META-ANALYSIS

Acute Renal Failure in the Intensive Care Unit: A Systematic Review of the Impact of Dialytic Modality on Mortality and Renal Recovery

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● **Background:** There is controversy about which dialytic modality should be used for the treatment of acute renal failure (ARF) in the intensive care unit. We performed a systematic review and meta-analysis to determine the relative risks (RRs) of mortality and renal recovery associated with intermittent hemodialysis (IHD) therapy compared with continuous renal replacement therapy (CRRT) in critically ill adults with ARF. **Methods:** Four databases (MEDLINE, Cochrane Library, Database of Abstracts and Reviews, and Science Citation Index), hand searching of conference proceedings and journals, manual review of bibliographies from identified articles, and contact with experts were used. All randomized trials (published or unpublished in any language) that compared mortality between intermittent and continuous treatments were eligible. Trials for which an RR for mortality could not be calculated or with multiple experimental interventions were excluded. Data were extracted separately by two authors and recorded on a standardized form. Disagreements were resolved by consensus. **Results:** Six eligible trials were identified; four of these provided data on renal outcomes. RR (mortality) for IHD was 0.96 (95% confidence interval [CI], 0.85 to 1.08; \( P = 0.50 \)), RR (renal death) was 1.02 (95% CI, 0.89 to 1.17; \( P = 0.78 \)), and RR (dialysis dependence) in survivors was 1.19 (95% CI, 0.62 to 2.27; \( P = 0.60 \); all compared with continuous therapy). Several sensitivity analyses did not change these results. Of the outcomes studied, the risk for dialysis dependence in survivors would be most sensitive to the addition of new trials. **Conclusions:** In comparison to IHD therapy, CRRT does not improve survival or renal recovery in unselected critically ill patients with ARF. Future studies should focus on well-defined subgroups of such patients using lessons learned from the trials in this meta-analysis. The high cost of chronic dialysis therapy and the relative instability of the RR for dialysis dependence suggest that future trials also should evaluate differences in renal recovery between dialytic modalities. Am J Kidney Dis 40:875-885. © 2002 by the National Kidney Foundation, Inc.

INDEX WORDS: Acute renal failure (ARF); hemodialysis (HD); meta-analysis.

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A CUTE RENAL failure (ARF) occurs in 20% to 25% of patients admitted to the intensive care unit (ICU) and is associated with adverse patient outcomes and high health care costs.\(^1\)\(^2\) For instance, a significant proportion of these patients will require dialysis therapy, with in-hospital mortality rates averaging 40% to 65%.\(^3\) Of patients who survive an episode of ARF in the ICU, 5% to 30% will remain on long-term dialysis therapy without renal recovery.\(^4\)

ARF in the ICU can be managed with intermit-
tent hemodialysis (IHD) therapy, in which intensive dialysis is performed for a few hours at variable intervals, or continuous renal replacement therapy (CRRT), during which treatment is performed continuously at lower blood flow rates.6 Although CRRT has several theoretical advantages compared with IHD,7 including enhanced hemodynamic stability, increased solute removal, and greater ultrafiltration capacity, individual randomized trials have not supported its superiority. Consequently, IHD continues to be widely used.8,9

Unfortunately, several such trials have not been published as full articles or appear to have baseline imbalances in illness severity between treatment groups despite randomization.10,11 At present, large practice variations exist with respect to the use of IHD and CRRT to manage ARF in the ICU,9,12,13 perhaps because of a lack of evidence about which therapy is superior.

We performed a systematic review and meta-analysis of published and unpublished randomized trials to quantify the relative risks (RRs) for mortality and renal recovery associated with IHD compared with CRRT in the treatment of ARF in the ICU. We also performed meta-regression to control for baseline differences in illness severity between treatment groups. Our goal is to synthesize the available information on this topic, with extensive use of sensitivity analysis to test the robustness of conclusions reached.

METHODS

Searching

We searched MEDLINE using the terms (kidney failure-acute OR “acute renal failure”) and (hemodialysis or haemodialysis or hemofiltration or haemofiltration), using databases from 1969 to January 2002. We also searched the Cochrane Library and the Database of Abstracts and Reviews using only the terms (kidney failure-acute OR “acute renal failure”). We manually reviewed reference lists from review articles identified in the search and examined abstracts of the major North American nephrology meeting (American Society of Nephrology) between 1990 and 2001. We used the Science Citation Index to identify investigations citing articles of interest. Tables of contents in four major nephrology journals and three major critical care journals were reviewed from January 2000 to January 2002 for articles that might be pertinent. Finally, we reviewed reference lists of investigations meeting our inclusion criteria for other potentially relevant studies. Any trial deemed worthy of manual review was recorded, as well as the reasons for subsequent exclusion (if applicable).

