

## Association Between Acute Kidney Disease and Intravenous Dye Administration in Patients With Acute Stroke A Population-Based Study

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**Background and Purpose**—Computed tomographic angiography and conventional angiography provide timely vascular anatomic information in patients with stroke. However, iodinated contrast dye may cause acute kidney injury (AKI). Within a large, biracial population, we examined in-hospital incidence of new or worsening kidney disease in patients with stroke and its association with administration of intravenous dye.

**Methods**—All adult residents of the Greater Cincinnati/Northern Kentucky region with acute ischemic stroke or intracerebral hemorrhage who presented to an emergency department in 2010 were included. Prevalence of unsuspected kidney disease at the time of emergency department presentation and the incidence of AKI after admission in 2 groups of patients—those who did and those who did not receive intravenous dye—were determined.

**Results**—In 2010, 2299 patients met inclusion criteria (89% ischemic stroke and 11% intracerebral hemorrhage); mean age 69 years (SD 15), 22% black, and 54% women. Among these patients, 37% had kidney disease at baseline, including 22% (516/2299) in whom this was unsuspected. Two percent (2%; 15/853) of patients with baseline kidney disease developed AKI during the hospital stay. Of those with no baseline kidney disease, 1% (14/14467) developed AKI. There was no association between dye administration and new or worsening kidney disease.

**Conclusions**—Although 22% of patients in the Greater Cincinnati/Northern Kentucky stroke population had unsuspected kidney disease, the incidence of new or worsening kidney disease was low, and AKI was not associated with dye administration. These findings confirm single-center reports that the risk of severe renal complications after contrast dye is small. (*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.014603.)

**Key Words:** acute kidney injury ■ contrast media ■ diagnostic imaging ■ epidemiology ■ stroke

In patients with acute ischemic or hemorrhagic stroke, early vascular imaging is important for medical and interventional management. However, iodinated radiographic contrast media carries a risk of renal toxicity and decreased renal function.<sup>1,2</sup>

Contrast-induced nephropathy (CIN) is defined as acute renal failure occurring within 24 to 72 hours after the administration of iodinated radiographic contrast media that cannot be attributed to other causes.<sup>3</sup> CIN is uncommon in patients with normal preexisting renal function, but it occurs more frequently in patients with underlying renal disease, particularly diabetic nephropathy.<sup>4</sup> CIN accounts for 12% of all cases of hospital-acquired acute renal failure,<sup>2</sup> and its occurrence can be associated with worse outcomes and increased healthcare costs.<sup>5</sup> The safety of administering contrast without regard to

renal function in a patient with acute stroke is controversial and much of the evidence that exists is limited to single-center retrospective studies.<sup>6,7</sup> Given the advanced age and vascular risk factors of patients with stroke, it is possible that the incidence of CIN may be significantly higher in these patients and that CIN might lead to higher rates of poor outcomes. The risk of CIN is a common rationale for delaying vascular imaging until a serum creatinine has been obtained, thus delaying identification of large-vessel occlusions and interventional therapy, in the case of ischemic stroke. Yet within the stroke population, the rates of unsuspected kidney disease (patients with elevated creatinine despite no known history of chronic kidney disease [CKD]) and the risk of new or worsened kidney disease after contrast-based imaging remain unknown.

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We therefore used data from the GCNKSS (Greater Cincinnati/Northern Kentucky Stroke Study), a large population-based stroke incidence study to pose the following questions: (1) what is the prevalence of unsuspected kidney disease in patients with stroke at the time of presentation, and (2) how often was administration of iodinated contrast during cerebrovascular imaging, associated with acute kidney injury (AKI) or renal failure requiring dialysis during their hospitalization? These data may help practitioners assess the risk of the first-line vascular imaging during acute evaluation of patients with stroke.

