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Renal Safety of Iodinated Contrast Media Depending on Their Osmolarity – Current Outlooks

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Summary

Iodinated contrast media (ICM) are commonly administered pharmaceutical agents. Most often they are used intravenously and intraarterially. Although iodinated contrast agents are relatively safe and widely used, adverse events occur and questions remain about their use, safety, and interactions. The most important adverse effects of contrast media include hypersensitivity reactions, thyroid dysfunction, and contrast-induced nephropathy. Radiologists must be aware of the risk factors for reactions to contrast media.

Nonionic iodinated contrast agents can be divided into monomeric, low-osmolar, and dimeric, iso-osmolar classes. The osmotic characteristics of contrast media have been a significant focus in many investigations of contrast-induced nephropathy.

MeSH Keywords: Acute Kidney Injury • Contrast Media • Osmolar Concentration

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Background

Iodinated contrast media (ICM) have found widespread use in diagnostic imaging and therapeutic procedures. Despite their generally high safety profile, possibility or adverse reactions should be taken into account every time they are used. The reactions may range from transient, mild allergic reactions to acute, directly life-threatening conditions.

It appears that the most important clinical challenge associated with the use of ICM is their potential nephrotoxicity. This includes both acute and delayed renal complications. Despite various controversies, most researchers agree that contrast-induced nephropathy (CIN) is of the highest clinical importance. It worsens the short-term (increased frequency of hospitalizations, dialysis, in-hospital mortality) as well as long-term prognoses for patients [1,2]. The objective of this study is to present the literature data on the safety of contrast media used in radiodiagnostics with particular focus on the differences in the presented opinions as discrepancies in positions on the safety of individual contrast media is of particular importance and requires special attention, particularly in terms of assessing the population sizes and methods used in the meta-analyses.

Non-Renal Adverse Reactions

The adverse reactions following the administration of contrast media may be classified as immediate or delayed. Most common (<3%) are immediate mild reactions such as nausea, vomiting, urticaria, pruritus, or cough [3]. Moderate and severe immediate adverse reactions are much less common (<0.04%). These include facial edema, laryngeal edema, bronchospasm, bradycardia, tachycardia, arrhythmias, hyper- or hypotension, coronary artery spasm, pulmonary edema, loss of consciousness or conditions requiring immediate treatment [3]. Death is a very rare consequence, its incidence being estimated at 1 per 1 million cases [3]. The reactions may develop along IgE-dependent or IgE-independent hypersensitivity mechanism [3].

Delayed adverse reactions are defined as occurring within the time frame between 1 hour and 1 week after administration of the contract medium. In most cases, these include skin reactions such as rash, erythema, or pruritus. The incidence of these reactions is difficult to establish (1–25% according to various sources). In author's opinion, part of the reported reactions may be mistakenly

Table 1. Risk factors of CIN according to the European Society of Urogenital Radiology.

Risk factors of CIN according to the European Society of Urogenital Radiology
eGFR <60 mL/min/1.73 m^2 before arterial administration of a contrast medium
eGFR <45 mL/min/1.73 m^2 before venous administration of a contrast medium
Diabetic nephropathy
Dehydration
Congestive heart failure (NYHA III and IV)
History of heart attack (<24 h)
Use of nephrotoxic drugs
Age >70
High dose of a contrast medium

associated with the contrast medium while being due to a completely different causal factor. Most reactions of this type are mild or moderate and resolve spontaneously. In practice, delayed reactions occur after the patient leaves the diagnostic lab. The mechanism of delayed skin reactions is not fully understood, being probably associated with cellular hypersensitivity reactions involving T lymphocytes [4].

An additional class consists of very late adverse reactions that occur later than 1 week after contract administration. In nearly all cases, they are associated with the thyroid function being disturbed after administration of the contrast medium. Biological effects of iodine contained within the contrast medium may consist in either hypo- or hyperthyroidism. High-risk groups include patients with untreated Graves' disease, patients with multinodular goiter and thyroid autonomy, particularly elderly patients and/or residents of areas characterized by iodine-deficient diets [3]. Patients with Hashimoto disease or patients after partial thyroidectomy are at a higher risk of radiocontrast-induced thyroid dysfunction [5].

Systemic effects may ensue following the administration of the contrast medium into the vascular system. The impact on the morphology (shape, plasticity) of erythrocytes is most probably due to the chemotoxic and dehydrating effects and may lead to disturbed microcirculation [6,7]. The process may be enhanced by interactions between the contrast medium with capillary endothelial cells [8]. The integrity of vascular endothelium may be compromised due to the deformation of endothelial cells and breakage of intercellular bridges leading to exposure of extracellular matrix [8].

