MAYO CLINIC

Acute Kidney Injury After Repeated Exposure to Contrast Material for Coronary Angiography

Aisha Betoko, PhD; Matthew B. Matheson, MS; Mohammad R. Ostovaneh, MD, MPH; Julie M. Miller, MD; Jeffrey Brinker, MD; Christopher Cox, PhD; João A.C. Lima, MD; and Armin Arbab-Zadeh, MD, PhD, MPH

Abstract

Objective: To assess the incidence of contrast-associated acute kidney injury (CAAKI) after repeated exposure to contrast material for computed tomography (CT) and conventional coronary angiography within short intervals.

Methods: We studied 651 patients enrolled in the CorE-64 (November 5, 2005—January 30, 2007) and CORE320 (October 21, 2009—August 17, 2011) multicenter studies. Participants with suspected obstructive coronary heart disease were referred for diagnostic cardiac catheterization and underwent coronary CT angiography for research before invasive angiography. Nonionic, low-osmolality iodinated contrast material was used for all imaging.

Results: The median age of the patients was 62 years, and 190 (29%) were women. Major risk factors for acute kidney injury were present in 277 of 651 (43%) patients. The median interval between CT imaging and invasive angiography was 3.1 days (interquartile range, 0.9-8.0 days). The median volume of contrast material was 100 mL for each test. In 16 (2.5%) of 651 patients, CAAKI developed. Of these cases, 1 occurred after the CT scan, whereas 6 were documented after invasive angiography (compared with post-CT creatinine concentration assessment). In 9 patients, CAAKI was found in comparing creatinine concentration after completion of both tests with baseline values (but not compared with post-CT imaging).

Conclusion: Acute kidney injury after repeated exposure to iodinated contrast media within a few days is uncommon even in a population of patients with highly prevalent risk factors. Withholding of clinically indicated contrast-enhanced imaging may therefore not be justified in this setting.

 ■ Mayo Clin Proc Inn Qual Out 2021;5(1):46-54

From the Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD (A.B., M.B.M., C.C.); and Johns Hopkins University School of Medicine, Baltimore, MD (M.R.O., J.M.M., J.B., J.A.C.L., A.A.-Z.).

Acute kidney injury attributed to application of iodinated contrast medium (contrast-associated acute kidney injury [CAAKI]) is a common concern in medical X-ray imaging. The diagnosis of CAAKI is challenging, however, because acute kidney injury may be caused by many mechanisms in patients undergoing imaging, who often have other risk factors for acute renal failure. Commonly, CAAKI after contrast medium exposure is suspected with a rise of serum creatinine concentration of at least 0.5 mg/dL (44 μmol/L) or by a relative increase of at least 25% from baseline occurring within 48 to 72 hours in the absence of an alternative cause.[1,2] Some consensus statements define acute kidney injury in 3 stages, requiring an increase of serum creatinine concentration of at least 50% or more than 0.3 mg from baseline.[3] In most cases, creatinine values return to baseline within 1 to 3 weeks.[4,5] However, clinical studies suggest that CAAKI is associated with increased morbidity and mortality after percutaneous coronary intervention (PCI).[6,7]

The reported incidence of CAAKI varies between 2% and 60%, depending on the definition, the population of patients, the mode of application, and the patient's baseline risk factors.[8,9] Risk factors for CAAKI include chronic kidney disease, advanced age, diabetes

TABLE 1. Baseline Characteristics and Clinical Data of the Study Participants[a,b,c]

