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Renal tolerability of iopromide and iodixanol in 562 renally impaired patients undergoing cardiac catheterisation: the DIRECT study

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KEYWORDS

- contrast-induced nephropathy
- iopromide
- iodixanol
- moderate renal dysfunction

Abstract

Aims: This multicentre, randomised, double-blind study compared the nephrotoxicity of low-osmolar, low-viscous iopromide and iso-osmolar, high-viscous iodixanol in Chinese patients with moderate renal dysfunction, after coronary angiography or percutaneous coronary intervention (PCI).

Methods and results: The primary endpoint was contrast-induced nephropathy (CIN) on day 3, defined as a post-dose increase in serum creatinine (SCr) of ≥50% from baseline. All patients were rigorously hydrated from six hours before intervention. In 562 evaluable patients (of 592 recruited), the contrast volume, presence of diabetes mellitus, mean baseline SCr and estimated glomerular filtration rate (eGFR) were comparable between the iopromide- and iodixanol-treated groups. SCr increases of ≥50% occurred in 1/278 (0.4%) of patients after iopromide and 1/284 (0.3%) after iodixanol. Incidences in the secondary endpoints were the following: SCr increases of ≥0.5 mg/dL, 1.4% and 0.7%, respectively; SCr increases of ≥25%, 5.4% and 2.8%; eGFR decreases of ≥25%, 3.6% and 2.5%. Only one patient showed renal failure, one week after dosing with iodixanol. All differences were statistically insignificant, in the overall collective group and in the subgroup with diabetes (n=170).

Conclusions: With rigorous hydration, the CIN incidence was very low in patients with moderate renal dysfunction who underwent coronary angiography or PCI. No difference in nephrotoxicity was found between iopromide and iodixanol.

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Introduction

Contrast-induced nephropathy (CIN; also referred to as contrast-induced acute kidney injury [CI-AKI]) is an acute impairment of renal function occurring after the administration of contrast-enhancement agents in the absence of other aetiologies[1,2]. CIN is a major complication of interventional coronary procedures, increasing morbidity and prolonging hospitalisation[3]. The number of cardiac angiography and percutaneous coronary interventions (PCI) has increased steadily in recent years[4]. Chronic kidney disease is the most important risk factor for CIN[5-8]. Modifiable risk factors for CIN include hydration (volume supplementation) status, the avoidance of first-generation ionic ("high-osmolar") contrast agents, the amount of contrast agent, use of concomitant nephrotoxic agents and recent administration of contrast agent[7,9-11]. Despite numerous studies and meta-analyses[12,13], the propensities of the various contrast agents to cause CIN have not been definitively established.

The NEPHRIC study[14] engendered the hypothesis, based on 129 cardiac-catheterisation patients, that iso-osmolar contrast agents are associated with better renal tolerance in patients with impaired renal function than low-osmolar contrast agents. The CARE study[15] concluded that the rate of contrast-induced nephropathy was not statistically different after the administration of low-osmolar iopamidol or iso-osmolar iodixanol in high-risk patients, and that any difference between the agents was unlikely to be clinically significant. Similar results were obtained for the low-osmolar agents, ioversol and iopromide in other multicentre studies[16,17].

In China, the number of cardiac catheterisation procedures is rising dramatically, with over 290,000 procedures in 2011. China now ranks number three in PCI procedures after the USA and Germany[18], but information regarding the prevalence of high-risk patients undergoing coronary angiography and regarding the incidence of CIN in high-risk patients who receive comprehensive prophylactic measures (such as rigorous hydration) is scarce. Results of single-centre investigations have been contradictory[19,20]. It was considered desirable to address these questions in an appropriate study.

We therefore conducted a large-scale, multicentre study to compare the nephrotoxicities of iopromide 370 and iodixanol 320 in Chinese patients with moderate renal dysfunction after coronary angiography or PCI. Additionally, we investigated the prevalence of baseline renal impairment among Chinese patients undergoing elective cardiac catheterisation.

Methods

The DIRECT study was a prospective, multicentre, randomised, double-blind, parallel group comparison of iopromide 370 and iodixanol 320 conducted at 19 centres in China between February 2009 and November 2010 (Clinical Trial Registration NCT00926562). The study was approved by the Institutional Review Board of each centre and performed in conformity with good clinical practice and the Declaration of Helsinki. Written informed consent was provided by all patients before enrolment.

PREVALENCE OF RENAL IMPAIRMENT AMONG PATIENTS UNDERGOING ELECTIVE CARDIAC CATHETERISATION

Initial recruitment rates were lower than anticipated. Therefore, between 1 June 2009 and 30 June 2010, we also investigated the prevalence of baseline renal function among 7,976 consecutive screened patients at 11 study centres. The eGFR calculated from the serum creatinine (SCr) level as an index of renal function was determined before administration of a contrast agent, using the abbreviated modification of diet in renal disease (MDRD) formula[21]. This was based on National Kidney Foundation definitions[5]: severe, eGFR <30 mL/min/1.73 m^2; moderate, 30 ≤ eGFR <60 mL/min/1.73 m^2; mild, 60 ≤ eGFR <90 mL/min/1.73 m^2.

