European Radiology (2019) 29:3927–3934
https://doi.org/10.1007/s00330-019-06147-2

CONTRAST MEDIA

Low incidence of nephrotoxicity following intravenous administration of iodinated contrast media: a prospective study

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Received: 16 November 2018 / Revised: 13 February 2019 / Accepted: 8 March 2019 / Published online: 11 April 2019

Abstract

Objectives To estimate the incidence of contrast-induced acute kidney injury (CI-AKI) after intravenous (iv) iodinated contrast material (ICM) exposure.

Methods This prospective cohort study included all consecutive patients who underwent radiological investigations using low-osmolar iopamidol 370 mg/ml in a regional hospital over a period of 36 months, without any exclusion criteria. The estimated glomerular filtration rate (eGFR) was evaluated using the MRDR equation before (2–10 days) and after (24–36 h) radiological investigations. CI-AKI was defined as a ≥25% decrease in eGFR from baseline. CI-AKI incidence was estimated using a binomial distribution. The association between CI-AKI and demographic and clinical characteristics was modeled using logistic regression.

Results The study included 1541 patients with a median age of 68 (1st–3rd quartiles 58–76) years with various comorbidities, 30% of whom had pre-existing CKD. Patients affected by stage III or IV chronic kidney disease (CKD) received an infusion of 0.9% normal saline (1.0–1.5 ml/kg/h) before and after iso-osmolar iodixanol administration. CI-AKI was observed in 33 patients (2.1%, 95% CI 1.5–3.0). The logistic regression analysis showed that antibiotic and statin therapies were significantly associated with CI-AKI. The probability of developing CI-AKI decreased by 80% in patients taking statins (OR = 0.20, 95% CI 0.03; 0.68) and increased approximately three times in patients with antibiotic therapy compared with those who did not take statins and antibiotics (OR = 2.92, 95% CI 1.21; 6.36).

Conclusions Our data suggest that low-osmolar iopamidol carries a low incidence of nephrotoxicity, even in subjects with various comorbid conditions or reduced renal function.

Key Points

- *IV administration of ICM carries a low incidence of nephrotoxicity, which was transient in observed patients.*
- *Statin therapy is negatively associated with AKI in patients exposed to ICM.*
- *Pre-existing impairment of renal function is not associated with AKI in patients exposed to ICM.*

Keywords Contrast material · Incidence · Glomerular filtration rate · Renal insufficiency

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00330-019-06147-2) contains supplementary material, which is available to authorized users.

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Abbreviations

CI-AKI	Contrast-induced acute kidney injury
CIN	Contrast-induced nephropathy
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
ICM	Intravenous iodinated contrast media
iv	Intravenous

Introduction

In the past 20 years, a large number of papers have warned of the risk of renal functional impairment following iodinated contrast material (ICM) administration [1].

As a consequence, radiologists developed increasing concerns for using ICM in clinical practice, irrespective of the type of investigation and the route of administration. In particular, much attention has been paid to patients with reduced renal function and/or those affected by diabetes mellitus or other comorbidities, since they are reported to be at a higher risk of acute kidney injury (AKI) [2].

This attitude may potentially cause a loss of diagnostic power in radiological investigation and, therefore, a loss of accuracy in the final diagnosis.

In clinical practice, the current absolute and indiscriminate fear of ICM administration—without any distinction among the various radiological investigations—seems to be the result of an incorrect perception of the problem. The majority of published papers ignore that renal function may worsen after ICM administration due to several factors that are frequently not directly related to contrast material toxicity.

In particular, among the possible causes, atheroembolic renal disease induced by cholesterol embolism is certainly an underdiagnosed cause of renal impairment occurring in patients undergoing intra-arterial procedures, without any relationship to ICM administration. In addition, in this setting, the risk of atheroembolic renal disease may be different, depending on the use of radial or femoral access, the latter being more frequently associated with side effects due to its proximity to the renal arteries [3, 4].

Lack of accuracy in diagnosing the type and mechanisms responsible for the decreased renal function reported after ICM radiological investigations, along with the different criteria used to define renal involvement, may explain the large variability reported in the incidence of so-called "contrast-induced nephropathy" (CIN). Indeed, the incidence of CIN ranges from 1 to 2% to 33%, depending on the severity of renal failure, the need for dialysis, and the long-term outcome of the patient [5].

