Extracorporeal Blood Purification Therapies for Prevention of Radiocontrast-Induced Nephropathy: A Systematic Review

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- **Background:** Radiocontrast-induced nephropathy (RCIN) causes acute kidney injury and increases mortality. Studies have examined the capacity of various forms of extracorporeal blood purification therapies for the prevention of RCIN, with conflicting results. We conducted a systematic review of published trials to determine whether periprocedural extracorporeal blood purification prevents RCIN.

- **Methods:** We searched PubMed, the Cochrane Collaboration Database, EMBASE, and CINAHL through January 2006 and bibliographies of retrieved articles and consulted with experts to identify relevant studies. Published studies of extracorporeal blood purification for the prevention of RCIN in patients receiving radiocontrast were included. Two authors reviewed all citations. The primary end point is the incidence of RCIN, defined as an increase in serum creatinine concentration (≥0.5 mg/dL [≥44 μmol/L]). Results were combined on the risk ratio scale. Random-effects models were used. Sensitivity analyses were performed to evaluate the effects of extracorporeal blood purification modality, study design, and sample size.

- **Results:** Eight trials (6 randomized controlled trials, 2 nonrandomized trials) were included in the analysis (pooled sample size, 412). Six trials assessed hemodialysis, whereas 1 trial each assessed continuous venovenous hemofiltration and continuous venovenous hemodiafiltration. The incidence of RCIN was 35.2% in the standard-medical-therapy group and 27.8% in the extracorporeal-blood-purification group. Extracorporeal blood purification did not decrease the incidence of RCIN significantly compared with standard medical therapy (risk ratio, 0.97; 95% confidence interval, 0.44 to 2.14); however, intertrial heterogeneity was high. Limiting analysis to only randomized trials did not eliminate heterogeneity, but limiting analysis to only hemodialysis trials did. Periprocedural hemodialysis did not decrease the incidence of RCIN.

- **Conclusion:** This critical analysis of the published literature suggests that periprocedural extracorporeal blood purification does not decrease the incidence of RCIN compared with standard medical therapy.


INDEX WORDS: Continuous renal replacement therapy; hemodialysis (HD); hemofiltration; meta-analysis; prevention; radiocontrast nephropathy.
of patients undergoing percutaneous coronary intervention, the incidence of RCIN was 3.3% overall and approximately 25% in patients with a baseline serum creatinine concentration of 2.0 mg/dL (177 μmol/L).5 Despite a high rate of recovery of renal function after RCIN, even small changes in serum creatinine concentration are associated with longer hospitalization and greater use of resources. Moreover, published data also strongly suggest an increase in mortality.5

Although the pathogenesis of RCIN has not been elucidated completely, a combination of renal ischemia and direct tubular epithelial toxicity is believed to be responsible. A direct toxic effect of radiocontrast on renal tubular epithelial cells is suggested by histopathologic changes, including epithelial cell vacuolization, interstitial inflammation, and cellular necrosis, as well as by increased excretion of enzymes in urine after contrast administration.6 Reactive oxygen metabolites may have a role in the pathogenesis of many renal diseases, and perhaps also in RCIN.7

Risk factors for RCIN include underlying kidney disease, diabetic nephropathy with renal insufficiency, advanced congestive heart failure or other prerenal state, multiple myeloma, and a high dose of radiocontrast agent.8,9 Radiocontrast nephropathy is decreased to some degree by limiting the volume of contrast used; periprocedural hydration (isotonic saline or isotonic sodium bicarbonate); use of low-osmolality or, more recently, iso-osmolar contrast agents; and withdrawal of agents that induce a prerenal state, such as diuretics, nonsteroidal anti-inflammatory agents, angiotensin-converting enzyme inhibitors, and angiotensin II type 1 receptor antagonist.8,9 In addition, although controversial, some clinical benefit may be gained with prophylactic use of N-acetylcysteine and theophylline.10,11

