayanon P, Piyayotai D. New strategy of α - and γ -tocopherol to prevent contrast-induced acute kidney injury in chronic kidney disease patients undergoing elective coronary procedures. *Nephrol Dial Transplant* 2013; **28**: 337-344 [PMID: 23314316 DOI: 10.1093/ndt/gfs525]
- 120 **Toso A**, Maioli M, Leoncini M, Gallopin M, Tedeschi D, Micheletti C, Manzone C, Amato M, Bellandi F. Usefulness of atorvastatin (80 mg) in prevention of contrast-induced nephropathy in patients with chronic renal disease. *Am J Cardiol* 2010; **105**: 288-292 [PMID: 20102936 DOI: 10.1016/j.amjcard.2009.09.026]
- 121 **Patti G**, Ricottini E, Nusca A, Colonna G, Pasceri V, D'Ambrosio A, Montinaro A, Di Sciascio G. 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* 2011; **108**: 1-7 [PMID: 21529740 DOI: 10.1016/j.amjcard.2011.03.001]
- 122 **Jo SH**, Koo BK, Park JS, Kang HJ, Cho YS, Kim YJ, Youn TJ, Chung WY, Chae IH, Choi DJ, Sohn DW, Oh BH, Park YB, Choi YS, Kim HS. 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* 2008; **155**: 499.e1-499.e8 [PMID: 18294484 DOI: 10.1016/j.ahj.2007.11.042]
- 123 **Barbieri L**, Verdoia M, Schaffer A, Nardin M, Marino P, De Luca G. The role of statins in the prevention of contrast induced nephropathy: a meta-analysis of 8 randomized trials. *J Thromb Thrombolysis* 2014; **38**: 493-502 [PMID: 24705677 DOI: 10.1007/s11239-014-1076-3]
- 124 **Quintavalle C**, Fiore D, De Micco F, Visconti G, Focaccio A, Golia B, Ricciardelli B, Donnarumma E, Bianco A, Zabatta MA, Troncone G, Colombo A, Briguori C, Condorelli G. Impact of a high loading dose of atorvastatin on contrast-induced acute kidney injury. *Circulation* 2012; **126**: 3008-3016 [PMID: 23147173 DOI: 10.1161/CIRCULATIONAHA.112.103317]
- 125 **Ludwig U**, Riedel MK, Backes M, Imhof A, Muche R, Keller F. MESNA (sodium 2-mercaptoethanesulfonate) for prevention of contrast medium-induced nephrotoxicity - controlled trial. *Clin Nephrol* 2011; **75**: 302-308 [PMID: 21426884]
- 126 **Bakris GL**, Lass NA, Glock D. Renal hemodynamics in radiocontrast medium-induced renal dysfunction: A role for dopamine-1 receptors. *Kidney Int* 1999; **56**: 206-210 [PMID: 10411694 DOI: 10.1046/j.1523-1755.1999.00528.x]
- 127 **Stone GW**, McCullough PA, Tumlin JA, Lepor NE, Madyoon H, Murray P, Wang A, Chu AA, Schaer GL, Stevens M, Wilensky RL, O'Neill WW. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *JAMA* 2003; **290**: 2284-2291 [PMID: 14600187 DOI: 10.1001/jama.290.17.2284]
- 128 **Bakris GL**, Burnett JC. A role for calcium in radiocontrast-induced reductions in renal hemodynamics. *Kidney Int* 1985; **27**: 465-468 [PMID: 2581011]
- 129 **Pflueger A**, Larson TS, Nath KA, King BF, Gross JM, Knox FG. Role of adenosine in contrast media-induced acute renal failure in diabetes mellitus. *Mayo Clin Proc* 2000; **75**: 1275-1283 [PMID: 11126837 DOI: 10.4065/75.12.1275]
- 130 **Wang A**, Holcslaw T, Bashore TM, Freed MI, Miller D, Rudnick MR, Szerlip H, Thames MD, Davidson CJ, Shusterman N, Schwab SJ. Exacerbation of radiocontrast nephrotoxicity by endothelin receptor antagonism. *Kidney Int* 2000; **57**: 1675-1680 [PMID: 10760103 DOI: 10.1046/j.1523-1755.2000.00012.x]
- 131 **Kurnik BR**, Allgren RL, Genter FC, Solomon RJ, Bates ER, Weisberg LS. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis* 1998; **31**: 674-680 [PMID: 9531185]
- 132 **Spargias K**, Adreanides E, Demerouti E, Gkouziouta A, Manginas A, Pavlides G, Voudris V, Cokkinos DV. Iloprost prevents contrast-induced nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation* 2009; **120**: 1793-1799 [PMID: 19841299 DOI: 10.1161/CIRCULATIONAHA.109.863159]
- 133 **Gurkowski L**, MacDougall M, Wiegmann T. Effects of Miso-prostol on Contrast-Induced Renal Dysfunction. *Am J Ther* 1995; **2**: 837-842 [PMID: 11854796]
- 134 **Onbasili AO**, Yenicierglu Y, Agaoglu P, Karul A, Tekten T, Akar H, Discigil G. Trimetazidine in the prevention of contrast-induced nephropathy after coronary procedures. *Heart* 2007; **93**: 698-702 [PMID: 17065180 DOI: 10.1136/hrt.2006.097477]
- 135 **Kolyada AY**, Liangos O, Madias NE, Jaber BL. Protective effect of erythropoietin against radiocontrast-induced renal tubular epithelial cell injury. *Am J Nephrol* 2008; **28**: 203-209 [PMID: 17960058 DOI: 10.1159/000110089]
- 136 **Yokomaku Y**, Sugimoto T, Kume S, Araki S, Isshiki K, Chin-Kanasaki M, Sakaguchi M, Nitta N, Haneda M, Koya D, Uzu T, Kashiwagi A. Asialoerythropoietin prevents contrast-induced nephropathy. *J Am Soc Nephrol* 2008; **19**: 321-328 [PMID: 18184858 DOI: 10.1681/ASN.2007040481]
- 137 **Toprak O**, Cirit M, Tanrisev M, Yazici C, Canoz O, Sipahioglu M, Uzum A, Ersoy R, Sozmen EY. Preventive effect of nebivolol on contrast-induced nephropathy in rats. *Nephrol Dial Transplant* 2008; **23**: 853-859 [PMID: 17933840 DOI: 10.1093/ndt/gfm691]
- 138 **Markota D**, Markota I, Starcevic B, Tomic M, Prskalo Z, Brizic I. Prevention of contrast-induced nephropathy with Na/K citrate. *Eur Heart J* 2013; **34**: 2362-2367 [PMID: 23349296 DOI: 10.1093/eurheartj/ehf009]
- 139 **Vogt B**, Ferrari P, Schönholzer C, Marti HP, Mohaupt M, Wiederkehr M, Cereghetti C, Serra A, Huynh-Do U, Uehlinger D, Frey FJ. Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful. *Am J Med*

2001; **111**: 692-698 [PMID: 11747848]

140 **Marenzi G**, Marana I, Lauri G, Assanelli E, Grazi M, Campodonico J, Trabattoni D, Fabbiochi F, Montorsi P, Bartorelli

AL. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med* 2003; **349**: 1333-1340 [PMID: 14523141 DOI: 10.1056/NEJMoa023204]

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