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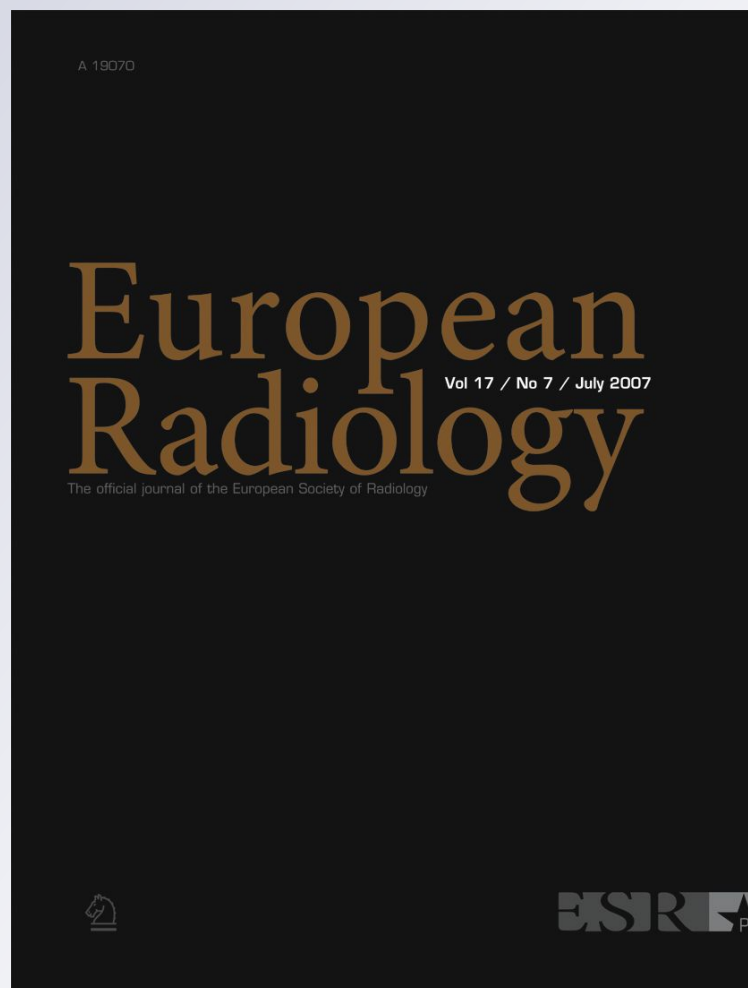
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# Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines

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## Abstract

**Purpose** The Contrast Media Safety Committee (CMSC) of the European Society of Urogenital Radiology (ESUR) has updated its 1999 guidelines on contrast medium-induced nephropathy (CIN).

**Areas covered** Topics reviewed include the definition of CIN, the choice of contrast medium, the prophylactic

measures used to reduce the incidence of CIN, and the management of patients receiving metformin.

## Key Points

- *Definition, risk factors and prevention of contrast medium induced nephropathy are reviewed.*
- *CIN risk is lower with intravenous than intra-arterial iodinated contrast medium.*

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- *eGFR of 45 ml/min/1.73 m<sup>2</sup> is CIN risk threshold for intravenous contrast medium.*
- *Hydration with either saline or sodium bicarbonate reduces CIN incidence.*
- *Patients with eGFR  $\geq$ 60 ml/min/1.73 m<sup>2</sup> receiving contrast medium can continue metformin normally.*

**Keywords** Contrast medium-induced nephropathy · Iodine-based contrast media · Gadolinium-based contrast media · Metformin · Renal failure

**MeSH terms** Contrast media · Renal insufficiency, chronic · Acute kidney injury · Iodopyridones · Gadolinium · Metformin

**Not MeSH but essential** Contrast-induced nephropathy

## Introduction

The Contrast Media Safety Committee of the European Society of Urogenital Radiology produced guidelines on CIN and on the use of metformin in patients receiving contrast medium in 1999 [1, 2]. These guidelines have already been slightly updated online [3]. The Committee decided to critically review the new literature and update its guidelines for reducing the risk of CIN and for the management of diabetic patients on metformin who receive contrast agents.

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## Materials and methods

The literature was systematically reviewed by repeatedly checking multiple databases (PubMed, Cochrane, EMBASE, Web of Science) for papers published from 1996 to April 2010. Search terms for iodine-based contrast medium (CM) induced nephropathy (CIN) included combinations of contrast media, contrast agent, induced, iodinated, nephropathy, nephrotoxicity, CIN, renal failure, kidney, renal, injury, acute, as well as the generic and brand names of the specific iodinated CM. Search terms for gadolinium CM-induced CIN included combinations of contrast media, contrast agent, induced, gadolinium, nephropathy, nephrotoxicity, CIN, renal failure, kidney, renal, injury, acute, as well as the generic and brand names of the specific gadolinium CM. Search terms for metformin included combinations of contrast media, contrast agent, induced, iodinated, nephropathy, nephrotoxicity, CIN, renal failure, kidney, injury, prevention, metformin, lactic acidosis as well as the generic and brand names of the specific metformin preparations. Search terms for interventions such as volume expansion, hydration, N-acetylcysteine, theophylline, aminophylline, fenoldopam etc. were added where appropriate. In total, more than 6,000 papers were screened during the period of preparation of the review. The type of study (randomised clinical trial, systematic review, meta-analysis) was not specifically used in the searches, but these terms were used when screening the abstracts. Cross-references were used when appropriate. Only manuscripts published in English and German were considered. The references from a previous literature search on this topic which involved one of the authors (F.S.) and collected 4,370 papers from 1966 to February 2005 were also considered [4].

The strength of recommendation and the level of evidence of different prophylactic strategies for CIN were weighted and graded according to pre-defined scales (Tables 1 and 2)

Successive draft proposals were extensively discussed among the academic CMSC members. The report was also reviewed by the representatives of the pharmaceutical companies who are consultants to the Committee. A consensus report was agreed at the CMSC business meeting in October 2010.

