Renal Replacement Therapy for Prevention of Contrast-Induced Acute Kidney Injury: A Meta-Analysis of Randomized Controlled Trials

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**Key Words**
Renal replacement therapy · Contrast-induced acute kidney injury · Hemodialysis · Hemofiltration

**Abstract**

**Background:** Contrast-induced acute kidney injury (CI-AKI) is an important cause of acute renal injury. Several clinical trials using renal replacement therapy (RRT) for prevention of CI-AKI yielded conflicting results. We performed a meta-analysis to assess the efficacy of prophylactic RRT on CI-AKI.

**Methods:** Randomized controlled trials on CI-AKI using RRT were identified without language restriction in Cochrane library, Pubmed and Embase. Data extracted from literature were analyzed with Review manager and Stata software.

**Results:** Nine randomized controlled trials involving 751 patients were included. Heterogeneity was found across trials ($p < 0.00001$). A random effect model was used to combine the data. RRT reduced the risk of CI-AKI by 26% compared with the control group, but statistical significance was not reached (risk ratio (RR) 0.74, 95% CI 0.35–1.60, $p = 0.45$). Subgroup analysis of modality indicated that hemodialysis was ineffective in reducing the risk of CI-AKI (RR 1.21, 95% CI 0.63–2.32, $p = 0.57$), while CRRT decreased the incidence of CI-AKI (RR 0.22, 95% CI 0.07–0.64, $p = 0.006$). Subgroup analysis according to the CKD stage did not record heterogeneity across trials. RRT increased the odds of CI-AKI in CKD stage 3 patients (RR 1.53, 95% CI 0.07–0.64, $p = 0.01$), but decreased the occurrence of CI-AKI in patients with CKD stage higher than 3 (RR 0.74, 95% CI 0.35–1.60, $p = 0.45$). The pooled RR of the need for permanent dialysis demonstrated an insignificant trend towards benefit in patients treated with RRT (RR 0.61, 95% CI 0.26–1.40, $p = 0.24$). RRT reduced in-hospital mortality compared with control group (RR 0.33, 95% CI 0.14–0.77, $p = 0.01$).

**Conclusion:** RRT fails to reduce the incidence of CI-AKI in patients with more advanced renal function. CRRT is more effective than hemodialysis for prevention of CI-AKI. RRT is effective in reducing the in-hospital mortality of CI-AKI patients.

**Introduction**
Contrast-induced acute kidney injury (CI-AKI) remains the common cause of acute renal injury [1], which accounts for 5–50% cases of hospital-acquired AKI depending on the population studied [2, 3]. CI-AKI has been a subject of concern to cardiologists and nephrolo-
Because of its association with an increased risk of morbidity, mortality and potentially irreversible reduction of renal function [4]. To date, the best prophylactic measure of CI-AKI has not been established. Periprocedural hydration and the use of low osmolar contrast are considered to be helpful, while other agents, such as dopamine, calcium channel blocker and N-acetylcysteine, have not been proven effective [5]. However, hydration involves a relatively high volume of saline infusion, which may aggravate hypertension or cardiac failure, especially for patients with preexisting renal or cardiac impairment.

Another important approach for prevention of CI-AKI is the early initiation of renal replacement therapy (RRT) during or after the administration of contrast. Generally, CI-AKI is a benign process, and the necessity of hemodialysis is rare [6]. However, in patients with preexisting renal insufficiency and diabetic mellitus, up to 7% of patients may require transient hemodialysis or progress to ESRD [7]. Although contrast can be effectively eliminated by hemodialysis and hemofiltration [8, 9], it is still controversial whether RRT is able to reduce the incidence of CI-AKI. Several randomized controlled trials (RCTs) were conducted on this issue [10–18], but the results have been inconsistent.

