Controversies in Contrast Material–induced Acute Kidney Injury: Closing in on the Truth?[1]

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Intravascular iodinated contrast material has been causally associated with the development of subsequent acute kidney injury, termed contrast material–induced nephropathy (CIN), or, more specifically, postcontrast acute kidney injury, for more than 60 years (1–3). As recently as 2010, exposure to iodinated contrast material had been implicated as the third most common cause of acute kidney injury and was reported to significantly increase the risk of dialysis and death (4,5). Although the causal association between exposure to intravenous contrast material and nephrotoxicity has been considered by many to be incontrovertible, recent debate and clinical evidence have emerged that cause us to question the incidence, severity, and in some cases, the existence of CIN (6–8). Iodinated contrast media are among the most commonly prescribed agents in current medical practice, with more than 30 million doses administered annually (9). It is, therefore, essential that the highest-quality evidence be obtained to understand the true incidence and clinical relevance of CIN.

Much of the existing literature on CIN is confounded by a variety of factors. Animal models of CIN suggest several potential nephrotoxic mechanisms, including vasoconstriction, the formation of reactive oxygen species, and direct tubular toxicity (2,10). However, because these models are often based on exaggerated renal insults and contrast material doses in excess of those experienced by human patients, their physiologic relevance in humans is controversial. In human studies, the most salient criticism of the existing literature is that much of it originates from uncontrolled studies after coronary angiography (7). This poses a problem for two reasons. First, such studies lack an appropriate control group of patients not receiving contrast material, which is necessary to properly discern causation. Second, the iatrogenic potential of intracardiac studies to cause acute kidney injury unrelated to contrast material administration (eg, renal atheroembolization) limits the generalizability of these studies to intravenous contrast material administration (11).

Two causes of contrast material–independent elevations in serum creatinine (SCr) levels are most likely to obscure a diagnosis of CIN. First, Newhouse et al (12) demonstrated that the state of hospitalization is associated with a high incidence of contrast-independent acute kidney injury. In their study, hospitalized patients not given contrast material experienced elevations in SCr at a rate similar to the reported incidence of CIN. Subsequently, Moore et al (13) examined 100 inpatients who developed postcontrast acute kidney injury after contrast material–enhanced CT and determined that 99 of 100 patients had at least one acute risk factor for acute kidney injury other than administration of contrast material, and the median number of nephrotoxic risk factors per patient was five. These findings suggest that inpatients are almost always exposed to contrast-independent causes of acute kidney injury, and that, on a per-patient basis, CIN is indistinguishable from acute kidney injury that occurs for other reasons. Second, temporal fluctuations in SCr levels secondary to physiologic variation could be mistaken for CIN, depending on the timing of the taking of blood samples for SCr measurements and the degree of preexisting renal dysfunction. Intraindividual SCr variability is substantially increased in patients with severely compromised renal function, and it is this subgroup that is purportedly at greatest risk of CIN (14). These confounding issues are important to consider, because,

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to date, there are no prospective randomized controlled human studies confirming the causal nephrotoxic potential of modern low- or iso-osmolality iodinated contrast material for either intravenous or intracardiac administration. CIN has long been accepted as fact without clear causal evidence in human subjects (7,15). For these reasons, postcontrast acute kidney injury after exposure to iodinated contrast material must be examined in more rigorous studies to determine the true incidence and severity of this clinical phenomenon.

Meta-Analysis

Although much of the existing literature on CIN originates from investigations of cardiac angiography, 13 controlled studies of intravenous administration were identified in systematic reviews conducted by Rao and Newhouse (15) in 2006 and McDonald et al (16) in 2013. In these studies, the incidence of acute kidney injury in the contrast material–naive control cohorts was often significantly higher than that observed in the contrast material–exposed cohorts. This excess of contrast-independent acute kidney injury in the control cohorts was almost certainly a manifestation of treatment bias, because physicians were less likely to administer intravenous contrast material to individuals with the most compromised renal function. While such bias does diminish the strength of this evidence, it provided initial evidence that the incidence of acute kidney injury after exposure to intravenous contrast material was likely far lower than what had been reported previously.

Authors of these systematic reviews identified several limitations in the existing literature on CIN. First, most of the identified studies were of limited sample size, and therefore, were insufficiently powered to allow adequate detection of clinically significant differences in acute kidney injury rates among patients with compromised renal function. Second, the results of all of these smaller retrospective studies were subject to the effects of treatment bias. Therefore, future studies would require substantially larger sample sizes and more rigorous methods to mitigate selection bias to provide a more accurate assessment of the incidence of CIN.

