Radiology

Kidney Injury after Intravenous versus Intra-arterial Contrast Agent in Patients Suspected of Having Coronary Artery Disease: A Randomized Trial

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See also the editorial by Einstein and Newhouse in this issue.

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Background: In the absence of randomized studies, it has been controversial whether the likelihood of acute kidney injury (AKI) differs between intravenous and intra-arterial contrast agent administration.

Purpose: To compare intravenous versus intra-arterial contrast agent administration in relationship to AKI and analyze the association between AKI and chronic kidney disease (defined as at least mildly decreased estimated glomerular filtration rates [eGFRs]).

Materials and Methods: This was a prospective study (*ClinicalTrials.gov*: NCT00844220) that involved randomizing participants with atypical chest pain and suspected coronary artery disease (CAD) between February 2009 and August 2015 to undergo coronary CT angiography with intravenous contrast agent administration or cardiac catheterization angiography with intra-arterial contrast agent administration. This prespecified secondary analysis compared AKI (serum creatinine increase of ≥ 25% or 0.5 mg/dL after 18–24 or 46–50 hours) determined by blinded investigators using absolute differences and relative risks, including two-sided 95% confidence intervals (CIs).

Results: A total of 320 participants (163 [50.9%] women; mean age, 60 years ± 11) were included. Baseline eGFR did not differ between the CT angiography group (84.3 mL/min/1.73 m^2 ± 17.2) and the catheterization group (87.1 mL/min/1.73 m^2 ± 16.7) (P = .14). AKI occurred in nine of 161 participants in the CT angiography group (5.6%; 95% CI: 3%, 10%) and in 21 of 159 participants in the catheterization group (13.2%; 95% CI: 9%,19%) (relative risk, 2.4; 95% CI: 1.1, 5.0; P = .02). Also in the subgroup of participants without obstructive CAD, in those not requiring coronary interventions, AKI was more common in the catheterization group (11.9%; 95% CI: 8%, 19%) than in the CT angiography group (4.3% [95% CI: 2%, 9%]; difference, 7.7% [95% CI: 1.3%, 14.1%]; relative risk, 2.8 [95% CI: 1.1, 7.0]; P = .02). Obstructive CAD (odds ratio [OR]: 2.7 [95% CI: 1.1, 6.6]; P = .02), femoral catheter access (OR: 2.5 [95% CI: 1.1, 5.6]; P = .04), and cine ventriculography were associated with AKI (OR: 2.3 [95% CI: 1.0, 4.9]; P = .03). In multivariable analysis, the presence of postcontrast AKI was associated with chronic kidney disease (hazard ratio: 12.4 [95% CI: 4.5, 34.6]; $P < .01$).

Conclusion: Acute kidney injury was more common after cardiac catheterization than after CT angiography in this prospective randomized study of patients suspected of having coronary artery disease.

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Our understanding of postcontrast acute kidney injury (AKI) (1,2) is limited by the lack of randomized control groups in clinical studies (3). Moreover, a recent reassessment of the risk resulting from exposure to contrast agents has questioned the existence of postcontrast AKI (4). While there is agreement that intra-arterial contrast agent administration can cause AKI (5), retrospective studies suggest that intravenous contrast material administration for CT has a similar risk of AKI to noncontrast CT (6–8). The latter finding was corroborated in a meta-analysis of 28 observational studies comparing CT studies performed with or without intravenous contrast material administration (9), while no randomized clinical trial has yet compared intravenous and intra-arterial contrast agent administration in relationship to AKI (10).

Although the exact underlying mechanisms are poorly understood (11), the intravenous route of contrast agent administration may reduce AKI compared with intra-arterial injection (12) by avoiding microembolization from the aorta to the kidneys (13) and reducing peak contrast agent concentration in the renal arteries (14). However, a recent paired cohort study found minimal differences between patients who received both intravenous and intra-arterial contrast agents, with AKI frequencies of 9.9% and 11%, respectively (15). Similar findings with minimal differences in AKI rates were obtained by Karlsberg et al (16) in an intraindividual comparison of CT angiography (7.6%) and peripheral angiography (8.7%). On the other hand, a nonrandomized study showed a higher rate of AKI after catheterization (4.4%) than after CT (1.2%) (17), and large observational studies

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Abbreviations

AKI = acute kidney injury, CAD = coronary artery disease, CAD-Man = Coronary Artery Disease Management, CCA = conventional coronary angiography, CI = confidence interval, eGFR = estimated glomerular filtration rate, IQR = interquartile range, KDIGO = Kidney Disease: Improving Global Outcomes, OR = odds ratio

Summary

In patients suspected of having coronary artery disease, intravenous contrast agent administration for coronary CT angiography had a lower rate of acute kidney injury compared with intra-arterial contrast agent administration for invasive coronary angiography, and postcontrast acute kidney injury was associated with chronic impairment of kidney function.