## Iodine-based contrast media

### Definition of CIN

In 1999, the CMSC gave the following definition of CIN: “Contrast-medium nephrotoxicity is a condition in

**Table 1** Classes of recommendations

Classes of recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

which an impairment in renal function (an increase in serum creatinine by more than 25% or 44  $\mu\text{mol/l}$ ) occurs within 3 days following the intravascular administration of a contrast medium in the absence of an alternative etiology” [1]. This definition is still widely used and has the merit of allowing valid comparison among different trials. However, a variety of questions arise. Is it still appropriate to consider absolute and relative increases in serum creatinine (SCr) together? Can the same thresholds still be used? Should the same time interval be considered? Can alternative explanations for the SCr changes be confidently excluded?

The Acute Kidney Injury Network (AKIN) suggested two separate CIN endpoints using both *absolute* and *relative* SCr changes [5, 6]. Their proposed diagnostic criteria for acute kidney injury (AKI) [7] include an absolute increase in serum creatinine level of  $\geq 0.3$  mg/dl (26.4  $\mu\text{mol/l}$ ), or a percentage increase in serum creatinine level of  $\geq 50\%$  (1.5-fold from baseline), or a reduction in urine output (documented oliguria of  $<0.5$  ml/Kg/h for  $>6$  h) within 48 h. The serum creatinine threshold of 0.3 mg/dl (26.4  $\mu\text{mol/l}$ ) was based on the evidence that even small changes in serum creatinine are associated with adverse outcomes, such as increases in short-term morbidity and mortality and in 1-year mortality. This is in agreement with the findings of Weisbord et al. [8] and Solomon et al. [9]. The AKIN recognised that these criteria might be over-sensitive, leading to an increase in

**Table 2** Levels of evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of the opinion of experts and/or small studies, retrospective studies, registries.

the number of false-positive diagnoses and suggested that further validation is required [6].

Calculations by Waikar and Bonventre [10] showed that increases in creatinine levels of 0.3 mg/dl (26.4  $\mu\text{mol/l}$ ) are only significant when they occur within 24 h, and that 0.5 mg/dl (44  $\mu\text{mol/l}$ ) at 48 h after CM may be a more appropriate cut-off.

Thomsen and Morcos [11] have suggested that an absolute increase in SCr  $\geq 0.5$  mg/dl (44  $\mu\text{mol/l}$ ) is preferable to a relative SCr measurement. Reddan et al. [12] considered that the relative measurement was probably unsuitable for patients with normal baseline SCr. They stated that an increase in SCr from 0.6 to 0.75 mg/dl (52.8 to 66  $\mu\text{mol/l}$ ) (25%) was unlikely to be of clinical importance. Toprak [13] and Waikar and Bonventre [10] supported this view. Based on these reports, an absolute increase in SCr seems a better threshold than a relative increase in SCr for the diagnosis of CIN.

A further suggestion for a threshold for the diagnosis of CIN is *a decrease of 25% from the baseline estimated glomerular filtration rate (eGFR)*. However, the accuracy of eGFR in patients with normal renal function (eGFR  $>60$  ml/min) has not yet been validated. In patients with reduced renal function (eGFR  $<60$  ml/min), eGFR may give a more accurate reflection of any change in GFR. The usefulness of defining CIN as a decrease in glomerular filtration rate (GFR) of 25% has not yet been established.

The *timing of SCr measurements after the procedure* is another topic of debate. The AKIN criteria suggested a period of 48 h for diagnosis to ensure that the process being diagnosed is acute and representative [6]. Waikar and Bonventre [10] agreed with this time period. They emphasised that patients with subacute rises in SCr may not be identified, but noted that the significance and prognosis of such subacute rises is unknown.

*The number of SCr measurements within the given period* also affects the findings and requires some standardisation. Reddan et al. [12] analysed data published by Davidson et al. [14] and showed that a single 24-h measurement would have missed 58.2% of the CIN cases that were detected by the 48-h measurement. McCullough et al. [15] found that SCr typically peaks 3–5 days after contrast medium administration and returns to baseline or near baseline within 1–3 weeks.

This topic is complex and understanding of it continues to evolve. At present, it seems appropriate to keep the definition agreed by the Committee in 1999 and to wait for possible future changes advised by nephrological experts.

Also, to avoid over-diagnosing CIN, it is important to remember physiological fluctuations in SCr levels and any concurrent pathological conditions and drugs that may affect renal function [16, 17]. It would be helpful if CIN studies focused more on serious clinical outcomes, especially long-term ones, such as renal replacement therapy. In CIN studies,



other causes of acute renal failure should be excluded by measuring the eGFR at least twice before CM administration to check that renal function is stable. If there are not two or more measurements, there may be a false-positive diagnosis of CIN.

#### Identifying risk factors for CIN

Identification of patients at risk of CIN before they receive contrast medium is essential.

#### Patient-related risk factors

In the previous guidelines a number of risk factors were listed: raised S-creatinine levels, particularly secondary to diabetic nephropathy; dehydration; congestive heart failure; age over 70 years; concurrent administration of nephrotoxic drugs, e.g. non-steroid anti-inflammatory drugs [1]. The significance of these risk factors has been confirmed by many studies and was supported by Toprak's review [18]. Guidelines about which patients should undergo serum creatinine measurement before administration of an iodine-based contrast medium have already been published by the CMSC [19].