Renal Adverse Reactions

Contrast induced nephropathy (CIN) is an acute renal insufficiency in a patient with normal renal function preceding the diagnostic procedure involving contrast administration or a significant worsening of renal function in patients previously diagnosed with chronic renal insufficiency. According to ESUR, significant worsening of renal function is determined on the basis of laboratory standards including creatinine clearance reduced by ≥25% or serum creatinine levels increased by ≥25% or ≥0.5 mg/dL (44.2 μmol/L) compared to the values before the procedure (within 3 days after contrast administration). The actual incidence of contrast-enhanced nephropathy is difficult to establish as it depends on the definition of CIN, the type of medical procedure, the route of contrast administration, differences in the distribution of risk factors in the study population and the methodology of assessment of renal parameters during the follow-up. Due to the number of variables being this high, literature reports differ in their estimations of the scale of the problem. Studies conducted in large populations of patients after intravenous administration of contrast media revealed acute worsening of renal function in 2.5–12% of patients [9,10]. Higher incidence of CIN, ranging from 7 to 50%, was observed in studies in which both the intravenous and the intraarterial route were taken into consideration [11,12]. The morbidity in the overall population of unburdened patients is below 2% [13]. The risk of CIN is significantly higher in patients of the high risk groups (Table 1), particularly in patients with comorbid diabetes [14]. Despite the many years of experience in the use of iodinated contrast media, the exact pathogenesis of contrast-induced nephropathy remains unknown. Numerous clinical studies are conducted to examine the impact of the molarity of the active substances on the renal function. The osmotic effect of contrast media on the kidneys involves increased release of sodium and water as well as a reduction in three parameters, namely renal blood flow (RBF), glomerular filtration rate (GFR), as well as filtration fraction (FF) [13]. Other factors that impair the renal blood flow include increased levels of vasoconstrictive factors such as adenosine or endothelin with simultaneous drop in the levels of vasodilators such as nitric oxide or prostacyclin [14]. Simultaneously, the toxic effect of contrast molecules on renal tubules exerted by means of reactive oxygen species is being highlighted [15,16].

Classification of Iodinated Contrast Media

The iodinated contrast media available at the market consist of one (monomers) or two (dimers) triiodinated benzene rings. Contrast media are divided into three basic groups

Table 2. Study list and details – intraarterial administration.

Publication	Patient population	Endpoints/definition of CIN	Study type	Sponsor	Procedure	Statistical sample power
Aspelin et al. [17]	Patients with CRI and diabetes	SCr ≥0.5 mg/dL 72 h after administration	Prospective, randomized Double-blinded	GEHC	PCI 42 CXA 126	80% N=129
Briguori et al. [18]	Patients with CRI	SCr ≥0.5 mg/dL 48 h after administration	Retrospective	Investigator	PCI 101 CXA 102	Not available N=225
Jo et al. [19]	Patients with CRI	SCr ≥0.5 mg/dL and/ or SCr ≥25% 1–2 days after administration	Prospective, randomized Double-blinded	Investigator	PCI 113 CXA 162	80% N=275
Rudnick et al. [20]	Patients with CRI	SCr ≥0.5 mg/dL 24, 48 and 72 h after administration	Prospective, randomized Double-blinded	GEHC	PCI CXA	90% N=299
Ni et al. [21]	Patients with CRI	SCr ≥25% 24 h after administration		Investigator	PCI	Not available N=285
Hérnandez F et al. [22]	Patients with diabetes	SCr ≥0.5 mg/dL and/or SCr ≥25% 72 h after administration	Prospective, not randomized	Investigator	PCI 102 CXA 148	Not available N=250
Solomon et al. [23]	Patients with CRI	SCr ≥0.5 mg/dL 48–72 h after administration	Prospective, randomized Double-blinded	Bracco	PCI 163 CXA 251	80% N=414
Nie et al. [24]	Patients with CRI	SCr ≥0.5 mg/dL and/or SCr ≥25% 1–2 days after administration	Prospective, randomized Double-blinded	Investigator	PCI 98 CXA 110	80% N=208
Wessely et al. [25]	Patients with CRI	SCr ≥0.5 mg/dL and/or SCr ≥25% 1-2 days after administration	Prospective, randomized Double-blinded	GEHC	PCI	90% N=324
Mehran et al. [26]	Patients with CRI	SCr ≥0.5 mg/dL and/or SCr ≥25% 1–2 days after administration	Prospective, randomized Double-blinded	Mallinckrodt and Guerbet	PCI 96 CXA 50	80% N=146
Laskey et al. [27]	Patients with CRI and diabetes	SCr ≥0.5 mg/dL 24, 48 and 72 h after administration	Prospective, randomized Double-blinded	GEHC	PCI 109 CXA 309	90% N=418
Shin et al. [28]	Patients with CRI	SCr ≥0.5 mg/dL 24, 48 and 72 h after administration	Prospective, randomized Double-blinded	Investigator	PCI 189 CXA 231	80% N=420
Bolognese et al. [29]	Patients with CRI	SCr ≥25% 72 h after administration	Prospective, randomized Single-blinded	Bayer Schering	PCI	8% N=475
Juergens et al. [30]	Patients with CRI	SCr ≥0.5 mg/dL and/or SCr ≥25% 48 h after administration	Prospective, randomized Double-blinded	Investigator	CXA 156 PCI 35	80% N=191
Chen et al. [31]	Patients with CRI	SCr ≥50% 72 h after administration	Prospective, randomized Double-blinded	Bayer HC	CXA 307 PCI 255	80% N=592

Table 3. Analysis of the results of studies listed in Table 2.

