Controversies in Contrast Material–induced Acute Kidney Injury: Propensity Score Matching of Patients with Different Dose/Absolute Glomerular Filtration Rate Ratios[1]

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Two large retrospective observational studies recently published in *Radiology* have led to questioning or downgrading the risk of contrast material–induced nephropathy (CIN) from intravenous administration of low- and iso-osmolality contrast material (LOCM and IOCM) at, for example, computed tomography (CT) (1–5), compared with that stated in guidelines (6–8). However, we believe that CIN still must be regarded as a real phenomenon and that existing guidelines should not be changed. There are several methodologic concerns regarding the two mentioned studies that may render the conclusions farfetched: *(a)* the use of relative rather than absolute glomerular filtration rate (GFR) in risk stratification, *(b)* the use of unenhanced CT as comparison group, *(c)* contrast material dose in relation to renal function was not used in the risk evaluation, and *(d)* limited attention to results stratified according to nonrenal risk factors. In addition, meta-analyses of randomized controlled trials between LOCM and IOCM after intra-arterial coronary procedures show clear evidence that at least LOCM is nephrotoxic (9,10).

Risk Stratification according to Absolute Instead of Relative GFR

Both McDonald et al (2) and Davenport et al (4) used estimated GFR adjusted for body surface area (ie, relative GFR in milliliters per minute per 1.73 m^2) in their risk stratification. However, for drugs such as contrast material, which are eliminated according to linear kinetics, the area under the plasma concentration time curve is proportional to the injected dose and absolute GFR (ie, an individual's actual renal function expressed as filtration volume per time unit in milliliters per minute) (11). As an example, absolute GFR for plasma clearance of an injected marker in milliliters per minute (eg, iodine-based contrast material) is calculated by dividing the amount of the injected marker by the area under the curve (12); accordingly, the area under the curve is equal to the dose divided by the absolute GFR. The area under the curve is a fundamental parameter used to express systemic exposure of drugs excreted by means of glomerular filtration that often correlates well with the drug's efficacy and toxicity and is, as such, a critical link between dosing and clinical end points (11,13). Therefore, absolute GFR should be used for evaluation of toxicity of drugs excreted by means of glomerular filtration (14).

Stratifying the propensity score analysis based on relative GFR will introduce misclassification on the basis of one of the major predictors of postcontrast acute kidney injury: absolute filtration volume per time unit. Our own unpublished data from a GFR validation study (15) indicate that 27% of the women (median body surface area, 1.75 m^2) and 38% of the men (median body surface area, 2.00 m^2) with GFRs of 30–44 mL/min per 1.73 m^2 (moderate to severe chronic kidney disease) (6) were reclassified to another range when data were expressed as absolute GFR in milliliters per minute. Most men were reclassified to a higher GFR range when the data were expressed as absolute GFR, whereas women were more evenly reclassified in both directions. Thus, with the use of relative GFR, small women with low absolute GFRs may be stratified to the same group as that of large men with substantially higher absolute GFRs in a certain relative GFR range, although their risk of postcontrast acute kidney injury may be substantially different. The consequences are more salient

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if only creatinine levels are used in the stratification, as seen in Table 1 of the original article by McDonald et al (1), in which a clear majority of the patients in the medium- and high-risk groups were men. For this reason, and in addition to using absolute GFR, we advocate for separate propensity matching for men and women.

Propensity Matching according to Contrast Material Dose/GFR Ratio

McDonald et al (2) and Davenport et al (4) included patients who had undergone nonenhanced CT as control group when evaluating the risk of GFR, a comparison which was likely to introduce selection bias, and strategies to adjust for such bias have been thoroughly discussed by others (16–18). We are not convinced that the analytical approach used, propensity score matching on the likelihood of receiving intravenous contrast material, sufficiently removes selection bias, even if relative GFR is replaced with absolute GFR and the matching is conducted separately for men and women. Furthermore, authors of neither of the two studies included contrast material dose in the analyses, although this seems fundamental to the analysis of a toxic agent excreted by means of glomerular filtration.