Key Points

- Acute kidney injury was more likely after intra-arterial (through a cardiac catheterization procedure) than after intravenous (through a coronary CT angiography procedure) contrast agent administration (13.2% vs 5.6%, respectively; relative risk, 2.4; $P = .02$).
- For individuals without obstructive coronary artery disease, acute kidney injury was more common in the catheterization group than in the CT angiography group (11.9% vs 4.3%; $P = .02$).
- Chronic kidney disease was more likely in individuals who had postcontrast acute kidney injury (12-fold greater risk, $P < .01$).

found a higher likelihood of AKI after intra-arterial (14.4%) (18) compared with intravenous contrast agent administration (6.4%) (19). Owing to a lack of randomized trials, it thus remains controversial whether AKI differs between intravenous and intra-arterial contrast medium administration.

We undertook the randomized Coronary Artery Disease Management (CAD-Man) study (20), which compared CT angiography (intravenous) and cardiac catheterization (intra-arterial) to address the primary hypothesis that procedural complications can be reduced by performing CT angiography instead of invasive catheter-based conventional coronary angiography (CCA) in patients with low-to-intermediate pretest probability for obstructive coronary artery disease (CAD). Results for the primary hypothesis of CAD-Man have been published (20), and in this prespecified secondary analysis of the CAD-Man study, we compared the impact of intravenous and intra-arterial contrast agent administration on the development of kidney injury.

Materials and Methods

This prospective randomized study and the study protocol (*ClinicalTrials.gov*: NCT00844220) were approved by the Charité ethics board and authorized by the German Federal Office for Radiation Protection. The study protocol has been published as an appendix to the main study publication (20). Enrolled participants provided written informed consent. The study's sponsor, the German Research Foundation, was not involved in any stage of the study design, data acquisition, data analysis, or manuscript preparation. The study's principal investigator (M.D.) had full control of the data.

Study Design

CAD-Man is a single-center randomized study that included 340 participants with atypical angina who were suspected of having CAD (20). Enrolled consecutive participants had a low-to-intermediate pretest probability of obstructive CAD according to the Duke score, which includes history, physical examination, and electrocardiographic (ECG) data (21), atypical presentation, and a clinical indication for cardiac catheterization including CCA (further explanations for these inclusion criteria can be found in Table E1 [online]). Exclusion criteria were history of obstructive CAD, signs of myocardial infarction, more than one positive ischemia test or highly positive exercise ECG study, non-sinus rhythm, history of hemodialysis, age less than 30 years, inability to hold breath for 5 seconds, and no negative pregnancy test 24 hours before procedures in women with child-bearing potential (further details are in Table E1 [online]). Participants and clinicians taking care of clinical care were blinded to the allocation sequence, but because of obvious differences between CT angiography and catheterization, could not be blinded to the tests. The primary outcome of CAD-Man was the occurrence of procedural complications observed within 48 hours, and the main study showed that CT angiography improved the diagnostic yield and was a safe gatekeeper for CCA, with no increase in long-term cardiovascular events.

AKI Substudy

This AKI substudy was a prespecified secondary analysis of all study participants predefined in the CAD-Man trial study protocol (20). There were no deviations from the prespecified objective to compare postcontrast AKI (aka "contrast-induced nephropathy") by using the most common definition (10): An increase in creatinine by 25% or 0.5 mg/dL or more from baseline to measurements obtained 18–24 and 46–50 hours after the procedures.

Randomization

Patients were referred for CCA because of suspected CAD and atypical chest pain. Study participants were randomly assigned (1:1) to either *(a)* CT angiography with intravenous contrast agent administration or *(b)* cardiac catheterization with CCA and intra-arterial contrast agent administration between February 17, 2009, and August 27, 2015. The randomization list was not stratified. It was generated by the statistician using nQuery 7.0 (Statistical Solutions, Cork, Ireland). Sequentially numbered, opaque, and sealed envelopes included the randomization group and were opened only when it was time to allocate the intervention (22). Because of obvious differences between CT angiography and catheterization, investigators and participants could not be blinded, while AKI outcomes were assessed by investigators masked to the allocated randomization group (20).

Study Procedures

CT and CCA were performed as previously described (20), and the same pre-warmed, low-osmolar, nonionic contrast agent (Iobitridol 350; Xenetix, Guerbet, Paris, France) with a concentration of 350 mg iodine per milliliter was used for CCA and CT angiography to avoid the bias that would have resulted from the use of different contrast agents in the two groups and to increase external validity. The contrast agent used for CT