Publication	Patient population	Endpoints/definition of CIN	Contrast media	Results
Aspelin et al. [17]	Patients with CRI and diabetes	SCr ≥0.5 mg/dL 72 h after administration	Iodixanol 320 (N=64) Iohexol 350 (N=65)	Iohexol >Iodixanol (26% *vs.* 3%, p < 0.05)
Briguori et al. [18]	Patients with CRI	SCr ≥0.5 mg/dL 48 h after administration	Iodixanol 320 (N=110) Iobitridol 350* (N=115)	No significant difference (Iodixanol 3%, Iobitridol 4%, p=n.s.)
Jo et al. [19]	Patients with CRI	SCr ≥0.5 mg/dL and/or SCr ≥25% 1–2 days after administration	Iodixanol 320 (N=140) Ioxaglate 320 (N=135)	Ioxaglate > Iodixanol (17% *vs.* 8%, p<0.05)
Rudnick et al. [20]	Patients with CRI	SCr ≥0.5 mg/dL 24, 48 and 72 h after administration	Iodixanol 320 (N=156) Ioversol 320 (N=143)	No significant difference (Iodixanol 22%, Ioversol 24%, p=n.s.)
Ni et al. [21]	Patients with CRI	SCr ≥25% 24 h after administration	Iodixanol (N=120) Iopamidol (N=165)	No significant difference (Iodixanol 11.7%, Iopamidol 19.4%, p=n.s.)
Hérnandez et al. [22]	Patients with diabetes	SCr ≥0.5 mg/dL and/or SCr ≥25% 72 h after administration	Iodixanol (N=118) Ioversol (N=132)	Ioversol > Iodixanol (8.3% *vs.* 2.5%, p<0.05)
Solomon et al. [23]	Patients with CRI	SCr ≥0.5 mg/dL 48–72 h after administration	Iodixanol 320 (N=210) Iopamidol 370 (N=204)	No significant difference (Iodixanol 7%, Iopamidol 4%, p=n.s.)
Nie et al. [24]	Patients with CRI	SCr ≥0.5 mg/dL and/or SCr ≥25% 1–2 days after administration	Iodixanol 320 (N=106) Iopromide 370 (N=102)	Iopromide >Iodixanol (16.7% *vs.* 5.7%, p<0.01.)
Wessely et al. [25]	Patients with CRI	SCr ≥0.5 mg/dL and/or SCr ≥25% 1–2 days after administration	Iodixanol 320 (N=162) Iomeprol 350 (N=162)	No significant difference (Iodixanol 22.2%, Iomeprol 27.7%, p=n.s.)
Mehran et al. [26]	Patients with CRI	SCr ≥0.5 mg/dL and/or SCr ≥25% 1–2 days after administration	Iodixanol 320 (N=72) Ioxaglate 320 (N=74)	No significant difference (Iodixanol 15.9%, Ioxaglate 24.2%, p=n.s.)
Laskey et al. [27]	Patients with CRI and diabetes	SCr ≥0.5 mg/dL 24, 48 and 72 h after administration	Iodixanol 320 (N=215) Iopamidol 370 (N=203)	No significant difference (Iodixanol 11%, Iopamidol 9%, p=n.s.)
Shin et al. [28]	Patients with CRI	SCr ≥0.5 mg/dL 24, 48 and 72 h after administration	Iodixanol 320 (N=215) Iopromide 300 (N=205)	No significant difference (Iodixanol 10.7%, Iopromide 7.8%, p=n.s.)
Bolognese et al. [29]	Patients with CRI	SCr ≥25% 72 h after administration	Iodixanol 320 (N=236) Iopromide 370 (N=239)	No significant difference (Iodixanol 13%, Iopromide 10%, p=n.s.)
Juergens et al. [30]	Patients with CRI	SCr ≥0.5 mg/dL and/or SCr ≥25% 48 h after administration	Iodixanol 320 (N=91) Iopromide 370 (N=100)	No significant difference (Iodixanol 12%, Iopromide 15%, p=n.s.)
Chen et al. [31]	Patients with CRI	SCr ≥50% 72 h after administration	Iodixanol 320 (N=284) Iopromide 370 (N=278)	No significant difference (Iodixanol 0.3%, Iopromide 0.4%, p=n.s.)

Table 4. Study list and details – intravenous administration.

