# Neurons Over Nephrons

## Systematic Review and Meta-Analysis of Contrast-Induced Nephropathy in Patients With Acute Stroke

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***Background and Purpose***—Because of the perceived risk of contrast-induced acute kidney injury (AKI), many centers require pre-imaging serum creatinine levels, potentially delaying care. We performed a systematic review and meta-analysis evaluating AKI rates in patients with acute ischemic stroke receiving computed tomographic angiography (CTA) and computed tomographic perfusion (CTP).

***Methods***—We searched MEDLINE, EMBASE, and the Web of Science through December 2016 for studies reporting on AKI in patients with acute ischemic stroke receiving CTA/CTP. Using a random-effects model, estimates were pooled across studies. Outcomes of interest were (1) the odds of AKI in patients receiving CTA/CTP versus noncontrast computed tomography, (2) overall rate of AKI and hemodialysis in patients with acute ischemic stroke undergoing CTA/CTP, and (3) the odds of CTA/CTP-associated AKI among patients with and without chronic kidney disease.

***Results***—Fourteen studies were included (6 case–control studies and 8 single-arm studies) with 5727 CTA/CTP and 981 noncontrast computed tomography patients. In case–control studies, AKI was significantly lower among CTA/CTP patients compared with noncontrast computed tomography patients (odds ratio=0.47; 95% confidence interval=0.33–0.68; $P<0.01$). Adjusting for baseline creatinine, there was no difference in AKI rates between groups (odds ratio=0.34; 95% confidence interval=0.10–1.21). The overall rate of AKI in CTA/CTP patients was 3% (95% confidence interval=2%–4%). The overall rate of hemodialysis in the CTA/CTP group was 0.07% (3 of 4373). There was no difference in AKI among CTA/CTP patients with and without chronic kidney disease (odds ratio=0.63; 95% confidence interval=0.34–1.12).

***Conclusions***—Nonrandomized evidence suggests that CTA/CTP are not associated with statistically significant increase in risk of AKI in patients with stroke, even those with known chronic kidney disease. (***Stroke*. 2017;48:1862-1868. DOI: 10.1161/STROKEAHA.117.016771.)**

**Key Words:** acute kidney injury ■ case-control studies ■ computed tomography angiography ■ creatinine ■ stroke



Noninvasive vascular imaging techniques, such as computed tomographic angiography (CTA) and CT perfusion (CTP), are becoming increasingly important in evaluation and triage of patients with acute ischemic stroke (AIS). In fact, recently published American Heart Association and American Stroke Association guidelines strongly recommend using CTA in evaluation of patients with AIS secondary to large vessel occlusion.[1] Evaluation of serum creatinine levels on arrival to the emergency department and before performing CTA/CTP has become an ingrained part of the workup of patients with AIS. Many centers have policies stating that CTA/CTP cannot be performed without a baseline serum creatinine level. However, waiting for these results to come back can cost the patient precious minutes and negatively impact neurological outcomes.[2] Furthermore, it is important to question whether or not it is justifiable to withhold a CTA or CTP, even in a patient with baseline chronic kidney disease (CKD) because of the perceived risk of acute kidney injury (AKI) secondary to contrast-induced nephropathy.

Although several studies have been performed to date evaluating the risk of AKI in patients with AIS undergoing CTA/CTP, the overall risks remain unclear, and there remains no change in practice patterns at most institutions.[3–18] We performed a systematic review and meta-analysis of the literature to (1) determine whether patients with AIS receiving CTA/CTP have higher rates of AKI than patients with AIS undergoing noncontrast computed tomography (NCCT) alone, (2) determine the overall rate of AKI among patients

Received January 18, 2017; final revision received March 24, 2017; accepted April 26, 2017.

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Guest Editor for this article was Gregory Albers, MD.

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***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.117.016771**

with AIS undergoing CTA/CTP, and (3) determine whether baseline CKD is a risk factor for AKI among patients undergoing CTA/CTP.