Characteristics	Overall (N=651)	CorE-64 (n=291)	CORE320 (n=360)
Male	461 (71)	221 (76)	240 (67)
Age (y)	62 (55-68)	61 (54-68)	62 (56-69)
Race			
Asian	194 (30)	74 (25)	120 (33)
Black	49 (8)	15 (5)	34 (9)
White	397 (61)	195 (67)	202 (56)
Other	11 (2)	7 (2)	4 (1)
Ethnicity			
Hispanic	29 (4)	0 (0)	29 (8)
Non-Hispanic	541 (83)	232 (80)	309 (86)
Other	81 (12)	59 (20)	22 (6)
BMI (kg/m^2)	27 (24-30)	27 (24-30)	27 (24-30)
Diabetic	196 (30)	76 (26)	120 (33)
Hypertension	480 (74)	200 (69)	280 (78)
Dyslipidemia	434 (68)	194 (67)	240 (68)
Family history of CAD	247 (39)	98 (34)	149 (44)
Prior MI	164 (25)	70 (24)	94 (26)
Prior PCI	150 (23)	44 (15)	106 (29)
Continent			
North America	188 (29)	106 (36)	82 (23)
South America	162 (25)	53 (18)	109 (30)
Europe	140 (22)	64 (22)	76 (21)
Asia	161 (25)	68 (23)	93 (26)
Heart failure	62 (10)	24 (8)	38 (11)
Beta blocker during CT scan			
Intravenous	172 (26)	79 (27)	93 (26)
Oral	293 (45)	56 (19)	237 (66)
Contrast agent dose during CTA and CTP (mL)	100 (80-120)	77 (73-80)	120 (120-120)
Contrast agent dose during ICA (mL)	100 (75-135)	100 (77-140)	100 (75-130)
Serum creatinine level (mg/dL)			
At baseline	0.89 (0.76-1.00)	0.90 (0.80-1.02)	0.85 (0.73-0.99)
Post-CT scan	0.84 (0.73-0.97)	0.90 (0.70-1.00)	0.83 (0.73-0.95)
Post-ICA	0.86 (0.76-1.00)	0.90 (0.80-1.00)	0.84 (0.74-0.95)
At discharge	0.90 (0.79-1.00)	0.88 (0.76-1.00)	0.90 (0.81-1.05)
Adverse events			
CAAKI, baseline to post-CT	1/188 (1)	1/70 (1)	0/118 (0)
CAAKI, post-CT to post-ICA	6/158 (4)	2/56 (4)	4/102 (4)
CAAKI, baseline to post-ICA	9/163 (6)	9/129 (7)	0/34 (0)
Contrast allergy	3 (<1)	3 (1)	0 (0)

[a]BMI, body mass index; CAD, coronary artery disease; CAAKI, contrast-associated acute kidney injury; CT, computed tomography; CTA, computed tomography angiography; CTP, computed tomography perfusion; ICA, invasive coronary angiography; MI, myocardial infarction; PCI, percutaneous coronary intervention.
[b]To convert creatinine values (mg/dL) to μmol/L, multiply by 88.4.
[c]Values are reported as number (%) or median (interquartile range).

mellitus, heart failure, and nephrotoxic drug use as well as procedure-related factors, such as route of administration of the contrast agent, osmolarity, and volume.[10-12]

A causal relationship between contrast material exposure and acute kidney injury has recently been questioned as a meta-analysis of more than 100,000 patients did not find an

TABLE 2. Timing of Creatinine Measurements After CT and ICA Procedures[a,b]

Measurement timing	CorE-64	CORE320	SCr rise from baseline[c]	SCr rise from post-CT imaging[c]
After CT	(n=114)	(n=274)		
0-11 hours	8 (7)	7 (3)	0	–
12-23 hours	35 (31)	16 (6)	0	–
1 day	16 (14)	71 (26)	1	–
2 days	11 (10)	24 (9)	0	–
3 days	9 (8)	28 (10)	–	–
4-7 days	18 (16)	70 (26)	–	–
≥8 days	13 (11)	57 (21)	–	–
Undetermined[d]	4 (4)	1 (<1)	–	–
After ICA	(n=253)	(n=247)		
0-11 hours	47 (19)	86 (35)	2	1
12-23 hours	76 (30)	52 (21)	4	1
1 day	47 (19)	29 (12)	2	2
2 days	18 (7)	17 (7)	1	2
3 days	15 (6)	15 (6)	–	–
4-7 days	16 (6)	23 (9)	–	–
≥8 days	31 (12)	25 (10)	–	–
Undetermined[d]	3 (1)	0 (0)	–	–