PATIENTS

Adult (≥18 years) Chinese patients of both sexes scheduled to undergo diagnostic cardiac angiography or elective PCI were screened. The principal inclusion criterion was moderate renal dysfunction (see above); patients with severe renal dysfunction were not included. Other principal exclusion criteria were pregnancy, lactation, intra-arterial or intravenous administration of an iodinated contrast agent from seven days before to 72 hours after the administration of a contrast agent, intake of any nephrotoxic medications 24 hours before or after the administration of a contrast agent, left ventricular ejection fraction (LVEF) <30% by ultrasound examination, cardiogenic shock, or other contraindications.

STUDY PROTOCOL

Patients included were randomised in equal numbers to receive iopromide (Ultravist, 370 mg I/ml; Bayer Healthcare, Berlin, Germany) or iodixanol (Visipaque, 320 mg I/ml; GE Healthcare, Chalfont St. Giles, UK) and underwent cardiac catheterisation. Double-blinding (up to database lock) was maintained by having the preparation, dispensation, administration and accounting of the contrast agents performed by a physician other than the investigator. Likewise, eligibility was assessed by physicians who did not participate in further study assessments before the blind was broken.

Procedures and interventions were performed according to standard practice at the study sites. The contrast agent was administered intra-arterially. The volume of contrast agent was determined by the patient's age, weight, clinical indication and examination technique. The volume of contrast agent was thus not standardised, and iodine concentration differences between iopromide 370 and iodixanol 320 were not adjusted.

Patients received prophylactic intravenous hydration with 500 ml 0.9% saline over at least the six hours up to the cardiac catheterisation procedure, followed by a further 1,000 ml after the start of the procedure; the rate of administration was 1-1.5 mL/kg per hour throughout. The hydration regimen was determined in advance by consensus of the responsible physicians, in relation to institutional practice and standard guidelines. Additional pharmacological prophylaxis (e.g., N-acetylcysteine) was not required.

Blood samples for baseline SCr and eGFR determination were obtained before hydration and again 72±12 hours after dosing (or as

closely to that as allowed by the patient's treatment regimen), to be repeated on day 7 if the SCr level increased to >0.5 mg/dL or by >25%. All SCr samples were analysed centrally.

Each patient was contacted by telephone 30 days after administration of the contrast agent, to ask whether hospitalisation, dialysis, any treatment(s) for acute renal failure, or death had occurred, and to record any adverse events.

ENDPOINTS

The primary endpoint was the incidence of relative increase in SCr of ≥50% from baseline to 72 hours after study agent administration. Non-inferiority of iopromide was tested for (see below). Secondary endpoints were a post-dose SCr increase of ≥25%, a post-dose SCr increase of ≥0.5 mg/dL, a post-dose eGFR decrease of ≥25% and the rate of renal failure 30 days post treatment. Adverse events were assessed.

STATISTICAL ANALYSIS

The sample size for this non-inferiority study was based on the proportion of patients with an SCr increase of ≥50%. This proportion was assumed to be 5% in both treatment groups. The non-inferiority margin was set at 5.5% by a combination of statistical reasoning and clinical judgement. It was estimated that with at least 80% power and a significance level of 0.025 (one-sided), a total sample size of 564 patients (282 patients per group) would be required to determine non-inferiority of iopromide. The sample size estimation was based on a one-sided Z-test with continuity correction (pooled). To allow for ~5% dropouts or non-evaluable patients, enrolment of a total of 590 patients was planned.

Data are presented as percentages or as mean±standard deviation (SD). Comparison of baseline data was performed using the χ^2 test or Fisher's exact test (categorical variables) and the Student t-test (continuous variables).

Eligibility for CIN analysis was prospectively defined to include patients who received a randomised contrast agent, underwent only one cardiac catheterisation procedure during the study period, had SCr measurements at baseline and 24-120 hours after dosing, and for whom no protocol violations (failure to meet inclusion criteria, meeting exclusion criteria, >1 angiographic procedure from the day of study treatment to the last study creatinine measurement, no cardiac catheterisation after randomisation, additional contrast medium, a critical clinical event during follow-up) occurred. Critical clinical events were defined as those very likely to compromise renal function (e.g., cardiac arrest, acute myocardial infarction, cardiovascular collapse, shock, or major surgery).

The difference in the incidences of CIN defined as an SCr increase of ≥50% (primary endpoint) were analysed by a Wald test for the risk difference on non-inferiority of iopromide (in this analysis "inferiority" is understood as a higher rate of a given potentially adverse safety result). In addition a superiority test was performed as a secondary analysis for primary and secondary definitions of CIN. One-sided p-values <0.025 were to be considered statistically significant in non-inferiority testing. In all other tests two-sided p-values <0.05 were to be considered statistically significant. The statistical analysis employed SAS version 9.13 (SAS Institute, Cary, NC, USA).

A literature search of prospective randomised trials comparing low-osmolar contrast agents with iso-osmolar iodixanol in renally compromised patients undergoing cardiac catheterisation was performed. All studies that met the search criteria starting from the publication of NEPHRIC in 2003 were included.

Results

Between February 2009 and November 2010, ~24,000 PCI candidate patients were surveyed/screened at centres in China.