## Methods

### Literature Search

This systematic review adheres to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). A comprehensive literature search of Ovid MEDLINE, Ovid EMBASE, and the Web of Science from their inception through December 2016 was performed to identify studies evaluating rates of AKI/contrast-induced nephropathy in patients undergoing CTA or CTP for evaluation of AIS. Initial search terms were AIS, stroke, cerebrovascular accident, AKI, nephropathy, contrast-induced nephropathy, and iodinated contrast. We also search references from multiple articles to find additional studies on risk of AKI in patients with AIS undergoing CTA or CTP.

Identified studies from the literature search were then further evaluated for inclusion in the meta-analysis. For the purposes of this meta-analysis, both case–control (NCCT versus CTA/CTP) and single-arm studies only including patients who underwent CTA/CTP were included. Additional inclusion criteria were the following: (1) studies only including patients undergoing imaging evaluation for AIS, (2) studies with at least 50 patients in each treatment group (if case–control) or 50 patients in the CTA/CTP group (single arm), and (3) studies reporting separate outcomes for patients undergoing CTA/CTP and NCCT. Exclusion criteria were the following: (1) case reports, (2) studies not separating outcomes by contrast administration status, and (3) studies with <50 patients in a given treatment arm. One author reviewed the article for inclusion. After selection of the articles, the data were abstracted by 1 author.

### Risk of Bias Assessment

Risk of bias assessment of the studies was performed using a modified Newcastle Ottawa Scale. This is a tool used for assessing the quality of nonrandomized studies included in systematic reviews or meta-analyses. Each study is judged on 8 item categorized into 3 groups: (1) selection of the study groups, (2) comparability of the study groups, and (3) ascertainment of the outcome of interest.[19] Factors that would make a study at low risk of bias would include (1) well-defined selection criteria; (2) similar baseline creatinine values between groups; (3) similar rates of baseline CKD, diabetes mellitus, and other relevant comorbidities between groups; and (4) well-defined criteria for AKI.

### Baseline Data and Outcome Variables

For the purposes of this study, we sought to evaluate the following outcomes: (1) determine if patients with AIS receiving CTA/CTP have higher rates of AKI than patients with AIS undergoing NCCT alone, (2) determine the overall rate of AKI and hemodialysis among patients with AIS undergoing CTA/CTP, and (3) determine if baseline CKD is a risk factor for AKI among patients undergoing CTA/CTP.

We collected the following information from each study: definition of AKI, mean age for each group, mean baseline creatinine for each group, number of patients with baseline CKD in each group, any pre- or post-intravenous contrast intervention (ie, fluids, N-acetyl cysteine, etc), standard contrast load, and number of patients who received CTA/CTP who required hemodialysis. Data were also collected on mean change in creatinine at follow-up, but these data were not meta-analyzed.

### Statistical Analysis

From each case–control study, we extracted a 2×2 table for binary outcomes and group sample size. Random-effects model was used to perform meta-analysis and combine the results of individual studies into a pooled estimate.[20] The $I^2$ statistic was used to express the proportion of inconsistency that is not attributable to chance.[21] For example, $I^2$ value of 60% means that 60% of the inconsistency in results is not because of chance but rather because of real differences across the studies in terms of population, comorbidities, and settings. Meta-analysis results were expressed as odds ratio (OR) for binary outcomes. For the analysis of single-arm studies (ie, CTA/CTP group only), we used a random-effects meta-analysis for combining incidence rates. We planned to explore the impact of publication bias by constructing funnel plots and testing their symmetry if a sufficient number of studies (>20) was available.

Because none of the studies were randomized controlled trials, we were concerned about lack of similarity between the 2 study groups (ie, patients with worse creatinine receiving 1 of the 2 interventions). Therefore, we planned to conduct a study-level meta-regression in which the dependent outcome was the effect size of each study (log of the OR of the primary outcome, the odds of AKI), and the explanatory variables (independent variables) were the mean baseline creatinine of the study and the type of computed tomography (NCCT versus CTA/CTP). Studies were weighted in meta-regression using their precision. The results of the meta-regression were presented as an OR adjusted for baseline creatinine. Analysis was conducted using Stata 14 software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

## Results

### Literature Search

Initial literature search yielded 431 unique articles. On review of abstracts and titles, 401 articles were immediately excluded. Thirty-two articles were retrieved for full text evaluation, of which 14 met inclusion criterial. Of the 14 studies, 6 were case–control (CTA/CTP versus NCCT) studies in which both groups consisted of patients with stroke.[3–10,12,14–18] Eight studies were single-arm studies that examined the rates of AKI among patients receiving CTA/CTP. Six studies provided data on the rates of AKI among CTA/CTP patients with and without baseline CKD. The literature search flow diagram is provided in Figure 1.