A recently published systemic review by Cruz et al. [19] demonstrated that RRT was ineffective in reducing the occurrence of CI-AKI. However, this review included two nonrandomized trials [20, 21], and heterogeneity was noted across the trials. In the present study, we combined evidence from nine RCTs to obtain current estimate on the effect of RRT for prevention of CI-AKI.

**Subjects and Methods**

**Literature Search Strategy**

RCTs that tested the effect of RRT on CI-AKI were retrieved from Cochrane library, Pubmed and Embase from 1966 to June 2010. The key words used included hemodialysis, hemofiltration, contrast-induced nephropathy, CRRT, CVVH and CVVHDF. Details of the searching process are shown in figure 1.

**Inclusion and Exclusion Criteria**

The inclusion criteria were as follows: (1) chronic kidney patients who received hemodialysis or CRRT before or after the administration of radiocontrast; (2) RCTs. We excluded trials without placebo or control group, as well as trials not accessible to full research data.

**Data Extraction**

Two reviewers (K.S. and S.J.) independently extracted the data from the primary trials. The primary outcome was the risk ratio (RR) for CI-AKI in patients treated with RRT and the standard therapy with saline infusion. CI-AKI was defined as a rise in serum creatinine of 0.5 mg/dl (44 μM) or a 25% increase from baseline value at 48 or 72 h after the exposure to contrast medium, which is a widely used definition by many studies [9, 12, 16, 18–20]. Secondary outcomes were the RRs of permanent dialysis dependence between groups by the end of follow-up and the in-hospital mortality.

**Assessment of Methodological Quality**

We assessed the quality of the trials with specific criteria (sequence generation, concealment allocation, blinded assessment, incomplete outcome data assessment and free of selective reporting), rather than any scale with regard to the limitation of this method [22]. The assessment was performed by two clinicians (K.S. and S.J.) who worked independently. Disagreement was adjudicated by consensus.

**Statistical Analysis**

Data from the trials were combined to calculate the overall RRs of primary and secondary outcomes in patients treated with RRT, compared with those who received hydration. Heterogeneity across trials was evaluated with Q and I² statistic, defined as p heterogeneity <0.1 or I² >50%. If heterogeneity existed, a random-effect model was used to assess the overall estimate. Otherwise, a fixed-effect model was chosen. Meta-regression was used to explore the cause of heterogeneity. Publication bias was employed by Egger’s test.

All analyses were performed using Intercooled STATA, version 10.0 (Stata, College Station, Tex., USA) and Review Manager, v5.0 (RevMan; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The level of statistical significance was set at p < 0.05.
Results

Trials Included in the Meta-Analysis

Among the 147 papers retrieved, nine RCTs articles fulfilled the inclusion criteria [10–18]. The fifth trial [14] presented the data with the change of serum creatinine over time, rather than the incidence of CI-AKI. As a result, this trial was not included in the analysis of the incidence of CI-AKI, but was included to analyze the need of permanent dialysis between RRT and control group. The study presented by Reinecke et al. [18] compared the effects of hydration, hemodialysis and N-acetylcysteine. We only extracted data of the first two parts with 273 subjects. The selection process of the trials is shown in figure 1.

Characteristics of the Trials

Characteristics of the trials are reported in table 1. A total of 751 patients were enrolled. Different types of radiocontrast were used, most of which were hypotonic contrast. Table 2 shows the protocols of the RRT.

Effect on Incidence of CI-AKI

Internal heterogeneity was significant as evaluated by the $I^2$ statistic and Q test ($p$ heterogeneity <0.0001, $I^2$ = 84%; fig. 2). Thus, a random-effect model was used. CI-AKI occurred in 181 of 751 patients studied (24.1%). Patients treated with RRT had a lower incidence of CI-AKI (20%) compared with those in the control group (28%), but statistic significance was not reached ($p = 0.45$, 95% CI 0.35–1.60; fig. 2).