A recent meta-analysis of controlled studies examining the incidence of CI-AKI in patients exposed to intravenous (iv) ICM failed to show any statistically significant difference between patients who received ICM and patients who did not [6]. In line with this evidence, the existence of CI-AKI has been questioned in several other studies [7–10]. In particular, these studies suggest that changes in serum creatinine levels observed after ICM exposure may reflect spontaneous fluctuations rather than "real" AKI. However, an important limitation of these studies is the lack of uniformity in data collection, i.e., the volume of administered ICM, creatinine values, and the time sequence between the administration of ICM and the appearance of AKI [8, 11]. It is widely accepted that CI-AKI develops within 24–72 h of ICM administration. Furthermore, eGFR is a more accurate method than creatinine alone to evaluate renal function, as it considers other factors such as age, race, and gender [12].

Thus, this study was designed to verify the real occurrence of CI-AKI after ICM administration in everyday clinical practice by studying prospectively an unselected population of patients who underwent radiological investigations in a single regional hospital.

Materials and methods

Study design and patients

The study was designed as a prospective cohort study with the aim of assessing the incidence of CI-AKI in patients that underwent any radiological diagnostic investigation with iv. ICM administration between 2012 and 2016 at the Radiology Department of the regional hospital of Ancona, Italy, without any inclusion or exclusion criteria.

Patients and data collection

Demographic and clinical data of the enrolled patients, including diabetes mellitus, hypertension, and cardiovascular diseases or pre-existing renal disease, were collected before radiological investigation.

Patients were defined as having diabetes mellitus or arterial hypertension if they received any glucose-lowering drug or antihypertensive medications.

In addition, any drug therapy was recorded. Finally, the type of radiological examination and the type and volume of ICM administered were collected, as well as the final radiological diagnosis and adverse drug reactions.

ICM and prophylaxis of renal function decrease

Patients affected by chronic kidney disease (CKD), stage III or IV, received iso-osmolar iodixanol (VISIPAQUE, GE Healthcare), while the remaining patients were administered the low-osmolar contrast material iopamidol at 370 mg/ml (Iopamiro, Bracco).

In accordance with the European Society of Urogenital Radiology guidelines, these patients also received an infusion of 0.9% normal saline (1.0–1.5 ml/kg/h) before and after ICM administration [13].

Evaluation of renal function

Nephrologists carried out the baseline patient evaluation by examining their clinical history, drawing special attention to events involving the kidneys and potential renal risk factors. CI-AKI was assessed before (2–10 days) and after (24–36 h) radiological investigation by measuring serum creatinine with a standardized method in the same laboratory. Estimated glomerular filtration rate (eGFR) was calculated using the MRDR equation [14]:

$$\mathrm{eGFR} = 175 \times (S_{Cr})^{-1.154} \times (\mathrm{age})^{-0.203} \times 0.742\ [\text{if female}] \times 1.212\ [\text{if African American}]$$

where S_{cr} is serum creatinine in milligrams per deciliter.

Patients with pre-existing CKD were identified and stratified according to the KDIGO guidelines [15] as follows:

- stage I: eGFR > 90%
- stage II: eGFR 60–89%
- stage III: eGFR 30–59%
- stage IV: eGFR 15–29%

A renal function change after contrast investigation was defined as a ≥ 25% reduction of calculated eGFR from baseline.

To investigate the possible relationship between eGFR changes and different variables, patients were divided into two groups according to whether they had a CI-AKI after ICM investigation.

Follow-up

Patients with a CI-AKI underwent extended follow-up to assess possible nephrological consequences.

- *Patients with normal renal function admission or stage I–II CKD*: creatinine levels were determined 1 week after the radiological investigation. If normal at 1 week, the follow-up stopped. Otherwise, a further follow-up visit was performed at 1 month, and then, if the creatinine level or eGFR was normal, the follow-up stopped.
- *Patients with stage III–IV CKD*: creatinine levels were determined 1 week and 1 month after the radiological investigation. If normal at 1 month, the follow-up stopped. Otherwise, a complete nephrological evaluation was performed in order to establish whether any underlying nephropathy, not directly related with CI-AKI, could be involved.

Statistical analysis

A non-parametric approach was used for the statistical analysis, since variables were not found to be normally distributed using the Shapiro test.

The incidence of CI-AKI was evaluated as point and 95% confidence interval (95% CI) estimates using the binomial distribution.

Quantitative variables were summarized using the median and interquartile range (first to third quartiles), and qualitative variables were summarized as the absolute and percentage frequencies.