There is general agreement that *chronic kidney disease* is the most significant risk factor for CIN and every multivariate analysis has shown that chronic kidney disease is an independent risk predictor for CIN [20–25]. Patients with chronic kidney disease are classified by the Kidney Disease Outcome Quality Initiative (KDOQI) according to GFR estimated by the Modification of Diet in Renal Disease (MDRD) formula that takes account of serum creatinine, age, gender and ethnicity.<sup>1</sup> However this equation is not suitable if renal function is unstable and is not accurate in patients with unusual dietary intake (e.g. vegetarian diet, high protein diet, creatine supplements), extremes of body composition (e.g. very lean, obese, paraplegia), or severe liver disease. In children, the Schwartz formula provides a clinically useful estimate of GFR [26]. The Chronic Kidney Disease–Epidemiology cooperation (CKD-EPI) creatinine equation was recently found to be more accurate and could eventually replace the MDRD study equation [27]. The KDOQI definition of chronic kidney disease (CKD) stages 3–5 does not require any evidence of renal damage and an eGFR <60 ml/min/1.73 m<sup>2</sup> is the threshold for the diagnosis [28]. Patients with eGFR >60 ml/min/1.72 m<sup>2</sup> should be regarded as normal unless they have other evidence of kidney disease [29].

<sup>1</sup> For MDRD formula go to internet address [http://www.nkdep.nih.gov/professionals/gfr\\_calculators/orig\\_con.htm](http://www.nkdep.nih.gov/professionals/gfr_calculators/orig_con.htm) or <http://nephron.com/cgi-bin/CGSIdefault.cgi> or [http://www.nephron.com/MDRD\\_GFR.cgi](http://www.nephron.com/MDRD_GFR.cgi)

The Committee already agreed that serum creatinine is not an ideal marker of renal function and that renal function is better estimated by using a specially derived predictive equation [19]. The Committee now supports using determination of eGFR to identify patients with impaired renal function, who are at risk of developing CIN.

*Diabetes mellitus* should probably be considered an independent risk factor for CIN [20, 23–25, 30], although there is no conclusive evidence that diabetic patients are at increased risk of CIN if their renal function is normal. Patients with chronic kidney disease and diabetes mellitus are at increased risk of CIN compared with those with the same degree of renal impairment who are not diabetic.

*Dehydration* is widely believed to be a risk factor for CIN based on clinical experience, but there are few trials demonstrating this.

A number of percutaneous coronary intervention (PCI) studies have shown that *congestive heart failure* (New York Heart Association [NYHA] grade 3–4) is associated with a higher incidence of CIN [20, 23, 24, 31]. Others have shown that recent (within 24 h) myocardial infarction and a low left ventricular ejection fraction (LVEF) are independent risk factors for CIN [24, 25]. All these data demonstrate that *poor cardiac function* is a risk factor for CIN.

*Advanced age* is associated with deterioration of renal function causing a higher risk of CIN. Some studies indicate that advanced age is an independent risk factor for CIN [23, 32]. The opinion of the Committee is that renal function should be measured in older patients (age over 70) before intravascular contrast medium administration.

The risk related to the concomitant use of *nephrotoxic drugs* is intuitive. It is poorly documented in the clinical literature [33], but has been shown in animal studies [34].

Recent data on *other risk factors* indicate the significance of haemodynamic instability (for example when an intra-aortic balloon pump is used), of reduction of the renal blood supply during vascular procedures (hypotension), or of reduction of the renal oxygen supply (anaemia) [20, 23, 25, 35, 36]. These factors have been added to the list of risk factors in the guidelines.

Also, the Committee agrees that patients susceptible to acute kidney damage (e.g. patients with unstable renal function) should be considered at risk of CIN, and therefore this clinical condition has been added to the list of risk factors.

Although in the past some dehydrated patients with multiple myeloma who underwent urography with high osmolality agents developed renal failure, there is no evidence that multiple myeloma is a risk factor for CIN in well-hydrated myeloma patients with normal renal function [37, 38]. However, patients with multiple myeloma often have reduced renal function and such patients are at risk of CIN.

### Procedure-related risk factors

In the previous guidelines, procedure-related risk factors were considered to be the use of high osmolar contrast media and large doses of CM.

**Route of contrast medium administration** Although trials directly comparing intravenous and intra-arterial CM are not available, increasing data supports a higher risk of renal complications including CIN after intra-arterial administration above the level of the renal arteries than after intravenous administration. Intravenous contrast medium for enhanced computed tomography (CT) is usually given in lower doses than for arteriography and lower concentrations of contrast medium reach the kidneys. Also, with enhanced CT, there are usually fewer haemodynamically unstable patients, and dislodged atheroemboli, which may occur during intra-arterial procedures, and result in cholesterol embolisation that can mimic CIN, are not a risk.

In the recent review by Katzberg and Lamba [39], the rate of CIN in patients with renal insufficiency who underwent enhanced CT was as low as 5%. However, the clinical studies they reviewed did not include many patients with marked reduction in renal function (CKD 4 and 5). The 5% figure is much lower than the rates reported in the cardiology literature for patients undergoing coronary angiography and percutaneous coronary intervention (PCI). Katzberg and Lamba [39] noted that their findings were even more significant when serious adverse effects after CM administration in cardiac catheter laboratories and in CT units were compared. They reviewed 1,075 patients with renal insufficiency in prospective CT trials and found that none had required dialysis and there were no deaths.

Following percutaneous coronary intervention with intra-arterial administration of CM, the need for dialysis depended on the patient's underlying disease and has been reported to vary from 0.7% [22] in the general patient population to 7% in patients with CKD [31]. Also, a large number of studies have showed that mortality, both during hospitalisation and at 1 year, is significantly increased in the patients who developed CIN [22, 24, 25, 31, 32].

The CMSC concludes that the risk of CIN is significantly lower following intravenous contrast medium administration. Evidence suggests that patients who are considered to be at risk in intra-arterial procedures may not be at risk in intravenous studies. Weisbord et al. [40] showed that the risk of developing CIN in outpatients who received intravenous CM increased significantly when the eGFR was less than 45 ml/min. Kim et al. [41] showed that the incidences of CIN after CT were 0.0%, 2.9% and 12.1% in patients with an eGFR of 45–59, 30–44 and <30 ml/min/1.73 m<sup>2</sup>, respectively. Katzberg and Lamba [39] concluded from their review of CT studies that there may be higher CIN rates in patients with an SCr of

2.0 mg/dl (176 μmol/l) or more or an eGFR of less than 40–45 ml/min. Also, some publications [42, 43] have suggested a change in the CKD classification, with subdivision of stage 3 into stage 3a with a GFR of 45–59 ml/min and 3b with a GFR of 30–44 ml/min [44]. The Committee concludes that patients referred for enhanced CT are genuinely at risk of CIN if they have CKD stage 3b, 4 and 5, and have an eGFR <45 ml/min.