PREVALENCE OF RENAL IMPAIRMENT IN CHINESE PATIENTS UNDERGOING CARDIAC CATHETERISATION (BASELINE SURVEY)

A baseline survey of 7,976 patients who underwent elective coronary angiography or PCI at 11 study centres revealed that the prevalence of normal and mild renal dysfunction was 50.67% and 40.95%, while the prevalence of moderate and severe renal insufficiency (eGFR of <60 mL/min/1.73 m^2) was 8.38% (moderate: 7.45%; severe: 0.93%; **Figure 1**). The patients with moderate renal impairment therefore accounted for about 90% of those at high risk of CIN (eGFR of <60 mL/min/1.73 m^2).

STUDY POPULATION

At 19 centres, 592 patients (6-84 per centre: median 31) were eligible and were enrolled in the study **(Figure 2)**.

Of the 562 evaluable patients, 278 received iopromide and 284 received iodixanol. The demographic, clinical, and procedural characteristics of the patients are shown in **Table 1**. The groups were comparable with regard to gender and race distribution, presence of diabetes mellitus, time-point of post-dose sampling, distribution

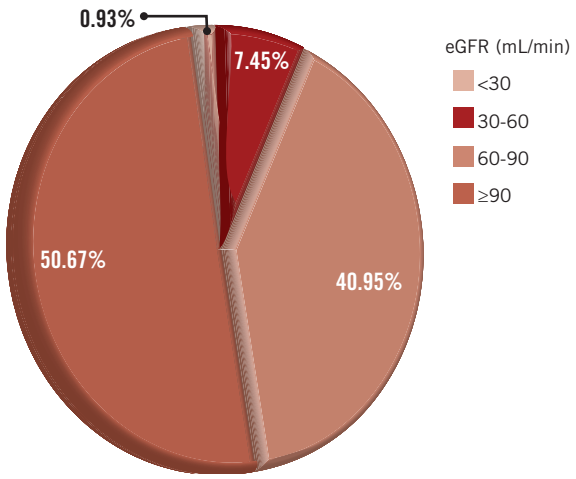

Figure 1. *Prevalence of renal insufficiency among patients who underwent elective cardiac catheterisation (baseline survey; n=7,976).*