Publication	Patient population	Endpoints/definition of CIN	Study type	Sponsor	Procedure	Statistical sample power
Carraro et al. [32]	Patients with mild to moderate CRI	SCr ≥50% 24 h after administration	Prospective, randomized Double-blinded	Investigator	i.v. urography	80% N=64
Chuang et al. [33]	Patients with CRI and/or diabetes	SCr ≥25% 72 h after administration	Prospective, randomized Double-blinded	Investigator	i.v. urography	Not available N=50
Barrett et al. [34]	Patients with moderate to severe CRI	SCr ≥0.5 mg/dL and/or SCr ≥25% 2–2 days after administration	Prospective, randomized Double-blinded	Bracco	CT	Not available N=153
Thomsen et al. [35]	Patients with moderate to severe CRI	SCr ≥0.5 mg/dL 24, 48 amd 72 h after administration	Prospective, randomized Double-blinded	Bracco	CT	Not available N=184
Nguyen et al. [36]	Patients with moderate to severe CRI	SCr ≥0.5 mg/dL 24, 48 and 72 h after administration	Prospective, randomized Double-blinded	GEHC	CT	95% N=117
Kuhn et al. [37]	Patients with moderate to severe CRI	SCr ≥25% 48–72 h after administration	Prospective, randomized Double-blinded	Bracco	CT	Not available N=248
Zo'o et al. [38]	Pediatric patients (aged 1-16) with normal renal function	SCr ≥0.5 mg/dL 48–72 h after administration	Prospective, randomized Double-blinded	Guerbet	CT	80% N=146

according to their osmolarity (the number of moles of the active substance dissolved in 1 kilogram of water) [15]. The oldest substances, referred to as high-osmolar contrast media (HOCM) are characterized by osmolarity of above 1500 mOsm/kg H_2O and are currently not recommended for intravascular use due to the high risk of adverse reactions. Low osmolar contrast media (LOCM) are characterized by osmolarities within a relatively wide range of 300–900 mOsm/kg H_2O, and are thus a heterogeneous group of compounds with different physicochemical parameters. These include iobitridol, iohexol, iomeprol, iopamidol, iopromide, ioversol, ioxaglate and ioxilan. The third group of iso-osmolar contrast media (IOCM) consists of iodixanol as the only member or the group. It is characterized by osmolarity level similar to that of blood (290 mOsm/kg H_2O) and dimeric and dimeric structure as opposed to monomeric HOCM and LOCM (except for ioxaglate which is an LOCM of a dimeric structure).

Analysis of Clinical Studies – Intraarterial Administration

Intraarterial administration is associated with the highest risk of adverse reactions. Clinical studies listed below (positions 17–31, Tables 2, 3) directly compared the iso-osmolar medium (dimer) with low-osmolar media (monomers) in terms of the incidence of contrast-induced nephropathy. Overall, 4621 patients were enrolled into 15 analyzed clinical studies. Low-osmolar contract media were administered to 2322 patients (iopamidol n=572; iopromide n=924; iomeprol n=162; iohexol n=65; iobitridol n=115; ioversol n=275;ioxaglate n=209), while the iso-osmolar contrast medium (iodixanol) was used in 2299 cases.

Four clinical studies (NEPHRIC, RECOVER, Hernandez et al., Nie et al.) conducted in 862 patients and comparing iso-osmolar iodixanol with low-osmolarity media (iohexol, ioxaglate, iopromide, ioversol) demonstrated a statistically significantly lower incidence of CIN complications following the administration of the former. The remaining 11 studies (3759 patients – iodixanol *vs.* iopamidol, iopromide, iomeprol, ioversol, ioxaglate) revealed no statistically significant differences in study endpoints or were suggestive of higher safety of LOCM.

Analysis of Clinical Studies – Intravenous Administration

This section deals with clinical studies (positions 32–38; Tables 4, 5) that assessed the incidence of CIN following

Table 5. Analysis of the results of studies listed in Table 4.

Publication	Patient population	Endpoints/definition of CIN	Contrast media	Results
Carraro et al. [32]	Patients with mild to moderate CRI	SCr ≥50% 24 h after administration	Iodixanol 320 (N=32) Iopromide 300 (N=32)	No significant difference
Chuang et al. [33]	Patients with CRI and/or diabetes	SCr ≥25% 72 h after administration	Iodixanol* (N=25) Iohexol* (N=25) *mgI/mL not available	No significant difference
Barrett et al. [34]	Patients with moderate to severe CRI	SCr ≥0.5 mg/dL 48–72 h after administration	Iodixanol 320 (N=76) Iopamidol 370 (N=77) Dose: 40 g I	No significant difference (2.6% *vs.* 0, p=0.3)
Thomsen et al. [35]	Patients with moderate to severe CRI	SCr ≥0.5 mg/dL 48–72 h after administration	Iodixanol 320 (N=72) Iomeprol 400 (N=76) Dose: 40 g I	Ioversol > Iomeprol (6.9% *vs.* 2.5%, p < 0.03)
Nguyen et al. [36]	Patients with moderate to severe CRI	SCr ≥0.5 mg/dL 24, 48 and 72 h after administration	Iodixanol 320 (N=61) Iopromide 370 (N=56) Dose: 37 g I	Iohexol > Iopromide (5.1% *vs.* 18.6%, p<0.04)
Kuhn et al. [37]	Patients with moderate to severe CRI	SCr ≥25% 48–72 h after administration	Iodixanol 320 (N=123) Iopamiron 370 (N=125) Dose: Iodixanol 32.5 g I Iopamidol 39.4 g I	No significant difference (4.9% *vs.* 5.6, p=1.0)
Zo'o et al. [38]	Pediatric patients (aged 1-16) with normal renal function	SCr ≥0.5 mg/dL 48–72 h after administration	Iodixanol 270 (N=71) Iobitridol 300 (N=74)	No significant difference (ITT 10.6% *vs.* 4.8%, p=0.72.) PP 10.3% *vs.* 0%, p=0.68)