Recent Studies

In 2013 and 2014, Davenport et al (17–18) and McDonald et al (19–20) published large controlled retrospective studies of postcontrast acute kidney injury after CT. Both groups used propensity score matching to mitigate treatment bias by simulating the randomization event that occurs in prospective randomized controlled studies. Both groups published results that were risk stratified according to the patient's baseline SCr level and baseline estimated glomerular filtration rate (GFR). After this propensity score adjustment, both groups were unable to identify a significant excess risk of CIN in patients with a baseline estimated GFR greater than 30 milliliters per minute per 1.73 m^2, translating to patients with Kidney Disease Outcomes Quality Initiative stages 1–3 chronic kidney disease. However, in patients with more severe chronic kidney disease (baseline estimated GFR $<$ 30 mL/min per 1.73 m^2, Kidney Disease Outcomes Quality Initiative stages 4–5), Davenport and colleagues (17) identified a significant excess of contrast material–associated acute kidney injury in the contrast-exposed group compared with the incidence of contrast-independent acute kidney injury in the control group that appeared to increase with worsening renal function (Fig 1). In contradistinction, McDonald and colleagues (19) were unable to identify a significant difference in the incidence of acute kidney injury between contrast-exposed and control groups in patients with baseline estimated GFR less than 30 mL/min per 1.73 m^2 (Fig 1).

The reasons for the divergent results in patients with baseline estimated GFR less than 30 mL/min per 1.73 m^2 could be explained by differences in the populations of patients with chronic renal disease, in institutional practice patterns in the treatment of patients with chronic renal failure, in preprocedural prophylaxis strategies, or in propensity score analysis methodologies. These and other hypotheses have been discussed in detail in other reviews (6,8,21). Nonetheless, in spite of their differences, the cumulative results from these large-sample studies from two large tertiary care centers suggest that the risk of CIN among patients with normal renal function and those with mild to moderate chronic renal impairment is extraordinarily low, if not zero. The divergent results in patients with severe renal impairment suggest that there may be some risk of CIN, but if so, this risk exists in a small subset ($<$ 5%) of all patients undergoing contrast-enhanced CT (22,23). These findings provide strong evidence that the incidence of CIN after intravenous iodinated contrast material administration is substantially lower than that previously suggested.

McDonald and colleagues (24) subsequently published a separate propensity score–adjusted study of the incidence of adverse clinical outcomes after administration of iodinated contrast material (24). In this study, the authors found that the propensity score–adjusted incidence of emergent dialysis and short-term mortality was not significantly different between patients exposed and those not exposed to intravenous iodinated contrast material. The presence of acute kidney injury was a significant risk factor for subsequent dialysis and 30-day mortality, but, as seen before in this population, this risk was found to be independent of contrast material exposure (Fig 2). These findings

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Abbreviations:
CIN = contrast material–induced nephropathy
GFR =glomerular filtration rate
SCr = serum creatinine

Conflicts of interest are listed at the end of this article.

See also the article by Nyman et al in this issue.

Figure 1

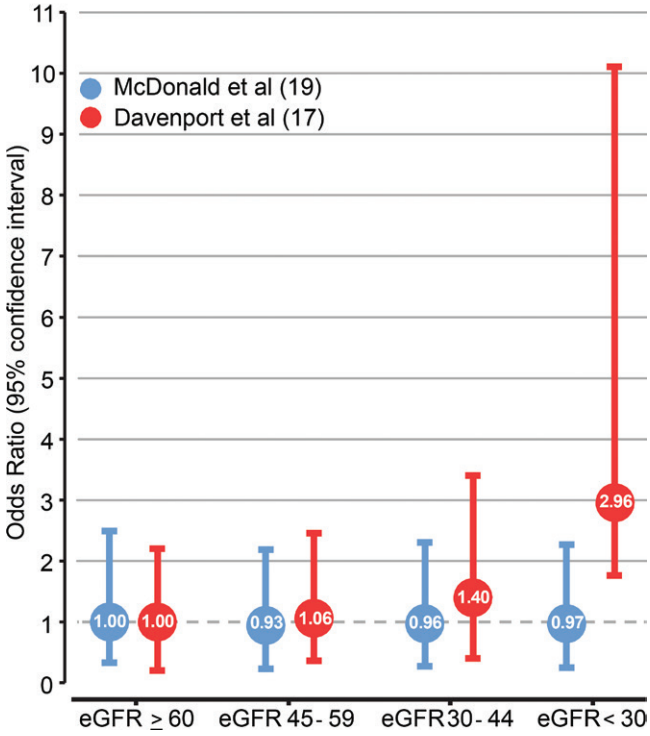

Figure 1: Reported odds ratios for acute kidney injury for contrast material recipients versus control patients for each estimated GFR (*eGFR*) subgroup in the McDonald et al (blue [19]) and Davenport et al (red [17]) studies.