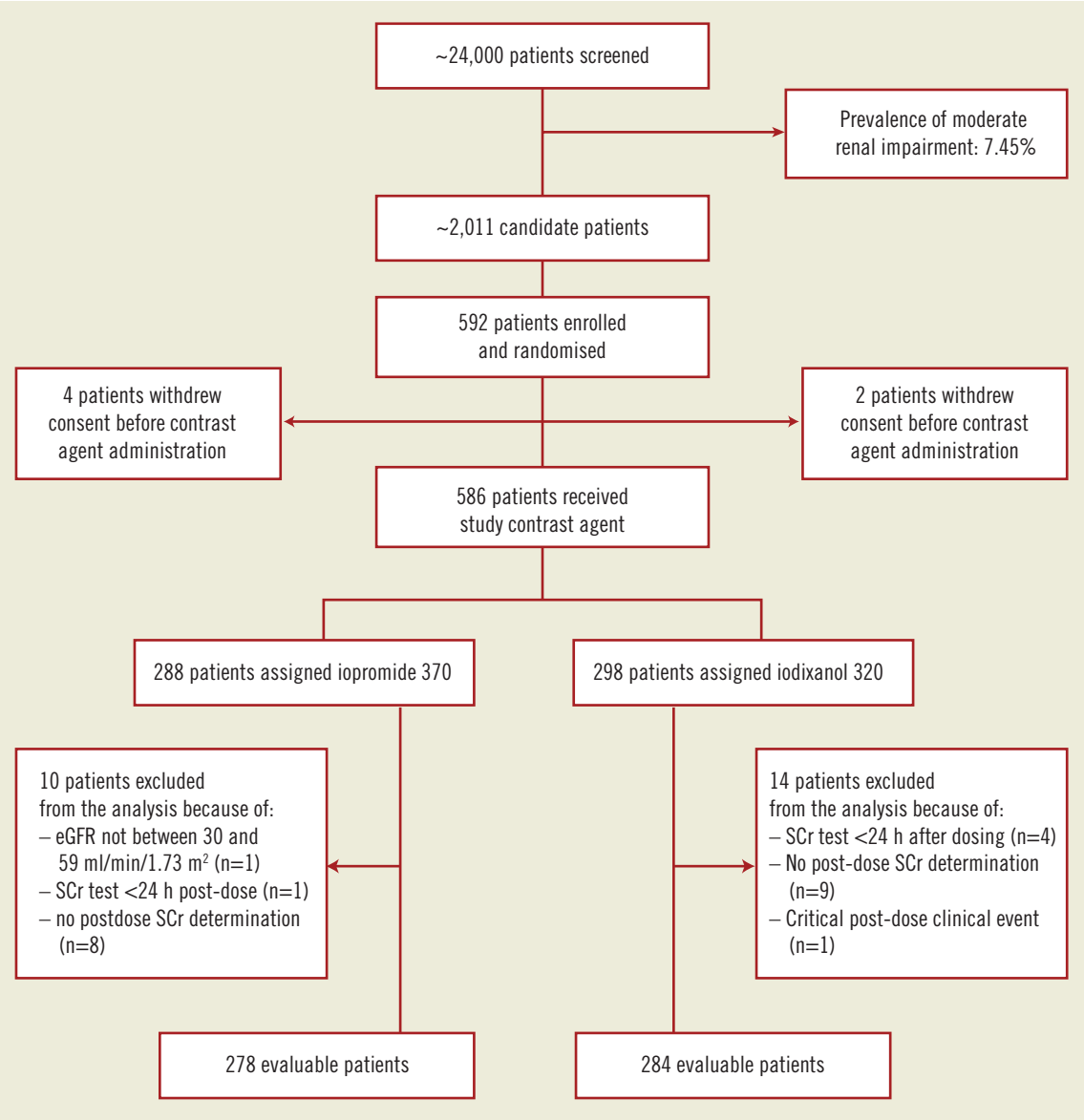

Figure 2. *Flow diagram for patients in the study.*

by type of procedure (diagnostic cardiac angiography or PCI). Baseline eGFR was also comparable: 49.56±8.10 mL/min per 1.73 m^2 in the iopromide group and 48.53±11.86 mL/ min per 1.73 m^2 in the iodixanol group (p=0.23). Details of pre-dose SCr are reported in **Table 2**. Patients who received iopromide received a larger volume of contrast agent. As iopromide 370 is also more concentrated than iodixanol 320, this resulted in a ~30% higher amount of iodine received by the patients in the iopromide group. The distribution of times of sampling for SCr was similar to that reported for the CARE study[15].

INCIDENCE OF CIN

The incidence of CIN did not differ statistically between the groups **(Table 3)**, irrespective of the definition used (see "endpoints"). Only one patient in each group had an increase in SCr from baseline of ≥50%, which was the prospectively defined primary endpoint. The incidences of CIN were 0.4% in the iopromide 370 group (1/278 patients) and 0.4% in the iodixanol 320 group (1/284 patients); the 95% confidence interval for the difference was -1.0% to +1.0%. Thus, non-inferiority of low-osmolar iopromide to iso-osmolar iodixanol was demonstrated, with p<0.001 **(Table 3)**.

In terms of the secondary endpoints, the incidence of an SCr increase of ≥0.5 mg/dL was close to 1% in both groups **(Table 3)**, while that of an SCr increase of ≥25% was higher in both groups (5.4% for iopromide 370 and 2.8% for iodixanol 320). Rates of eGFR decreases of ≥25% were similar **(Table 3)**.

The average dose of contrast agent (in ml) was three times below the eGFR (in mL/min/1.73 m^2; **Table 1**), a value previously cited as critical[22,23]. To look for any possible dose effect, we compared the rates of CIN among patients for whom this ratio was >3 and ≤3.

Table 1. Baseline clinical characteristics of the study population.

Characteristic	Iopromide 370 (n=278)	Iodixanol 320 (n=284)	*p*-value
Age (years)	69.0±10.5	70.0±9.25	0.235
Gender, M/F (%)	67.6/32.4	66.9/33.1	0.858
Weight (kg)	70.8±12.5	70.2±12.5	0.569
Diabetes (%)	27.7	32.7	0.200
eGFR (mL/min/1.73 m^2) *	49.6±8.1	48.5±11.9	0.229
PCI (%)	46.8	44.0	0.553
Volume of CE (ml)	129.1±83.0	115.5±64.2	0.031
Dose of iodine (g)	47.8±30.7	37.0±20.6	<0.01
Time of post-CE SCr (h)			
24-48 hours (%)	6.8	8.5	
48-72 hours (%)	76.6	78.2	0.119
72-96 hours (%)	15.8	10.9	
>96 hours (%)	0.7	2.5	

CE: contrast-enhancing agent; *: baseline value for both groups together - 48.70±8.13

Table 2. Baseline SCr level (mg/dL) of study patients.

	Iopromide 370 n, mean±SD	Iodixanol 320 n, mean±SD	*p*-value
Total population	278, 1.39±0.41	284, 1.43±0.29	0.221
Patients with DM	77, 1.37±0.31	93, 1.45±0.31	0.080
Patients without DM	201, 1.40±0.44	191, 1.41±0.28	0.669
Diagnostic coronary angiography	148, 1.38±0.27	159, 1.44±0.30	0.036
PCI	130, 1.41±0.53	125, 1.40±0.42	0.970

DM: diabetes mellitus

Among 222 patients with a ratio >3, six (2.7%) experienced CIN; of the 340 patients with a ratio ≤3, 19 (5.6%) also did so. Thus, a higher rate of CIN accompanying a higher ratio of contrast agent volume to eGFR was not observed.

SUBGROUP ANALYSIS

CIN occurrence in patients with diabetes mellitus (the NEPHRIC population[14]) also showed no significant difference between the groups, regardless of the CIN endpoint **(Table 4)**. In 170 diabetic patients, an SCr increase of ≥50% occurred in 1.3% after iopromide (1/77 patients) and 0% after iodixanol (0/93; p=0.27). Again, non-inferiority of iopromide was demonstrated. For the secondary endpoints: respective SCr increases of ≥25% were 8.5% and 3.5% (p=0.34), SCr increases of ≥0.5 mg/dL were 1.3% and 0% (p=0.27), rates of eGFR decreases of ≥25% were 3.9% and 4.3% (p=0.90).

Owing to the low CIN rate, no additional subgroup analyses were performed. Our results are compared with those of published prospective comparative trials in **Table 5**.