In total, 6708 patients were included. Of these, 5727 received CTA or CTP and 981 received NCCT alone. The most common definition of AKI was a >25% increase in creatinine (10 of 14 studies). Mean baseline creatinine in the CTA/CTP group ranged from 0.9 to 1.2 and mean baseline creatinine in the NCCT group ranged from 1.0 to 1.4. Typical volume of iodinated contrast injected ranged from 70 to 200 cc with most studies in the range of 100 to 140 cc. Three studies were categorized as low risk of bias because of the fact that both CTA/CTP groups had similar baseline creatinine and similar rates of baseline CKD, well-defined outcomes, and near-complete long-term follow-up. The remainder of the studies was categorized as moderate risk of bias. No studies had a high risk of bias. Two studies had standardized hydration protocols for patients receiving CTA/CTP. These data are summarized in Table.

### Case–Control Studies

A total of 6 case–control studies were included in meta-analysis. Among case–control studies, all but 1 required baseline creatinine on admission. In the CTA/CTP group, 2.3% (70 of 3057, 95% confidence interval [CI]=1.8%–2.9%) of patients developed AKI compared with 6.3% (60 of 951, 95% CI=4.9%–8.1%) in the NCCT group. On meta-analysis, patients in the CTA/CTP group had lower odds of developing AKI than

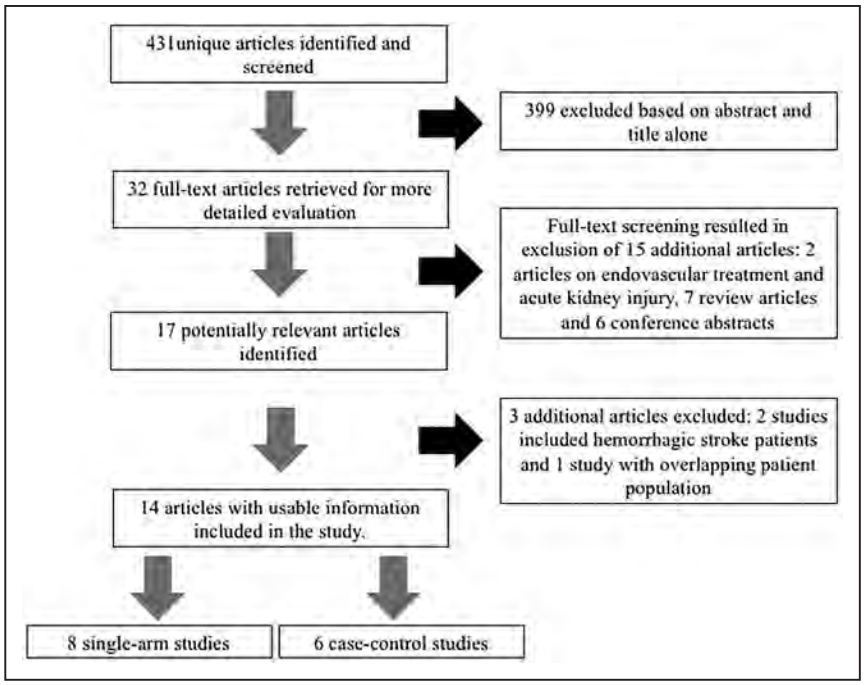


**Figure 1.** Literature search flow chart.

patients in the NCCT group (OR=0.47; 95% CI=0.33–0.68; $P<0.01$). $I^2$ value was 0% indicating no substantial heterogeneity. Forest plots are provided in Figure 2. Meta-regression adjusting for baseline creatinine demonstrated no difference in AKI rates between groups (OR=0.34; 95% CI=0.10–1.21). Inspection of the funnel plot (Figure 3) shows some asymmetry suggesting the possibility of publication bias (ie, studies showing lower incidence of AKI with CTA/CTP were less likely to be published). However, the number of studies included in this analysis was small (6 studies), making conclusions about publication bias unreliable.