Moreover, the odds ratios (OR) of CI-AKI for the main risk factors considered were estimated by means of logistic regression analysis.

Drugs used by patients were recorded at baseline, and their distributions were evaluated according to the presence or absence of CI-AKI. Comparisons between the two groups were performed using Fisher's exact test. A Wilcoxon-Mann-Whitney test was used to compare quantitative variables between participants and non-participants and between CKD and non-CKD patients.

A multiple logistic analysis was used to estimate the association between demographic and clinical characteristics and CI-AKI. All estimates were expressed as OR and 95% CIs. A likelihood ratio test was used to select the most parsimonious model and to evaluate the model's goodness of fit.

A level of probability lower than 0.05 was used to assess the statistical significance, and the statistical analyses were performed using R version 3.4.3 [16].

Good clinical practice and ethical aspects

The study was registered under the European Clinical Trials Database (reference number: EudraCT 2012-004742-16) and was approved by the Region Marche Ethics Committee. All patients were consecutively enrolled, informed about the study design and gave written informed consent to participate.

Results

The study was conducted in a hospital-based radiology department in which both routine and emergency computed tomography requiring iv ICM administration are carried out. A total of 2271 patients were enrolled, but it was not possible to fully evaluate 730 of the patients. No significant differences were found between participants in the study and nonparticipants with regard to their main characteristics, with the exception of

age and the presence of hypertension (Supplementary material, Table 1). Patients participating in the study were significantly older and had hypertension significantly more frequently. The final analysis was carried out on 1541 subjects, whose main demographic and clinical features are reported in Table 1.

Approximately one-third (28%) of the patients included in the study had pre-existing impaired renal function. The patients with CKD stage III or IV (201, 13% of patients included) received prophylactic measures as above described and were studied using iso-osmolar iodixanol as the contrast material. Six hundred thirty-nine (42%) patients were enrolled from internal wards of the hospital. After the radiological procedure, CI-AKI was observed in 33 patients (2.1%, 95% CI 1.5–3.0). At the first follow-up (1 week), in all of the 33 patients who developed CI-AKI, renal function had returned to baseline values (Fig. 1), and none of the patients developed renal failure requiring dialysis treatment. As shown in Table 2, the risk of CI-AKI was not significantly associated with clinical conditions such as cardiovascular diseases, diabetes, or hypertension or with renal function impairment before ICM administration. Moreover, the frequency of CI-AKI was not significantly different between in- and outpatients (16 (2.5%) vs 17 (1.9%), respectively, $p = 0.534$). The median percentage variation of eGFR was 0% (first to third quartiles − 8.5 to 9) in non-CKD patients and − 5.4% (first to third quartiles − 15.6 to 1.7) in CKD patients ($p < 0.001$).

The distribution of drugs used by the patients evaluated in the study at baseline, according to the presence of CI-AKI, is reported in Table 3. The majority of patients received several drugs; the percentage of patients receiving antibiotic therapy was significantly higher in patients who developed CI-AKI than in those who did not. The percentage of patients receiving beta-blockers and of those receiving statin therapy was significantly higher in the group of individuals who did not develop CI-AKI than in those who did. Regarding antibiotic therapy, eight patients belonging to the CI-AKI group were treated with fluoroquinolones, penicillin, or aminoglycoside.

The regression analysis showed that statin and antibiotic therapies were significantly associated with AKI: the probability of developing CI-AKI decreased by 80% in patients taking statins and increased about three times in patients with antibiotic therapies with respect to those that did not received statins and antibiotics, respectively (Table 4).

Table 1 Distribution of the main characteristics of the patients at baseline according to their inclusion in the study. Fisher's exact test; chi-square test; Wilcoxon-Mann-Whitney test

Variables	$N = 1541$
Age, years (median (1st–3rd quartiles))	68 (58–76)
Gender males	959 (62.2%)
Cardiovascular disease	570 (36.9%)
Diabetes	237 (15.3%)
Hypertension	764 (49.5%)
Monoclonal gammopathy	11 (0.7%)
Pharmacological therapy*	1286 (83.4%)
Chronic kidney disease	
No	1109 (71.9%)
Stage I	9 (0.58%)
Stage II	222 (14.0%)
Stage III	151 (9.7%)
Stage IV	50 (3.2%)

Numbers in the table refer to absolute (percentage) frequencies otherwise indicated. *Any concomitant pharmacological treatments to which the patients were exposed