MEAN PEAK CHANGES IN SCR LEVEL

Mean peak changes in SCr seemed to favour iopromide, but no significant difference was found between iopromide and iodixanol in the total population (–3.38±34.27 versus –2.37±17.844, p=0.6589) or in patients with diabetes mellitus (–0.60±18.997 versus 1.31±17.389, p=0.4940; **Figure 3**). An important observation was that the mean post-dose SCr levels decreased compared with mean pre-dose SCr levels, both in the total population and in diabetic patients receiving iopromide, whereas the mean post-dose SCr level was increased in diabetic patients after iodixanol exposure.

Table 3. Incidence of CIN, total population.

Definition of CIN	Iopromide 370 (n=278)	Iodixanol 320 (n=284)	95% CI of difference	*p*-non-inf	*p*-sup
SCr >50% ↑ n (%)	1 (0.4%)	1 (0.3%)	–1.0%, 1.0%	<0.001	0.99
SCr >25% ↑ n (%)	15 (5.4%)	8 (2.8%)	–0.7%, 5.9%	–	0.12
SCr >0.5 mg/dl ↑ n (%)	4 (1.4%)	2 (0.7%)	–1.0%, 2.4%	–	0.40
eGFR> 25% ↓ n (%)	10 (3.6%)	7 (2.5%)	–1.7%, 4.0%	–	0.43

↑: increase; ↓: decrease; non-inf: in test for non-inferiority of iopromide; sup: in test for superiority of iopromide

Table 4. Incidence of CIN, patients with diabetes mellitus.

Definition of CIN	Iopromide 370 (n=77)	Iodixanol 320 (n=93)	95% CI of difference	*p*-non-inf	*p*-sup
SCr >50% ↑ n (%)	1 (1.3%)	0 (0.0%)	–1.2%, 3.8%	<0.001	0.27
SCr >25% ↑ n (%)	6 (8.5%)	4 (3.5%)	–3.8%, 10.8%	–	0.34
SCr >0.5 mg/dl ↑ n (%)	1 (1.3%)	0 (0.0%)	–1.2%, 3.8%	–	0.27
eGFR> 25% ↓ n (%)	3 (3.9%)	4 (4.3%)	–6.4%, 5.6%	–	0.90

↑: increase; ↓: decrease; non-inf: in test for non-inferiority of iopromide; sup: in test for superiority of iopromide

Table 5. Comparative CIN studies with iodixanol in renally impaired patients who underwent cardiac catheterisation (CIN endpoint: increase of >0.5 mg/dL within 3 days after the administration of contract agent).

Study	Recruitment period	Low-osmolar comparator agent	Total no. of patients	Rigorous pre-procedure hydration of all patients?	Baseline renal function (eGFR, mL/min/ 1.73 m²)*		Incidence of CIN		
					Comparator agent	Iodixanol	Comparator agent	Iodixanol	*p*
NEPHRIC[14]	1999-2001	Iohexol	129 ◊	No	47.3±16.6	50.1±12.8	26.2%	3.1%	<0.01
ICON[24]	2001-2004¶	Ioxaglate	146	Yes	45.9±18.9	44.5±14.1	18.2%	15.9%	ns
VALOR[16]	2001-2004	Ioversol	299 ◊	Yes	38.8±11.1	36.5±11.3	23.8%	21.8%	ns
RECOVER[25]	2004	Ioxaglate	275	Yes	44.9±10.3	45.2±11.4	8.9%	3.6%	ns‡
Juergens et al[19]	2003-2006	Iopromide	191	Yes	49.3±16.7	50.0±17.2	7%	3%	ns
Nie et al[20]	2005-2006	Iopromide	208	Yes	46.8±11.7	46.3±12.1	10.8%	3.8%	0.05‡
CARE[15]	2005-2006	Iopamidol	414 ◊	Yes	49.3±11.6	50.2±13.0	4.4%	6.7%	ns
Laskey et al[26]	2005-2007	Iopamidol	418 ◊	Yes	47.9±22.1	45.5±22.1	5.4%§	9.3%§	ns
Shin et al[17]	2009-2010	Iopromide	420 ◊	Yes	42.1±12.2	42.1±11.8	6.3%	6.5%	ns
DIRECT#	2009-2010	Iopromide	562 ◊	Yes	49.6±8.1	48.6±11.9	1.3%	0%	ns

◊ Multi-centric trials. All trials except NEPHRIC included patients with and without diabetes mellitus. The CONTRAST trial[27] did not report this endpoint, and is therefore not listed, but it also found no significant differences between low-osmolar iomeron and iodixanol. *: eGFR estimations were inconsistently performed using either MDRD or Cockroft-Gault formulae; ¶: estimated - dates not clearly reported - recruitment ended well before 2005; ‡: significant differences reported with less specific CIN endpoint; §: rate of "conservative" CIN, where creatinine changes deemed unrelated to the contrast agent application were excluded; #: this work; ns: not significant