### Incidence Rates in Uncontrolled Studies

Of the 5727 patients in the CTA/CTP group, 128 (2.2%) developed AKI. Random-effects meta-analysis found an overall AKI rate of 3.0% (95% CI=2.0%–4.0%) with an $I^2$ value of 65%, indicating substantial heterogeneity. Among studies reporting rates of hemodialysis following CTA/CTP, 0.07% (3 of 4373) of patients underwent hemodialysis. Forest plots are provided in Figure 4.

### Outcomes of Patients With and Without CKD

A total of 6 studies reported AKI rates of CTA/CTP patients with and without CKD. Among patients with CKD, the overall rate of AKI following CTA/CTP was 2.3% (14 of 609) compared with 3.7% for the non-CKD group (65 of 1780). On unadjusted meta-analysis, patients with CKD had similar odds of developing AKI than patients without CKD (OR=0.63; 95% CI=0.35–1.12; $P>0.05$). $I^2$ value was 74.9%, indicating substantial heterogeneity.

## Discussion

This systematic review and meta-analysis of >6000 patients found that the rate of AKI among patients receiving CTA/CTP for evaluation of AIS is low at ≈3%. Hemodialysis rates among patients with stroke receiving CTA/CTP are exceedingly low at 0.07%. When adjusting for baseline creatinine, patients in the CTA/CTP group had similar odds of developing AKI when compared with patients receiving NCCT alone. Interestingly, in our meta-analysis of CTA/CTP patients with and without CKD, there was no statistical difference in AKI rates between groups. These findings are important as they suggest that withholding or delaying acute stroke vascular/perfusion imaging because of creatinine values may be unnecessary.[22,23] Future randomized controlled trials are needed to confirm the results of this study.

Several large studies have been published which question the association between iodinated contrast administration and AKI. In a propensity score-based 1:1 matched analysis of 21 346 patients who received contrast-enhanced computed tomographies and NCCTs, one study found that the rates of AKI, emergent dialysis, and 30-day mortality were not significantly different between groups. Among patients who developed AKI, contrast exposure was not an independent risk factor for mortality or dialysis.[24] In a separate propensity score-matched analysis of 12 508 patients with contrast-enhanced and noncontrast-enhanced scans based on baseline glomerular filtration rate, one study found that there was no difference in the rates of AKI at multiple baseline glomerular filtration rate levels, including patients with a glomerular filtration rate<30 mL/min per 1.73 $m^2$.[25] Similar to the findings of our meta-analysis, one recently published meta-analysis of case–control studies found no difference in the rates of AKI, death, and dialysis among patients undergoing contrast-enhanced and noncontrast-enhanced computed tomographic examinations.[26] Our meta-analysis differs from these previously published studies because we studied the rates of AKI in a disease-specific population (AIS), which has a high prevalence of multiple cardiovascular risk factors that are associated with higher rates of renal dysfunction.