Discussion

The results of our prospective study suggest that iv ICM administration carries a low incidence of nephrotoxicity. As described, many subjects included in the study suffered from diabetes mellitus or cardiovascular disease and, even more relevant to the aim of the study, one-third of them had CKD ranging from stage II to stage IV. Previously reported papers have associated these conditions with increased risk of nephrotoxicity [17–24]. In contrast, only 2.1% of the patients (33 patients) included in the present study experienced changes in eGFR measured after the radiological survey (24–36 h) that were greater than 25% compared with the value obtained before the radiological survey (2–10 days). It is very interesting to note that 29 of the 33 patients with CI-AKI belonged to the group with normal renal function, suggesting that compromised renal function does not increase the risk of CI-AKI after administration of iv ICM. These data are consistent with a previous study conducted by McDonald et al. In particular, this retrospective study was conducted on 12,508 internal patients (stratified for renal function) that underwent CT with or without ICM. The authors concluded that the risk of CI-AKI is independent of contrast material exposure, even in patients with low eGFR [25].

In addition, in our study, only two patients with stage III–IV CKD developed a CI-AKI that resolved within 7 days. Considering that only patients with stage III–IV CKD had received prophylactic treatment, our results may suggest that prophylactic hydration in patients with stage III–IV CKD can be convenient since the risk of CI-AKI in these patients was not significantly different from that of patients with no CKD or stage I–II CKD. No definitive guidelines indicating a prophylaxis protocol are currently available; hence, in the literature, the results are conflicting and new approaches are under consideration [26–28]. For instance, the prospective study conducted by Nijsse E et al concludes that hydration does not reduce the risk of CI-AKI in the population with moderate

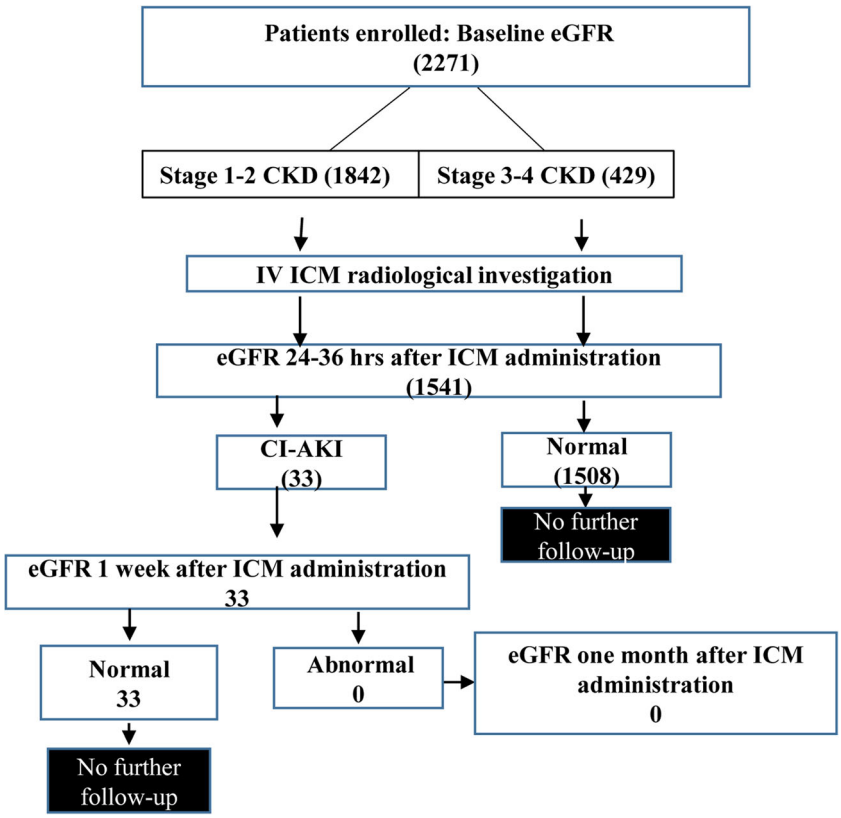

Fig. 1 Enrollment and follow-up of study participants

Table 2 Odds ratio and 95% confidence interval of CI-AKI according to the main demographic and clinical factors evaluated at baseline