intravenous administration of iso-osmolar contrast medium compared to low-osmolarity media (Tables 4, 5). A total of 7 clinical studies with the total number of 925 patients were analyzed. Low-osmolar contrast media were administered to 465 patients (iopamidol n=202; iopromide n=88; iomeprol n=76; iohexol n=25; iobitridol n=74), while the iso-osmolar contrast medium (iodixanol) was used in 460 cases. One of the analyzed studies, conducted in 117 patients (Nguyen et al; iodixanol n=61 *vs.* iopromide n=56) revealed a lower number of CIN cases following administration of IOCM. The remaining 6 studies conducted in the overall population of 808 patients revealed no superiority of iso-osmolar medium (iodixanol) or were suggestive of the superiority of low-osmolar contrast media (iopamidol, iopromide, iomeprol, iohexol, iobitridol).

Meta-Analysis, Summary Reports

This section presents summary reports of multiple studies (positions 39–47; Table 6). When analyzing the presented data, one should consider the lack of unanimous definition of CIN, differences in patient groups and different types of studies. It is therefore difficult to draw explicit conclusions; however, the data reveal some important, mutually confirming correlations. Of much importance are the study endpoints including the incidence of CIN. The higher the incidence, the less safe the contrast medium.

The results of metaanalyses are suggestive of a very important hypothesis, according to which low-osmolarity contrast media (LOCM) are not a homogeneous group of compounds. Of note are the repeatedly poorer results for iohexol and ioxaglate as compared to the remaining LOCM. The data support the thesis regarding the benefits of iodixanol (IOCM) as compared to particular agents from the LOCM group such as iohexol and ioxaglate while not confirming the superiority of iodixanol over other low-osmolarity media.

Conclusions

The discussion on the safety of contrast media and the clinical importance of their individual properties is far from being closed. Each new study is a source of new data. Due to the non-homogeneous patient groups, differences in the definitions of CIN as well as differences in the study methodologies assumed by the authors, it is difficult to carry out a comparative analysis of individual products. Careful analysis of the results published in recent years suggests high degree of arbitrariness in the choice of methodologies, potentially leading to low conformity of data and formulation of false conclusions. Taking these limitations into consideration, one may conclude that despite the lower osmolarity of the dimeric medium, clinical practice and, most of all, the results of randomized studies confirm the comparably high level of safety as regards nephrotoxicity of the iso-osmolar medium and most low-osmolar media, which

Table 6. Meta-analyses.

Publication	Patient population	Endpoints/definition of CIN	Contrast media	Results
McCullough et al. [39]	Patients with normal renal function (N=3,008)	SCr ≥0.5 mg/dL 18 h – 7 days after administration	• Iodixanol 320 (N=1,382) • Ioxaglate (N=789) • Iohexol (N=381) • Iopromide (N=106) • Iopamidol (N=69)	• Iohexol and Ioxaglate > Iodixanol
Sharma et al. [40]	Patients with CRI(N=560)	SCr ≥0.5 mg/dL and/or SCr ≥25% 48–72 hours after administration	• Iodixanol 320 (N=209) • Iohexol (N=106) • Iopamidol (N=245)	• Iohexol > Iodixanol • Iohexol > Iopamidol • Iopamidol = Iodixanol
Solomon [41]	Patients with CRI (N=1,365)	SCr ≥0.5 mg/dL and/or SCr ≥25% 1–7 days after administration	• Iodixanol 320 (N=263) • Iohexol (N=431) • Iopamidol (N=400) • Other LOCM (N=271)	• Iohexol > Iodixanol • Iohexol > Iopamidol • Iopamidol = Iodixanol
Solomon and DuMouchel [42]	Patients with CRI(N=3.112)	SCr ≥0.5 mg/dL and/or SCr ≥25% 1–7 days after administration	• Iodixanol 320 (N=569) • Iohexol (N=677) • Iopamidol (N=652) • Ioversol (N=447) • Other LOCM (N=767)	• Iohexol > Iodixanol • Iohexol > Iopamidol • Iohexol = Ioversol • Iopamidol = Visipaque
Heinrich et al. [43]	3,270 patients	25 randomized studies Administration route: 17 i.a. / 8 i.v.	• Iodixanol (N=1,701) • LOCM (N=1,569)	• Iohexol > Iodixanol after i.a. administration • No difference with LOCM other than iohexol
Reed et al. [44]	2,763 patientsów	16 randomized studies Administration route: 11 i.a. / 5 i.v.	• Iodixanol (N=1383) • Ioversol (N=1380)	• Iohexol and Ioxaglate > Iodixanol • No difference with LOCM other than iohexol and ioxaglate
From et al. [45]	7,166 patients	36 randomized studies 1966–2009 Administration route: 27 i.a. / 9 i.v.	• Iodixanol (N=3672) • LOCM (N=3494)	• Iohexol > Iodixanol • No superiority of IOCM as compared LOCM other than iohexol
Dong et al. [46]	3,129 patients	18 randomized studies Administration route: 11 i.a. / 7 i.v.	• Iodixanol (N=1604) • LOCM (N=1525)	• Iodixanol > LOCM after i.a. administration
Biondi-Zoccai et al. [47]	10,048 patients	42 randomized studies Administration route: 32 i.a. / 10 i.v.	• Iodixanol *vs.* Iohexol (N=982) • Iodixanol *vs.* Iopromide (N= 2202) • Iodixanol *vs.* Iomeron (N=1667) • Iodixanol *vs.* Ioxaglate (N=2826) • Iodixanol *vs.* Ioversol (N=334)	• Iohexol > Iodixanol • Iopamidol, Iomeprol, Ioversol and Iodixanol had similar safety profiles • Further studies are required for Iopromide