help explain much of the confusion perpetuated by uncontrolled investigations of contrast material–associated clinical outcomes, in which much if not all of the significant risk of dialysis and mortality was likely inappropriately attributed to contrast material exposure. These results suggest that the clinical risks associated with CIN have been greatly overstated.

Ongoing Controversies

Despite the wealth of recent data indicating that intravascular iodinated contrast material is associated with significantly lower rates of acute kidney injury, morbidity, and mortality than previously thought, controversy surrounding these findings persists. The most significant criticisms of these recent data are related to methodologic concerns regarding their retrospective study designs, how propensity score adjustment may have altered the results, failure to control or account for periprocedural CIN prophylaxis measures, and the continued use of SCr level–based assays to detect nephrotoxicity.

Although retrospective, the recent studies by Davenport et al and McDonald et al were collectively far larger in sample size than were previously published studies, with more than 40 000 patients. Furthermore, despite slight methodologic differences in application of propensity score adjustment, both groups arrived at similar results that showed a greatly decreased incidence of CIN. Although propensity score adjustment might be perceived as statistical voodoo, the theory behind logistic regression that forms the basis of a propensity score is firmly established in mathematics and statistics as a robust method of bias reduction (25–27). As it relates to the study of postcontrast acute kidney injury, both groups built fairly robust propensity score models to mitigate treatment bias. Such models, while not exhaustive, provide a reasonable approximation of the variables used by physicians in the clinical decision-making process with respect to contrast material administration. As both groups clearly demonstrated, these models greatly reduced the covariate heterogeneity, and therefore, approximated the process of randomization. Furthermore, sensitivity analyses performed by McDonald et al (24) demonstrated through exhaustive iterative bootstrapping of multiple propensity score–matching methods that the observed findings are highly reproducible and not likely the result of anomalous logistic regression results.

Notwithstanding the results of these large propensity score–adjusted studies, there are challenges and limitations to examining causality through retrospective studies. Most notably, unmeasured differences between recipients of contrast material and control patients may have remained that confounded the link between contrast agents and kidney injury. However, three facts minimize this potential bias. First, in both large studies at separate institutions, separate investigators arrived at similar conclusions. Second, a subsequent study in which McDonald et al (28) incorporated numerous additional variables into their propensity score model, including year of CT scan and administration of intravenous fluid and medication, showed results similar to those of their prior studies. Third, the counterfactual analysis performed by McDonald et al (20) did not show a significant excess of postcontrast acute kidney injury in the contrast-exposed group that would have been expected with strong causal relationships. Retrospective studies are limited to available patients and to laboratory tests of renal function that were ordered during the course of routine clinical care. It is likely that patients in these studies with the greatest degree of renal dysfunction, and therefore the greatest purported risk of CIN, were receiving prophylactic measures (eg, isotonic volume expansion) expressly