Risk factors	No CI-AKI ($n = 1508$)	CI-AKI ($n = 33$)	OR (95% CI)	p
Age, years (median (1st–3rd quartiles))	67.7 (58.2; 75.6)	68.6 (58.1; 74.5)	0.99 (0.97; 1.02)	0.576
Gender (n (%))				
Males	944 (62.6)	15 (45.5)		
Females	564 (37.4)	18 (54.5)	2.01 (1.00; 4.07)	0.050
Cardiovascular disease (n (%))				
No	924 (62.3)	23 (69.7)		
Yes	560 (37.7)	10 (30.3)	0.72 (0.32; 1.48)	0.385
Diabetes (n (%))				
No	1259 (84.5)	27 (81.8)		
Yes	231 (15.5)	6 (18.2)	1.21 (0.45; 2.78)	0.675
Hypertension (n (%))				
No	740 (49.7)	19 (57.6)		
Yes	750 (50.3)	14 (42.4)	0.73 (0.36; 1.45)	0.370
Chronic kidney disease (n (%))				
No	1080 (71.6)	29 (87.9)		
Stage I	9 (0.6)	0 (0)		
Stage II	220 (14.6)	2 (6.1)	0.34 (0.05; 1.13)	0.141
Stage III	149 (9.9)	2 (6.1)	0.51 (0.08; 1.68)	0.346
Stage IV	50 (3.3)	0 (0)		
ICM administrated volume (median (1st–3rd quartiles))	100 (85; 110)	100 (90; 110)	1.01 (0.99; 1.03)	0.281

Table 3 Drugs used in patients evaluated in the study at baseline, according to the presence of CI-AKI

n (%)	No CI-AKI (*n* = 1474)	CI-AKI (*n* = 33)	*p*
ACE Inhibitors			
No	1269 (86.1)	31 (93.9)	0.303
Yes	205 (13.9)	2 (6.1)	
Angiotensin II receptor antagonists			
No	1184 (80.3)	27 (81.8)	1
Yes	290 (19.7)	6 (18.2)	
Diuretics			
No	1139 (77.3)	25 (75.8)	0.834
Yes	335 (22.7)	8 (24.2)	
FANS			
No	1208 (82)	25 (75.8)	0.362
Yes	266 (18)	8 (24.2)	
Calcium channel blockers			
No	1274 (86.4)	31 (93.9)	0.302
Yes	200 (13.6)	2 (6.1)	
Beta-blockers			
No	1108 (75.2)	30 (90.9)	0.04
Yes	366 (24.8)	3 (9.1)	
Antiplatelet			
No	1302 (88.3)	30 (90.9)	1
Yes	172 (11.7)	3 (9.1)	
Anticoagulants			
No	1276 (86.6)	30 (90.9)	0.61
Yes	198 (13.4)	3 (9.1)	
Oral hypoglicemic agents			
No	1314 (89.1)	29 (87.9)	0.776
Yes	160 (10.9)	4 (12.1)	
Statins			
No	1090 (73.9)	31 (93.9)	0.008
Yes	384 (26.1)	2 (6.1)	
Antibiotics			
No	1346 (91.3)	25 (75.8)	0.007
Yes	128 (8.7)	8 (24.2)	
Antineoplastics			
No	1394 (94.6)	33 (100)	0.416
Yes	80 (5.4)	0 (0)	
Antiviral, antifungals, and pesticides			
No	1437 (97.5)	32 (97)	0.573
Yes	37 (2.5)	1 (3)	
Corticosteroids			
No	1292 (87.7)	26 (78.8)	0.176
Yes	182 (12.3)	7 (21.2)	
Generic antihypertensive drug			
No	1349 (91.5)	32 (97)	0.517
Yes	125 (8.5)	1 (3)	
Analgesics			
No	1354 (91.9)	27 (81.8)	0.051
Yes	120 (8.1)	6 (18.2)	
Other			
No	584 (39.6)	9 (27.3)	0.207
Yes	890 (60.4)	24 (72.7)	

p value refers to Fisher's exact test

renal impairment. Furthermore, Liu Y et al suggest that excessive high volume of hydration may not be associated with a reduced risk of CI-AKI. These conflicting data suggest that further studies are needed to definitively clarify a prophylaxis protocol. On the basis of these findings, we hypothesize that data extrapolation from cardiological procedures (with infusion of the ICM through percutaneous catheterization) may

Table 4 Estimate of the association between clinical factors and the probability of CI-AKI. Results of the logistic regression analysis

Independent variables	OR	95% CI	*p*
Statins therapy (yes vs no)	0.20	0.03; 0.68	0.030
Antibiotic therapy (yes vs no)	2.92	1.21; 6.36	0.012

led to overestimation of ICM renal toxicity. In support of this hypothesis, some authors suggest that CI-AKI may be induced by different factors, sometimes merely due to transient hemodynamic fluctuation [7–10, 29, 30] or to the damage of renal structure, frequently observed in the clinical setting of ICM radiological investigation [31].