**Choice of contrast medium** High osmolality CM are a risk factor for CIN, although the evidence is limited to intra-arterial studies in patients with chronic kidney disease [45].

An important question is whether there are significant differences in renal safety between the low osmolar CM (the non-ionic monomers or the ionic dimer ioxaglate) and an iso-osmolar CM (the non-ionic dimer iodixanol). As the risk of CIN is greater with intra-arterial than with intravenous CM, it is important to consider the two routes of administration separately in studies comparing different CM.

Aspelin et al. [46], in the NEPHRIC trial, compared intra-arterial iohexol and iodixanol in 129 patients with chronic kidney disease and diabetes mellitus and showed a significantly higher incidence of CIN after iohexol (26%) than after iodixanol (3%). Subsequently, a large number of different studies have compared the non-ionic dimer iodixanol with different non-ionic monomers given intra-arterially. Jo et al. [47], in the RECOVER trial, evaluated 275 patients with chronic kidney disease and showed that iodixanol was less nephrotoxic than ioxaglate in some subgroups (e.g. patients with diabetic nephropathy). Nie et al. [48] found significantly lower CIN rates with iodixanol (5.7%) than with iopromide (16.7%) in 208 patients with chronic kidney disease.

Other recent multicenter prospective angiographic trials have been unable to show significant differences between iodixanol and different non-ionic monomers in patients with CKD. In particular, no significant differences were detected by Rudnick et al. [49] (VALOR trial, 299 patients, iodixanol vs ioversol), by Solomon et al. [50] (CARE trial, 414 patients, iodixanol vs iopamidol), by Wessely et al. [51] (CONTRAST trial, 324 patients, iodixanol vs iomeprol) and by Laskey et al. [52] (418 patients with CKD and diabetes, iodixanol vs iopamidol). Results from the latter study are particularly interesting, because the trial design closely resembles that of Aspelin et al. [46] as it studied patients with CKD and diabetes, who are at greatest risk of CIN. Other comparative intra-arterial trials evaluating smaller number of patients were also unable to detect significant differences in CIN rates between iodixanol and different low osmolar agents [53–57].

There have been relatively few trials comparing intravenous use of different CM. Two trials have suggested differences between contrast agents. Nguyen et al. [58] showed lower nephrotoxicity of iodixanol than iopromide used for enhanced

CT in 117 patients. However, Thomsen et al. [59] in the ACTIVE trial found lower nephrotoxicity with iomeprol than with iodixanol in 148 patients who had enhanced CT. Other studies after intravenous contrast medium have failed to show significant differences between iodixanol and non-ionic monomers [60–62].

A number of meta-analyses of the nephrotoxicity of different contrast media have been published. The recent meta-analysis by Heinrich et al. [63] considered 25 trials that compared non-ionic agents and indicated that iodixanol is not associated with a reduced risk of CIN after intravenous administration. After intra-arterial contrast medium injection iohexol was associated with a greater risk of CIN than iodixanol in patients with renal insufficiency, whereas no significant difference was found between iodixanol and other non-ionic monomers. Similar results were reported in a recent meta-analysis by Reed et al. [64]. The earlier meta-analysis of 16 angiographic studies by McCullough et al. [65], which evaluated the iodixanol database owned by GE Healthcare, suggested that iodixanol was less nephrotoxic than the other agents with low osmolarity. However, the meta-analysis only included data up to 2003, and most of these trials compared ioxaglate and iohexol with iodixanol.

The previous CMSC guideline suggested the use of CM with low or iso-osmolarity in patients with risk factors for CIN. Having considered the many studies published in recent years, the Committee considers that this previous guideline should not be changed.

**Dose of CM** The incidence of CIN is related to the dose of CM and unnecessarily large doses should be avoided in all patients, especially in at risk patients. Recent studies have tried to identify the maximum amount of CM that can safely be injected during PCI. Possible limits that have been suggested are a CM dose in grams of iodine numerically equal to the eGFR value in ml/min or keeping the ratio of the CM volume to the creatinine clearance below 3.7 [66, 67].

These recommendations cannot be directly applied to intravenous use such as in enhanced CT or intravenous urography, but they give a pointer for future studies. A “safe” dose does not exist and even very limited doses of CM may cause CIN in high-risk patients [68]. Therefore, in all patients, only the minimum amount of contrast medium necessary to answer the clinical diagnostic question should be used.

**Multiple studies** The previous guideline suggested avoiding multiple studies with CM within a short period of time in at-risk patients. No controlled trials providing evidence from repeated procedures have been published. The CMSC is aware of the significance of this issue in daily practice and of the importance of providing recommendations for the optimal time interval between procedures that require intravascular CM administration. Ideally, the interval

between procedures should be 2 weeks, the expected recovery time of the kidney after acute injury, but when this is not possible, the interval should be as long as is acceptable clinically.

#### Prophylactic strategies

When patients at risk of CIN are referred for a procedure that necessitates intravascular CM, it is very important first to establish the clinical need for the examination, and whether another procedure not requiring the use of iodine-based CM could provide the required diagnostic information. The situation has been complicated by the recognition of the risk of inducing nephrogenic systemic fibrosis (NSF) after some of the gadolinium contrast media used for magnetic resonance imaging (MRI) (refer to the NSF guideline at [www.esur.org](http://www.esur.org)).

If the procedure using iodinated CM is deemed essential, preventive measures should be used [69].