Radiocontrast media is excreted by the kidneys, and its elimination is delayed in patients with underlying kidney disease. For this reason, enhancing the total clearance of radiocontrast media with extracorporeal blood purification therapies is proposed as a potential method for the prevention of RCIN in patients with advanced kidney disease. Several studies showed efficient removal of radiocontrast through hemodialysis and, more recently, continuous renal replacement therapies (CRRTs).12,13 However, the ability of these therapies to prevent the occurrence of RCIN or any of its clinical sequelae is not clear. Conflicting results, mostly negative, exist regarding the utility of extracorporeal removal of radiocontrast (hemodialysis and CRRT) to prevent acute kidney injury. These results leave the clinician without a true recommendation for using this modality in the prevention of RCIN in high-risk patients. The Acute Dialysis Quality Initiative Workgroup adopted the term “extracorporeal blood purification” to refer to the use of extracorporeal therapies for nonrenal indications, from sepsis to end-stage liver disease.14 This term also can be used here because the therapies are being used for the prevention, rather than treatment, of acute kidney injury. This systematic review aims to describe the published experience with extracorporeal blood purification therapies for the prevention of RCIN, as well as the methodological quality of these studies, and estimate the magnitude of effect reported in these studies.

METHODS

Study Selection, Data Abstraction, and Validity Assessment

The search strategy and data abstraction were defined by using a prospective protocol. Radiocontrast nephropathy for the purpose of this review is defined as an increase in serum creatinine concentration of at least 0.5 mg/dL (44 μmol/L), the most common definition used in the literature. In addition, this degree of incremental increase in serum creatinine concentration was associated with increases in in-hospital mortality and length of hospital stay.15 All published studies that compared the incidence of radiocontrast nephropathy between groups of patients treated with periprocedural extracorporeal blood purification therapy versus standard medical therapy for the prevention of RCIN were eligible for inclusion. Trials that involved multiple experimental interventions were excluded. We performed a literature search without language restriction using the terms (radiocontrast) and (hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration), using databases through January 2006. Eligible trials were identified through PubMed, Cochrane Collaboration, EMBASE, and CINAHL. Full-text articles were retrieved for further assessment when any of the investigators considered a citation to be potentially relevant. We manually reviewed reference lists from review articles identified in the search, investigations meeting our inclusion criteria, and selected conference proceedings and consulted with experts in nephrology, cardiology, and radiology for other potentially relevant studies. Any trial deemed worthy of manual review was recorded. Trials with a nonrandomized design were eligible, but sensitivity analyses were performed later to
evaluate the effect of the experimental design. All data were extracted separately by 2 authors and results were compared; disagreements were resolved by consensus with the aid of a third party. Extracted data were recorded on a standardized form. If multiple publications existed by the same investigator, the studies were reviewed carefully and/or the investigator was contacted to ensure that no data were analyzed in duplicate. At least 3 attempts were made to contact the corresponding and/or first investigator. Methods included E-mail and mailed or faxed letters. Two investigators independently assessed trial quality by examining how well the allocation to intervention groups was concealed: A indicates adequate concealment of the allocation (eg, use of sealed opaque envelopes), B indicates uncertainty about whether the allocation was adequately concealed (eg, when the method of concealment is not stated in the report), C indicates the allocation definitely was not adequately concealed (eg, open random number lists or quasirandomization, such as alternate patients), and D indicates randomization was not used.16

**Outcome Measures**

The primary outcome is the pooled estimate of the risk ratio (RR) for RCIN, as defined, for patients treated with extracorporeal therapies for the prevention of RCIN compared with “standard” medical therapy. Some studies described changes in renal function or used a definition of RCIN that differed from our a priori definition. In such a case, we attempted to contact the investigators to ask for their primary data. Not all investigators provided the information requested. In some cases, updated information was available for inclusion. All patients were included in analyses irrespective of follow-up (intention to treat). If outcome data were missing, we used carry forward of the last-observed response. Because extracorporeal blood purification is an invasive and costly procedure, we considered it acceptable as a prophylactic measure for RCIN if a 15% absolute risk reduction could be achieved. Assuming a 35% incidence of RCIN in the standard-medical-therapy group, α of 0.05, and 80% power, a sample size of at least 151 subjects in each arm is needed.