## Methods

Details of the design and conduct of the GCNKSS have been described elsewhere.<sup>8</sup> Briefly, in calendar year 2010, all acute ischemic strokes and intracranial hemorrhages among the ≈1.3 million residents of the GCNK region were ascertained by identifying inpatient discharge *International Classification of Diseases-Ninth Revision* codes 430 to 436 at 15 area adult hospitals. We have previously found that residents in this population exclusively seek care at these hospitals.<sup>9</sup> All residents of the region ≥20 years of age with acute ischemic stroke or intracranial hemorrhage who presented to an emergency department and survived at least 2 days were included in this analysis. Medical records from the acute hospitalization were retrospectively reviewed by study nurses, and designation of stroke and stroke type were verified by study-physician review. Age, race, sex, stroke risk factors, admission serum creatinine (Cr), and vascular imaging were among the items included in the abstraction. Either history of CKD or elevated Cr at the time of presentation represented baseline renal insufficiency in this study. Undiscovered kidney disease was defined as a Cr ≥1.2 on presentation, without previous history of CKD or end-stage renal disease (ESRD) as provided by chart review or patient history. The decision of whether intravenous dye was administered hyperacutely was made by individual emergency department physician and individual physicians who are part of the University of Cincinnati Stroke Team based on their clinical judgment.

Our study methodology systematically reviews each patient's record for medical comorbidities, as detailed previously.<sup>10</sup> Development of an AKI during the hospital stay was defined as chart documentation of acute renal failure, new dialysis, or renal insufficiency documented in a patient with no previous history of such. Worsening kidney disease was determined by physician documentation of acute or chronic renal failure, new dialysis, or tunnel dialysis catheter insertion in patients with history of CKD or ESRD. Incidence of new or worsening kidney function was assessed and stratified by use of intravenous dye.

## Data Analysis

SAS, version 9.4 (SAS Institute, Cary NC) was used for analysis. Univariate analysis was used to examine distributions of continuous variables and frequency of categorical variables. *t* test and  $\chi^2$  analysis were used as appropriate to compare groups (those with versus without renal insufficiency, and those with and without use of dye). Results were used to determine potential predictors of unsuspected renal insufficiency; variables associated with unsuspected renal insufficiency at  $P < 0.20$  were included in the initial multiple logistic regression model. Fisher exact test was used to test the association of use of dye with new or worsening kidney function individually as numbers were too small for using multiple logistic regression analysis to examine multiple predictors of this outcome. Multiple logistic regression was used to examine the association of dye administration with the combined outcome of new or worsening kidney function, adjusting for the a priori chosen covariates of renal function at baseline, history of renal disease and age.

## Results

In 2010, 2299 patients among residents of the GCNK region who presented to an emergency department with acute ischemic stroke (89%) or intracranial hemorrhage (11%) met inclusion criteria for this analysis. The mean age was 69 years (SD 15); 22% of the cohort was black, and 54% were women. Among all 2299 patients, 283 (12%) had intravenous dye-based vascular imaging, and 853 (37%) had either history of kidney disease ( $n=337$ ) or elevated Cr ( $n=516$ ) at the time of presentation (Table 1). Older age, black race, male sex, history of diabetes mellitus, and history of hypertension were associated with the finding of CKD at baseline. Current smoking and intracranial hemorrhage were more prevalent in the group without CKD at baseline.

### Characteristics of Patients Stratified by Baseline Renal Function and Contrast Exposure

We evaluated differences in baseline characteristics between those who received contrast for vascular imaging and those who did not and stratified by baseline renal function (Table 2). We found that in the 1447 patients without baseline kidney disease, 204 (14%) received dye. Patients without baseline kidney disease who received dye were younger, had less hypertension, were more commonly current smokers, and were more likely to be men when compared with those without baseline kidney disease

**Table 1. Characteristics of Patients With Ischemic and Hemorrhagic Stroke in the Greater Cincinnati/Northern Kentucky Stroke Study of 2010, Stratified by Baseline Renal Function**

|                   | Total Population<br>( $n=2299$ ) | Without Kidney Disease at<br>Baseline ( $n=1446$ ; 62.9%) | With Kidney Disease at<br>Baseline ( $n=853$ ; 37.1%)* | <i>P</i> Value† |
|-------------------|----------------------------------|---|--|-----------------|
| Age, mean (SD), y | 69.3 (15.0)                      | 67.3 (15.3)   | 72.7 (14.0)  | <0.0001         |
| Race (black)      | 513 (22.3%)                      | 281 (19.4%)   | 232 (27.2%)  | <0.0001         |
| Sex (women)       | 1241 (54.0%)                     | 855 (59.1%)   | 386 (45.2%)  | <0.0001         |
| HTN               | 1853 (80.6%)                     | 1085 (75.0%)  | 768 (90.0%)  | <0.0001         |
| DM                | 775 (33.7%)                      | 410 (28.4%)   | 365 (42.8%)  | <0.0001         |
| Current smoking   | 629 (27.4%)                      | 429 (29.7%)   | 200 (23.4%)  | 0.001           |
| ICH               | 258 (11.2%)                      | 181 (12.5%)   | 77 (9.0%)  | 0.01            |

Data presented as mean (SD) or  $n$  (%). DM indicates diabetes mellitus; HTN, hypertension; and ICH, intracerebral hemorrhage.