Figure 2

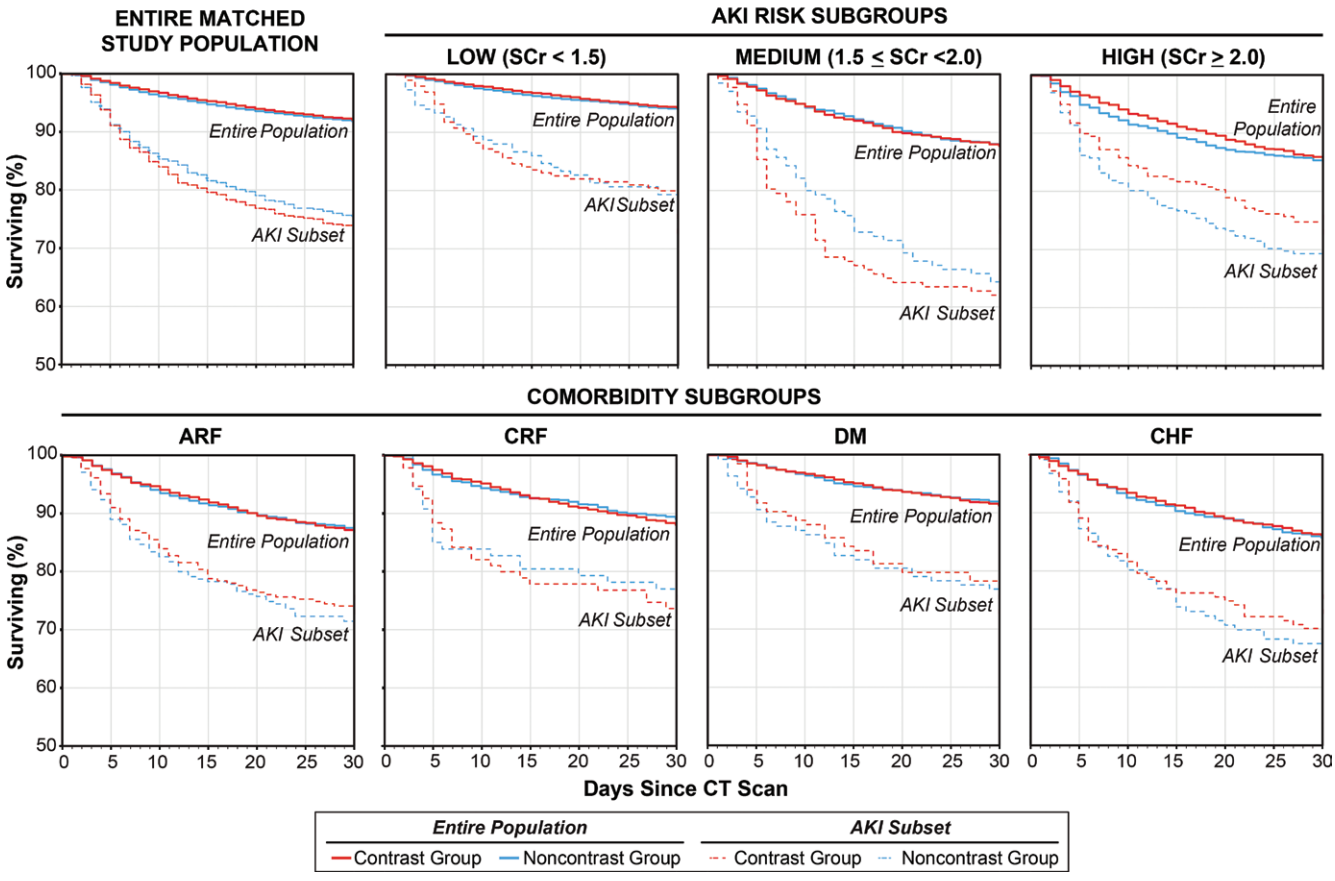

Figure 2: Survival analysis of contrast material recipients and propensity score–matched control patients for the entire population, acute kidney injury risk subgroups, and comorbidity subgroups as published in McDonald et al (24). For each analysis, survival was compared between contrast material recipients (contrast group, red line) and control patients (noncontrast group, blue line) for the entire population (solid line) and the subset of patients who developed acute kidney injury (dashed line). *AKI* = acute renal injury, *ARF* = acute renal failure, *CRF* = chronic renal failure, *DM* = diabetes mellitus, *CHF* = congestive heart failure.

to mitigate the likelihood of CIN occurring; therefore, such retrospective studies (regardless of size) do not directly inform a practice alternative in which no prophylactic measures are performed and no preprocedural renal function screening is conducted. Prospective randomized controlled trials are necessary to determine whether intravascular iodinated contrast agents cause kidney injury, and if so, in which patients. It would be informative to perform such studies with a combination of traditional SCr level–based assays (to allow comparison to prior studies and maintain relevance to clinical care) and novel renal biomarkers (to improve upon the weaknesses inherent to SCr-based assessments).

Point-Counterpoint

The concerns over the use of SCr level–based assays to detect and risk stratify nephrotoxicity raised by Nyman et al (29) are valid but not without caveats. SCr level–based assays of renal function are subject to variance from intrinsic physiologic, dietary, and fluid-related causes. While estimated GFR improves SCr levels by linearizing the distribution of renal function and controlling for race-, age-, and sex-based variation in SCr measures, it is also subject to the limitations inherent to measuring SCr levels (eg, unreliability in a nonsteady-state, physiologic variation) because it is ultimately derived from the same laboratory assay. Absolute GFR, an alternative calculated method of deriving GFR that is also based fundamentally on SCr, can be helpful for calculating the dose of a drug when a patient's body size is much larger or smaller than average (30,31).