[a]CT, computed tomography; ICA, invasive coronary angiography; SCr, serum creatinine.
[b]Values are reported as number (%).
[c]Indicates an increase of serum creatinine concentration by ≥25% or ≥0.5 mg/dL.
[d]Indicates creatinine sample was taken >1 day before the scan.

increased risk of acute nephropathy in patients receiving contrast medium for computed tomography (CT) imaging vs those who underwent a non-contrast-enhanced scan.[13] An alternative explanation for acute kidney injury observed after invasive coronary angiography (ICA) is the possibility of renal insult mediated by mechanisms other than contrast agent toxicity, for example, by atheroembolism.[14,15] In the prospective CorE-64 and CORE320 trials,[16,17] participants received CT scans and ICA within a short sequence, thus providing the opportunity for comparing the risk of acute kidney injury after repeated exposure and after intravenous and intra-arterial application (and associated risk of atheroembolism) in the same patients. We hypothesized that repeated application of contrast medium is associated with low risk of acute kidney injury and that the risk of kidney injury is greater after invasive angiography than after CT angiography (CTA), given the additional risk of atheroembolism associated with invasive angiography.

METHODS

For this analysis, we combined data from the CorE-64 and CORE320 prospective clinical studies, given their similar study protocol and population.[16,17] Both studies were approved by local Institutional Review Boards of participating centers, and all patients provided written informed consent.

CorE-64 Study Design and Data Collection

The Coronary Artery Evaluation Using 64-Row Multi-detector Spiral Computed Tomography Angiography (CorE-64) study investigated the diagnostic accuracy of CTA for detecting obstructive coronary heart disease in comparison to ICA.[16,18] The methods of the CorE-64 study have been previously detailed.[18] The study enrolled 371 participants aged 40 years and older at 9 international centers from November 5, 2005, to January 30, 2007.[19] Patients were excluded from participation if they had any of the following: history of allergic reaction to iodinated contrast media, history of contrast-induced nephropathy, history of multiple myeloma or previous organ transplant, elevated serum creatinine concentration (>1.5 mg/dL; to convert to μmol/L, multiply by 88.4) or calculated creatinine clearance of less than 60 mL/min (using the Cockcroft-Gault formula), atrial fibrillation or uncontrolled tachyarrhythmia, advanced atrioventricular block (second- or third-degree heart block), evidence of severe symptomatic heart failure (New York Heart Association class III or IV), known or suspected moderate or severe aortic stenosis, previous coronary artery bypass or other cardiac surgery, coronary artery intervention within the last 6 months, known or suspected intolerance of or contraindication to beta blockers (including known allergy to beta blockers, history of moderate to severe bronchospastic lung disease including moderate to severe asthma, and severe pulmonary disease), body mass index >40 kg/m^2, or any other history or condition that the investigator judged to be a significant reason for exclusion.[18] Patients underwent the study-related CTA scan, followed by clinically driven ICA within 30 days.

CORE320 Study Design and Data Collection

The prospective, multicenter CORE320 study (www.clinicaltrials.gov, NCT00934037) enrolled 381 symptomatic individuals, aged

Mayo Clin Proc Inn Qual Out ■ February 2021;5(1):46-54 ■ https://doi.org/10.1016/j.mayocpiqo.2020.08.012
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45 to 85 years referred for ICA with suspected obstructive coronary heart disease, at 16 sites in 8 countries from October 21, 2009, to August 17, 2011.[17] CORE320 aimed to examine the diagnostic accuracy of combined 320-row CTA and CT myocardial perfusion imaging in comparison to the combination of ICA and single-photon emission CT myocardial perfusion imaging. The study design and CT methods have been reported in detail.[20,21] Exclusion criteria were similar to those of CorE-64: known allergy to iodinated contrast media, elevated serum creatinine concentration (>1.5 mg/dL) or calculated creatinine clearance of less than 60 mL/min, atrial fibrillation, second- or third-degree atrioventricular block, previous cardiac surgery, coronary intervention within the past 6 months, evidence of acute coronary syndrome with thrombolysis, myocardial infarction risk score of 5 or higher or elevated cardiac enzyme activities in the past 72 hours, high radiation exposure (≥5.0 rem) in the 18 months before consent, and body mass index above 40 kg/m^2, among others.[21]