**Data Analysis**

Data from eligible studies were combined by using a random-effects model. Intertrial heterogeneity was estimated by means of chi-square test. To evaluate effects of extracorporeal blood purification modality, study quality, and sample size, additional analysis was performed combining only trials using intermittent hemodialysis, randomized trials, and those with sample sizes of at least 20 in each group. Analyses were performed with Review Manager, version 4.2 (RevMan; The Nordic Cochrane Centre, The Cochrane Collaboration 2003, Copenhagen, Denmark). Level of statistical significance is set at P less than 0.05. Values for RR are expressed as a point estimate with 95% confidence intervals (CIs) and P. All RRs refer to risk for extracorporeal blood purification compared with standard medical therapy (labeled as “EBP” and “Standard” in graphs).

**RESULTS**

**Identification of Eligible Trials**

Seventy-eight abstracts were reviewed. Of these, 34 articles were deemed worthy of further exploration and retrieved for review. Five articles were either single case reports or deemed irrelevant. Fifteen studies were excluded because they evaluated only the clearance of contrast medium by dialysis using various filters, rather than clinical outcome. We identified 14 studies that compared renal outcomes between patients undergoing and those not undergoing extracorporeal blood purification for RCIN.13,17-29 Of these, 9 dealt with hemodialysis for the prevention of RCIN: 5 were randomized trials,17,18,20-22 and the sixth used a case-control design.19 The seventh study described results in the context of previous studies without their own comparison group and therefore was not eligible.23 The eighth study was a similar report in German of the same patients reported in an English language journal and also was excluded.24 The ninth article was a letter to the editor describing the outcome of some of the patients reported in a previous study.25 The remaining 5 studies dealt with CRRT, but 2 articles published by the same investigator involved the same patients in a randomized trial.26,27 There was a fourth article on CRRT for the treatment of patients with established acute renal failure caused by RCIN,28 and the fifth involved 2 variations of hemofiltration in separate treatment arms.29 These were not included in the analysis. Therefore, 6 hemodialysis studies (5 randomized controlled trials) and 2 CRRT studies (1 randomized controlled trial) were included in the final analysis (Table 1). Of the 6 hemodialysis studies, 1 expressed results in terms of mean change in renal function over time, rather than incidence of RCIN, and we were not able to retrieve additional data despite attempts to contact the investigators.18 It was not included in the analysis for the incidence of RCIN. However, it was included in the analysis for the need for acute temporary RRT and renal death.
Characteristics of Patients and Interventions

The 8 trials included 412 patients, 203 in the extracorporeal-blood-purification group and 209 in the standard-medical-therapy group. Of the 8 trials, all reported the mean age of patients (range, 57.6 to 72 years), 5 reported the proportion of men (range, 55.3% to 83.3%), and 8 reported the proportion of patients with diabetes (range, 29.8% to 64.7%). Characteristics of the included studies are listed in Table 1. Eligibility criteria in 1 study used different levels of serum creatinine for patients with and without diabetes (lower in patients with diabetes), and median baseline serum creatinine concentrations for each subgroup are listed in Table 1.21

Several types of radiological procedures were involved (Table 2); some patients underwent multiple procedures simultaneously.

Details of extracorporeal blood purification therapy are listed in Table 3. For the prevention of RCIN, a single session of periprocedural hemodialysis was performed with contrast exposure. In 1 study, hemodialysis was performed simultaneously with the radiocontrast procedure.18 In the 5 hemodialysis studies, mean or median delay time ranged from 63 to 106 minutes from contrast exposure to the beginning of hemodialysis.17,19-22 Heparin was used in at least 1 hemodialysis study17; use or nonuse of heparin was not mentioned in the others. In the 2 CRRT studies, modalities used were continuous venovenous hemodiafiltration (CVVHDF) performed simultaneously with the radiocontrast procedure13 and continuous venovenous hemofiltration (CVVH) that was initiated 4 to 6 hours before, interrupted during, and resumed after the radiocontrast procedure.26 In the standard-medical-therapy group, saline was administered in varying amounts: isotonic saline, 83 mL/h, for 12 hours before and after contrast20; 1 L 6 hours before and after contrast18; 1 mL/kg/h 12 hours before and after contrast22; 1 mL/kg/h 6 to 8 hours before and 24 hours after contrast26; 2 to 2.5 L of fluid orally or intravenously 12 hours before and in the 24 hours after contrast21; 0.45 sodium chloride, 1 L, 12 hours before contrast17; and not specified.13,19 Other renoprotective measures included administration of a calcium channel blocker if the patient was not already administered one,20,21 administration of aminophylline in 5 of 40 patients,19 and temporary withholding of such potentially nephrotoxic agents as angiotensin-converting enzyme inhibitors and metformin.18,21,22 No study reported administration of N-acetylcysteine.