Sub-analysis of trials with hemodialysis resulted in a moderate intertrial heterogeneity ($p$ heterogeneity = 0.07,
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I^2 = 69%; fig. 3). Six out of seven studies demonstrated that hemodialysis did not reduce the risk of CI-AKI. The aggregate incidence of CI-AKI between hemodialysis and the control group was comparable (21 vs. 24%, p = 0.45, 95% CI 0.63–2.32; fig. 3).

Two trials used CVVH for preventing CI-AKI. Sub-analysis of this subgroup revealed a significant decrease in occurrence of CI-AKI compared with the control group (10.8 vs. 51.1%, p = 0.006; fig. 3). There was statistical heterogeneity among studies as evaluated by the I^2 statistic of 68%.

Sub-analysis of trials involving CKD stage 3 patients suggested a significant decrease in incidence of CI-AKI in the control group compared with the hemodialysis group (17.2 vs. 27.8%, p = 0.45, 95% CI 0.63–2.32; fig. 3). By comparison, trials with patients whose baseline CKD stage was over 3 showed that RRT decreased the incidence of CI-AKI compared with the control group (9.25 vs. 49.2%, p < 0.0001, 95% CI 0.08–0.43; fig. 3). Of interest, heterogeneity across studies was not found in these two analyses.

**Effect on Incidence of Permanent Hemodialysis**

Permanent hemodialysis was reported in five studies. Heterogeneity was not found among the trials (p heterogeneity = 0.11, I^2 = 48%; fig. 4). The RR of incidence of permanent dialysis between the HD and control group was insignificant (p = 0.24; fig. 4).

**Effect on In-Hospital Mortality**

In-hospital mortality was reported in four trials [13, 15, 16, 18]. As the intertrial heterogeneity was not significant, a fixed effect model was used. RRT for CI-AKI resulted in a lower in-hospital mortality compared with the control group (2.5 vs. 6.4%, p = 0.01, 95% CI 1.10–2.12; fig. 5).