is reflected in current guidelines proposed by competent scientific associations (Table 7). This conclusion pertains to both intravenous and intraarterial administration. At the same time, low-osmolarity contrast media should not be considered a homogeneous group.

In case of high-risk patients, on the basis of the currently available literature data, all contrast media, including the iso-osmolar dimer, iodixanol, may be potentially nephrotoxic and relying on a particular agent with the purpose of reducing the risk of CIN may be deceptive. The safest way to minimize the risk of CIN is to use the possibly lowest dose of a low- or iso-osmolar contrast medium while ensuring appropriate hydration.

Table 7. Guidelines of scientific associations.

Scientific association	Recommendations
American College of Radiology [48]	"Studies [. . .] revealed no evident superiority of iso-osmolar iodixanol over low-osmolar contrast media with respect to the incidence of CIN A meta-analysis conducted in 2009 on cumulative data of 25 clinical trials revealed no difference in the incidence of CIN between iodixanol and low-osmolar contract media following intravenouis administration [. . .]"
ESUR Contrast Media Safety Committee [49]	"The previous recommendations [of the Safety Committee] proposed that low-osmolar or iso-osmolar contrast media be used in patients with CIN risk factors. Having considered numerous studies published in recent years, the Committee found no grounds for changing this position"
Canadian Association of Radiologists [50]	"Larger studies and meta-analyses revealed no significant difference between iodixanol and most low-osmolar contrast media. [. . .] Currently, the Canadian Associstion of Radiologists recommends the use of iso- or low-osmolar contrast media in patients with GFR <45 mL/ min in intravenous administration and GFR <60 mL/min at intraarterial administration"
The Renal Association, British Cardiovascular and Intervention Society and The Royal College of Radiologists [51]	"We are suggesting that a lowest possible volume of a low- or iso-osmolar contrast medium is used in patients with risk factors of acute contrast-induced nephropwthy."
American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions [52]	"[The volume of] contrast media should be minimized, and low-osmolar or iso-osmolar contrast media should be used"
European Society of Cardiology [53]	"In patients with mild, moderate or severe chronic renal insufficiency, low-osmolar or iso-osmolar contrast media are recommended at doses of <350 mL or 4 mL/kg [of body weight]"
Asian Society of Cardiovascular Imaging [54]	"Low- or iso-osmolar contrast media are recommended"

References:

