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

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
and factors of renal function is determined on the basis of laboratory insufficiency. According to ESUR, significant worsening in patients previously diagnosed with chronic renal dysfunction or a significant worsening of renal function preceding the diagnostic procedure involving 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 and 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 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 m² before arterial administration of a contrast medium |
| eGFR <45 mL/min/1.73 m² 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 |

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].
### 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 | 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 |
| 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 |
| 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 Double-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        | Iodixanol 320 (N=64)  lohexol 350 (N=65) | Iodexol > Iodixanol (26% vs. 3%, p < 0.05)                              |
| Briguiori et al. [18]| Patients with CRI                     | SCr ≥ 0.5 mg/dL 48 h        | Iodixanol 320 (N=110)  lohexol 350* (N=115) | No significant difference (Iodixanol 3%, lohexol 4%, p=n.s.)           |
| Jo et al. [19]       | Patients with CRI                     | SCr ≥ 0.5 mg/dl and/or      | 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 | 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         | Iodixanol (N=120)  Iopamidol (N=165) | No significant difference (Iodixanol 11.7%, Iopamidol 19.4%, p=n.s.)  |
| Hernandez et al. [22]| Patients with diabetes                | SCr ≥0.5 mg/dL and/or      | 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    | 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      | 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      | 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      | 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 | 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 | 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        | 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      | 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        | Iodixanol 320 (N=284)  Iopromide 370 (N=278) | No significant difference (Iodixanol 0.3%, Iopromide 0.4%, p=n.s.)      |
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$_2$O 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$_2$O, 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$_2$O) 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...

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### 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 and 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                 |
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.

| 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) Iopamidol 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) |

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 osmolality 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
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, ioxixanol, 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.

| Publication                  | Patient population | Endpoints/definition of CIN | Contrast media | Results                                                                 |
|------------------------------|--------------------|-----------------------------|----------------|-------------------------------------------------------------------------|
| McCullough et al. [39]       | Patients with normal renal function (N=3,008) | $\mathrm{SCr} \geq 0.5 \, \text{mg/dL}$ 18 h – 7 days after administration | • Iodixanol 320 (N=1,382)     | lohexol and loxaglate > iodixanol                                      |
| Sharma et al. [40]           | Patients with CRI (N=560) | $\mathrm{SCr} \geq 0.5 \, \text{mg/dL}$ and/or $\mathrm{SCr} \geq 25\%$ 48–72 hours after administration | • Iodixanol 320 (N=209)     | lohexol > iodixanol                                                     |
| Solomon [41]                 | Patients with CRI (N=1,365) | $\mathrm{SCr} \geq 0.5 \, \text{mg/dL}$ and/or $\mathrm{SCr} \geq 25\%$ 1–7 days after administration | • Iodixanol 320 (N=263)     | lohexol > iodixanol                                                     |
| Solomon and DuMouchel [42]   | Patients with CRI (N=3,112) | $\mathrm{SCr} \geq 0.5 \, \text{mg/dL}$ and/or $\mathrm{SCr} \geq 25\%$ 1–7 days after administration | • Iodixanol 320 (N=569)     | lohexol > iodixanol                                                     |
| Heinrich et al. [43]         | 3,270 patients     | 25 randomized studies 17 i.a. / 8 i.v. | Iodixanol (N=1,701)     | lohexol > iodixanol after i.a. administration |
| Reed et al. [44]             | 2,763 patients     | 16 randomized studies 11 i.a. / 5 i.v. | Iodixanol (N=1383)     | lohexol and loxaglate > iodixanol                                      |
| From et al. [45]             | 7,166 patients     | 36 randomized studies 27 i.a. / 9 i.v. | Iodixanol (N=3672)     | lohexol > iodixanol                                                     |
| Dong et al. [46]             | 3,129 patients     | 18 randomized studies 11 i.a. / 7 i.v. | Iodixanol (N=1604)     | lohexol > LOCM after i.a. administration                               |
| Biondi-Zoccai et al. [47]    | 10,048 patients    | 42 randomized studies 32 i.a. / 10 i.v. | Iodixanol vs. lohexol (N=982) | lohexol > iodixanol                                                     |

Table 6. Meta-analyses.

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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) • lohexol > iodixanol • No superiority of LOCM 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) • lohexol > 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. lohexol (N=982) • Iodixanol vs. iomeron (N=2202) • Iodixanol vs. loxaglate (N=2826) • Iodixanol vs. ioversol (N=334) • lohexol > iodixanol • Iopamidol, Iomeprol, Ioversol and Iodixanol had similar safety profiles • Further studies are required for ioversol
Recommendations

“The previous recommendations [of the Safety Committee] proposed that low-osmolar or iso-osmolar contrast media are recommended in patients with mild, moderate or severe chronic renal insufficiency, low-osmolar or iso-osmolar contrast media should be used.

Larger studies and meta-analyses revealed no significant difference between iodixanol and low-osmolar contrast media. [. . .] Currently, the Canadian Association 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.”

Larger studies and meta-analyses revealed no evident superiority of iso-osmolar iodixanol over low-osmolar contrast media following intravenous administration [. . .]”

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.”

“We are suggesting that the lowest possible volume of a low- or iso-osmolar contrast medium is used in patients with risk factors of acute contrast-induced nephropathy.”

“The volume of contrast media should be minimized, and low-osmolar or iso-osmolar contrast media should be used”

“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)”

“Low- or iso-osmolar contrast media are recommended”

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 a cumulative data of 25 clinical trials revealed no difference in the incidence of CIN between iodixanol and low-osmolar contrast media following intravenous administration [. . .]” |
| ESUR Contrast Media Safety Committee [49] | “The previous recommendations [of the Safety Committee] proposed that low-osmolar or iso-osmolar contrast media are recommended at doses of <350 mL or 4 mL/kg (of body weight)” |
| Canadian Association of Radiologists [50] | “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.” |
| The Renal Association, British Cardiovascular and Intervention Society and The Royal College of Radiologists [51] | “We are suggesting that the lowest possible volume of a low- or iso-osmolar contrast medium is used in patients with risk factors of acute contrast-induced nephropathy.” |
| 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” |

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