However, in most patients, the estimated GFR and absolute GFR are similar with respect to chronic kidney disease classification (30), estimated GFR is a much more common measure of renal function in clinical work and in prospective trials, and in each of the aforementioned large propensity-adjusted studies, the dose of contrast material was fixed throughout estimated GFR classes. Measured GFR is the most direct method of determining

renal function, but it is too costly and time consuming to be used outside of specific prospective studies. In addition, although absolute and measured GFR may be more precise, there is no evidence that either allows more accurate prediction of postcontrast acute kidney injury risk compared with that with estimated GFR.

Nyman et al (29) note that newer sensitive biomarkers may be used to detect subclinical renal injury in the absence of traditional measurable changes in renal function; however, the clinical relevance of these findings is, thus far, conjecture. There is certainly no evidence that several such microinjuries lead to clinically relevant functional decline, and the absence of such data in subjects exposed to numerous doses of iodinated contrast material raises doubt about that possibility. Despite the limitations of the SCr level–based assay for the diagnosis and risk stratification of acute kidney injury, SCr level– and estimated GFR–based assessments remain the standard of care and are essential components of CIN studies (32,33). Furthermore, because CIN has been universally defined by changes in SCr level, we are obligated to investigate if SCr-defined CIN is a diagnosis of misattribution or a discrete clinical entity that can be verified by using appropriately designed controlled studies.

As important as investigating these issues may be, we feel it is important not to lose perspective about the real risks to our patients. By now it is apparent that the likelihood of CIN from intravenous administration of iodinated contrast material—whatever its exact incidence—is small, and the likelihood of clinically relevant renal damage is low in patients receiving current standard-of-care methods of prophylaxis. Given that many of the methodologic issues that have plagued studies of intravenous contrast material have so far yet to be addressed for coronary angiography, the risk of true CIN from intracardiac injection (separated from atheroemboli and other confounding factors) is unknown and likely also overstated. However, an unreasonable fear of CIN persists among radiologists and their referring colleagues. This fear often leads to withholding contrast material when it would otherwise be indicated without substantial regard for the diagnostic benefits it might impart. The American College of Radiology Appropriateness Criteria confirm what radiologists already know: intravascular contrast material significantly improves diagnostic sensitivity for many serious diseases. The danger of diagnostic error may, in many cases, be greater than the danger of intravascular contrast material, and we have a central duty to consider this. This not only requires that we modify our behavior, but that we educate our clinical colleagues about the results of recent investigations clarifying the negligible risk of CIN in most patients. In the risk-benefit analysis that should precede all medical tests, consideration must be given to both sides of the equation, with decision-making guided by fact instead of fear and misinformation.

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References

1. American College of Radiology. ACR Manual on Contrast Media. Version 9. http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/Contrast Manual/2013_Contrast_Media.pdf. Published 2013. Accessed October 14, 2013.
2. Seeliger E, Sendeski M, Rihal CS, Persson PB. Contrast-induced kidney injury: mechanisms, risk factors, and prevention. Eur Heart J 2012;33(16):2007–2015.
3. Stacul F, van der Molen AJ, Reimer P, et al. Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. Eur Radiol 2011;21(12):2527–2541.
4. Mitchell AM, Jones AE, Tumlin JA, Kline JA. Incidence of contrast-induced nephropathy after contrast-enhanced computed tomography in the outpatient setting. Clin J Am Soc Nephrol 2010;5(1):4–9.
5. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis 2002;39(5):930–936.
6. Davenport MS, Cohan RH, Khalatbari S, Ellis JH. The challenges in assessing contrast-induced nephropathy: where are we now? AJR Am J Roentgenol 2014;202(4):784–789.
7. Katzberg RW, Newhouse JH. Intravenous contrast medium-induced nephrotoxicity: is the medical risk really as great as we have come to believe? Radiology 2010;256(1):21–28.
8. Newhouse JH, RoyChoudhury A. Quantitating contrast medium-induced nephropathy: controlling the controls. Radiology 2013;267(1):4–8.
9. Solomon R. Contrast media: are there differences in nephrotoxicity among contrast media? BioMed Res Int 2014;2014:934947.
10. Wong PC, Li Z, Guo J, Zhang A. Pathophysiology of contrast-induced nephropathy. Int J Cardiol 2012;158(2):186–192.
11. Stratta P, Bozzola C, Quaglia M. Pitfall in nephrology: contrast nephropathy has to be differentiated from renal damage due to atheroembolic disease. J Nephrol 2012;25(3):282–289.
12. Newhouse JH, Kho D, Rao QA, Starren J. Frequency of serum creatinine changes in the absence of iodinated contrast material: implications for studies of contrast nephrotoxicity. AJR Am J Roentgenol 2008;191(2):376–382.
13. Moore A, Dickerson E, Dillman JR, et al. Incidence of nonconfounded post-computed tomography acute kidney injury in hospitalized patients with stable renal function receiving intravenous iodinated contrast material. Curr Probl Diagn Radiol 2014;43(5):237–241.
14. Ricós C, Iglesias N, García-Lario JV, et al. Within-subject biological variation in disease: collated data and clinical consequences. Ann Clin Biochem 2007;44(Pt 4):343–352.
15. Rao QA, Newhouse JH. Risk of nephropathy after intravenous administration of contrast material: a critical literature analysis. Radiology 2006;239(2):392–397.
16. McDonald JS, McDonald RJ, Comin J, et al. Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis. Radiology 2013;267(1):119–128.
17. Davenport MS, Khalatbari S, Cohan RH, Dillman JR, Myles JD, Ellis JH. Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material: risk stratification by using estimated glomerular filtration rate. Radiology 2013;268(3):719–728.