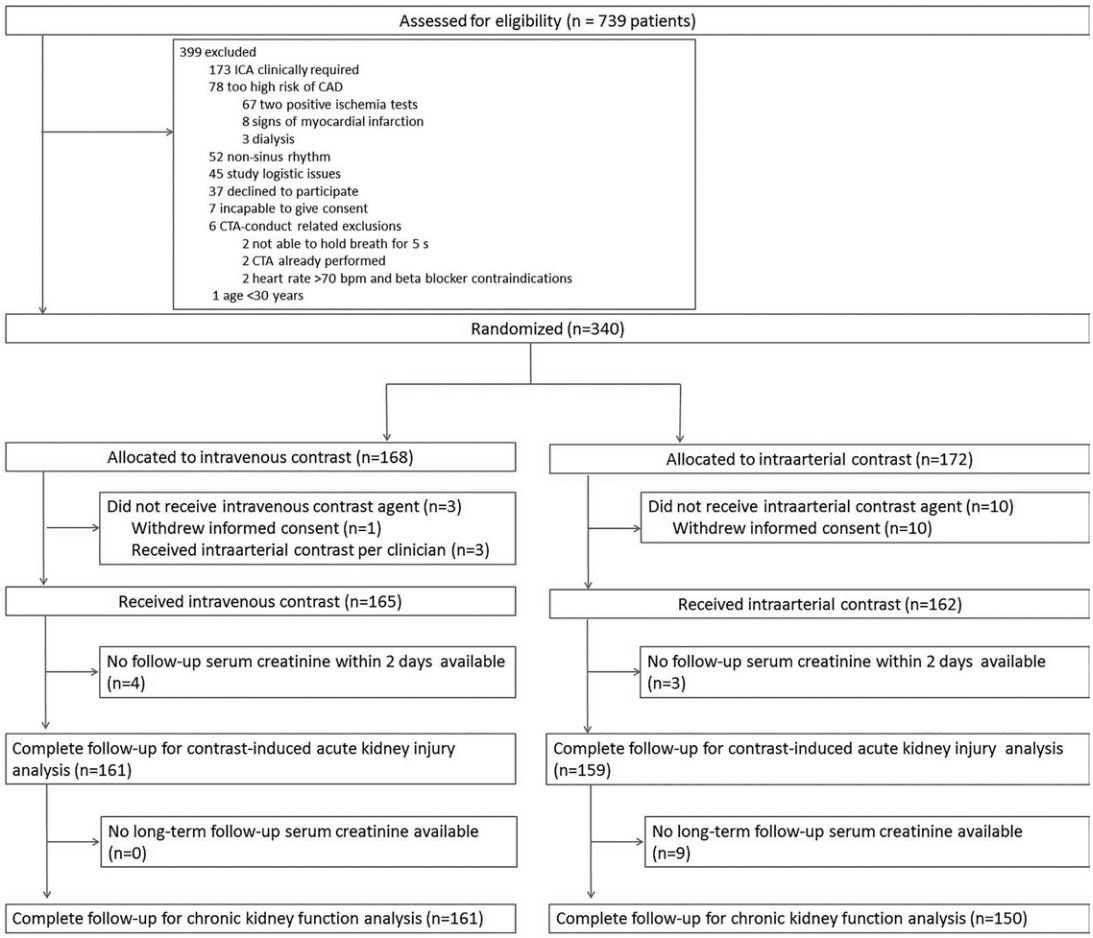

Figure 1: Flowchart of patients shows how many patients were possibly eligible, how many were included and excluded, and how many had available data on kidney injury in the two groups. CAD = coronary artery disease, CTA = CT angiography, ICA = invasive (conventional catheter-based) coronary angiography.

angiography and CCA belongs to the group of low-osmolar nonionic contrast agents, which are considered noninferior to iso-osmolar agents (23).

For CCA, the contrast agent was injected directly into the right and left coronary arteries for projectional luminography, which was repeated from different angulations as clinically needed. The contrast agent volume used for cine ventriculography and for percutaneous coronary intervention performed as part of catheterization was included.

In participants undergoing CT angiography, the same contrast agent used for CCA was injected intravenously as a single bolus. Body weight was used to individually stratify the contrast agent volume and flow rate (≤60 kg: 50 mL, 4 mL/sec; > 60 ≤ 80 kg: 60 mL, 5 mL/sec; > 80 kg: 70 mL, 5 mL/sec) as well as the subsequent isotonic saline injection (≤60 kg: 40 mL, 4 mL/sec; > 60 ≤ 80 kg: 40 mL, 5 mL/sec; > 80 kg: 40 mL, 5 mL/sec). Further information about saline injections and additional medications for the two imaging procedures in the two groups are provided in Tables E2 and E3 (both online). Additional intra-arterial contrast agent volumes required in participants from the CT angiography group for subsequent cardiac catheterization, if done, might also have contributed to kidney injury and were thus included if they were performed before the last short-term creatinine measurement.

In participants with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2, the following preparation was recommended to physicians responsible for the clinical care of patients, according to evidence at the initiation of our study (24,25): intravenous hydration using 500 mL of isotonic sodium chloride and 600 mg of *N*-acetylcysteine twice during the 4 hours before and after the procedures. Other measures (eg, withholding ACE inhibitors or diuretics before procedures) were at the discretion of the responsible physicians in the two study groups.

At long-term clinical follow-up, all participants were eligible for assessment of renal safety parameters to identify chronic changes in serum creatinine and eGFR. These parameters were determined and compared after a median of 1.9 years.

Outcomes and Measurements

Postcontrast AKI according to the most common definition (10) was the prespecified end point of this substudy and was analyzed after excluding patients who withdrew written informed consent or did not undergo the randomized procedure (Fig 1). The primary end point of this substudy was an

increase in serum creatinine of 25% or 0.5 mg/dL or greater within 3 days of contrast agent administration. To optimally cover this time window and the peak of injury at 24 and 48 hours (26), serum creatinine measurements were repeated after baseline by an independent laboratory after 18–24 and 46–50 hours. Secondary end points included the following: AKI in the subgroup of participants without obstructive CAD defined by CT angiography or CCA, a multivariable analysis of factors associated with postcontrast AKI in all participants, and multivariable analysis of factors associated with postcontrast AKI in relation to long-term serum creatinine after a median follow-up of 1.9 years. AKI in participants without obstructive CAD was added to the outcomes of this study to investigate AKI in participants not receiving interventions according to the most common definition (10) and according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition of AKI as creatinine increase of 50% or 0.3 mg/dL or greater (27). Serum creatinine was measured by independent investigators, Labor Berlin (blinded to the randomization group), on Roche/Hitachi Cobas C systems (Roche Diagnostics, Mannheim, Germany) using a kinetic colorimetric assay based on the Jaffe method standardized against isotope dilution mass spectroscopy. The eGFR was calculated by using the Chronic Kidney Disease Epidemiology collaboration equation (28).