**Hydration (volume expansion)** Randomised double-blinded trials comparing hydration with a proper control group of no hydration are not available. However, conducting such randomised trials would be ethically unacceptable given the current understanding of CIN. Based on clinical experience, there is broad consensus that volume expansion reduces the risk of CIN. Adequate volume expansion improves renal blood flow, induces diuresis with dilution of contrast material within the tubules, reduces the activation of the renin-angiotensin system, suppresses the secretion of the anti-diuretic hormone, and minimises reductions in the renal production of endogenous vasodilators such as nitric oxide and prostacycline [70].

Although the literature published since the original CMSC guidelines has favoured volume expansion with intravenous fluid over oral hydration, there has not been adequate research on this topic. Trivedi et al. [71] compared intravenous saline 0.9% at 1 ml/kg/h from 12 h before and until 12 h after CM administration with unrestricted oral fluids. CIN occurred significantly less frequently in the intravenous saline group (3.7%), compared with the oral fluid group (34.6%). However, oral hydration was shown to be effective by Dussol et al. [72] who compared oral salt capsules and normal water intake with intravenous saline hydration before a variety of procedures. Prevention of CIN in the oral hydration group was comparable with that in the intravenous hydration group. In a small study by Taylor et al. [73], patients scheduled for coronary angiography showed similar CIN rates after being given either an “outpatient preparation” of overnight oral hydration with 1,000 ml of fluid, plus intravenous saline 0.45% at a rate of 300 ml/h starting 1 h before angiography and continuing for 6 h thereafter, or an



“in-patient preparation” with intravenous half-saline at 75 ml/h during the 12 h before and after CM.

Normal saline (0.9%) appears to be more effective than half-normal saline (0.45%) [74].

To determine the optimal amount of volume expansion, correlation with the body weight seems reasonable and the literature suggests 1.0–1.5 ml/kg/h. However, there is no clear evidence on the optimal rate and duration of infusion. There is evidence that intravenous saline given for 24 h before and after the procedure provides better protection than hydration only during the procedure [75, 76]. Most papers on coronary angiography and PCI suggest starting intravenous saline 12 h before the procedure and continuing for 12 h after. The most effective regime for intra-arterial procedures appears to be 1.0–1.5 ml/kg/h 12 h before and 12 h after the procedure. However, this regime is clearly not practical for outpatients.

The use of sodium bicarbonate instead of sodium chloride has been advocated. It is suggested that the resulting urine alkalisation reduces the generation of free radicals. Bicarbonate appears capable of scavenging reactive oxygen species, as well as increasing urine flow. Also, the large amounts of chloride in isotonic saline may cause constriction of the renal vasculature [77]. Merten et al. [78] published the first trial comparing infusion of sodium bicarbonate (154 mEq/l in dextrose 5% water) with sodium chloride. Infusion was started 1 h before the CM injection at a rate of 3 ml/kg/h and continued for 6 h after at a rate of 1 ml/kg/h. A number of further trials followed and their results have been pooled in recent meta-analyses [77–83]. These suggest that sodium bicarbonate may provide better protection against CIN than normal saline. However, in all these meta-analyses study heterogeneity was reported and there was even publication bias in some studies. When heterogeneity is present, meta-analysis is not the right tool for summarising data [84].

However, a more recent meta-analysis showed no evidence of heterogeneity or publication bias and favours hydration with sodium bicarbonate [85]. The diminished risk of CIN after sodium bicarbonate does not seem to translate into decreased mortality or a reduced need for haemodialysis, but the incidence of these complications is low and a pooled analysis is probably underpowered to detect significant differences [81]. The safety of sodium bicarbonate in cardiac patients might be a source of concern, but sodium bicarbonate does not appear to cause deterioration in congestive heart failure or to trigger acute pulmonary oedema [82].

In conclusion, it appears that sodium bicarbonate provides equal or superior protection to isotonic saline. Therefore, the Committee considers that there is enough evidence to recommend that either volume expansion regimen may be used. When normal saline is used, the

Committee recommends an intravenous regime of 1.0–1.5 ml/kg/h for at least 6 h before and after contrast medium administration. For sodium bicarbonate, the most widely used regimen (3 ml/kg/h for 1 h before contrast medium followed by 1 ml/kg/h for 6 h after) seems appropriate, although the dose of sodium bicarbonate should be increased until urine alkalisation is achieved [81]. The sodium bicarbonate protocol is quicker than the optimal isotonic saline regimen and might be useful for outpatients. Additional studies are required to assess whether a single bolus of sodium bicarbonate administered just before contrast medium administration is effective as Tamura et al. [86] suggested, as this protocol would be extremely useful in daily practice.

*Hydration (volume expansion): class of recommendation I, level of evidence C*

*Pharmacological prophylaxis* No drugs have been approved by the regulatory authorities for the prevention of CIN and the CMSC did not support pharmacological prophylaxis for preventing CIN in its previous guidelines [1] because none of the pharmacological manipulations had been shown to offer consistent protection.

A number of trials of different drugs have been published recently and have been reviewed by the Committee. For most of the drugs tested, including fenoldopam, dopamine, calcium channel blockers, atrial natriuretic peptide, L-arginine, prostaglandin E<sub>1</sub>, furosemide, mannitol and endothelin receptor antagonist [70, 72, 87–90], the evidence is limited, conflicting or even negative. Some drugs that appear potentially beneficial, such as theophylline/aminophylline, statins, ascorbic acid and iloprost [72, 91–101], require further evaluation. None of these drugs was consistently effective, and some of them (e.g. theophylline/aminophylline) may have harmful side effects. The use of these drugs for the prophylaxis of CIN cannot be supported.

N-acetylcysteine (NAC) has received considerable attention during the last decade following the paper by Tepel et al. [102] and deserves a more detailed analysis. NAC is cheap, widely available, is considered safe, and may be beneficial because of its antioxidant and vasodilatory effects. The drug has been used orally, in variable doses, and intravenously, with even more variable protocols. The most popular protocol was an oral regime of 600 mg twice daily for 24 h the day before and on the day of the procedure. Most of the studies involved patients undergoing coronary angiography or PCI. More than 30 randomised controlled trials have evaluated the efficacy of NAC for preventing CIN, with the largest studies being Azmus et al., Briguori et al., Kay et al., Marenzi et al. and Webb et al. [103–108]. The results were conflicting, with some reporting a decreased incidence of CIN, and others showing no significant benefit. It has been suggested that higher doses (a double oral dose) might give better protection

[105, 109]. However, intravenous NAC at higher doses may be associated with significant side effects, such as hypotension and bronchospasm.