Method Quality of Included Studies

Allocation concealment was deemed adequate in 2 trials17,26 and uncertain in 4 trials18,20,22 (Figs 1 to 3). The remaining 2 studies used a retrospective or historic control group.13,19

Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Year Published</th>
<th>Country of Origin</th>
<th>Radiocontrast Agent</th>
<th>Extracorporeal Blood Purification</th>
<th>Standard Medical Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No. of Patients/Mean Baseline Serum Creatinine*(mg/dL)</td>
<td>Technique</td>
</tr>
<tr>
<td>20</td>
<td>1998</td>
<td>Germany</td>
<td>Iopentol</td>
<td>15/2.58</td>
<td>HD</td>
</tr>
<tr>
<td>21</td>
<td>2000</td>
<td>Sweden</td>
<td>Iohexol, iodoxanol, ioxaglat</td>
<td>153.36-3.86*</td>
<td>HD</td>
</tr>
<tr>
<td>22</td>
<td>2001</td>
<td>Switzerland</td>
<td>Nonionic low-osmolality</td>
<td>55/3.58</td>
<td>HD</td>
</tr>
<tr>
<td>17</td>
<td>2001</td>
<td>Germany</td>
<td>Iopromid</td>
<td>7/2.9</td>
<td>HD</td>
</tr>
<tr>
<td>18</td>
<td>2003</td>
<td>Germany</td>
<td>Iomeprol</td>
<td>7/3.9</td>
<td>HD</td>
</tr>
<tr>
<td>13</td>
<td>2003</td>
<td>Italy</td>
<td>Ioversol</td>
<td>26/2.6</td>
<td>CVVHDF</td>
</tr>
<tr>
<td>26</td>
<td>2003</td>
<td>Italy</td>
<td>Iopentol</td>
<td>58/3.0</td>
<td>CVVH</td>
</tr>
<tr>
<td>19</td>
<td>2005</td>
<td>Taiwan</td>
<td>Iopromid</td>
<td>20/3.9</td>
<td>HD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>203</td>
</tr>
</tbody>
</table>

NOTE. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4.

Abbreviation: HD, hemodialysis.

*Different inclusion criteria for serum creatinine level for patients with and without diabetes; median value is given for each subgroup.

†Mean value not stated in report.
<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Angiography</th>
<th>Radiological Intervention</th>
<th>Amount of Contrast (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coronary</td>
<td>Renal</td>
<td>Cerebral/ Carotid</td>
</tr>
<tr>
<td>20</td>
<td>EBP, 13/15</td>
<td>EBP, 2/15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S, 14/15</td>
<td>S, 1/15</td>
<td></td>
</tr>
<tr>
<td>21†</td>
<td>EBP, 15/15</td>
<td>EBP, 13/58</td>
<td>EBP, 23/58</td>
</tr>
<tr>
<td></td>
<td>S, 17/17</td>
<td>EBP, 13/58</td>
<td>EBP, 13/58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S, 1/8</td>
<td>EBP, 0/7</td>
</tr>
<tr>
<td>22</td>
<td>EBP, 4/7</td>
<td>EBP, 2/7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S, 6/8</td>
<td>EBP, 0/7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S, 0/8</td>
<td>EBP, 1/7</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>EBP, 7/7</td>
<td>EBP, 1/7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S, 10/10</td>
<td>EBP, 1/7</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>EBP, 15/26</td>
<td>EBP, 11/26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S, 15/25</td>
<td>EBP, 11/26</td>
<td></td>
</tr>
<tr>
<td>13†‡</td>
<td>EBP, 58/58</td>
<td>EBP, 10/58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S, 56/56</td>
<td>EBP, 51/58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S, 8/56</td>
<td>EBP, 48/56</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td>EBP, 12/20</td>
</tr>
<tr>
<td></td>
<td>S, 1/20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EBP, extracorporeal-blood-purification group; NS, not stated in article; S, standard-medical-therapy group.