Sample Size Determination

The CAD-Man study was planned to randomly allocate 320 participants for the examination of procedural complications as the primary outcome. With a two-sided α of .05 and use of a χ^2 test with correction for continuity and anticipating procedural complications in five and 15% of participants, 160 participants per group provided an 80% power. Postcontrast AKI was a planned secondary objective in the study protocol and thus not part of the sample size estimation. An ex-post analysis revealed that, with 30 events (9.4%), differences of approximately 10% (4.5% vs 14.2%) could have been identified with 80% power.

Statistical Analysis

Postcontrast AKI was compared between study arms calculating absolute differences and relative risks, including two-sided 95% confidence intervals (CIs) (29). Significance was tested by using the χ^2 test with continuity correction, and the Fisher exact test was used in case of low cell counts. Only participants with serum creatinine at baseline and at least one time point after the procedure were included in our analysis.

We additionally compared contrast agent volumes between the two groups and in participants with and those without AKI and in those without obstructive CAD using a Wilcoxon rank sum test. Logistic regression was used for a multivariable analysis of risk factors for AKI and chronic kidney disease. Also, in the statistical analysis of the association of contrast agent volumes and hydration with postcontrast AKI, logistic regression was used for a multivariable analysis. For these analyses, we included adjusted odds ratios (ORs) and hazard ratios with two-sided 95% CIs. We also compared the groups in terms of possible differences in hydration.

A linear mixed model with random intercept was applied to analyze the short-term change in absolute creatinine. Study group was coded as a binary factor, and time was coded as a factor with three levels. The interaction of study group with time (df = 2) was analyzed to compare the increase in creatinine levels from baseline to 18–24 and 46–50 hours between the CT and CCA groups. In a secondary analysis, time to short-term AKI was analyzed by using the Kaplan-Meier method and the log-rank Mantel-Cox test. We used the multiple Cox proportional hazard model including forward selection for prognostic variables for analyses of long-term serum creatinine (chronic kidney disease). Computations were performed by using the freely available statistical software R (3.4) *(http://www.R-project.org)* and commercial software SPSS, version 24.0 (SPSS, Chicago, Ill). The level of significance was .05 (two sided).

Results

A total of 739 patients were assessed during the study period for fulfillment of the eligibility criteria (Table E1 [online]), and 340 participants were randomized (168 to intravenous and 172 to intra-arterial contrast agent administration, Fig 1). Short-term follow-up creatinine was available for 161 of 165 participants (98%) who received intravenous contrast agent in the CT angiography group and for 159 of 162 participants (98%) who received intra-arterial contrast agent in the CCA group. Specifically, creatinine was available after 18–24 hours in 315 of 320 participants (156 after CCA, 159 after CT angiography) and after 46–50 hours in 307 of 320 participants (152 after CCA, 155 after CT angiography). The population available for analysis with creatinine available at least at one time point consisted of 320 participants (Fig 1, 50.9% female [163]) with a mean age of 60.5 years ± 11.4. Participant characteristics, including baseline creatinine levels and eGFR, which was greater than 60 mL/min/1.73 m^2 in more than 90% of patients, were well balanced, and both sexes were equally represented (Table 1). Thirteen participants in the CT angiography group suspected of having CAD underwent additional CCA within the short-term creatinine follow-up interval after a median of 25.7 hours (interquartile range [IQR]: 12.5–37.4 hours; Table 2) and remained in the CT angiography group for the analysis of AKI.

AKI Findings

AKI occurred in nine of 161 participants (5.6%; 95% CI: 3%, 10%) in the intravenous (CT angiography) group and in 21 of 159 participants in the intra-arterial contrast agent administration (direct CCA) group (13.2%; 95% CI: 9%, 19%; relative risk, 2.4; 95% CI: 1.1, 5.0; P = .02; Table 3). The Kaplan-Meier analysis showed lower probability of postcontrast AKI in the intravenous contrast agent group than in the CCA group (P = .03; Fig 2). Relative, individual, and absolute changes in short-term creatinine are shown in Figures E1–E3 (all online). Approximately half of the 30 participants with postcontrast AKI showed increased creatinine after both 18–24 hours and 46–50 hours (Fig E2 [online]). In the mixed model, the short-term increase in absolute creatinine levels was higher in the CCA group than in the CT angiography group in all partici-