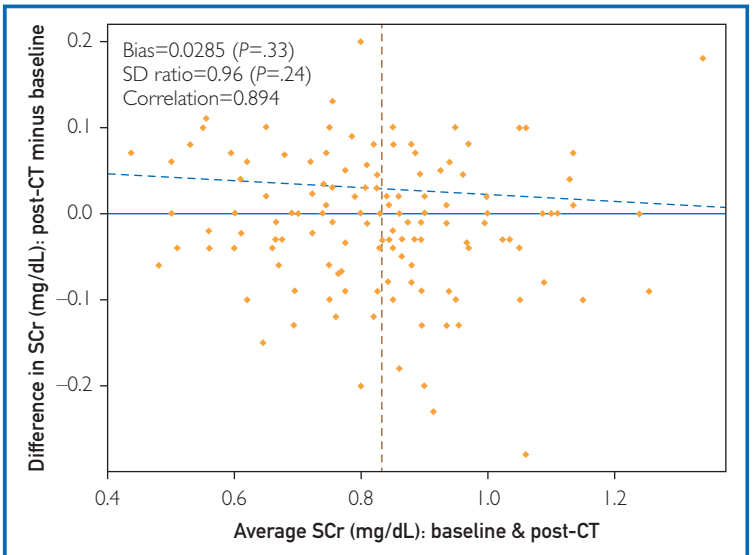

FIGURE 1. Bland-Altman plot of serum creatinine (SCr) changes after computed tomography (CT) angiography. A Bland-Altman graph is provided for the difference of SCr after CT scan and baseline SCr against the average of both values. The difference was computed as post-CT SCr minus baseline SCr. Correlation coefficient is 0.89 (95% CI, 0.86 to 0.92), the mean difference is 0.03 mg/dL (95% CI, −0.03 to 0.09), and the standard deviation ratio is 0.96 (95% CI, 0.90 to 1.03). The plot demonstrates that very little change occurred in SCr levels before and after exposure to contrast media during CT scan.

Study Population

Of the 752 participants from the combined CoreE-64 and CORE320 cohorts, 87 were excluded from this analysis because creatinine measurements were available only at baseline, and another 14 were excluded because the creatinine value was not available at baseline. The remaining 651 had baseline creatinine values as well as at least 1 subsequent assessment of serum creatinine concentration after 1 or both procedures.

Contrast Medium Application for CTA

Before the CT scan, patients were given intravenous hydration with normal saline (250-500 mL) to minimize the risk of CAAKI and to avoid hypovolemia before administration of the vasodilator stressor. Sublingual nitroglycerin was given before scanning. Real-time contrast bolus tracking and a prospective electrocardiography-triggered scan protocol were applied over 1 to 2 heart beats. For CT perfusion imaging in CORE320, contrast medium application was repeated 20 minutes later, after adenosine infusion (140 μg/kg per minute) by a similar protocol as for rest CT.[21] Iopamidol (ISOVUE-370, Bracco Diagnostics) was administered for all imaging by a power injection with flow rates of 4 to 5 mL/s and a triphasic injection protocol (100% contrast agent, followed by 30% contrast agent and 70% saline mix, followed by 100% saline chaser).[18,21]

Contrast Medium Application for ICA

Conventional coronary angiography was performed within 60 days of multidetector CTA by standard techniques at the participating centers.[18,21] The specific choice of the contrast agent was left to the discretion of the study site investigators, but nonionic, low-osmolality iodinated contrast material was used for all imaging, administered by manual or power injection through coronary angiography catheters. Contrast agent volume was assessed separately after diagnostic coronary angiography and coronary intervention. Standard hydration procedures were performed before exposure to the contrast material.