1. Brown JR, Malenka DJ, DeVries JT et al: Transient and persistent renal dysfunction are predictors of sur vival after percutaneous coronary intervention: Insights from the Dartmouth Dynamic Registry. Cathet Cardiovasc Interven, 2008; 72: 347–54
2. Bartholomew BA, Harjai KJ, Dukkipati S et al: Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. Am J Cardiol, 2004; 93: 1515–19
3. Thomson KR, Varma DK: Safe use of radiographic contrast media. Australian Prescriber, 2010; 33: 19–22
4. Loh S, Bagheri S, Katzberg RW et al: Delayed adverse reaction to contrast-enhanced CT: A prospective single-center study comparison to control group without enhancement. Radiology, 2010; 255: 764–71
5. Gartner W, Weissel M: Do iodine-containing contrast media induce clinically relevant changes in thyroid function parameters of euthyroid patients within the first week? Thyroid, 2004; 7: 521–24
6. Kerl JM, Nguyen SA, Lazarchick J et al: Iodinated contrast media: effect of osmolarity and injection temperature on erythrocyte morphology *in vitro*. Acta Radiol, 2008; 49: 337–43
7. Jung F, Mrowietz C, Rickert D et al: The effect of radiographic contrast media on the morphology of human erythrocytes. Clin Hemorheol Microcirc, 2008; 38: 1–11
8. Franke RP, Fuhrmann R, Hiebl B et al: Influence of various radiographic contrast media on the buckling of endothelial cells. Microvasc Res, 2008; 76: 110–13
9. Weisbord SD, Mor MK, Resnick AL et al: Incidence and outcomes of contrast-induced AKI following computed tomography, Clin J Am Soc Nephrol, 2008; 3(5): 1274–81
10. Mitchell AM, Kline JA: Contrast nephropathy following computed tomography angiography of the chest for pulmonary embolism in the emergency department. J Thromb Haemost, 2007; 5(1): 50–54
11. McCullough PA, Wolyn R, Rocher LL et al: Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med, 1997; 103(5): 368–75
12. Chen SL, Zhang J, Yei F et al: Clinical outcomes of contrast-induced nephropathy in patients undergoing percutaneous coronary intervention: A prospective, multicenter, randomized study to analyze the effect of hydration and acetylcysteine. Int J Cardiol, 2008; 126(3): 407–13
13. Berg KJ: Nephrotoxicity related to contrast media. Scand J Urol Nephrol, 2000; 34: 317–22
14. Gleeson TG, Bulugahapitiya S: Contrast-induced Nephropathy. Am J Roentgenol, 2004; 183(6): 1673–89
15. Bucher AM, De Cecco CN, Schoepf UJ et al: is contrast medium osmolality a causal factor for contrast-induced nephropathy? BioMed Research International, 2014; Article ID 931413
16. Katzberg R: Contrast medium – induced nephrotoxicity: Which pathway? Radiology, 2005; 235: 752–55
17. Aspelin P, Aubry P, Fransson SG et al: Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med, 2003; 348: 491–99
18. Briguori C, Colombo A, Airoldi F et al: Nephrotoxicity of low-osmolality versus iso-osmolality contrast agents: Impact of nacetylcysteine. Kidney Int, 2005; 68: 2250–55
19. Jo SH, Youn TJ, Koo BK et al: 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: 924–30
20. Rudnick MR, Davidson C, Laskey W et al: 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; 1: 1–7
21. Ni J, Zhang R, Zhang J et al: Safety of iso-osmolar nonionic dimer during percutaneous coronary intervention J Interv Radiol (Chinese), 2006; 15: 327–29