Table 1: Baseline Participant Characteristics in the Two Groups

Characteristic	CT Angiography (n = 161)	CCA (n = 159)
Age (y)	60.6 ± 11.3	60.5 ± 11.5
Men	55.8 ± 11.6	57.6 ± 11.3
Women	64.9 ± 9.3	63.4 ± 11.0
No. of women*	87 (54.0)	76 (47.8)
Body mass index (kg/m^2)	27.3 ± 4.7	27.0 ± 4.6
Risk factors for postcontrast acute kidney injury		
Age > 70 years*	41 (25.5)	40 (25.1)
Weight (kg)	79.1 ± 15.4	79.7 ± 16.4
Presence of NYHA class II disease or higher*	39 (24.2)	47 (29.5)
Obstructive coronary artery disease*	20 (12.4)	25 (15.7)
Hyperlipidemia*	93 (57.8)	81 (51.0)
Arterial hypertension*	107 (66.4)	110 (69.2)
Diabetes mellitus*	15 (9.3)	30 (18.9)
Smoking*	38 (23.6)	33 (20.7)
Chronic kidney disease		
Baseline creatinine level (mg/dL)	0.87 ± 0.2	0.84 ± 0.2
eGFR (mL/min/1.73 m^2)*	84 (17)	87 (17)
eGFR category G1 (≥90 mL/min/1.73 m^2)*	65 (40.4)	78 (49.1)
eGFR category G2 (60–89 mL/min/1.73 m^2)*	83 (51.5)	71 (44.6)
eGFR category G3a (45–59 mL/min/1.73 m^2)*	8 (4.9)	8 (5.0)
eGFR category G3b (30–44 mL/min/1.73 m^2)*	5 (3.1)	2 (1.2)
Pretest probability of coronary artery disease according to the Duke score (21)	32 ± 26	38 ± 25
Medications*		
Diuretic	22 (13.7)	20 (12.6)
Statin	42 (26.1)	41 (25.8)
Acetylsalicylic acid	46 (28.6)	40 (25.1)
β-blocker	69 (42.8)	69 (43.4)
Insulin	3 (1.8)	3 (1.9)
Oral antidiabetic	11 (6.8)	17 (10.7)
ACE inhibitor	38 (23.6)	42 (26.4)
Hospital admission status at time of randomization*		
Inpatient	88 (54.6)	93 (58.5)
Outpatient	73 (45.4)	66 (41.5)

Note.—Unless otherwise specified, data are means ± standard deviations. The only difference between the two groups was for pretest probability, which was higher for patients with diabetes mellitus, which was more common in the coronary angiography group. Although diabetes was significantly more frequent in the conventional coronary angiography (CCA) group, there was no confounding with treatment regarding the primary outcome, as diabetes was not associated with acute kidney injury (AKI) in the multivariable analysis (Table E4 [online]). Two of 15 and three of 30 patients with diabetes in the CT angiography and CCA groups, respectively, developed AKI. ACE = angiotensin-converting enzyme, eGFR = estimated glomerular filtration rate, NYHA = New York Heart Association (classification of heart failure, with class II indicating slight limitation of physical activity due to dyspnea).

* Data are numbers of participants, with percentages in parentheses.

pants (overall, P = .02) and in participants with postcontrast AKI (P = .001).

Postcontrast AKI in Subgroups

In the subgroup of participants without obstructive CAD, AKI was also more common in the CCA group (11.9% [95% CI: 8%, 19%] vs 4.3% [95% CI: 2%, 9%]; P = .02; Table 3). No participant without obstructive CAD in the CT angiography group had AKI according to the KDIGO definition, but five of the 134 participants in the CCA group did (Table 3; P = .03). All participants fulfilling the KDIGO classification had stage 1 AKI. Absolute differences between the two groups in postcontrast AKI according to the most common definition were similar in women and men (Table 3).

Contrast Agent Volumes and Hydration

The median total contrast agent volume was significantly higher in the CCA group (78 mL; IQR, 64–95 mL) than in the CT angiography group (66 mL; IQR, 60–70 mL; P = .01; Table 2). In participants without CAD, the total contrast agent volume was also higher in the CCA group (P < .001; Table 2). No association was found in the multivariable analysis between the contrast agent volume and AKI, either in the univariable or in the multivariable analysis (Table E4, Fig E4 [both online]).

Table 2: Imaging Procedure Characteristics in the Two Groups

Characteristic	CT Angiography (n = 161)	CCA (n = 159)
Imaging procedures		
Total contrast agent volume (mL)	66 (60–70)	78 (64–95)
Total contrast agent volume in patients without CAD (mL)	65 (60–70)	74 (60–85)
CT angiography*	161 (100)	0
Intravenous contrast agent volume for CT angiography (mL)	65.7 ± 11.8	0
CCA*†	13 (8.1)	159 (100)
Intra-arterial contrast agent volume for CCA (mL)	120.7 ± 66.9	85.8 ± 40.0
PCI*	8/13 (61.5)	19 (11.9)
Intra-arterial contrast agent volume for PCI (mL)	40.0 ± 37.4	53.8 ± 58.6
Cine ventriculography during catheterization*	9/13 (69.2)	136 (85.5)
Contrast agent volume for cine ventriculography (mL)	28.8 ± 3.4	28.2 ± 3.5
Radial access*	1 (7.7)	10 (6.3)
Femoral access*	12 (92.3)	149 (93.7)

Note.—Unless otherwise specified, data are means ± standard deviations or medians with interquartile ranges in parentheses. CAD = coronary artery disease, CCA = conventional coronary angiography, PCI = percutaneous coronary intervention.