More than 15 meta-analyses have been performed, and the more recent are Kelly et al., Fishbane, Gonzales et al., Pannu et al., Sinert and Doty, and Zagler et al. [97, 110–114]. Their results were again conflicting. Most studies were underpowered and Gonzales et al. [111] noted that the apparent benefit of NAC was essentially limited to early trials, which were small in size and of poorer quality. It is puzzling that different meta-analyses reached different conclusions. Papers analysing the meta-analyses revealed statistical and clinical heterogeneity, variable quality of reporting and publication bias [84, 115–117]. Furthermore, there has been speculation about whether NAC may lower SCr without affecting GFR and so without any benefit to renal function [118, 119]. Other authors [120] could not reproduce these results.

In conclusion, the current opinion of the CMSC is that the efficacy of NAC and other drugs in reducing the incidence of CIN remains unproven and their use cannot be recommended.

*Pharmacological prophylaxis: class of recommendation IIb, level of evidence A*

**Haemodialysis and haemofiltration** Haemodialysis immediately after CM administration removes the contrast material but is not effective in preventing CIN [121]. Therefore, the CMSC does not recommend prophylactic haemodialysis.

Haemofiltration has been discussed in the recent literature [122, 123] but requires management in the intensive care unit (ICU), is costly and affects creatinine levels per se. Additional data may eventually support its use in very high-risk patients, such as those in CKD grade 5, or those in ICUs, who require interventional vascular procedures.

*Prophylactic haemodialysis: class of recommendation III, level of evidence A Haemofiltration: class of recommendation IIb, level of evidence B*

**Withdrawal of nephrotoxic drugs** The use of nephrotoxic drugs is likely to increase the risk of developing CIN. This is supported by experimental observations [34], but clinical data are lacking. A trend towards a higher incidence of CIN in patients receiving loop diuretics, non-steroidal anti-inflammatory drugs, coxibs, aminoglycosides or amphotericin B has been reported [33]. CIN in patients treated with cisplatin has also been described. Conflicting data have been reported on angiotensin-converting enzyme (ACE) inhibitors, with some suggesting an increased risk of CIN, and others suggesting a decreased risk. A more comprehen-

sive list of nephrotoxic drugs, including others that have not been reported in the medical history of patients who developed CIN, has been published [124, 125].

Withdrawal of nephrotoxic drugs at least 24 h before CM administration in at-risk patients was suggested in the previous guidelines. Current literature supports this advice, but the recommendation is poorly followed in clinical practice [126, 127]. It seems reasonable to continue the use of ACE-inhibitors, loop-diuretics and small doses of nonsteroidal antiinflammatory drugs (NSAIDs) for antiplatelet treatment in patients with stable renal function, because temporary cessation may be more harmful for the patient.

The CMSC agreed that lack of evidence makes it difficult to produce a definitive statement about nephrotoxic drugs. The Committee therefore recommends that the possible withdrawal of nephrotoxic drugs before contrast medium in patients at risk of CIN should be discussed with the referring physician and that their judgement should balance the relative benefits and harms.

*Withdrawal of nephrotoxic drugs: Class of recommendation IIa, level of evidence C*

## Gadolinium-based contrast media

Nephrotoxicity of gadolinium-based CM has been observed. The CMSC position is that gadolinium-based CM are more nephrotoxic than iodine-based CM in equivalent x-ray attenuating doses [128–131] and should not be used for radiographic examinations such as angiography and CT. The use of gadolinium-based CM for angiography or CT is not an approved indication anywhere in the world.

A number of retrospective [132, 133] and prospective [134, 135] clinical studies have supported the safety of gadolinium-based CM when used for MRI in patients with renal impairment. No deterioration of renal function was reported in any of these patients. The same applies to a study of 21 patients with chronic kidney disease who were given gadobutrol intravenously but did not undergo MRI [136].

There are only a few reports of CIN following gadolinium contrast agents. Sam et al. evaluated 153 patients with chronic renal insufficiency who received a triple dose of gadolinium DTPA during MR angiography (MRA). Three out of 153 patients (1,9%), who had received a dose ranging from 0.31 to 0.41 mmol/kg developed acute renal failure with anuria [137]. Another retrospective study analysed 473 patients with chronic renal failure who underwent MRA at a dose of 0.2 mmol/Kg. In the subgroup of 91 patients with stage 3 or 4 renal failure, who had a median eGFR of 33 ml/min/kg/1.73 m<sup>2</sup>, one of three different gadolinium-based CM

**Table 3** Guideline

Definition: CIN is a condition in which a decrease in renal function occurs within 3 days of the intravascular administration of a CM in the absence of an alternative aetiology. An increase in serum creatinine by more than 25% or 44  $\mu\text{mol/l}$  (0.5 mg/dl) indicates CIN

### 1. RENAL ADVERSE REACTIONS TO IODINE-BASED CONTRAST MEDIA

#### RISK FACTORS FOR CONTRAST MEDIUM-INDUCED NEPHROPATHY

Patient-related	<ul style="list-style-type: none"> <li>• eGFR less than 60 ml/min/1.73 m<sup>2</sup> before intra-arterial administration</li> <li>• eGFR less than 45 ml/min/1.73 m<sup>2</sup> before intravenous administration</li> <li>• In particular in combination with               <ul style="list-style-type: none"> <li>○ Diabetic nephropathy</li> <li>○ Dehydration</li> <li>○ Congestive heart failure (NYHA grade 3-4) and low LVEF</li> <li>○ Recent myocardial infarction (&lt;24 h)</li> <li>○ Intra-aortic balloon pump</li> <li>○ Peri-procedural hypotension</li> <li>○ Low haematocrit level</li> <li>○ Age over 70</li> <li>○ Concurrent administration of nephrotoxic drugs</li> </ul> </li> <li>• Known or suspected acute renal failure</li> </ul>
Procedure-related	<ul style="list-style-type: none"> <li>• Intra-arterial administration of contrast medium</li> <li>• High osmolality agents</li> <li>• Large doses of contrast medium</li> <li>• Multiple contrast medium administrations within a few days</li> </ul>