**Meta-Regression**

Meta-regression was performed to assess the factors which may have resulted in heterogeneity. Of interest, this analysis suggested that heterogeneity was predominantly explained by the baseline CKD stage (coefficient −1.67, p = 0.01, 95% CI −2.32 to −1.02). Other meta-regres-
**Fig. 3.** Effect of baseline CKD stage on CI-AKI.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>RRT</th>
<th>Control</th>
<th>Weight</th>
<th>RR, random, 95% CI</th>
<th>Year</th>
<th>RR, random, 95% CI</th>
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<tbody>
<tr>
<td></td>
<td>events</td>
<td>total</td>
<td>events</td>
<td>total</td>
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<tr>
<td>1.2.1 Baseline CKD stage 3</td>
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<tr>
<td>Lehnert [10]</td>
<td>8</td>
<td>15</td>
<td>6</td>
<td>15</td>
<td>13.8%</td>
<td>1.33 (0.61, 2.91)</td>
</tr>
<tr>
<td>Sterner [11]</td>
<td>6</td>
<td>15</td>
<td>4</td>
<td>17</td>
<td>12.3%</td>
<td>1.70 (0.59, 4.90)</td>
</tr>
<tr>
<td>Berger [12]</td>
<td>3</td>
<td>7</td>
<td>1</td>
<td>8</td>
<td>7.6%</td>
<td>3.43 (0.45, 25.93)</td>
</tr>
<tr>
<td>Vogt [13]</td>
<td>24</td>
<td>55</td>
<td>20</td>
<td>58</td>
<td>15.2%</td>
<td>1.27 (0.80, 2.01)</td>
</tr>
<tr>
<td>Reinecke [18]</td>
<td>22</td>
<td>134</td>
<td>10</td>
<td>139</td>
<td>14.1%</td>
<td>2.28 (1.12, 4.64)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>226</strong></td>
<td><strong>237</strong></td>
<td><strong>62.9%</strong></td>
<td><strong>1.53 (1.10, 2.12)</strong></td>
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</tr>
<tr>
<td><strong>Total events</strong></td>
<td>63</td>
<td>41</td>
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<tr>
<td>Heterogeneity: $\chi^2 = 2.63$, d.f. = 4 (p = 0.62), $I^2 = 0%$</td>
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<tr>
<td>Test for overall effect: $Z = 2.54$ (p = 0.01)</td>
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<tr>
<td>1.2.2 Baseline CKD stage higher than 3</td>
<td></td>
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<tr>
<td>Marenzi [15]</td>
<td>4</td>
<td>58</td>
<td>32</td>
<td>56</td>
<td>12.7%</td>
<td>0.12 (0.05, 0.32)</td>
</tr>
<tr>
<td>Marenzi [16]</td>
<td>9</td>
<td>62</td>
<td>12</td>
<td>30</td>
<td>13.9%</td>
<td>0.36 (0.17, 0.77)</td>
</tr>
<tr>
<td>Lee [17]</td>
<td>2</td>
<td>42</td>
<td>18</td>
<td>40</td>
<td>10.5%</td>
<td>0.11 (0.03, 0.43)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>162</strong></td>
<td><strong>126</strong></td>
<td><strong>37.1%</strong></td>
<td><strong>0.19 (0.08, 0.43)</strong></td>
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<tr>
<td><strong>Total events</strong></td>
<td>15</td>
<td>62</td>
<td></td>
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<tr>
<td>Heterogeneity: $\chi^2 = 4.24$, d.f. = 2 (p = 0.12), $I^2 = 53%$</td>
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<tr>
<td>Test for overall effect: $Z = 3.90$ (p &lt; 0.0001)</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>388</strong></td>
<td><strong>363</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.74 (0.35, 1.60)</strong></td>
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</tr>
<tr>
<td><strong>Total events</strong></td>
<td>78</td>
<td>103</td>
<td></td>
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<tr>
<td>Heterogeneity: $\chi^2 = 43.86$, d.f. = 7 (p &lt; 0.0001), $I^2 = 84%$</td>
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<tr>
<td>Test for overall effect: $Z = 0.76$ (p = 0.45)</td>
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</tbody>
</table>

**Fig. 4.** Effect of RRT on permanent dialysis of CI-AKI.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>RRT</th>
<th>Control</th>
<th>Weight</th>
<th>RR, fixed, 95% CI</th>
<th>Year</th>
<th>RR, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>events</td>
<td>total</td>
<td>events</td>
<td>total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vogt [13]</td>
<td>3</td>
<td>55</td>
<td>2</td>
<td>58</td>
<td>22.7%</td>
<td>1.58 (0.27, 9.11)</td>
</tr>
<tr>
<td>Frank [14]</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>10</td>
<td>23.9%</td>
<td>1.43 (0.26, 7.86)</td>
</tr>
<tr>
<td>Marenzi [15]</td>
<td>2</td>
<td>58</td>
<td>11</td>
<td>56</td>
<td>32.6%</td>
<td>0.18 (0.04, 0.76)</td>
</tr>
<tr>
<td>Reinecke [18]</td>
<td>2</td>
<td>135</td>
<td>1</td>
<td>137</td>
<td>12.2%</td>
<td>2.03 (0.19, 22.12)</td>
</tr>
<tr>
<td>Lee [17]</td>
<td>0</td>
<td>42</td>
<td>5</td>
<td>40</td>
<td>8.5%</td>
<td>0.09 (0.00, 1.52)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>297</strong></td>
<td><strong>301</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.61 (0.26, 1.40)</strong></td>
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</tr>
<tr>
<td><strong>Total events</strong></td>
<td>9</td>
<td>21</td>
<td></td>
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<tr>
<td>Heterogeneity: $\chi^2 = 7.64$, d.f. = 4 (p = 0.11), $I^2 = 48%$</td>
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<tr>
<td>Test for overall effect: $Z = 1.17$ (p = 0.24)</td>
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</table>
sion analyses revealed that heterogeneity were not accounted for by study type (coefficient –1.74, 95% CI –3.78 to 0.29, p = 0.081) or membrane type (coefficient 1.50, 95% CI –3.54 to 0.54, p = 0.122).