* Data are numbers of participants, with percentages in parentheses.

† CCA performed in the CT angiography group in patients suspected of having obstructive CAD at CT angiography was included when performed within the short-term creatinine follow-up time window.

Hydration was recommended for 12 of the 161 participants in the CT angiography group (7.5%) and for 11 of the 159 participants in the CCA group (6.9%) (Table E5 [online]). No association was found in the multivariable analysis between hydration and postcontrast AKI (Table E4 [online]).

Risk Factors Associated with AKI in Both Groups

In the multivariable analysis, the following factor was associated with AKI in both groups: presence of obstructive CAD (OR, 2.7; 95% CI: 1.1, 6.6; P = .02), and, as part of CCA, femoral access (OR, 2.5; 95% CI: 1.1, 5.6; P = .04) and cine ventriculography (OR, 2.3; 95% CI: 1.0, 4.9; P = .03; Table E4 [online]).

Postcontrast AKI Depending on Procedures

Whether or not cine ventriculography or femoral access was used for CCA did not result in different AKI frequency in either group (Table 4). In the participants who received a total contrast agent volume of less than 70 mL, there were fewer cases of AKI in the CT angiography group than in the CCA group (6% [five of 83 participants] vs 17% [nine of 53 participants]; difference, 11.0%; 95% CI: −0.4%, 22.3%; relative risk, 2.8; 95% CI: 1.0, 8.0; P = .048; Table 4).

Long-term Serum Creatinine

Long-term follow-up was available in 97% of study participants (311 of 320 participants; Fig 1 and Figs E5–E7 [online]). After a median of 1.9 years (IQR, 1.1–4.5 years), a greater proportion of participants with postcontrast AKI still had increased creatinine by 25% or 0.5 mg/dL or greater (38% vs 6%; $P < .001$) and at least mildly decreased eGFR (86%, 73.2 mL/min/1.73 m^2 ± 20.2 vs 61%, 82.7 mL/min/1.73 m^2 ± 17.5; P = .02; Fig 3) compared with participants without postcontrast AKI. In the long-term multivariable analysis, only postcontrast AKI (hazard ratio: 12.4; 95% CI: 4.5, 34.6; $P <$ .01) and age greater than 70 years (hazard ratio: 3.1; 95% CI: 1.3, 7.9; P = 0.01) were associated with chronic kidney disease (Table E6 [online]).

Discussion

In the absence of randomized studies, it has so far been controversial whether the likelihood of acute kidney injury (AKI) differs between the intravenous and intra-arterial routes of administration. The principal findings of this randomized clinical study of patients with atypical angina, possible coronary artery disease (CAD), and normal baseline kidney function were (*a*) AKI is more likely after an intra-arterial contrast agent procedure (13.2%, cardiac catheterization) than after intravenous contrast agent administration (5.6%, CT angiography), with a relative risk of 2.4; and (*b*) chronic kidney disease was more likely in participants included in both groups with postcontrast AKI, with a 12-fold greater risk. The lower AKI risk after CT angiography compared with conventional coronary angiography (CCA) was similarly found in all participants and in those without obstructive CAD. After a median follow-up of 1.9 years, increased creatinine levels and poorer estimated glomerular filtration rate categories were found in participants who had developed postcontrast AKI, corroborating the relationship of postcontrast AKI and chronic kidney disease.

AKI frequencies similar to our study have been reported in observational studies after CT angiography (6.4%) (19) and CCA (14.4%) (18). AKI frequency was also comparable in a large retrospective cohort study of CT with and CT without intravenous contrast agents (7% and 9%) (30). An inpatient registry study in the United States showed that AKI developed at similar rates in patients who received a contrast agent (by any route) and patients who did not receive a contrast agent (5.5%

Table 3: AKI in All Patients and Subgroups

AKI Definition and Subgroup	CT Angiography (n = 161)	CCA (n = 159)	P Value*	Absolute Difference in Percentage†	Relative Risk†
Postcontrast AKI according to most common definition in all patients‡	9 (5.6)	21 (13.2)	.02	7.6 (1.3, 14.4)	2.4 (1.1, 5.0)
Patients without obstructive CAD					
Most common definition‡	6/141 (4.3)	16/134 (11.9)	.02	7.7 (1.3, 14.1)	2.8 (1.1, 7.0)
KDIGO definition§	0/141 (0)	5/134 (3.7)	.03	3.7 (0.5, 6.9)	NA‖
Women					
Most common definition‡	5/87 (5.7)	10/76 (13.2)	.11	7.4 (−1.6, 16.4)	2.3 (0.8, 6.4)
KDIGO definition§	0/87 (0)	2/76 (2.6)	.22	2.6 (−1.0, 6.2)	NA‖
Men					
Most common definition‡	4/74 (5.4)	11/83 (13.3)	.11	7.8 (−1.1, 16.8)	2.5 (−0.8, 7.4)
KDIGO definition§	2/74 (2.7)	6/83 (7.2)	.28	4.5 (−2.2, 11.2)	2.7 (0.6, 12.9)

Note.—Unless otherwise specified, data are numbers of participants, with percentages in parentheses. AKI = acute kidney injury, CAD = coronary artery disease, CCA = conventional coronary angiography, KDIGO = Kidney Disease: Improving Global Outcomes, NA = not applicable. CAD was defined as at least one ≥ 50% coronary diameter stenosis at CT angiography or CCA.