Selection and Data Abstraction

The search strategy and data abstraction were defined by a prospective protocol. To minimize effects of publication bias, all studies that compared mortality between contemporaneous groups of critically ill patients treated with CRRT and IHD for ARF were eligible for inclusion, whether published or unpublished. We did not restrict the search to the English language. Exclusion criteria were designed to reduce the risk for selection bias. Trials for which an RR for mortality or renal recovery could not be determined, that involved multiple experimental interventions, or that included children were excluded. Trials with a nonrandomized design were eligible for sensitivity analyses (discussed later), but were not used in assessment of the primary or secondary end points.

If multiple publications existed by the same investigator, the studies were carefully reviewed and/or the investigator was contacted to ensure that no data were analyzed in duplicate. Some studies did not contain all the required information; a note was made of this in the log to facilitate a later inquiry to the investigators. All data were extracted separately by two 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.

At least three attempts were made to contact the corresponding and/or first investigator on every included randomized controlled trial (RCT). Methods included mailed or faxed letters, E-mail, and telephone calls. Not all investigators provided the information requested. Data used in meta-analysis of RCTs was confirmed by five of the six original investigators. In some cases, updated information was available for inclusion.

Outcome Measures

The primary outcome was the pooled estimate of the RR for mortality for patients with ARF in the ICU treated with IHD compared with CRRT, obtained from RCTs only. The definition of mortality varied among studies (some used inhospital rates, and others used mortality at ICU discharge). We used these outcomes interchangeably in our analysis because the same definition was used for both arms of any given study. Although this may affect the estimate of the absolute risk for death in patients requiring dialysis therapy for ARF, it should not affect the difference in outcomes between treatments. If both in-hospital and ICU discharge mortality rates were available, the former was used. Intention-to-treat results were used when available.

Secondary outcomes included RRs for renal death (death or dialysis dependence at study end) and dialysis dependence among survivors. Renal death and the presence or absence of dialysis dependence among survivors were determined at hospital or ICU discharge, as available.

Validity Assessment

We attempted to assess the quality of each eligible study, using a previously validated instrument.14 Unfortunately, many studies had missing data or were only published in abstract form. Even after including information obtained directly from the investigators, we could not calculate these
scores appropriately in most cases. We therefore abandoned the attempt to use a composite scoring system to rate study quality. Instead, we provided qualitative details (when available) on methods likely to influence the internal validity of randomized trials.15

Assessment of Trial Heterogeneity

We plotted mortality rates for IHD against those for CRRT to visually inspect their distribution. The Q statistic was calculated to provide a numerical measure (and significance test) of heterogeneity for each analysis.16 This statistic tests the null hypothesis that the underlying effect measured by each of the pooled studies is equivalent. For $P$ less than 0.05 for $Q$, this assumption is invalid and heterogeneity exists.

Quantitative Data Synthesis

We first performed a funnel plot of sample size against RR (mortality) for nonrandomized trials.17 A funnel plot was not produced for randomized trials because of the small number of studies and because several of these studies were unpublished, making the plot difficult to interpret. Next, data from the 18 eligible studies were combined using fixed and random-effect (DerSimonian and Laird18) models. $P$ is reported for fixed-effects models if the $Q$ statistic suggested no heterogeneity of effect; in all other cases, random-effects models were used.

In addition to the primary and secondary outcomes (based on RCTs only), we also evaluated the effect of study quality on RR (mortality) by performing the modeling procedure in two additional groups: nonrandomized trials alone and all eligible trials. Because nonrandomized trials may be more likely to favor IHD (because sicker patients often undergo CRRT in clinical practice), this served as a form of sensitivity analysis for RR (mortality).19 We did not perform this analysis for renal outcomes because of the small number of nonrandomized studies with the requisite data.

We used random-effects meta-regression20 to control for baseline differences in mean Acute Physiology and Chronic Health Evaluation II (APACHE II) scores between treatment arms. Although RCTs do not normally require adjustment for baseline factors, it appears that significant differences in baseline factors exist in at least one RCT.21,22-40 Two potentially eligible studies were excluded because the CRRT group also underwent IHD41 or involved children.42 A number of seemingly relevant studies were multiple publications and therefore excluded. The remaining studies either did not compare IHD and CRRT directly or did not provide data on mortality or renal recovery.

Six studies were RCTs,21,25,33,35,37,40 of which 3 studies were published only in abstract form25,33,37; 2 studies, as full articles21,40; and 1 study, as a thesis.35 APACHE II scores were available for 11 studies. Information on individual studies is listed in Tables 1 and 2. Four studies used intention-to-treat analyses, and 1 study did not35 (this information was not available in one case33). Allocation concealment was adequate in 1 study,21 inadequate in a second study,40 and not assessed in the remainder.