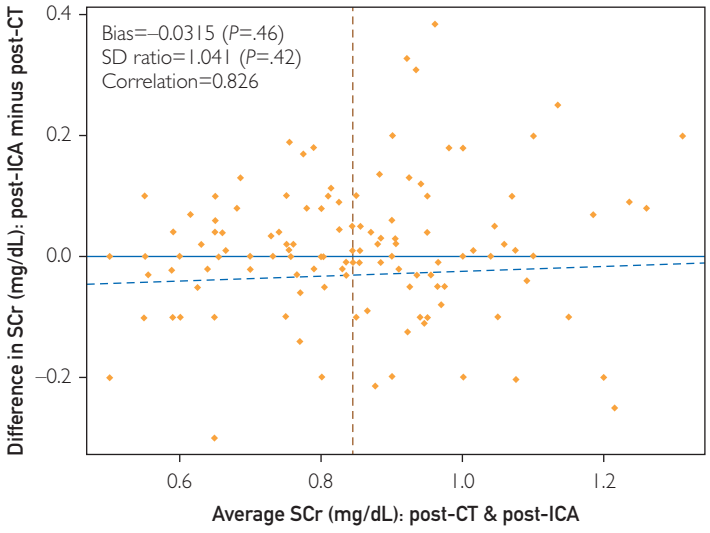

FIGURE 2. Bland-Altman plot of serum creatinine (SCr) changes after computed tomography (CT) angiography and invasive coronary angiography (ICA). A Bland-Altman graph is shown for the mean difference of SCr after ICA and after CT against the average of both values. The difference was computed as post-ICA SCr minus post-CT SCr. Correlation coefficient is 0.83 (95% CI, 0.77 to 0.87), the mean difference is −0.03 mg/dL (95% CI, −0.11 to 0.05), and the standard deviation ratio is 1.04 (95% CI, 0.94 to 1.15). Very little change is observed in SCr level before and after exposure to contrast media during ICA.

Blood Sample Acquisition and Clinical Follow-up

The study protocols requested blood samples to be collected and serum creatinine concentration to be analyzed at baseline (pre-CT imaging), 72 hours after CT, 72 hours after ICA, and before discharge to monitor renal function. Clinical follow-up of the enrolled patients occurred at 30 days, 6 months, and 1 year. Minor and major adverse events related to contrast media injection were recorded.

Data Analyses

Contrast-induced nephropathy (CAAKI) was defined as an increase in serum creatinine concentration by 0.5 mg/dL or more or an increase in serum creatinine concentration to 25% or higher from baseline, which was known or presumed to have occurred within 72 hours after intravenous administration of contrast material. Baseline characteristics of the patients were expressed as median (interquartile range [IQR]) for continuous variables and as proportions for categorical variables. Bland-Altman analyses and figures were used to assess change in creatinine values from baseline to subsequent measurements. This was done by regressing the difference between the post−baseline value and the baseline value on the sample-centered average of the 2; the coefficients of this regression estimate bias (intercept) and log-ratio of dispersion (slope). Statistical analyses were performed using SAS 9.4 (SAS Institute).

RESULTS

Demographic and clinical characteristics of study participants are provided in Table 1. Of the 651 patients, 190 (29%) were women; median age was 62 years. There were 277 (43%) patients who had either diabetes mellitus or a history of heart failure or were at least 75 years old, thus carrying major risk factors for CAAKI.[22] The median interval between CT scans and ICA was 3.13 days (IQR, 0.91-7.96 days). The interval was shorter in CorE-64 than in CORE320, 0.82 (IQR, 0.17-3.91) days vs 5.86 (2.21-11.01) days, respectively. The median volume of the iodinated contrast material in the overall population was 100 (80-120) mL during CT scans (77 [73-80] mL for a single application of contrast agent in CorE-64 and 120 [120-120] mL for 2 applications [CTA and CT perfusion imaging] in CORE320) and 100 (75-140) mL for ICA. Of 651 patients undergoing ICA, 88 (13.5%) underwent PCI in the same session, affecting the median volume of contrast material given for ICA. Creatinine samples were obtained within 72 hours of CT imaging in 188 of 388 (48%) and in 372 of 500 (74%) for ICA. Details on all creatinine measurements are provided in Table 2.