**Assessment of Methodological Quality**

The quality of the included trials was relatively low (table 3). Most of the trials (77%) did not describe the specific methods of randomization. Those trials simply mentioned that patients were randomly selected. Only Marenzi’s trials used computer-generated random numbers. All trials used open-label design, as allocation concealment and blinding are impossible to perform in this kind of procedure.

**Publication Bias**

Egger’s test indicated that publication bias was insignificant (p = 0.792, 95% CI –5.3 to 4.22; fig. 6).

**Discussion**

Our meta-analysis revealed that RRT was unable to reduce the occurrence of CI-AKI in patients with renal failure in contrast to the saline infusion (p = 0.45, 95% CI 0.35–1.60; fig. 2). In addition, considerable heterogeneity across trials was found. Sub-analysis of RRT modality demonstrated that prophylactic hemodialysis could not reduce the incidence of AI-CKI, while CRRT exhibited a lower risk of CI-AKI.

A possible explanation for the detrimental effect of HD is that HD per se is a ‘renal toxic’ procedure [23]. Hy-
potenstion and the release of inflammatory factor during hemodialysis contribute to acute kidney injury. Removal of contrast media results in the alteration of osmotic pressure, leading to the extravascular shift of water, which can cause the depletion of volume. The subsequent activation of sympathetic nervous system might induce the ischemia of medulla, which may further aggravate the renal function [24].

The CRRT trials were both conducted by Marenzi and provoked considerable controversy. The first study was criticized for the methodological flaw using serum creatinine to evaluate the renal function and for the insufficient clearance of contrast with a low dosage of substitution solution [25]. Several potential reasons for the efficacy of CVVH, such as the use of heparin and bicarbonate-based solution, have been raised, but none of them seemed plausible. In 2006, Marenzi published a second trial with CRRT, in which he compared the effects of two hemofiltration protocols on CI-AKI. Pre/posthemofiltration was found more effective in lowering the occurrence of CI-AKI than posthemofiltration, indicating that high-volume controlled hydration before contrast media may explain the mechanism of the beneficial effect of CRRT [16].

As sub-analysis of modality did not eliminate heterogeneity, we performed meta-regression to explore the source of heterogeneity, which showed a relation between the RR of CI-AKI and the baseline CKD stage. We therefore analyzed the effects in the subgroups of baseline CKD stage 3 and higher. Interestingly, heterogeneity was not found in these subgroups. Patients in Lee and Marenzi’s studies represented a more severely ill population compared with other trials (CKD stage 4–5 vs. stage 3). The discrepancy of the selected population could account for the cause of heterogeneity. When analysis was restricted to studies involving CKD stage 3 patients, we recorded a significant increase in RR of hemodialysis (RR = 1.53, p = 0.01). This finding indicated that hemodialysis was ineffective, or even harmful for prevention of CI-AKI in this selected population.

By comparison, analysis of trials with patients involving CKD stage 4–5 revealed an overwhelming favorable effect of RRT over standard treatment in reducing the incidence of CI-AKI (RR = 0.19, p < 0.001). Patients in this population are more vulnerable to contrast injury and are unable to effectively eliminate contrast medium. As there were only three trials in this subgroup, further studies are needed to elucidate the effect of RRT in this population.

We also explored secondary outcomes which were irrelevant to serum creatinine. As expected, heterogeneity across trials was also found. The overall RR on the need for permanent HD was comparable between RRT and control groups (RR 0.61, 95% CI 0.26–1.40, p = 0.24; fig. 4). RRT did not exhibit beneficial effect on the need for permanent dialysis. However, in-hospital mortality was reduced by RRT (RR 0.33, 95% CI 0.14–0.77, p = 0.01; fig. 5). This favorable effect may be possible due to the inclusion of trials with CRRT, as a recent systemic review has confirmed that CRRT is able to reduce the mortality of critically ill patients [26].