**Table. Included Studies**

| Author, Journal, Year | Study Design | n CTA/CTP: n NCCT | Definition AKI | Mean Baseline Cr, mg/dL CTA/CTP:NCCT | Standard Contrast Dose, cc | Mandatory Serum Cr Pre-CTA/CTP | Risk of Bias |
|---|---|---|---|---|---|---|---|
| Yeo et al, *Aktualnosci Neurologiczne*, 2016[3] | Case–control | 372:93 | >50% increase in Cr within 5 d | 0.9:1.0 | 70 | No | L |
| Ehrlich et al, *Stroke*, 2016[4] | Case–control | 157:132 | >25% increase in Cr within 2 d | 1.1:1.4 | 70–100 | Yes | M |
| Luitse et al, *Int J Stroke*, 2015[6] | Single arm | 731:NA | >25% or >44 μmol/L within 3 d | NA | NA | Yes | M |
| Ang et al, *Int J Stroke*, 2015[7] | Single arm | 623:NA | NA | 1.1:NA | 100–150 | Yes | M |
| Bill et al, *Eur J Neurol*, 2015[5] | Case–control | 1721:273 | >25% increase in Cr over baseline within 1 d | 1.0:1.3 | 50–150 | Unclear | M |
| Lima et al, *Am J Neuroradiol*, 2010[8] | Case–control | 575:343 | >25% increase in Cr over baseline | 1.0:1.2 | 100–140 | Yes | L |
| Aulicky et al, *JNIS*, 2009[9] | Case–control | 164:77 | Cr increase by ≥44 mmol/L within 24–72 h | 1.2:1.2 | 140 | Yes | L |
| Krol et al, *Stroke*, 2007[10] | Single arm | 224:NA | >25% increase in serum Cr within 5 d | NA | 75–100 | No | M |
| Matias-Guiu et al, *Neurologia,* 2014[12] | Single arm | 157:NA | >25% increase in Cr or increase in 0.5 mg/dL | NA | 100 | Unclear | M |
| Campbell et al, *JNNP*, 2013[14] | Single arm | 475:NA | NA | NA | 150–220 | Yes | M |
| Mehdiratta et al, *JSCVD*, 2008[15] | Case–control | 68:63 | >25% increase in Cr within 3 d | NA | 70–100 | Unclear | M |
| Langner et al, *AJNR*, 2008[16] | Single arm | 100:NA | >25% increase in Cr or increase in 0.5 mg/dL | 1.0:NA | 120 | Yes | M |
| Hopyan et al, *AJNR*, 2008[17] | Single arm | 198:NA | >25% increase in Cr within 3 d | 1.0:NA | 90–130 | Yes | M |
| Dittrich et al, *J Neurol*, 2007[18] | Single arm | 162:NA | >25% increase in Cr or increase in 0.5 mg/dL | 1.1:NA | 140 | Unclear | M |

AKI indicates acute kidney injury; Cr, creatinine; CTA/CTP, computed tomographic angiography/computed tomographic perfusion; L, low; M, medium; NA, not applicable; and NCCT, noncontrast computed tomography.

Understanding whether or not iodinated contrast is a risk factor for AKI in the stroke population is important for several reasons. First, several studies have demonstrated that renal dysfunction and AKI are risk factors for poor outcomes after AIS.[27–29] In a study of >4.5 million hospital admissions for AIS and intracranial hemorrhage from the Nationwide Inpatient Sample, Nadkarni et al[29] found that AKI was associated with an 18% higher likelihood of adverse discharge, including significantly higher rates of mortality. Given that poorer outcomes are seen in patients with AKI and stroke, identifying and eliminating risk factors for AKI are particularly important. Our results make it clear that the iodinated contrast required for CTA/CTP does not increase the risk of AKI in patients with acute stroke. Furthermore, this reassuring evidence is

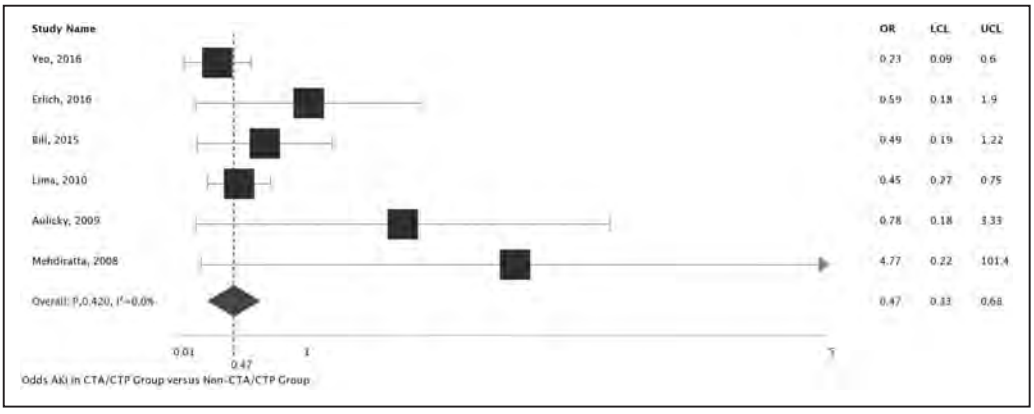


**Figure 2.** Meta-analysis of acute kidney injury rates: case–control studies. CTA/CTP indicates computed tomographic angiography/computed tomographic perfusion.