* According to Fisher exact test because of low cell counts.

† Data in parentheses are 95% confidence intervals.

‡ Defined as an increase in creatinine of ≥ 25% or 0.5 mg/dL.

§ Defined as an increase in creatinine of ≥ 50% or 0.3 mg/dL.

‖ Relative risk was not calculated in case of zero frequencies.

vs 5.6%), suggesting that the risk may be overstated in the literature and overestimated by clinicians (31).

There may be multiple pathophysiologic mechanisms leading to a lower risk of AKI after intravenous contrast material administration for coronary CT angiography. The contrast agent volume used in the CT angiography group was significantly smaller and might have contributed to the lower frequency of AKI seen after CT angiography. However, we did not find an association between contrast agent volume and AKI in either our univariable or multivariable analysis. Thus, we can exclude possible confounding of our results by contrast agent volume. Introducing catheters, as required for CCA, may result in microshowers of cholesterol emboli into the renal arteries (13). Also, the multiple injections during the intra-arterial procedure versus the single injection for intravenous procedures may explain our results. Moreover, catheter access via the femoral artery was associated with a higher absolute risk for AKI by 2% in a randomized study in patients in an acute setting (32). Our study also showed a greater risk of AKI after femoral access in our multivariable analysis, suggesting that radial access may provide an opportunity to reduce the AKI risk of CCA. Microembolization is more likely if substantial atherosclerosis is present, as in patients with obstructive CAD, who also had a greater risk for AKI in our study. During cine ventriculography, the contrast agent concentration in renal artery blood is higher and changes much more rapidly (14), explaining why cine ventriculography was associated with AKI in our analyses and suggesting that this part of the CCA procedure should be avoided if possible.

Hydration by administration of intravenous saline and intravenous *N*-acetylcysteine was considered most effective based on randomized studies available at the time when our randomized study was protocolized. The PRESERVE trial in patients with stage 3 or 4 chronic kidney disease undergoing invasive angiography found that oral acetylcysteine did not lower the risk of major adverse kidney events, death, or AKI compared with placebo (33). Our observations confirm the

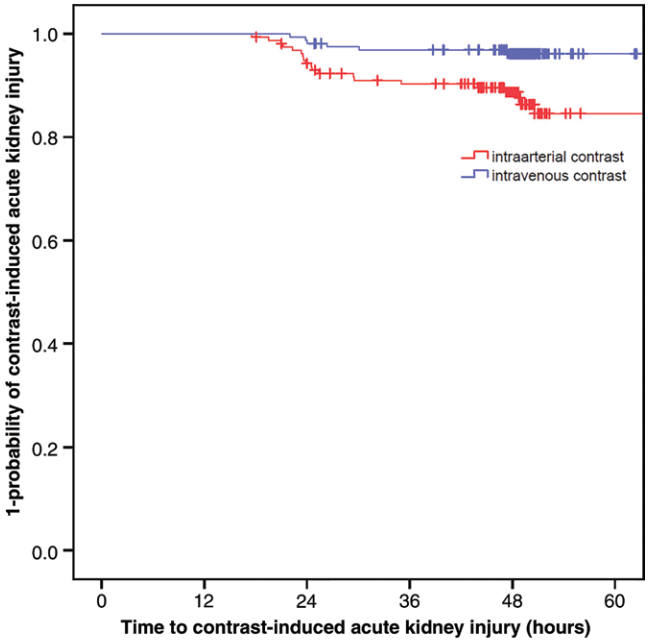

Figure 2: Kaplan-Meier curve of postcontrast acute kidney injury in the two groups. There is a lower probability of postcontrast acute kidney injury in the intravenous (CT angiography) than in the intra-arterial (conventional coronary angiography) contrast agent group (P = .03). Vertical lines on the graphs = censored data and the corresponding x values at the time when censoring occurred.

Table 4: AKI in Relation to Procedural Measures

Procedural Measures and AKI Definition	CT Angiography (n = 161)	CCA (n = 159)	P Value*	Absolute Difference in Percentage†	Relative Risk†
Cine ventriculography performed					
Most common definition‡	1/9 (11.1)	18/136 (13.2)	>.99	2.1 (−19.2, 23.4)	1.2 (0.2, 8.0)
KDIGO definition§	1/9 (11.1)	8/136 (5.9)	.45	−5.2 (−26.1, 15.7)	0.53 (0.07, 3.83)
Femoral access					
Most common definition‡	1/12 (8.3)	20/149 (13.4)	>.99	5.1 (−11.5, 21.7)	1.6 (0.2, 11.1)
KDIGO definition§	1/12 (8.3)	7/149 (4.7)	.47	−3.6 (−19.6, 12.4)	0.6 (0.1, 4.2)
Total contrast agent volume < 70 mL					
Most common definition‡	5/83 (6.0)	9/53 (17.0)	.048	11.0 (−0.4, 22.3)	2.8 (1.0, 8.0)
KDIGO definition§	0/83 (0)	0/53 (0)	>.99	0.0 (NA)‖	NA#

Note.—Unless otherwise specified, data are numbers of participants, with percentages in parentheses. AKI = acute kidney injury, CCA = conventional coronary angiography, KDIGO = Kidney Disease: Improving Global Outcomes, NA = not applicable.