#### 1.1. Time of referral

##### ELECTIVE EXAMINATION

##### IDENTIFY PATIENTS WHO REQUIRE MEASUREMENT OF RENAL FUNCTION

- Patients with known eGFR less than 60 ml/min/1.73 m<sup>2</sup> Determine eGFR (or SCr) within 7 days of contrast medium administration
- Patients who will receive intra-arterial contrast medium
- Age over 70
- Patients with a history of:
  - Renal disease
  - Renal surgery
  - Proteinuria
  - Diabetes mellitus
  - Hypertension
  - Gout
  - Recent nephrotoxic drugs

##### EMERGENCY EXAMINATION

Identify at-risk patients (see above) if possible:

- Determine eGFR if the procedure can be deferred until the result is available without harm to the patient
- If eGFR cannot be obtained, follow the protocols for patients with eGFR less than 60 ml/min/1.73 m<sup>2</sup> for intra-arterial administration and eGFR less than 45 ml/min/1.73 m<sup>2</sup> for intravenous administration as closely as clinical circumstances permit.

#### 1.2. Before the examination

##### ELECTIVE EXAMINATION

- |                              |   |
|------------------------------|---|
| At risk patients (see above) | <ul style="list-style-type: none"> <li>• Consider an alternative imaging method not using iodine-based contrast media</li> <li>• Discuss the need to stop nephrotoxic drugs with the referring physician</li> <li>• Start volume expansion. A suitable protocol is intravenous normal saline, 1.0-1.5 ml/kg/h, for at least 6 h before and after contrast medium. An alternative protocol is intravenous sodium bicarbonate, 3 ml/kg/h for 1 h before contrast medium and 1 ml/kg/h for 6 h after contrast medium.</li> </ul> |
|------------------------------|---|

##### EMERGENCY EXAMINATION

- |                              |  |
|------------------------------|--|
| At risk patients (see above) | <ul style="list-style-type: none"> <li>• Consider an alternative imaging method not using iodine-based contrast media.</li> <li>• Start volume expansion as early as possible before contrast medium administration (See elective examination).</li> </ul> |
|------------------------------|--|

**Table 3** (continued)**1.3. Time of examination**

At-risk patients (see above)	<ul style="list-style-type: none"> <li>• Use low or iso-osmolar contrast media</li> <li>• Use the lowest dose of contrast medium consistent with a diagnostic result</li> </ul>
Patients not at increased risk	<ul style="list-style-type: none"> <li>• Use the lowest dose of contrast medium consistent with a diagnostic result</li> </ul>

**1.4. After the examination**

At-risk patients	<ul style="list-style-type: none"> <li>• Continue volume expansion</li> <li>• Determine eGFR 48–72 h after contrast medium</li> </ul>
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Note: No **pharmacological prophylaxis** (with renal vasodilators, receptor antagonists of endogenous vasoactive mediators or cytoprotective drugs) has yet been shown to offer consistent protection against contrast medium-induced nephropathy.

**2. RENAL ADVERSE REACTIONS TO GADOLINIUM-BASED CM (NON-ORGAN SPECIFIC).****MR EXAMINATIONS**

- The risk of nephrotoxicity is very low when gadolinium-based CM are used in approved doses.
- In patients with reduced renal function refer to ESUR guidelines on NSF.

**RADIOGRAPHIC EXAMINATIONS**

- Gadolinium-based CM should not be used for radiographic examinations in patients with renal impairment.
- Gadolinium-based CM are more nephrotoxic than iodine-based CM in equivalent X-ray attenuating doses.

**3. PATIENTS TAKING METFORMIN****3.1 Iodine-based contrast media**

- 1) *Patients with eGFR equal to or greater than 60 ml/min/1.73 m<sup>2</sup> (CKD 1 and 2)* can continue to take metformin normally.
- 2) *Patients with eGFR 30–59 ml/min/1.73 m<sup>2</sup> (CKD3)*
  - a) Patients receiving intravenous contrast medium with eGFR equal to or greater than 45 ml/min/1.73 m<sup>2</sup> can continue to take metformin normally.
  - b) Patients receiving intra-arterial contrast medium, and those receiving intravenous contrast medium with an eGFR between 30 and 44 ml/min/1.73 m<sup>2</sup>, should stop metformin 48 h before contrast medium and should only restart metformin 48 h after contrast medium if renal function has not deteriorated.
- 3) *Patients with eGFR less than 30 ml/min/1.73 m<sup>2</sup> (CKD 4 and 5), or with an intercurrent illness causing reduced liver function or hypoxia.* Metformin is contraindicated and iodine-based contrast media should be avoided.
- 4) *Emergency patients.* Metformin should be stopped from the time of contrast medium administration. After the procedure, the patient should be monitored for signs of lactic acidosis. Metformin should be restarted 48 h after contrast medium if serum creatinine/eGFR is unchanged from the pre-imaging level.

**3.2 Gadolinium-based contrast media**

No special precautions are necessary when diabetic patients on metformin are given gadolinium-based CM.

(gadopentetate dimeglumine, gadodiamide, or gadoterate) was administered. Eleven out of 91 (12.1%) developed CIN (defined as an increase of  $\geq 0.5$  mg/dl (44  $\mu\text{mol/l}$ ) in SCr level over baseline). None required dialysis and their mean eGFR after the procedure was 16 ml/min/kg/1.73 m<sup>2</sup>. Lower eGFR and diabetic nephropathy were statistically significant independent risk factors [138]. There are some case reports of diabetic patients who underwent MRI with gadolinium-based CM at low doses and developed CIN [139, 140].