18. Davenport MS, Khalatbari S, Dillman JR, Cohan RH, Caoili EM, Ellis JH. Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material. Radiology 2013;267(1):94–105.

19. McDonald JS, McDonald RJ, Carter RE, Katzberg RW, Kallmes DF, Williamson EE. Risk of intravenous contrast material-mediated acute kidney injury: a propensity score-matched study stratified by baseline-estimated glomerular filtration rate. Radiology 2014;271(1):65–73.

20. McDonald RJ, McDonald JS, Bida JP, et al. Intravenous contrast material-induced nephropathy: causal or coincident phenomenon? Radiology 2013;267(1):106–118.

21. Davenport MS, Cohan RH, Ellis JH. Contrast media controversies in 2015: imaging patients with renal impairment or risk of contrast reaction. AJR Am J Roentgenol 2015;204(6):1174–1181.

22. Davenport MS, Khalatbari S, Cohan RH, Ellis JH. Contrast medium-induced nephrotoxicity risk assessment in adult inpatients: a comparison of serum creatinine level– and estimated glomerular filtration rate–based screening methods. Radiology 2013; 269(1):92–100.

23. Herts BR, Schneider E, Poggio ED, Obuchowski NA, Baker ME. Identifying outpatients with renal insufficiency before contrast-enhanced CT by using estimated glomerular filtration rates versus serum creatinine levels. Radiology 2008;248(1):106–113.

24. McDonald RJ, McDonald JS, Carter RE, et al. Intravenous contrast material exposure is not an independent risk factor for dialysis or mortality. Radiology 2014;273(3):714–725.

25. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46(3):399–424.

26. McDonald RJ, McDonald JS, Kallmes DF, Carter RE. Behind the numbers: propensity score analysis-a primer for the diagnostic radiologist. Radiology 2013;269(3):640–645.

27. Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med 1997;127(8 Pt 2):757–763.

28. McDonald JS, McDonald RJ, Lieske JC, et al. Risk of acute kidney injury, dialysis, and mortality in patients with chronic kidney disease after intravenous contrast material exposure. Mayo Clin Proc 2015;90(8):1046–1053.

29. Nyman U, Aspelin P, Jakobsen J, Björk J. Controversies in contrast material–induced acute kidney injury: propensity score matching of patients with different dose/absolute glomerular filtration rate ratios. Radiology 2015;277(3):633–637.

30. National Kidney Foundation. Frequently asked questions about GFR estimates. https://www.kidney.org/sites/default/files/docs/12-10-4004_abe_faqs_aboutgfrrev1b_singleb.pdf. Published 2014. Accessed March 1, 2015.

31. Nyman U, Björk J, Bäck SE, Sterner G, Grubb A. Estimating GFR prior to contrast medium examinations-what the radiologist needs to know! Eur Radiol 2015 May 28. [Epub ahead of print]

32. Ad-hoc working group of ERBP, Fliser D, Laville M, et al. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy. Nephrol Dial Transplant 2012;27(12):4263–4272.

33. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11(2):R31.