Our meta-analysis has some limitations. Firstly, our conclusion may be underpowered as most of the eligible trials were small and many of them were of low quality. Secondly, most trials used serum creatinine to evaluate renal function. As RRT can decrease the level of creatinine, the use of creatinine may create a bias in the assessment of kidney function. However, as the definition of CI-AKI with creatinine is widely accepted by most references, it is impossible to avoid using this parameter. Two trials delineated the change of serum creatinine levels over time, which demonstrated that the serum concentration after RRT was decreased sharply in the first 24 h and progressively returned to baseline by 48 h [10, 13]. Four trials also used creatinine clearance or GFR to assess renal function, and showed no between-group difference in the occurrence of CI-AKI [12, 14, 17, 18]. Therefore, we held that the definition of CI-AKI with serum creatinine could not be viewed as unreasonable. In spite of this, studies presented with GFR are believed to be more appropriate to assess the effect of RRT on the incidence of CI-AKI.

In conclusion, our study suggested that RRT failed to reduce the incidence of CI-AKI in CKD stage 3 patients, but may be beneficial in patients with more advanced renal function. CRRT is more effective than hemodialysis for prevention of CI-AKI. Further studies, especially trials involving severely impaired renal function patients are needed to define the appropriate strategy for the application of RRT in CI-AKI patients.

References


To the Editor

We read with interest the meta-analysis by Song et al. [1] on renal replacement therapy (RRT) for the prevention of contrast-induced acute kidney injury (CI-AKI). In principle we agree that whatever benefit prophylactic RRT may offer, this is likely limited to a high-risk population with a high pretest probability of CI-AKI, including those with severe chronic kidney disease (CKD). While this seems quite intuitive, we might argue that this remains speculative and not borne out by the meta-analysis.

In table 1, the 9 studies are classified by CKD stage: 5/9 directly reported a mean estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl). Among these, the mean CrCl in Frank et al. [2] was 17.4–19.4 ml/min; such patients would be classified as stage 4 rather than stage 3 as erroneously indicated in table 1.

The remaining 4/9 studies reported only mean serum creatinine (sCr) values, mean age and genders of both study arms. We would presume therefore that CKD staging was performed by approximating eGFR based on these available data. Since all 4 studies were conducted in Europe, the subjects are likely to be predominantly Caucasian. If so, the lowest possible approximate eGFR would be obtained by using the higher mean age and sCr, selecting ‘male’ gender and sCr non-traceable by isotope dilution mass spectrometry. The highest possible eGFR would be obtained by using the lower mean age and sCr, selecting ‘female’ gender and sCr traceable by isotope dilution mass spectrometry. The range of imputed eGFRs would therefore be 13–19 [3], 11–26 [4], 16–28 [5] and 19–32 [6], ml/min/1.73 m². Therefore only the study by Lehner et al. [6] could conceivably be classified as CKD stage 3–4, while the others are stage 4. Song et al. inappropriately classified these studies as stage 3.

Furthermore, in figure 3 of Song et al. [1], they indicate the number of patients who develop CI-AKI for each study. The primary end point in the study of Lee et al. [7] was the change in CrCl between baseline and the fourth day; the incidence of CI-AKI was not among their reported end points. What they did report was that 18 patients in the control group and 2 in the RRT group had permanent renal damage with an increase in sCr >1 mg/dl or required permanent dialysis after discharge. Clearly this is not an end point that can be combined with the others in figure 3.

If the misclassification of CKD stages and the aberrant data abstraction for the study of Lee et al. are taken into consideration, the meta-analysis no longer demonstrates a differential effect between CKD stage 3 and CKD stage 4–5.

References