(The topic of NSF is outside the scope of this paper. For further information, refer to the NSF guideline published online by the CMSC at [www.esur.org](http://www.esur.org)).

**Metformin**

The biguanide metformin is the drug of first choice in adults with non-insulin-dependent diabetes mellitus, not controlled by diet and exercise [141, 142]. Metformin is absorbed quickly from the gut, with peak blood levels at

2.5 h. It is then rapidly excreted by the kidneys, by both glomerular filtration and tubular secretion, with 90% excreted in the first 12 h [143]. Slow-release metformin tablets, which have recently been introduced, have a layer of polymer around the active metformin core, and this slows and smoothes absorption. Peak blood levels occur at 7 h, but thereafter handling of the metformin is identical to the immediate release preparation [144].

An earlier biguanide, phenformin, introduced in the late 1950s, was associated with an unacceptably high risk of lactic acidosis and was withdrawn in 1977. Metformin was estimated to have a 10–20 times lower risk of causing lactic acidosis than phenformin [143], but concerns about its use persisted. The risk of metformin-induced lactic acidosis in diabetics is now recognised to be very low, with rates of 4.3 and 9 cases per 100,000 patient years reported [145, 146]. The risk of lactic acidosis with metformin appears to be no greater than that with sulphonylurea [146, 147].

In renal impairment, metformin excretion is reduced, for example by 74–78% in moderate or severe renal impairment



[148] and blood metformin levels may be many times greater than the therapeutic level [149], potentially increasing the risk of lactic acidosis. Renal impairment has therefore been considered to be a contraindication to the use of metformin and the Summaries of Product Characteristics (SPCs) issued by the manufacturers of metformin state that it should not be prescribed when the eGFR is less than 60 ml/min/1.73 m<sup>2</sup> [150]. Other contraindications to metformin are conditions that predispose to lactic acidosis, particularly liver disease and conditions causing hypoxia or reduced peripheral perfusion, such as cardiac or respiratory failure and severe infection [143].

As the low incidence of lactic acidosis associated with metformin has been recognised, it has been suggested that metformin can be prescribed to patients with CKD 3 (GFR 30–59 ml/min/1.73 m<sup>2</sup>) [151–153]. In a series of 2,500 patients in whom a variety of contraindications to metformin were ignored, there was only one case of lactic acidosis [151]. Clinical guidelines issued by the UK National Institute for Clinical Excellence (NICE), updated in 2009, state that metformin can be prescribed to patients with an eGFR of 45 ml/min/1.73 m<sup>2</sup> or more (or serum creatinine less than 130 µmol/l), that the metformin dose should be reviewed if the eGFR is less than 45 ml/min/1.73 m<sup>2</sup>, and that metformin should be stopped if the eGFR falls below 30 ml/min/1.73 m<sup>2</sup> (serum creatinine exceeds 150 µmol/l) [142].

Diabetics with renal impairment are at higher risk of CIN after intravascular iodinated contrast media than are non-diabetics with the same degree of renal impairment [30, 154, 155]. The risk of CIN is very low in diabetic patients with normal renal function [30, 155]. Anxieties about the use of iodinated contrast agents in diabetics taking metformin relate to the possibility of producing CIN, thus leading to retention of metformin, with an associated increased risk of lactic acidosis. In the absence of direct studies on the subject, guidelines for radiologists produced since the 1990s have had to be based on the consensus of experts familiar with metformin pharmacokinetics and the pathophysiology of CIN [156, 157].

In 1999, the first ESUR CMSC guideline on metformin stated that patients with normal renal function should stop metformin from the time of administration of intravascular iodinated contrast medium for 48 h and only restart after the serum creatinine had been shown to be normal. Patients with abnormal serum creatinine should stop metformin 48 h before contrast medium administration and only restart metformin 48 h afterwards if their serum creatinine is unchanged [2]. As confidence about the safety of metformin increased, a relaxation of the guidelines for metformin was proposed [158, 159]. A new ESUR guideline released online in 2009 stated that patients on metformin with an eGFR of 60 ml/min/1.73 m<sup>2</sup> or more could continue to take metformin

as usual if they received intravascular iodinated contrast medium. For patients with eGFR between 30 and 59 ml/min/1.73 m<sup>2</sup> it was recommended that metformin was stopped 48 h before contrast medium administration, and only restarted if the eGFR measured 48 h afterwards was unchanged [3].

The Committee has updated this 2009 guideline in the light of its new CIN recommendations and of the recent NICE guideline [142]. The new ESUR guideline states that patients with an eGFR of 45 ml/min/1.73 m<sup>2</sup> or greater can continue to take metformin normally if they receive intravenous iodinated contrast medium. Patients receiving intra-arterial iodinated contrast medium with an eGFR of 30–59 ml/min/1.73 m<sup>2</sup> and patients receiving intravenous contrast medium with an eGFR 30–44 ml/min/1.73 m<sup>2</sup> should stop taking metformin 48 h before contrast medium administration. Renal function should be re-assessed 48 h after contrast medium and metformin should only be restarted if it has not deteriorated further.

Although CIN has been reported after gadolinium contrast media [140], it is very rare when approved doses only are used. No special precautions are needed when patients receiving metformin are given gadolinium-based contrast agents.

## Conclusion

Evaluation of the current literature, summarised in this report, indicates the need for a number of changes to the previous guidelines [1, 3]. The Committee agreed that the risk of CIN is lower after intravenous than after intra-arterial contrast medium administration (at a similar dose) and considered that only patients with an eGFR less than 45 ml/min/1.73 m<sup>2</sup> are at risk of CIN before intravenous administration of iodinated contrast media. Additionally, the Committee agreed that volume expansion with either sodium bicarbonate or normal saline is effective in preventing CIN and that either can be used. The guidelines for the use of CM in diabetic patients on metformin have been relaxed. These, and some further minor changes have been incorporated into the new guidelines which are presented in Table 3.

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