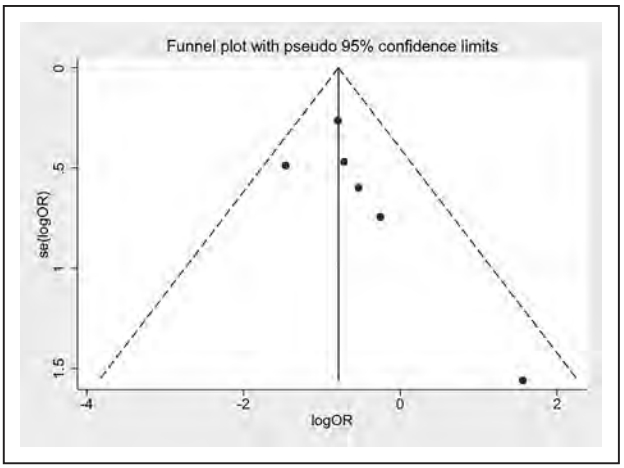


**Figure 3.** Funnel plot, acute kidney injury (AKI) rates: case–control studies. Inspection of the funnel plot shows some asymmetry suggesting the possibility of publication bias (ie, studies showing lower incidence of AKI with computed tomographic angiography/computed tomographic perfusion were less likely to be published). However, the number of studies included in this analysis was small (6 studies), making conclusions about publication bias unreliable. OR indicates odds ratio.

consistent as none of the studies included in this meta-analysis found an association between contrast administration and AKI.[3–10] Thus, physicians managing patients with stroke in the acute setting should not be feeling they are facing a dilemma between losing neurons or nephrons when ordering CTA/CTP because these contrast scans do not have a major deleterious effect on renal function.

It is conceivable that the contrast loads of a CTA or CTP examination added to those of angiography performed during mechanical thrombectomy could increase the rates of AKI among patients with AIS. However, 2 recently published studies have found that this is not the case.[30,31] In a study of 99 patients who underwent mechanical thrombectomy, many of whom had received pre-treatment CTA/CTP, Loh et al[30] found that the rate of AKI was just 3% and that the average creatinine change was just 4.6% at 48 hours post-operatively. In a study of 194 patients who underwent mechanical thrombectomy, Sharma et al[31] found that the rate of AKI was just 1.5% with none of the patients having permanent renal dysfunction as a result of treatment. The rates of AKI in these studies are similar to the overall rate of 2.4% seen in our meta-analysis, thus suggesting that CTA/CTP and mechanical thrombectomy probably do not result in any substantial increase in the risk of developing AKI.

## Limitations

Our study has limitations. First, none of the included studies were randomized controlled trials; consequently, many of the studies were likely affected by some degree of selection bias because it can be assumed that patients with known markedly elevated serum creatinine values were less likely to undergo CTA/CTP examinations than those with normal creatinine values. However, in subgroup analysis of patients with and without CKD, we still found no association between elevated baseline creatinine and risk of AKI among stroke patients undergoing CTA/CTP. Testing for publication bias suggested that studies showing lower incidence of AKI with CTA/CTP were less likely to be published. Therefore, publication bias is unlikely to change the conclusion of this meta-analysis about lack of association between contrast and AKI. There was some heterogeneity in the definitions of AKI between studies although most studies considered AKI to be defined as an increase in creatinine value of 25% from baseline. We conducted a study-level