The median serum creatinine concentration was 0.89 (IQR, 0.76-1.00) mg/dL at baseline, 0.84 (0.73-0.97) mg/dL after CT, and 0.86 (0.76-1.00) mg/dL after ICA. Among the 188 (29%) participants who had serum creatinine concentration measured less than 72 hours after the CT examination, there was no significant increase (Figure 1). The difference between baseline and post-CT serum creatinine concentration was 0.03 mg/dL on average (standard error [SE], 0.03), and the correlation between both measurements was

Mayo Clin Proc Inn Qual Out ■ February 2021;5(1):46-54 ■ https://doi.org/10.1016/j.mayocpiqo.2020.08.012
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0.89. Similarly, among the 158 (24%) participants who had serum creatinine concentration measured between CT and ICA and again within 72 hours after the ICA examination, there was no significant change in the serum creatinine value (Figure 2). The average difference between post-CT and post-ICA serum creatinine concentration was −0.03 mg/dL (SE, 0.04), with a correlation of 0.83 between the 2 values. Among the 163 (25%) participants who had post-ICA serum creatinine concentration measured within 72 hours after the CT scan, there was a nonsignificant decrease of −0.07 mg/dL (SE, 0.05) from baseline, with a correlation of 0.75 between the 2 values (Figure 3). The serum creatinine value of the 175 (27%) participants with available serum creatinine concentration at discharge was 0.05 mg/dL (SE, 0.05) higher than at baseline (Figure 4).

Incidence of CAAKI

Among the 651 participants, 16 cases of acute kidney injury (2.5% [95% CI, 1.4 to 4.0]) were associated with application of contrast material. The rate of CAAKI was low in both cohorts but higher in CorE-64 (4.1 [2.4-7.1]) than in CORE320 (1.1 [0.4-2.8]) despite the use of more contrast material in CORE320 (detailed results are provided in the Supplemental Table, available online at http://mcpiqojournal.org). CAAKI developed in 1 patient after the CT scan, whereas 6 patients met criteria for CAAKI after ICA compared with post-CT serum creatinine assessment. Nine patients were noted to have CAAKI within 48 hours after ICA and completion of both tests compared with baseline (but not compared with post-CT evaluation). Because of the low incidence of CAAKI, we did not formally test for a difference of CAAKI after CT vs after ICA. Of all 16 patients with incident CAAKI, 8 had no event within 30 days after CT and ICA, 5 had PCI during ICA, 2 had PCI within 1 week of ICA, and 1 had coronary artery bypass graft surgery 21 days after ICA. Three patients in our sample experienced "allergic" reactions to contrast material exposure. Four others enrolled in CorE-64 or CORE320 were noted to have adverse events, but these were not included in this analysis because of insufficient data on renal function.