*Includes computed tomographic scan.
†Amount of contrast stated in grams.
‡An unspecified number of patients also underwent angioplasty.
§Data from a subset of 12 patients in whom pharmacokinetics of radiocontrast were studied.
||Some patients underwent multiple procedures.
Effects on RCIN

In 7 of 8 studies, the incidence of RCIN, defined as an increase in serum creatinine concentration of at least 0.5 mg/dL (44 μmol/L), was available from either the original publication or communication with the investigators. Incidence of RCIN was 35.2% in the standard-medical-therapy group and 27.8% in the extracorporeal-blood-purification group. Overall, extracorporeal blood purification did not appear to decrease the incidence of RCIN significantly compared with standard medical therapy (Fig 1; RR, 0.97; 95% CI, 0.44 to 2.14). For the study by Gabutti et al,13 although sample size for the CVVHDF group was 26, this included 2 patients who already had acute kidney injury from acute tubular necrosis who therefore were not included in the denominator for calculating the incidence of RCIN. However, they were included in analysis for other end points.

Intertrial heterogeneity was significant in this analysis (P = 0.0002). The analysis then was

Table 3. Treatment Details of Extracorporeal Blood Purification

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Time From Contrast Exposure to Start of Extracorporeal Blood Purification (h)</th>
<th>Duration of Extracorporeal Blood Purification (h)</th>
<th>Filter</th>
<th>Blood Flow (mL/min)</th>
<th>Dialysate Flow (mL/min)</th>
<th>Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>63 ± 6 min</td>
<td>3</td>
<td>Fresenius F50 (Fresenius Medical Care, Bad Homburg, Germany)</td>
<td>139 ± 8</td>
<td>500</td>
<td>NS</td>
</tr>
<tr>
<td>21</td>
<td>Maximum, 3 h</td>
<td>4</td>
<td>Low-flux cellulose acetate or diacetate</td>
<td>200</td>
<td>500</td>
<td>NS</td>
</tr>
<tr>
<td>22</td>
<td>120 min (median) 30-280 min (range)</td>
<td>3.1</td>
<td>Fresenius F50, F60 (Fresenius Medical Care)</td>
<td>180</td>
<td>500</td>
<td>NS</td>
</tr>
<tr>
<td>17</td>
<td>106 ± 25 min</td>
<td>2-3</td>
<td>Fresenius F6 (Fresenius Medical Care)</td>
<td>220</td>
<td>500</td>
<td>Heparin</td>
</tr>
<tr>
<td>18</td>
<td>0 (simultaneous)</td>
<td>4</td>
<td>Fresenius F60 (Fresenius Medical Care)</td>
<td>200</td>
<td>500</td>
<td>NS</td>
</tr>
<tr>
<td>13</td>
<td>0 (simultaneous)</td>
<td>10</td>
<td>Prisma M100 (Prisma, Hospal, Mirandola, Italy)</td>
<td>150</td>
<td>Replacement and dialysate 2,000 mL/h</td>
<td>Heparin</td>
</tr>
<tr>
<td>26</td>
<td>0*</td>
<td>22-30</td>
<td>Renalflow HF700 (Gambro, Mirandola, Italy)</td>
<td>100</td>
<td>Replacement 1,000 mL/h; no dialysate</td>
<td>Heparin</td>
</tr>
<tr>
<td>19</td>
<td>NS “as soon as technically feasible”</td>
<td>4</td>
<td>AM-Bio HX90 (Asahi Medical Co, Ltd, Tokyo, Japan)</td>
<td>200</td>
<td>500</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not stated in article.

*CVVH was started before, interrupted during, and resumed immediately after the radiocontrast procedure.