\*Defined as either elevated creatinine ( $\geq 1.2$ ) on arrival or history of kidney disease.

†Comparison of patients with and without kidney disease at baseline.

**Table 2. Characteristics of Patients With Ischemic and Hemorrhagic Stroke in the Greater Cincinnati Northern Kentucky Stroke Study, Stratified by the Presence or Absence of Contrast Administration for Cerebrovascular Imaging**

|                   | Stroke Patients Without Kidney Disease at Baseline (n=1446; 62.9%) |                 |         | Stroke Patients With CKD or Elevated Cr at Baseline (n=853; 37.1%) |                |         |
|-------------------|--|-----------------|---------|--|----------------|---------|
|                   | Received Dye (n=204)   | No Dye (n=1242) | P Value | Received Dye (n=79)  | No Dye (n=774) | P Value |
| Age, y            | 58.2 (14.6)  | 68.8 (14.9)     | <0.0001 | 68.5 (13.4)  | 73.1 (14.0)    | 0.005   |
| Race (black)      | 45 (22.1%)   | 236 (19.0%)     | 0.31    | 16 (20.2%)   | 216 (27.9%)    | 0.15    |
| Sex (women)       | 100 (49.0%)  | 755 (60.8%)     | 0.002   | 33 (41.8%)   | 353 (45.6%)    | 0.51    |
| HTN               | 132 (64.7%)  | 953 (76.7%)     | 0.0002  | 72 (91.1%)   | 696 (89.9%)    | 0.73    |
| DM                | 49 (24.0%)   | 361 (29.1%)     | 0.14    | 33 (41.8%)   | 332 (42.9%)    | 0.85    |
| Smoking (current) | 77 (37.8%)   | 352 (28.3%)     | 0.006   | 24 (30.4%)   | 176 (22.7%)    | 0.13    |
| ICH               | 26 (12.8%)   | 155 (12.5%)     | 0.92    | 3 (3.8%)   | 74 (9.6%)      | 0.10    |

Data presented as mean (SD) or n (%). CKD indicates chronic kidney disease; Cr, serum creatinine; DM, diabetes mellitus; HTN, hypertension; and ICH, intracerebral hemorrhage.

who did not receive intravenous dye. In the 853 patients with baseline kidney disease, 79 (9%) received contrast. Patients with baseline kidney disease who received contrast were younger, but no other characteristics were significantly different between those receiving dye and those not receiving dye.

### Unsuspected Kidney Disease

In this population of 2299 patients with stroke, 1962 had no history of CKD. Using Cr of  $\geq 1.2$  on presentation as a definition of unsuspected renal insufficiency, 516 of these patients (26%) presented with unsuspected kidney disease (Table 3). Multivariable logistic regression analysis showed that older age, black race, male sex, hypertension, and diabetes mellitus were all independently associated with unsuspected kidney disease ( $R^2=0.14$ ). However, current smoking and stroke type were not statistically significant. Adjusted odds ratios are shown in Table 3.

Of the 516 patients with unsuspected kidney disease, 53 received intravenous contrast for vessel imaging. Comparison

of characteristics, between those who did and those who did not receive intravenous dye, revealed the only significant difference between groups was mean age (67.1 versus 72.8 years;  $P=0.003$ ), with older patients less likely to receive contrast.

Of note, 40 patients with a history of CKD had normal Cr on arrival, that is, they had unsuspected renal sufficiency.

### Incidence of New or Worsening Renal Insufficiency in Patients With Acute Stroke Stratified by Contrast Exposure

Only 29 cases (1.3%) of the total cohort (n=2299) had either AKI or worsening kidney disease. After adjusting for renal function at baseline, history of renal disease and age, the administration of dye was not statistically significant for increasing the odds of the outcome of acute or worsening kidney disease,  $P=0.69$ ; adjusted odds ratio, 1.125 (95% confidence interval, 0.42–3.70).