In our opinion, a more appropriate approach is to restrict the analysis to the contrast material–enhanced CT group and propensity match patients at various absolute GFR ranges with different contrast material dose/absolute GFR ratios, with the ratio (which equals the area under the curve) reflecting the degree of potentially nephrotoxic exposure that the patient has received (11,19–22). Such propensity matching most likely reduces the problem of selection bias, since all included patients have received contrast material but at different dose/absolute GFR ratios. Ordinal regression analysis (23) can be used to model propensities for more than two levels of the contrast material dose/absolute or estimated GFR ratio. As an example, grams of iodine/absolute GFR ratio ranges of less than 0.5, 0.5–0.9, and greater than or equal to 1.0 may be used. An analysis of coronary studies indicates that a grams of iodine/GFR ratio exceeding 1.1 is a significant and independent predictor of postcontrast acute kidney injury, although the propensity approach was not used in these studies (24).

Results Stratified according to Nonrenal Risk Factors

The propensity score models in Davenport et al (4) and McDonald et al (2) can be used to identify factors that are associated with the likelihood of receiving contrast material. If CIN exists, then it would be most likely to occur in patients who have received contrast material despite the presence of nonrenal risk factors for which contrast material is contraindicated (ie, in patients with low propensity scores). Therefore, it is important to pay attention to results stratified according to propensity scores so that the effect of contrast material can be assessed in the presence of nonrenal risk factors at various absolute GFR intervals. McDonald et al (1) presented results stratified according to the propensity scores only in their first article ([1], Table E2 [online]) but did not comment on the specific results. The results for the median-risk group actually showed a significantly elevated risk for postcontrast acute kidney injury in the subgroup with the lowest propensity scores (odds ratio, 1.68; $P < .001$; 95% confidence interval: 1.35, 2.10). A similar elevation was not seen in the high-risk group, but here the subgroup with the lowest propensity scores was hampered by low statistical power. These results should, of course, also be treated with caution because of our other previously stated arguments.

Other Issues

In addition to the major concerns, there are also other issues that add to the uncertainty in the two mentioned observational studies (2,4). Adopting GFR equations requires local creatinine assay calibrations equal to those used when the equations were developed to avoid over- or underestimation of renal function (25,26) because of substantial interlaboratory variation in analytical results (27). According to our experience, this is consistently missing in articles on postcontrast acute kidney injury and also is not available in the studies by Davenport et al (4) and in that by McDonald et al (2) published before 2006 (after which McDonald et al used creatinine assays traceable to the international standard method, isotope dilution mass spectrometry). In addition, both the McDonald (2) and Davenport (4) groups collected their patient materials during a 10-year period during which shifts in creatinine calibration may have occurred (28). Changes in creatinine calibration may cause bias in the propensity score analysis if changes occur over time and the propensity matching does not include time. Another issue is the uncertainty of GFR estimations in general. Approximately 20%–30% of GFR estimations have an error exceeding 30% in relation to measured GFR, mainly large overestimations (15), which may lead to additional misclassification of GFR stages (14).

Existence of CIN and Guidelines

The weaknesses of the observational data at hand make it hazardous to disregard the risk of CIN. Meta-analyses of LOCM and IOCM at intra-arterial coronary procedures based on randomized controlled trials, providing a higher degree of evidence than observational

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Abbreviations:
CIN = contrast material–induced nephropathy
GFR = glomerular filtration rate
IOCM = iso-osmolality contrast material
LOCM = low-osmolality contrast material

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

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

studies, strongly indicate that at least LOCM are potentially nephrotoxic (9,10). Although meta-analyses of studies on intravenous administration of contrast material did not demonstrate any significant difference in postcontrast acute kidney injury between the use of LOCM and that of IOCM, patients at high risk (eg, those with unstable renal function, heart failure, hemodynamic instability, uncontrolled diabetes, recent examinations with contrast material enhancement) are often excluded (29–32).