22. Hernández F, Mora L, García-Tejada J et al: Comparison of iodixanol and ioversol for the prevention of contrast-induced nephropathy in diabetic patients after coronary angiography or angioplasty. Source Rev Esp Cardiol, 2009; 62/12: 1373–80
23. Solomon RJ, Natarajan MK, Doucet S et al: 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: 3189–96
24. Nie B, Cheng WJ, Li YF et al: A prospective, double-blind, randomized, controlledtrial on the efficacy and cardiorenal safety of iodixanol *vs.* iopromide in patients with chronic kidney disease undergoing coronary angiography with or without percutaneous coronary intervention. Catheter Cardiovasc Interv, 2008; 72(7): 958–65
25. Wessely R, Koppara T, Bradaric C et al: Choice of contrast medium in patients with impaired renal function undergoing percutaneous coronary intervention. Circ Cardiovasc Intervent, 2009; 2: 430–37
26. Mehran R, Nikolsky E, Kirtane AJ et al: Ionic low-osmolar versus nonionic iso-osmolar contrast media to obviate worsening nephropathy after angioplasty in chronic renal failure patients. The ICON (Ionic versus non-ionic Contrast to Obviate worsening Nephropathy after angioplasty in chronic renal failure patients) Study. JACC Cardiovasc Interv, 2009; 5: 451–21
27. Laskey W, Aspelin P, Davidson C et al: Nephrotoxicity of iodixanol versus iopamidol in patients with chronic kidney disease and diabetes mellitus undergoing coronary angiographic procedures. Am Heart J, 2009; 158: 822–28
28. Shin DH, Choi DJ, Youn TJ et al: Comparison of contrast-induced nephrotoxicity of iodixanol and iopromide in patients with renal insufficiency undergoing coronary angiography. Am J Cardiol, 2011; 108: 189–94
29. Bolognese L, Falsini G, Schwenke C et al: Impact of iso-osmolar versus low-osmolar contrast agents on contrast-induced nephropathy and tissue reperfusion in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (from the Contrast Media and Nephrotoxicity Following Primary Angioplasty for Acute Myocardial Infarction [CONTRAST-AMI] Trial). Am J Cardiol, 2012; 109: 67–74
30. Juergens CP, Winter JP, Nguyen-Do P et al: Nephrotoxic effects of iodixanol and iopromide in patients with abnormal renal function receiving N-acetylcysteine and hydration before coronary angiography and intervention: a randomized trial. Intern Med J, 2009; 39: 25–31
31. Chen Y, Hu S, Liu Y et al: Renal tolerability in 562 renally impaired patients undergoing cardiac catheterisation: the DIRECT study. EuroIntervention, 2012; 8: 830–38
32. Carraro M, Malalan F, Antonione R et al: Effects of a dimeric *vs.* a monomeric nonionic contrast medium on renal function in patients with mild to moderate renal insufficiency: a double-blind, randomized clinical trial. Eur Radiol, 1998; 8(1): 144–47
33. Chuang FR, Chen TC, Wang IK et al: Comparison of iodixanol and iohexol in patients undergoing intravenous pyelography: A prospective controlled study. Renal Failure, 2009; 31(3): 181–88
34. Barrett BJ, Katzberg RW, Thomsen HS et al: Contrast-induced nephropathy in patients with chronic kidney disease undergoing computed tomography. A double-blind comparison of iodixanol and iopamidol. Invest Radiol, 2006; 41: 815–21
35. Thomsen HS, Morcos SK, Erley CM et al.; 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 patientswith chronic kidney disease undergoing abdominal computed tomography. Invest Radiol, 2008; 43: 170–78
36. Nguyen SA, Suranyi P, Ravenel JG et al: Iso-osmolality versus low-osmolality iodinated contrast medium at intravenous contrast-enhanced CT: Effect on kidney function. Radiology, 2008; 248: 97–105
37. Kuhn MJ, Chen N, Sahani DV et al: The PREDICT Study: A randomized double-blind comparison of contrast-induced nephropathy after low- or isoosmolar contrast agent exposure. Am J Roentgenol, 2008; 191(1): 151–57
38. Zo'o M, Hoermann M, Balassy C et al: Renal safety in pediatric imaging: randomized, double-blind phase IV clinical trial of iobitridol 300 versus iodixanol 270 in multidetector CT. Pediatr Radiol, 2011; 41: 1393–400
39. 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(4): 692–99
40. Sharma SK, Kini A et al: Effect of nonionic radiocontrast agents on the occurrence of contrast-induced nephropathy in patients with mild-moderate chronic renal insufficiency: Pooled analysis of the randomized trials. Catheter Cardiovasc Interv, 2005; 65: 386–93
41. Solomon R: The role of osmolality in the incidence of contrast-induced nephropathy: A systematic review of angiographic contrast media in high risk patients. Kidney Int, 2005; 68: 2256–63
42. Solomon R, DuMouchel W: Contrast media and nephropathy: findings from systematic analysis and food and drug administration reports of adverse effects. Invest Radiol, 2006; 8: 651–60
43. Heinrich MC, Häberle L, Müller V et al: Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low-osmolar contrast media: meta-analysis of randomized controlled trials. Radiology, 2009; 250: 68–86
44. Reed M, Meier P, Tamhane UU et al: The relative renal safety of iodixanol compared with low-osmolar contrast media: a meta-analysis of randomized controlled trials. JACC Cardiovasc Interv, 2009; 2: 645–54
45. From AM, Al Badarin FJ, McDonald FS et al: Iodixanol versus low-osmolar contrast media for prevention of contrast induced nephropathy: Meta-analysis of randomized, controlled trials. Circ Cardiovasc Interv, 2010; 3(4): 351–58
46. Dong M, Jiao Z, Liu T et al: Effect of administration route on the renal safety of contrast agents: a meta-analysis of randomized controlled trials. J Nephrol, 2012; 25(3): 290–301
47. Biondi-Zoccai G, Lotrionte M, Thomsen HS et al: Nephropathy after administration of iso-osmolar and low-osmolar contrast media: Evidence from a network meta-analysis. Int J Cardiol, 2014; 172: 375–80
48. ACR Manual on Contrast Media 2013 (Version 9). *http://www.acr.org/quality-safety/resources/contrast-manual*
49. Stacul F, van der Molen AJ, Reimer P et al: Contrast induced nephropathy: Updated ESUR Contrast Media Safety Committee guidelines. Eur Radiol, 2011; 21: 2527–41
50. Owen RJ: Canadian Association of Radiologists consensus guidelines for the prevention of contrast-induced nephropathy: update 2012. Can Assoc Radiol J, 2014; 65(2): 96–105
51. *http://www.renal.org/docs/default-source/guidelines-resources/joint-guidelines/Prevention_of_Contrast_Induced_Acute_Kidney_Injury_CI-AKI_In_Adult_Patients.pdf*
52. Bashore TM, Balter S, Barac A et al: American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions Expert Consensus Document on Cardiac Catheterization Laboratory Standards Update. J Am Coll Cardiol, 2012; 59(24): 2221–305
53. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI), Wijns W, Kolh P, Danchin N et al: 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 for Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J, 2010; 31: 2501–55
54. ASCI CCT & CMR Guideline Working Group, Jinzaki M, Kitagawa K, Tsai IC et al: ASCI 2010 contrast media guideline for cardiac imaging: a report of the Asian Society of Cardiovascular Imaging cardiac computed tomography and cardiac magnetic resonance imaging guideline working group. Int J Cardiovasc Imaging, 2010; 26: 203–12