Those who developed new or worsening kidney disease were stratified by baseline renal function and by whether

**Table 3. Characteristics of Patients With Unsuspected Kidney Disease\* Within the GCNK Stroke Study (Greater Cincinnati/Northern Kentucky)**

|                   | Stroke Patients With No History of Kidney Disease at Baseline (n=1915†) |                                     |         |                              |
|-------------------|---|-------------------------------------|---------|------------------------------|
|                   | Serum Creatinine <1.2 (n=1399)  | Serum Creatinine $\geq 1.2$ (n=516) | P Value | Adjusted Odds Ratio (95% CI) |
| Age, y            | 67.3 (15.3)   | 72.2 (14.2)                         | <0.0001 | 1.20‡ (1.15–1.26)            |
| Race (black)      | 268 (19.2%)   | 130 (25.2%)                         | 0.004   | 1.82 (1.40–2.37)             |
| Sex (women)       | 847 (60.5%)   | 204 (39.5%)                         | <0.0001 | 0.32 (0.26–0.41)             |
| HTN               | 1045 (74.7%)  | 444 (86.0%)                         | <0.0001 | 1.70 (1.26–2.29)             |
| DM                | 391 (28.0%)   | 177 (34.3%)                         | 0.007   | 1.23 (0.98–1.56)             |
| Smoking (current) | 410 (29.3%)   | 142 (27.5%)                         | 0.44    | 1.19 (0.91–1.56)             |
| ICH               | 176 (12.6%)   | 49 (9.5%)                           | 0.06    | 0.70 (0.49–1.00)             |

Data presented as mean (SD) or n (%). CI indicates confidence interval; DM, diabetes mellitus; HTN, hypertension; and ICH, intracerebral hemorrhage.

\*Unsuspected kidney disease was defined as a patient who had no previous history of kidney disease, but who had a creatinine  $\geq 1.2$  on initial serum testing on presentation for acute stroke.

†47 patients with no baseline serum creatinine were excluded from this analysis.

‡Per 5-year increment.

contrast was administered for cerebrovascular imaging (Table 4). There was no significant difference in the incidence of new or worsening kidney disease between patients who received intravenous contrast for acute stroke vessel imaging and those who did not receive contrast. Of the 79 patients with baseline kidney disease who received dye, only 1 (1.3%) developed worsening renal function, compared with 14 (1.8%) of the 774 who did not receive dye. Among the 53 patients with unsuspected kidney disease who received intravenous dye, 1 (1.9%) had worsening creatinine during their hospital stay compared with 4 (0.9%) of the 463 who did not receive dye ( $P=0.42$ ). Independent predictors of new or worsening kidney disease among patients who received intravenous dye cannot be determined because of the small number of patients with the outcomes of interest. Similar proportions were seen in the group of patients with normal renal function at baseline, in which 3 (1.5%) of the 204 who received dye versus 11 (0.9%) of the 1242 who did not receive dye developed an AKI ( $P=0.43$ ).

None of the patients who had contrast-based cerebrovascular imaging developed AKI requiring dialysis during their hospitalization. Only 1 patient required new dialysis during stroke admission; this patient did not receive intravenous contrast.

### Discussion

In this population-based study, we found that although 1 in 4 patients presented with unsuspected kidney disease, the overall incidence of an AKI after intravenous contrast administration in patients with stroke was extremely low. These findings are consistent with previous single-center studies of contrast-induced nephropathy after cerebrovascular imaging in patients with acute stroke,<sup>11</sup> but have not been previously reported in a population-based analysis.

Previous studies estimate that the incidence of CIN from intravenous dye given in an emergency department for all diagnoses is  $\approx 7\%$  to  $11\%$ .<sup>12,13</sup> In a large, retrospective case-control study of 10121 patients who received low osmolar iodinated contrast media and 10121 control patients, a difference in nephrotoxicity was observed only in patients with estimated glomerular filtration rate (eGFR)  $<30$  mL/min per  $1.73$  m<sup>2</sup>. No difference was seen in the incidence of acute renal failure, dialysis, or death between groups in this study.<sup>14</sup> Furthermore, many studies have shown that kidney function usually returns to preexisting levels within 7 days,<sup>15</sup> and AKI after radiocontrast administration rarely requires acute

dialysis treatment.<sup>16</sup> Finally, a single-center study found that after adjusting for differences in presumed risk factors of CIN, noncontrast computerized tomographic scans were at equivalent risk of serum creatinine-defined AKI compared with recipients of contrast-enhanced computerized tomographic scans, regardless of baseline renal function,<sup>17</sup> suggesting that baseline kidney function alone may not be the best predictor for those who will go on to develop an AKI after receiving intravenous dye. Although these studies have similar conclusions, they were not limited to patients with stroke or to neurovascular imaging.