The McDonald group (1) used IOCM for patients with serum creatinine levels greater than 2 mg/dL (177 μmol/L; an approximate GFR of <40 mL/min per 1.73 m^2) (2), and all others received LOCM. Although the authors argue that there are studies showing no difference between IOCM and LOCM, "no difference" does not necessarily prove similarity. Bruce et al (33) noted that LOCM had a higher incidence of postcontrast acute kidney injury at serum creatinine values greater than 1.8 mg/dL (159 μmol/L) than did IOCM and a control group not receiving contrast material. Thus, McDonald et al may have confirmed the results of Bruce et al that only IOCM may not have apparent nephrotoxic potential at contrast-enhanced CT. Observational studies that yield negative results should thus not be interpreted as the nonexistence of CIN. Another interpretation could be that contrast material is indeed nephrotoxic but that adoption of guidelines is sufficient to avoid the increased risk for kidney injury.

We also want to emphasize that defining postcontrast acute kidney injury in terms of a cut-off value (dichotomous; ie, a certain increase in serum creatinine level) may be misleading, because an increase to below the defined value may be interpreted as no injury to the kidneys. New concepts indicate that kidney injury may occur even in the absence of alterations in kidney function (ie, structural subclinical injuries that may be detected with new biomarkers [34]). Although authors of a few recent studies (35–37) of these new biomarkers have shown different results, one cannot exclude the possibility of injuring many nephrons each time contrast material is injected. Repeated contrast-enhanced examinations in patients with, for example, oncologic or vascular diseases theoretically may contribute to progressive diminished functional reserve of the kidneys even if filtration function appears unaltered each time. Studies are warranted to clarify this aspect of potential contrast material nephrotoxicity.

The recently published American College of Radiology guidelines (38) state that "there is very little evidence that intravenous iodine-based contrast material is an independent risk factor for acute kidney injury in patients with estimated GFRs greater than or equal to 30 mL/min per 1.73 m^2" and "if a threshold for CIN risk is used at all, 30 mL/min per 1.73 m^2 seems to be the one with the greatest level of evidence." However, considering (a) the highlighted methodologic weaknesses of currently available evidence, *(b)* that patients with GFR of 30–44 mL/min per 1.73 m^2 had a borderline risk of CIN according to Davenport et al (4), *(c)* the unreliability of GFR equations with approximately 20%–30% large errors, and *(d)* the possible effect of type and number of hitherto presumed nonrenal risk factors, we regard the present (eg, European [7] and Canadian [8]) guidelines as still appropriate for maintaining a reasonable safety margin in a risk-benefit analysis. These guidelines recommend that efforts to reduce the risk of CIN after CT be concentrated on patients with GFR of less than 45 mL/min per 1.73 m^2 (although an absolute GFR threshold should, in our opinion, be used, ie, < 45 mL/min) and patients with multiple nonrenal risk factors. GFR equations are only intended for patients with stable renal function and cannot be used in unstable conditions, because serum creatinine levels lag behind changes in renal function, as also pointed out in the American College of Radiology manual.

Finally, we wish to emphasize the lack of guidelines that include consideration of the actual contrast material dose used in relation to renal function for assessment of the risk of CIN (eg, grams of iodine/GFR ratio). Davenport et al (4) used approximately 40 g of iodine in most patients, and McDonald et al (1) used 25–60 g of iodine. Postcontrast acute kidney injury intra-arterial coronary procedures often occur with mean doses of 40–90 g of iodine (24). By using a low–tube voltage CT technique, possibly combined with hybrid iterative reconstruction, contrast material doses may be reduced substantially (39–41), (eg, from a median dose of 28–55 g of iodine at 120–140 kVp pulmonary CT arteriography [42] to 10 g of iodine at 80 kVp [39]). Thus, an 80-kVp technique may, to a large extent, solve the problem of performing CT in patients at high risk for CIN.

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