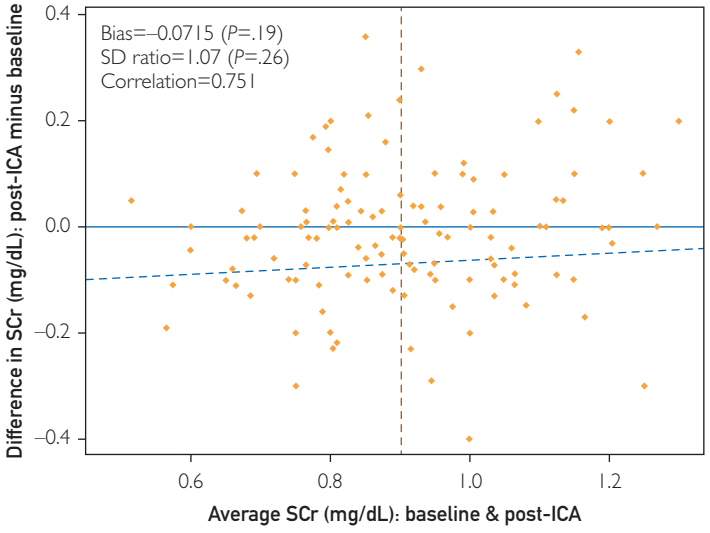

FIGURE 3. Bland-Altman plot of serum creatinine (SCr) changes after invasive coronary angiography (ICA) vs baseline. A Bland-Altman graph is provided for the mean difference of SCr after ICA and baseline SCr against the average of both values. The difference was computed as post-ICA SCr minus baseline SCr. Correlation coefficient is 0.75 (95% CI, 0.67- to 0.81), the mean difference is −0.07 mg/dL (95% CI, −0.18 to 0.04), and the standard deviation ratio is 1.07 (95% CI, 0.95 to 1.20). Very little change is observed in SCr level before and after exposure to contrast media during CT and ICA.

DISCUSSION

We found low rates of acute kidney injury in patients receiving repeated doses of contrast material for CT and ICA within 3 days despite high prevalence of risk factors for CAAKI in our study population. More patients fulfilled criteria for CAAKI after invasive vs CT coronary angiography, but the numbers were too small for conclusive analyses. The rate of CAAKI was greater in CorE-64 than in CORE320, which had longer intervals between exposure, although rates were low in both cohorts.

Our results are relevant for pragmatic and mechanistic considerations. Hospitalized patients often undergo X-ray tests with application of contrast material, and there is a concern for increased risk of CAAKI with repeated exposure to contrast agents within short intervals. Such concern may lead to withholding of tests, which may delay patient care and even place patients at risk by denying critical treatment (eg, coronary artery interventions). Only

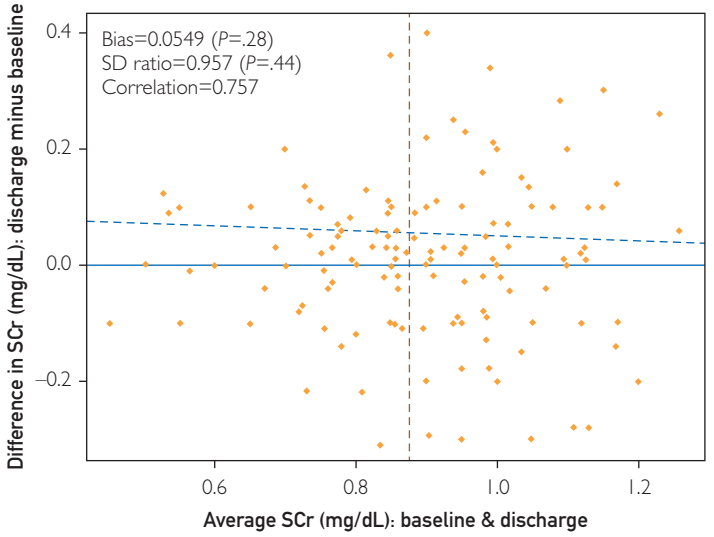

FIGURE 4. Bland-Altman plot of serum creatinine (SCr) changes at discharge vs baseline. A Bland-Altman graph is shown for the mean difference of SCr at discharge and baseline SCr against the average of both values. The difference was computed as SCr at discharge minus baseline SCr. Correlation coefficient is 0.76 (95% CI, 0.68 to 0.81), the mean difference is 0.05 mg/dL (95% CI, −0.05 to 0.15), and the standard deviation ratio is 0.96 (95% CI, 0.86 to 1.07). Very little change is observed in SCr level at baseline and at discharge, after exposure to contrast media during computed tomography and invasive coronary angiography.

scarce data are available on the risk of CAAKI after repeated exposure to contrast material. Trivedi and Foley[23] found a 14% CAAKI rate among 28 patients who received a total of 130 mL of iodinated contrast agent in 2 exposures 20 days apart. Conversely, Dinesch et al[24] did not observe CAAKI among 17 patients who underwent CTA and ICA within 24 hours. To the best of our knowledge, our study is the largest prospective evaluation of CAAKI in patients undergoing repeated exposure to contrast material for X-ray imaging within a few days.