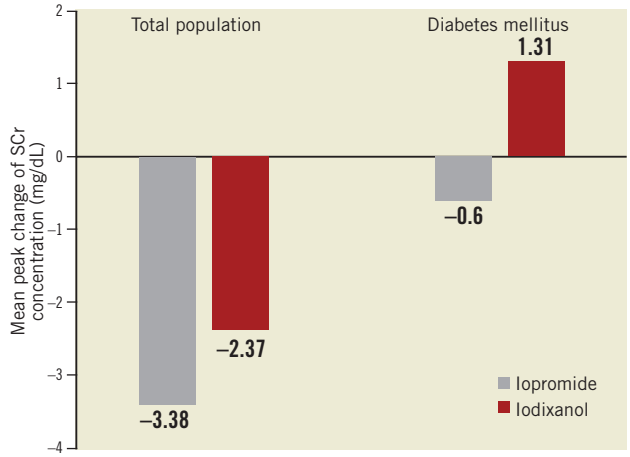

Figure 3. *Serum creatinine: mean peak changes (mg/dL) from baseline.*

RENAL FAILURE DURING 30-DAY FOLLOW-UP

No patient required haemodialysis; no study-related deaths were reported. Only one patient in the iodixanol group, who was not diagnosed with CIN on day 3, was found to have an SCr level that increased by ≥25% one week after discharge from hospital. During a one-year post-treatment follow-up his overall condition was stable with his SCr level remaining high at around 2.26 mg/dL.

NON-RENAL ADVERSE EVENTS

Adverse events were recorded for 50 of the 592 patients (8.4%), 30 (10.3%) in the iopromide group and 20 (6.7%) in the iodixanol group (p=0.1392). Most (10.3% and 6.7%, respectively) of these were non-serious and resolved spontaneously. In the iodixanol group one patient died after surgery, which was considered by the investigator to be unrelated to the study agent.

Discussion

Our study has revealed that, in the population of Chinese patients with moderate renal dysfunction, undergoing cardiac catheterisation and with rigorous hydration, CIN was very infrequent. We found no significant difference in its occurrence between those receiving the low-osmolar, non-ionic monomer iopromide 370 and those receiving the iso-osmolar dimer iodixanol 320. Non-inferiority of iopromide compared with iodixanol was demonstrated. During the 30-day follow-up, no patient required haemodialysis. A survey conducted in 11 of the 19 study centres showed that the prevalence of moderate and severe renal insufficiency among patients undergoing coronary angiography and elective PCI were 7.45% and 0.93%, respectively, and thus lower than anticipated.

The primary endpoint used –changes in SCr– has been used as a surrogate parameter in renal function safety trials[14,15,25]. Less specific thresholds of the surrogate definition of CIN may be prone to spurious effects unrelated to contrast application[28], so the threshold for "renal risk" (the incidence of relative increase in SCr by ≥50%, as defined by the RIFLE criteria developed by the Acute Dialysis Quality Initiative (ADQI) group for the nephrological scientific community[29,30]) was used as the primary endpoint in this study.

Secondary endpoints were chosen for comparability with earlier CIN studies in this area[14,15,25]. Criteria to be considered include clinical importance, responsiveness to the intervention, precision definition, and accuracy and feasibility of measurement[29]. None of the surrogate endpoints has been validated prospectively against hard

clinical endpoints; association between post-procedural SCr increases in renal risk patients and morbidity/mortality has been seen in large cardiological registries[8]. It remains unclear which definition of post-procedural SCr changes is the most appropriate to describe the risk for the patients.

However, the two major findings of this study are unaffected by the choice of endpoint: rates of CIN were low, and they did not differ statistically between the groups (iopromide: 0.4%; iodixanol: 0.3%). This absence of a significant difference was found throughout the study. This corresponds to earlier data on the renal tolerance of low-osmolar compared with iso-osmolar contrast agents. **Table 5** lists all published randomised comparative trials, and shows clearly that the NEPHRIC hypothesis could not be confirmed. This may be ascribed to the limitations of the NEPHRIC study (small sample size, baseline imbalance, inconsistent hydration of the patients). Our results are in line with the other data, and with 562 patients this study is to date the largest prospective, randomised, double-blind comparison of nephrotoxicity between contrast agents in high-risk patients undergoing cardiac catheterisation.

The rates of post-procedural SCr increase that we observed are lower than in earlier trials, although this difference is not great **(Table 5)**. Using the less sensitive increase of ≥0.5 mg/dL listed in **Table 5**, the rates found in this study are not far from the lowest rates seen in other trials (rates of 3-4% have been reported in several trials). A 50% increase in SCr was not reported in most of the other trials, but so-called "severe CIN" rates, such as increases of 1.0 mg/dL, have frequently been investigated and have been shown to have a very low rate as well (e.g., 0% for iodixanol in NEPHRIC and 2.9% for all patients by Shin et al). If the threshold defining the SCr increase is lowered, then the calculated incidence rates in all studies become higher, but again the rates we found are not much lower than those lowest rates reported from other studies. The low rates may be explained by study-specific factors such as the more homogenous study population and, especially, hydration (all the patients in our study received rigorous, prolonged hydration, with appropriate caution in older patients or in those with known reduced LVEF); also, the present study population was less severely impaired, consistent with the lower incidence of CIN that we observed[14,15,19,25,26].

A surprising observation was the difference in contrast agent volume between the treatment groups **(Table 1)**. However, as stated above, this was not fixed by the study protocol, but was determined by local standard procedures, so we infer that it was a random effect. Importantly, the volume of study drug was greater than that of control drug; consequently, the conclusion of the study is not affected, as the overall exposure to the study drug was greater.

We conclude that it is reasonable to infer that the tendency to develop CIN is very low for most high-renal risk patients given low-osmolar contrast media (LOCM) or iso-osmolar contrast media (IOCM) for elective coronary angiography or PCI, as long as they receive rigorous hydration. This conclusion is supported by a recent review that proposes possible mechanisms of contrast agent-related kidney injury[2].