* According to Fisher exact test because of low cell counts.

† Data in parentheses are 95% confidence intervals.

‡ Defined as an increase in creatinine of ≥ 25% or 0.5 mg/dL.

§ Defined as an increase in creatinine of ≥ 50% or 0.3 mg/dL.

‖ The 95% confidence interval was not calculated for zero frequencies.

\# The relative risk was not calculated for zero frequencies.

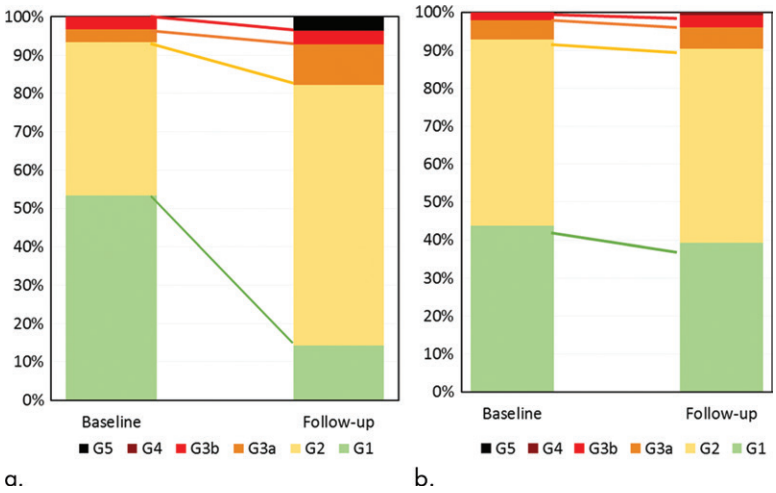

Figure 3: Graphs show long-term estimated glomerular filtration rate (eGFR) categories in patients with and those without acute kidney injury (AKI). **(a)** Graph shows poorer long-term eGFR categories (representing chronic kidney function) at a median follow-up of 1.9 years in patients with postcontrast AKI (results available for 28 of 30 patients). **(b)** Graph shows almost stable long-term eGFR categories in patients without postcontrast AKI (results available for 283 of 290 patients). eGFR categories are as follows: normal or high (G1, eGFR ≥ 90 mL/min/1.73 m^2), mildly decreased (G2, eGFR = 60–89 mL/min/1.73 m^2), mildly to moderately decreased (G3a, eGFR = 45–59 mL/min/1.73 m^2), moderately to severely decreased (G3b, eGFR = 30–44 mL/min/1.73 m^2), severely decreased (G4, eGFR = 15–29 mL/min/1.73 m^2), and kidney failure (G5, eGFR < 15 mL/min/1.73 m^2).

known variability of clinical caretakers in following hydration recommendations. Interestingly, hydration was not protective in the recent AMACING trial with AKI in 2.6% and 2.7% of the patients, respectively, and creatinine measured once at 2–6 days (34). Our multivariable analysis also found no effect of hydration. We encountered higher rates of AKI possibly because we performed two short-term creatinine measurements.

Our study had some limitations. First, it was powered to investigate procedural complications, and kidney injury was a prespecified secondary outcome. Second, it was a randomized single-center study, and results might be different in other centers. Third, data for albuminuria and proteinuria were not consistently available. Fourth, our results may apply only to patients suspected of having CAD and atypical angina, a group with almost always normal baseline renal function, as in our study. Fifth, diabetes mellitus was more common and the pretest probability of CAD was higher in the CCA group. However, there was no confounding with treatment regarding the primary outcome, as diabetes was not associated with AKI in the multivariable analysis and obstructive CAD was not more common in the CCA group. Importantly, 98% of study participants had complete short-term (18–24 or 46–50 hours after the procedure) follow-up creatinine, and, after a median of 1.9 years, long-term follow-up creatinine was available in 97% of the 320 participants.

This randomized study, however, cannot assess the causality of whether intravenous contrast agent (for CT angiography) is associated with AKI, as no comparison group without any contrast agent administration was available. Further studies should investigate this relevant clinical question, preferably using a randomized or intraindividual comparison. Low-osmolar nonionic contrast agents have been shown to be noninferior to iso-osmolar agents (23) for AKI, suggesting that our results also apply to iso-osmolar agents. Policies for clinical decision making about the testing of patients eligible for either intravenous or intra-arterial contrast agent procedures should be revised to reflect the greater

risk of AKI after intra-arterial contrast agent procedures (1,2). Moreover, our results allow better informed risk-benefit decision making, and clinical practice guidelines (35) should include stronger recommendations for coronary CT angiography as a diagnostic test in patients suspected of having CAD and low-to-intermediate pretest probability, reflecting the reduced AKI risk found in our study.

In summary, in patients suspected of having coronary artery disease, intravenous contrast agent administration for coronary CT angiography yielded a lower rate of acute kidney injury (AKI) than intra-arterial administration for conventional coronary angiography, and postcontrast AKI is associated with chronic impairment of kidney function.

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