Fig 1. RR for RCIN: primary analysis.
repeated, limiting studies to randomized trials only (RR, 0.95; 95% CI, 0.34 to 2.60) and trials with sample sizes larger than 20 (RR, 0.60; 95% CI, 0.15 to 2.30). Intertrial heterogeneity remained significant in these secondary analyses (P < 0.0001 for both). We repeated the analysis, limiting the studies to those performing hemodialysis only, and intertrial heterogeneity became nonsignificant (P = 0.77). In this subgroup of 230 patients (hemodialysis, n = 112; standard, n = 118), a detrimental effect of hemodialysis on incidence of RCIN approached statistical significance, favoring standard medical therapy (Fig 2; RR, 1.35; 95% CI, 0.93 to 1.94).

**Effects on Need for Acute Temporary RRT and Renal Death**

Data for the need for acute temporary RRT were available from either the original publication or communication with the investigators (n = 412). The indication(s) for this in 1 study was oligoanuria for more than 48 hours despite administration of more than 1 g/24 h of intravenous furosemide or earlier in the event of concomitant overt heart failure. Unfortunately, specific indications for acute hemodialysis or hemofiltration were not mentioned in the other studies. Need for acute temporary RRT was 8.1% in the standard-medical-therapy group and 5.4% in the extracorporeal-blood-purification group. This analysis shows that extracorporeal blood purification did not significantly affect the need for acute dialysis (RR, 0.92; 95% CI, 0.09 to 9.30). Unfortunately, this event was rare, and in 5 studies, the need for acute temporary RRT was zero in both arms, severely limiting our ability to perform this analysis. In addition, intertrial heterogeneity was significant (P = 0.006). Because of the small number of trials in which the event occurred, no further analysis was carried out for this outcome.

Data for death and need for permanent RRT were available from 4 studies (284 patients). Incidences of renal death were 12.5% in the standard-medical-therapy group and 7.9% in the extracorporeal-blood-purification group.
icated that extracorporeal blood purification did not appear to decrease the incidence of renal death significantly compared with standard medical therapy (Fig 3; RR, 0.82; 95% CI, 0.27 to 2.47). Intertrial heterogeneity was not significant in this analysis ($P = 0.11$).

**Adverse Events**

Reported adverse events in the extracorporeal-blood-purification group were few and included clotting of blood tubing ($n = 1$), catheter dysfunction ($n = 1$), arteriovenous fistula formation at the access site ($n = 1$), bleeding at the vascular access site ($n = 3$), and need for blood transfusion ($n = 1$). In 1 study, 7 patients had palpable groin hematomas, but because this also was the site of the arterial catheter for the coronary angiogram, the exact location of the local bleeding could not be determined.

**DISCUSSION**

This review of 8 studies that included more than 400 patients treated in 5 countries compared the effect of extracorporeal blood purification with standard medical therapy for the prevention of RCIN. Extracorporeal therapies, such as intermittent hemodialysis, CVVH, and CVVHDF, did not appear to have a significant effect on either the incidence of RCIN or need for dialysis. As stated, because of the invasive nature of extracorporeal blood purification and costs involved in performing extracorporeal blood purification, we would consider it to be an acceptable prophylactic measure if it decreased the absolute risk for RCIN by 15%. This systematic review had adequate power to detect a risk reduction of this magnitude if it was present. However, intertrial heterogeneity was significant in these primary analyses. Limiting the analysis for the incidence of RCIN to randomized trials only or those with at least a modest sample size did not eliminate heterogeneity. However, in trials that performed only hemodialysis, heterogeneity became nonsignificant. With this analysis, there was a trend favoring standard therapy compared with prophylactic hemodialysis, but this failed to reach statistical significance. Because there were only 2 CRRT studies, with different study designs and CRRT modalities, we were unable to perform further analysis of this subgroup.