The incidence of CAAKI increases with the number of risk factors for acute kidney injury (eg, as low as 1.2% for patients without risk factors and up to 31% for patients with ≥2 risk factors).[4,8,22] The mechanisms leading to CAAKI, however, are poorly understood.[9] Observational data have challenged the common perception that intravenous application of iodinated contrast material for X-ray imaging is associated with risk of acute kidney injury and raised the question of whether creatinine concentration rises after exposure are unrelated to the contrast medium.[13] Furthermore, acute kidney injury after intra-arterial catheterization (eg, ICA) may by caused by atheroembolism and not by the contrast medium itself (or by a combination).[14,15]

Our data were inconclusive regarding the question of whether acute kidney injury is more common after catheter-mediated angiography vs intravenously applied contrast material (of the same type and volume) for noninvasive angiography by CT, probably because of the low incidence of kidney injury and the associated low statistical power. However, a trend of greater acute kidney injury risk after ICA vs CTA was observed, which warrants further investigation.

Our study has considerable strength, including that it is the largest investigation of its kind, the use of an identical volume among the imaging tests, and a prospective (parent) study design. On the other hand, we acknowledge several limitations of our study. Foremost, an observed increase in creatinine concentration after exposure to a contrast agent does not prove contrast-induced acute kidney injury—or even any acute kidney injury for that matter. Even though all patients were prospectively enrolled, the data for our analysis were derived from 2 parent studies that were not designed—and therefore not powered—to address the question of acute kidney injury after application of contrast material. Accordingly, we lack statistical power to conclusively elucidate the underlying mechanisms of acute kidney injury, and our results may prompt larger investigations. Furthermore, despite being part of the study protocols, many blood samples for testing were not obtained because of logistic reasons, which led to imbalanced sampling after the individual imaging tests. The availability of laboratory data may be subject to bias, although it is reassuring to note equal distribution among samples at various time points. We did not determine the impact of individual maximum radiographic contrast agent dose, given that almost all participants had normal baseline

Mayo Clin Proc Inn Qual Out ■ February 2021;5(1):46-54 ■ https://doi.org/10.1016/j.mayocpiqo.2020.08.012
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kidney function. Last, we excluded patients with preexisting renal failure, and our results therefore may not be applicable to this population.

CONCLUSION

Acute kidney injury after repeated exposure to iodinated contrast material within a few days is uncommon even among patients with risk factors for renal failure. It is conceivable that different mechanisms are responsible for acute kidney injury in patients undergoing noninvasive or invasive application of iodinated contrast agents. Larger, dedicated studies may provide further insights into the relationship of contrast material exposure and acute kidney injury.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CAAKI** = contrast-associated acute kidney injury; **CTA** = computed tomography angiography; **ICA** = invasive coronary angiography; **IQR** = interquartile range; **PCI** = percutaneous coronary intervention; **SE** = standard error

Grant Support: The parent studies (but not the present investigation) were funded by Canon (formerly Toshiba) Medical Systems. Contrast material for computed tomography imaging in CorE-64 and CORE320 was provided by Bracco Diagnostics.

Potential Competing Interests: Armin Arbab-Zadeh receives research grant support from Canon Medical Systems.

Correspondence: Address to Armin A. Zadeh, MD, PhD, MPH, Department of Medicine/Division of Cardiology, Johns Hopkins University, 600 N Wolfe St, Halsted 562, Baltimore, MD 21287-0409 (azadeh1@jhmi.edu; Twitter: @armin_zadeh).

ORCID

Armin Arbab-Zadeh: https://orcid.org/0000-0003-2516-9083

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