Our baseline survey showed that the prevalence of moderate and severe renal insufficiency was respectively 7.45% and 0.93% among Chinese patients undergoing coronary angiography and elective PCI, which is lower than had been anticipated. Patients with moderately impaired renal dysfunction accounted for ~90% of the renal-risk population.

The study's most important limitation is that the incidence rates assumed for the primary endpoint were anticipated to be 5%, which proved to be an overestimation. Of the secondary endpoints, only the incidence of an SCr increase of >25% in the iopromide group (5.4%) was close to 5%. Thus, robustly adequate powering would have required a study at least three times larger (even though this study was the largest of its kind to date). Nevertheless, the primary objective (to demonstrate non-inferiority of iopromide over iodixanol) was achieved.

A second limitation is that a measurement of SCr on day 7 was available for only 8.5% of the study patients (48/562). This was because, following clinical routine, most patients were discharged on day 3 and did not return to the hospital on day 7. Of the 48 patients with an SCr increase of >25% on day 7, four did not show an SCr increase of >25% on day 3. This accords with other reports that SCr may not peak until 4-5 days after contrast agent administration[31]. Consequently, future CIN trials of this kind should include measurements on day 7, or even later, after contrast agent administration.

One strength of our study is its relatively large and homogenous study population, yielding a robust comparability of the two study groups and reducing the probability of spurious effects. We see no reason to suppose that our conclusion could not be generalised to patients of any ethnicity. A repetition with severely renally impaired patients would be desirable, but probably impracticable given the logistical, ethical and cost hurdles.

Conclusions

The DIRECT study is to date the largest prospective randomised, double-blind comparison of the nephrotoxicity between different contrast-enhancement agents. It focused on patients at high risk of renal complications after cardiac catheterisation. The results demonstrate that the patients with moderate renal dysfunction account for most of the high-risk patients for CIN, and that adhering to a rigorous hydration regimen in patients at risk results in a very low incidence of CIN as revealed by relevant changes in SCr level. The nephrotoxicity of iopromide was found not to be statistically different from that of iodixanol 320. The attention of the treating physician can therefore shift from the question of the choice of contrast or the type of prophylaxis towards focusing on the actual core task, i.e., performing a successful cardiac catheterisation even in a patient at high risk of renal complications.

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Conflict of interest statement

Y. Chen has received speaker's expenses from Bayer Healthcare. All of the other authors have no conflicts of interest to declare.

References

1. Murphy SW, Barrett BJ, Parfrey PS. Contrast nephropathy. *J Am Soc Nephrol.* 2000;11:177-82.

2. Seeliger E, Sendeski M, Rihal CS, Persson PB. Contrast-induced kidney injury: mechanisms, risk factors, and prevention. *Eur Heart J.* 2012;33:2007-15.

3. Mehran R, Brar S, Dangas G. Contrast-induced acute kidney injury. Underappreciated or a new marker of cardiovascular mortality? *J Am Coll Cardiol.* 2010;55:2210-1.

4. Thom T, Haases N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng ZJ, Flegal K, O'Donnell C, Kittner S, Lloyd-Jones D, Goff DC Jr, Hong Y, Adams R, Friday G, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V, Sidney S, Sorlie P, Steinberger J, Wassertheil-Smoller S, Wilson M, Wolf P. Heart disease and stroke statistics - 2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2006;113:e85-e151.

5. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39:S1-266.

6. Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. *Kidney Int.* 2006;69: S11-5.

7. Schweiger MJ, Chambers CE, Davidson CJ, Zhang S, Blankenship J, Bhalla NP, Block PC, Dervan JP, Gasperetti C, Gerber L, Kleiman NS, Krone RJ, Phillips WJ, Siegel RM, Uretsky BF, Laskey WK. Prevention of contrast induced nephropathy: recommendations for the high risk patient undergoing cardiovascular procedures. *Catheter Cardiovasc Interv.* 2007;69:135-40.

8. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN, Holmes DR Jr. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation.* 2002;105:2259-64.

9. Barrett BJ, Parfrey PS. Clinical practice. Preventing nephropathy induced by contrast medium. *N Engl J Med.* 2006;354:379-86.

10. Nikolsky E, Mehran R, Turcot D, Aymong ED, Mintz GS, Lasic Z, Lansky AJ, Tsounias E, Moses JW, Stone GW, Dangas GD. Impact of chronic kidney disease on prognosis of patients with diabetes mellitus treated with percutaneous coronary intervention. *Am J Cardiol.* 2004;94:300-5.

11. Lautin E, Freeman NJ, Schoenfeld AH, Bakal CW, Haramati N, Friedman AC, Lautin JL, Braha S, Kadish EG, Sprayregen S. Radiocontrast-associated renal dysfunction: incidence and risk factors. *AJR Am J Roentgenol.* 1991;157:49-58.

12. Heinrich MC, Häberle L, Müller V, Bautz W, Uder M. Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low-osmolar contrast media: meta-analysis of randomized controlled trials. *Radiol.* 2009;250:68-86.

13. Reed M, Meier P, Tamhane UU, Welch KB, Moscucci M, Gurm HS. The relative renal safety of iodixanol compared with low-osmolar contrast media: a meta-analysis of randomized controlled trials. *JACC Cardiovasc Interv.* 2009;2:645-54.

14. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med.* 2003;348:491-9.

15. Solomon RJ, Natarajan MK, Doucet S, Sharma SK, Staniloae CS, Katholi RE, Gelormini JL, Labinaz M, Moreyra AE; Investigators of the CARE study. Cardiac Angiography in Renally Impaired Patients (CARE) study: a randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease. *Circulation.* 2007;115:3189-96.

16. Rudnick MR, Davidson C, Laskey W, Stafford JL, Sherwin PF; VALOR Trial Investigators. Nephrotoxicity of iodixanol versus ioversol in patients with chronic kidney disease: the Visipaque Angiography/Interventions with Laboratory Outcomes in Renal Insufficiency (VALOR) Trial. *Am Heart J.* 2008;156:776-82.

17. Shin DH, Choi DJ, Youn TJ, Yoon CH, Suh JW, Kim KI, Cho YS, Cho GY, Chae IH, Kim CH. Comparison of contrast-induced nephrotoxicity of iodixanol and iopromide in patients with renal insufficiency undergoing coronary angiography. *Am J Cardiol.* 2011;108:189-94.

18. China Cath: Gao RL, Chairman CIT 2011, Welcome to CIT 2011 in Partnership with TCT, CIT 2011, Beijing, China.

19. Juergens CP, Winter JP, Nguyen-Do P, Lo S, French JK, Hallani H, Fernandes C, Jepson N, Leung DY. Nephrotoxic effects of iodixanol and iopromide in patients with abnormal renal function receiving N-acetylcysteine and hydration before coronary angiography and intervention: a randomized trial. *Intern Med J.* 2009;39:25-31.

20. Nie B, Cheng WJ, Li YF, Cao Z, Yang Q, Zhao YX, Guo YH, Zhou YJ. A prospective, double-blind, randomized, controlled trial on the efficacy and cardiorenal safety of iodixanol vs. iopromide in

patients with chronic kidney disease undergoing coronary angiography with or without percutaneous coronary intervention. *Catheter Cardiovasc Interv.* 2008;72:958-65.

21. Johnson C, Levey AS, Coresh J, Levin A, Lau J, Eknoyan G. Clinical practice guidelines for chronic kidney disease in adults: Part II. Glomerular filtration rate, proteinuria, and other markers. *Am Fam Physician.* 2004;70:1091-7.

22. Mager A, Vaknin Assa H, Lev EI, Bental T, Assali A, Kornowski R. The ratio of contrast volume to glomerular filtration rate predicts outcomes after percutaneous coronary intervention for ST-segment elevation acute myocardial infarction. *Catheter Cardiovasc Interv.* 2011;78:198-201.

23. Gurm HS, Dixon SR, Smith DE, Share D, Lalonde T, Greenbaum A, Moscucci M; BMC2 (Blue Cross Blue Shield of Michigan Cardiovascular Consortium) Registry. Renal function-based contrast dosing to define safe limits of radiographic contrast media in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol.* 2011;58:907-14.

24. Mehran R, Nikolsky E, Kirtane AJ, Caixeta A, Wong SC, Teirstein PS, Downey WE, Batchelor WB, Casterella PJ, Kim YH, Fahy M, Dangas GD. Ionic low-osmolar versus nonionic iso-osmolar contrast media to obviate worsening nephropathy after angioplasty in chronic renal failure patients: the ICON (Ionic versus non-ionic Contrast to Obviate worsening Nephropathy after angioplasty in chronic renal failure patients) study. *JACC Cardiovasc Interv.* 2009;2:415-21.

25. Jo SH, Youn TJ, Koo BK, Park JS, Kang HJ, Cho YS, Chung WY, Joo GW, Chae IH, Choi DJ, Oh BH, Lee MM, Park YB, Kim HS. Renal toxicity evaluation and comparison between visipaque (iodixanol) and hexabrix (ioxaglate) in patients with renal insufficiency undergoing coronary angiography. *J Am Coll Cardiol.* 2006;48:924-30.

26. Laskey W, Aspelin P, Davidson C, Rudnick M, Aubry P, Kumar S, Gietzen F, Wiemer M; DXV405 Study Group. Nephrotoxicity of iodixanol versus iopamidol in patients with chronic kidney disease and diabetes mellitus undergoing coronary angiographic procedures. *Am Heart J.* 2009;158:822-8.

27. Wessely R, Koppara T, Bradaric C, Vorpahl M, Braun S, Schulz S, Mehilli J, Schomig A, Kastrati A. Choice of contrast medium in patients with impaired renal function undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv.* 2009;2:430-7.

28. Newhouse JH, Kho D, Rao QA, Starren J. Frequency of Serum Creatinine Changes in the Absence of Iodinated Contrast Material: Implications for Studies of Contrast Nephrotoxicity. *AJR Am J Roentgenol.* 2008;191:376-82.

29. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care.* 2004;8:R204-12.

30. Kellum JA. Acute kidney injury. *Crit Care Med.* 2008;36: S141-5.

31. McCullough PA, Adam A, Becker CR, Davidson C, Lameire N, Stacul F, Tumlin J; CIN Consensus Working Panel. Epidemiology and prognostic implications of contrast-induced nephropathy. *Am J Cardiol.* 2006;98:5K-13K.