One confounding aspect to consider in these studies is the use of serum creatinine concentration to define the presence or absence of RCIN. Because extracorporeal therapies decrease serum creatinine concentration, this end point would favor extracorporeal blood purification over standard therapy. However, because the most commonly used definition of RCIN in the literature relies on the measurement of serum creatinine concentration, this aspect cannot be completely avoided in the context of a systematic review. Also, the cosmetic effect of hemodialysis or CRRT on serum creatinine concentration can be expected to persist for only a day after the treatment; thus, measurements at 48 to 72 hours after prophylactic dialysis or other extracorporeal blood purification procedure would not be unreasonable. In general, serum creatinine and blood urea nitrogen concentrations decreased in the first 24 hours after extracorporeal blood purification as a consequence of their removal by dialysis and ultrafiltration and, in the case of hemofiltration, simultaneous dilution of blood through fluid replacement. Thereafter, values progressively returned to baseline values. In at least 2 studies, some attempt was made to measure renal function by another method, such as 24-hour urine collection for creatinine clearance and plasma and renal clearance of iohexol, and likewise, there were no significant differences between the extracorporeal-blood-purification and standard-medical-therapy groups. Perhaps future studies using other renal function markers, such as cystatin C, or markers of acute kidney injury, such as kidney injury molecule 1, cysteine rich protein 61, or neutrophil gelatinase-associated lipocalin, would help elucidate matters.

We attempted to examine other relevant clinical end points that do not depend solely on measurement of serum creatinine. The need for acute temporary RRT increases both the length and cost of hospitalization and is associated with an increase in mortality. In terms of the need for acute RRT, this event occurred in only 3 of the included trials, which severely limited our ability to analyze this outcome. Two studies had point estimates of risk favoring standard medical therapy, but were not statistically significant. One CRRT study found a statistically significant decrease in the need for acute tempo-
rinary RRT in the group that underwent periproce-
dural CVVH.26 As expected, intertrial heteroge-
nity was significant in this analysis, and we did not find a significant difference between the extracorporeal-blood-purification and standard-
medical-therapy groups. Because of the limited data available for this particular end point, we did not attempt further analysis.

Other than mortality, another pertinent clinical end point is chronic kidney disease stage 5 requiring long-term dialysis treatment. Long-term dialysis therapy is associated with significant impairment in health-related quality of life. Moreover, long-term dialysis therapy is expensive, costing an average of US $69,751/year.34 Because the majority of this cost is from outpatient dialysis treatments, greater rates of renal recovery might save significant resources. We therefore tried to evaluate the effect of extracorporeal blood purification on renal death, defined as a combined end point of death and/or need for permanent RRT, and found no benefit.

One factor that may explain the low prophylactic value of extracorporeal blood purification in general might be a delayed start of treatment after contrast exposure. Hemodynamic changes induced by contrast medium are mediated by such rapidly released transmitters as oxygen free radicals and adenosine and occur within a few seconds of contrast administration.7 Histomor-
phic changes, such as vacuolization of tubular cells, are apparent 15 minutes after contrast me-
dium application.35 A dialysis that, for practical reasons, is initiated at least 30 minutes after contrast medium exposure might be too late for pathophysiologic reasons, especially in the case of time-consuming interventional procedures. This is 1 of the potential reasons that hemodialysis performed after radiological procedures has not improved the outcome. Even when the intent was to start hemodialysis “as soon as technically feasible,” the mean or median time from contrast procedure to initiation of hemodialysis reported in the literature ranges from 63 to 120 min-
utes.17,20,22 One study performed hemodialysis simultaneously with the radiological proce-
dure.18 Unfortunately, results of this study were reported as change in renal function over time, rather than incidence of RCIN. This study con-
cluded that although simultaneous hemodialysis significantly reduced the area under the curve of iomeprol, it did not affect peak plasma concentra-
tion or influence renal function or incidence of end-stage renal disease. However, 1 of the limita-
tions of this study is its small sample size (n = 17). In addition, simultaneous CVVHDF also did not show benefit.13 The incidence of RCIN in the CVVHDF group was reported as 37% versus 24% in a group of historic controls. In this study, ioversol removal by CVVHDF was believed to be modest. It was equal to the intrinsic renal removal of radiocontrast, with a mean ioversol urinary/CVVHDF extraction rate of 1.00 ± 0.46. However, only 1 dose of CVVHDF was studied. It is not clear whether greater ultrafiltration rates would have resulted in significantly better ioversol clearance and better clinical outcome.