This toxicity may occur immediately or shortly after ICM administration, and recovery generally takes place in a few days. In contrast, the latter is induced by the embolism of cholesterol crystals mobilized by catheterization, leading to a more severe irreversible renal failure. It typically occurs after 4–5 days after the procedure, and it is sometimes associated with systemic symptoms such as blue toes and frequently requires dialysis.

Another critical point is the extremely variable definition of CI-AKI, which makes the reported studies poorly comparable and, usually based on changes in serum creatinine, led to the misleading assumption that every fluctuation occurring after ICM administration was due to CI-AKI. Furthermore, an increase in serum creatinine was observed even in patients who did not receive ICM [6–10].

The correct diagnosis of CI-AKI should be made on the basis of renal histological examination showing typical tubular lesions but, of course, a study including this invasive procedure is not feasible in a large cohort of patients and is not ethical.

Our results are in line with other studies carried out in patients who underwent contrast-enhanced computed tomography, where renal consequences of ICM administration were scanty [32–34]. Of note, subjects included in our study were not only inpatients but also outpatients, which are more vulnerable to CI-AKI [35]. Interestingly, even patients with established CKD were not more prone to AKI following ICM administration than people who had a normal eGFR. One should consider that all the patients with abnormal renal function received hydration with saline solution before ICM infusion and that the radiological procedure was carried out with isosmolar contrast material, according to the European Society of Urogenital Radiology guidelines. Whether these measures could have influenced the observed results is questionable.

Similarly, there is still doubt regarding the role of iso-osmolar contrast media in preventing eGFR changes. Some studies comparing contrast agent with different osmolality led to controversial results, and the majority of the studies and meta-analyses failed to demonstrate that iso-osmolar contrast

materials are less nephrotoxic than the low-osmolar agents [36–40].

In our study, the results of the CKD risk stratification as a function of the baseline eGFR indicate that the incidence of CI-AKI is similar in all patient subgroups. In line with this finding, a recent large retrospective study excluded that any eGFR subgroup is a risk factor for CI-AKI [25].

The role of concomitant drug therapies in patients undergoing radiological investigations with ICM is an interesting issue, considering the potential nephrotoxicity of many drugs and their possible interaction with ICM, which might negatively affect renal function in some clinical settings.

With regard to drug administration, the present study assessed an association between different classes of drugs and CI-AKI. Our results suggest a negative association of statins with AKI after ICM administration. This relationship is consistent with findings already described in the literature [41, 42], and it may rely on the "pleiotropic" effect of statins, along with their ability to increase endothelial nitric oxide and to reduce endothelin [43, 44].

On the other hand, in line with the literature, antibiotic therapy seems to increase the probability of renal function impairment after ICM, as shown by the multivariable logistic regression analysis.

Our study has two main limitations. First, the creatinine value needed for eGFR calculation after the radiological survey was not available for all of the patients (32%, excluded patients). All of these patients were outpatients, so we do not know if they developed CI-AKI or other abnormalities. However, these patients did not differ from those included in the study in terms of general characteristics. Second, the measurement of creatinine before the radiological survey for outpatients was performed 2–10 days before the radiological survey, whereas for inpatients, creatinine was measured 1–2 days before the survey. Nevertheless, no significant difference in the CI-AKI development was found between in- and outpatients. Third, in our study, different ICM agents were used, depending on the presence or absence of pre-existing CKD, even though a retrospective study [11] has shown that the risk of CI-AKI is independent of the ICM administered.

In conclusion, this study was performed in an unselected cohort of patients, mostly elderly, with various comorbidities, including patients with impaired renal function. The study therefore reflected everyday clinical practice. Furthermore, the results confirmed that iv ICM administration carries a low incidence of renal impairment.

Saline infusion and iso-osmolar contrast media used in patients with more advanced renal failure might have contributed to the observed results, although their role in preventing CI-AKI is still controversial [13].

We believe that ICM can be administered to all patients, albeit with the necessary precautions as indicated by the guidelines.

Funding This study has received funding by Agenzia Italiana del Farmaco (AIFA) (FARM823BHC).

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Salvatore Amoroso.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry Luigi Ferrante and Edlira Skrami have significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Prospective
- Performed at one institution

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