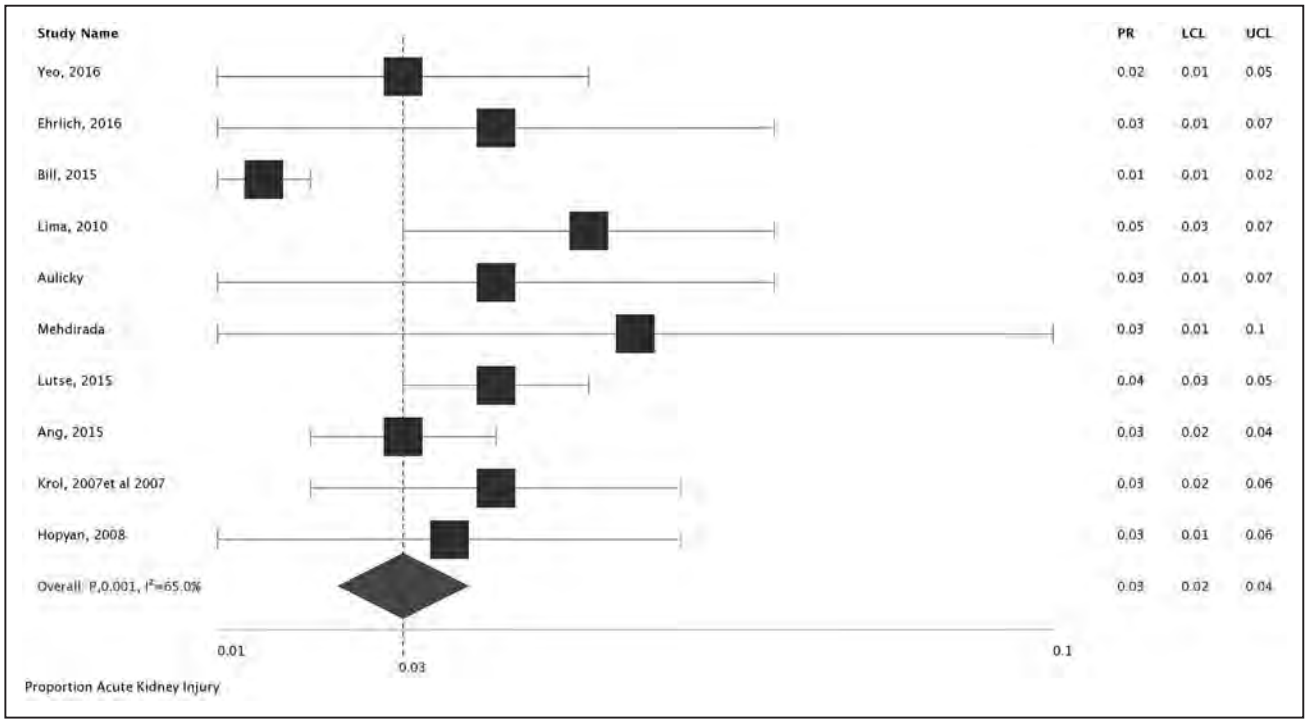


**Figure 4.** Meta-analysis of overall acute kidney injury rates.

meta-regression that is subject to ecological bias. In addition, there is heterogeneity in the amount of contrast dye administered, as well as the type/brand of contrast administered. Overall, the certainty in the present evidence is low because of the observational nature of studies and possible bias.[32]

## Conclusions

This systematic review and meta-analysis including >6000 patients found no association between contrast administration for CTA/CTP and development of AKI in patients with AIS. These findings suggest that delays in imaging and care because of absent or elevated creatinine values are not acceptable. Concern about AKI should not deter physicians from pursuing their optimal imaging strategy for the management of patients with AIS.

## Disclosures

Dr McDonald received research grant from GE healthcare (significant, >10% or 5%), and he is the advisory board member for Iodinated Contrast at GE Healthcare (no compensation). Dr Kallmes received research grant from GE Healthcare for separate but related project (significant, >10 K or 5%), and he is the member of Cost-Effectiveness Advisory Board for GE Healthcare (modest, <10 K or <5%). Dr Demchuk received honoraria for CME Events from Medtronic (significant, >10 K or 5%), and he is the member of advisory board for Pulse Therapeutics (modest, <10 K or <5%). He served as consultant for Neural Analytics (modest, <10 K or <5%). The other authors report no conflicts.

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