Because of the potential side effects, the American College of Radiology, the Canadian Association of radiologists, and the European Society of Urogenital Radiology have each published guidelines for intravenous contrast medium administration based on various and conflicting serum creatinine values. This practice translates into fewer intravenous contrast-based studies being completed at the expense of diagnostic accuracy.

With the recent publication of positive endovascular trials,<sup>18–21</sup> the need for hyperacute vessel evaluation and endovascular treatment is now the standard of care. The recent Focused Update of the American Heart Association Guidelines for the Early Management of Patients with Acute Ischemic Stroke Regarding Endovascular Treatment updated their imaging recommendations:

*If endovascular therapy is contemplated, a noninvasive intracranial vascular study is strongly recommended during the initial imaging evaluation of the acute stroke patient (Class I; Level of Evidence A).<sup>22</sup>*

Waiting for a creatinine on patients with acute stroke before administering contrast may significantly delay treatment and decrease the chance for a good outcome, given that a 45-minute delay in reperfusion translates to a 10% decreased likelihood of a good outcome.<sup>23</sup> Our data suggest that it is generally safe to administer contrast for cerebrovascular imaging because the incidence of CIN nephropathy is extremely low, even in patients with known CKD and the  $\approx 27\%$  of patients with stroke with unsuspected renal insufficiency.

There are limitations in the interpretation of our results because of their retrospective nature. Serial creatinine laboratory values were not collected and therefore clinical chart review and subjective data were used to define both CKD and AKI in this study. Despite this drawback, we are confident that the risk of missed dialysis patients is low. In addition, the

**Table 4. Kidney Disease–Related Outcomes in Patients With Normal Renal Function, Known Chronic Kidney Disease, and Unsuspected Renal Insufficiency Stratified by IV Dye Administration**

|                          | Normal Renal Function at Baseline<br>(n=1446) |                    |          | Baseline Kidney Disease*<br>(n=853) |                   |          | Unsuspected Renal Insufficiency<br>(n=516 of the 853) |                   |          |
|--------------------------|---|--------------------|----------|-------------------------------------|-------------------|----------|---|-------------------|----------|
|                          | Received IV Dye (n=204)                       | No IV Dye (n=1242) | P Value† | Received IV Dye (n=79)              | No IV Dye (n=774) | P Value† | Received IV Dye (n=53)                                | No IV Dye (n=463) | P Value† |
| Acute kidney injury      | 3 (1.5%)                                      | 11 (0.9%)          | 0.43     |                                     |                   |          |   |                   |          |
| Worsening kidney disease |   |                    |          | 1 (1.3%)                            | 14 (1.8%)         | 1.0      | 1 (1.9%)  | 4 (0.9%)          | 0.42     |

IV indicates intravenous.

\*Defined as either elevated serum creatinine on arrival or history of chronic kidney disease.

†Fisher exact test.

creatinine threshold used to define CKD in this study is lower than most definitions; yet we still found extremely low incidence of new AKI. Another important limitation is selection bias. Physicians were likely selecting healthier patients with stroke to receive intravenous contrast dye, which was reflected in the multiple differences in baseline characteristics between those who received and those who did not receive intravenous contrast. Furthermore, patients who died within 2 days, presumably the sickest patients, were not included, thus creating further selection bias. We are therefore unable to determine risk factors for CIN in all patients, and we can comment only on the complications among those selected to receive dye by the treating physicians. A prospective trial to answer this question is unlikely to be completed and ultimately the risk of renal failure must be weighed against the benefits of rapid assessment of the cerebrovasculature in patient's suspected of having an ischemic stroke.

### Conclusions

Data from a population-based epidemiology study do not show any increase in AKI in those receiving dye for imaging studies. Although further study is needed, our results support previous work showing low risk. Given the potential benefit of acute vascular imaging, available data suggest that concern the risk of contrast-induced nephropathy should not delay the first-line cerebrovascular imaging that may be useful for acute stroke therapy.

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