On visual inspection, it is evident that the CVVH trial is a significant factor in heterogeneity among trials. To date, this is the only center in which extracorporeal therapy for RCIN yielded positive results. Other than a decreased likelihood of RCIN, this study also showed decreases in requirement for acute temporary RRT, in-house mortality, and 1-year mortality.26 Results differ from that of the CVVHDF study.13 The difference in results may be caused by differences in study populations, amounts of radiocontrast administered, the CRRT technique itself, or ancillary care. It is worth noting that the CRRT dose used in both studies is less than that recommended by our group for the treatment of patients with acute kidney injury.36 It was hypo-
thesized that heparin may be responsible for the clinical benefit seen in the study by Marenzi et al.26 Heparin was shown to inhibit acute inflammation, attenuate ischemia-reperfusion injury, and may have a suppressant action on oxidant stress.37 This does not seem to be a plausible explanation at this point because both CRRT studies and at least one of the intermittent hemodialysis studies also used hepa-
rin.13,17,26 Another potential explanation for the renal protective effect seen with hemofiltration is the use of an alkalinizing bicarbonate-based solution during hemofiltration, as suggested by a recent study.38 However, this seems less likely because bicarbonate-based solutions were used in both CRRT studies. The study by Marenzi et al26 also was criticized for the inequality of nursing care received by the extracorporeal-blood-purification and control groups because the former was in the intensive care unit, whereas the latter was in a stepdown unit.25,30 Although patient location was
not stated by Gabutti et al, it is plausible that a difference in location and/or staffing ratio also occurred in this study. At this time, reasons for the difference in observed clinical benefits in these 2 CRRT studies remain unclear. It is worth noting that Marenzi et al recently published a second randomized study showing a beneficial effect of CVVH performed before and after the contrast procedure on the incidence of RCIN, need for acute temporary RRT, and in-hospital mortality. The effect of postcontrast CVVH was less marked, but still appeared to decrease the need for acute temporary RRT and in-hospital mortality.

This review has potential limitations. Meta-analyses are observational by nature and therefore may be affected by bias or confounding. We performed a limited number of predefined subgroup analyses. Results of these analyses should be interpreted with caution, and prospective validation is needed before causal inferences can be made. Sample sizes of included trials generally are small: only 4 studies had at least 20 patients in each group, and of these 4 studies, only 2 studies used a randomized design. The small trials therefore may have generated false-negative conclusions because of random error alone. As mentioned, for this review, RCIN is defined as an incremental change in serum creatinine concentration, the value of which is affected directly by extracorporeal therapies and therefore may not be the best indicator of RCIN. In addition, another potential cause of acute kidney injury during angiographic procedures is multiple cholesterol emboli syndrome. The definition of RCIN used does not allow us to distinguish this from acute kidney injury caused by atheroembolic disease. Moreover, incremental increases in serum creatinine concentrations as small as 0.2 to 0.3 mg/dL (17.7 to 26.5 μmol/L) were associated with poor outcomes, particularly in cardiac populations. It is possible that our definition of RCIN set at an incremental increase of at least 0.5 mg/dL (44 μmol/L) was not sensitive enough to detect a difference between extracorporeal blood purification and standard therapy. However, as mentioned, this was 1 of the most common definitions used in the literature. Ideally, additional analyses should be performed looking at the effects of diabetes, severity of preexisting renal insufficiency, type of contrast procedure, and amount of contrast. However, the limited amount of published data precludes these subgroup analyses at this time.

Putting these data into perspective, this critical analysis found no difference in the incidence of RCIN between patients treated with periprocedural extracorporeal blood purification compared with standard medical therapy. The potential benefit of CVVH published by a single center should be confirmed with additional studies before it can be recommended or disregarded, and higher doses of CRRT also may merit further investigation. In addition, future studies should consider other novel extracorporeal blood purification techniques (sustained low-efficiency dialysis), as well as standard use of bicarbonate-based hydration and/or N-acetylcysteine in the medical-therapy arm. Last, because reactive oxygen metabolites are thought to have a role in the pathogenesis of RCIN, this also may suggest a potential role for extracorporeal blood purification using membranes that have the ability to inhibit lipid peroxidation by interacting with scavengers, such as vitamin E–coated dialyzers, in the prevention of RCIN.

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