Two RCTs excluded patients with severe hypotension,21,35 Timing of and indications for dialysis were determined clinically in most cases; one study each followed a detailed protocol for adjustment of vasopressors40 and dialysis dose.37 Delivered dialysis dose was equivalent between arms in two studies,25,37 apparently greater for CRRT in one study,21 and not available for the remainder. Dialysis membranes used in each arm were made of the same material in three cases25,37,40 and appeared to be of similar biocompatibility in one additional trial.35

Quantitative Data Synthesis

Meta-analysis (mortality). The funnel plot of N against effect size showed an absence of small nonrandomized studies that found RR (mortality) less than 1, suggesting at least some de-
<table>
<thead>
<tr>
<th>Reference</th>
<th>Publication Year</th>
<th>Country of Origin</th>
<th>IHD Technique</th>
<th>IHD No.</th>
<th>IHD APACHE II</th>
<th>IHD Mortality</th>
<th>IHD Renal Death</th>
<th>IHD Dialysis Dependence</th>
<th>CRRT Technique</th>
<th>CRRT No.</th>
<th>CRRT APACHE II</th>
<th>CRRT Mortality</th>
<th>CRRT Renal Death</th>
<th>CRRT Dialysis Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simpson and Allison&lt;sup&gt;33&lt;/sup&gt;</td>
<td>1993</td>
<td>UK</td>
<td>CUP membrane</td>
<td>58</td>
<td>NA</td>
<td>0.83</td>
<td>NA</td>
<td>NA</td>
<td>CAVHDF, CVVHDF, PS membranes</td>
<td>65</td>
<td>NA</td>
<td>0.71</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kierdorf&lt;sup&gt;35&lt;/sup&gt;</td>
<td>1994</td>
<td>Germany</td>
<td>PMMA membrane 6-7 × wk</td>
<td>52</td>
<td>24.8 ± 5.8</td>
<td>0.64</td>
<td>NA</td>
<td>NA</td>
<td>CVVHF, PAN membrane</td>
<td>48</td>
<td>26.0 ± 4.0</td>
<td>0.63</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sandy et al&lt;sup&gt;37&lt;/sup&gt;</td>
<td>1998</td>
<td>US</td>
<td>PS membrane, dialysis dose = CRRT 3.5 × wk</td>
<td>40</td>
<td>24.5 ± 7.7</td>
<td>0.60</td>
<td>0.87</td>
<td>0.69</td>
<td>CVVHD, PS membrane</td>
<td>39</td>
<td>21.4 ± 6.1</td>
<td>0.71</td>
<td>0.821</td>
<td>0.36</td>
</tr>
<tr>
<td>John et al&lt;sup&gt;40&lt;/sup&gt;</td>
<td>2001</td>
<td>Germany</td>
<td>PS membrane, dialytic technique not standardized</td>
<td>20</td>
<td>33 ± 4</td>
<td>0.70*</td>
<td>0.8*</td>
<td>0.33*</td>
<td>CVVHF, PS membrane, dialytic technique not standardized</td>
<td>10</td>
<td>34 ± 5</td>
<td>0.70*</td>
<td>0.8*</td>
<td>0.33*</td>
</tr>
<tr>
<td>Mehta et al&lt;sup&gt;21&lt;/sup&gt;</td>
<td>2001</td>
<td>US</td>
<td>CUP, CA, PMMA, PS, PAN membranes 5 × wk</td>
<td>82</td>
<td>20.6</td>
<td>0.48</td>
<td>0.634</td>
<td>0.07</td>
<td>CAVHDF/CVVHDF, PS or PAN membrane</td>
<td>84</td>
<td>25.3</td>
<td>0.66</td>
<td>0.667</td>
<td>0.14</td>
</tr>
<tr>
<td>Uehlinger et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>2001</td>
<td>Switzerland</td>
<td>PS membrane, dialysis dose = CRRT 5-7 × wk</td>
<td>55</td>
<td>NA</td>
<td>0.51</td>
<td>0.49</td>
<td>0.02</td>
<td>CVVHDF, PAN membrane</td>
<td>71</td>
<td>NA</td>
<td>0.47</td>
<td>0.48</td>
<td>0.02</td>
</tr>
</tbody>
</table>

NOTE. Values expressed as mean ± SD when appropriate. All outcomes are at hospital discharge, unless otherwise stated. Renal death indicates death or need for dialysis at end of study; dialysis dependence refers to proportion of survivors requiring dialysis at study end.

Abbreviations: CAVHDF, continuous arteriovenous hemodiafiltration; CVVHDF, continuous venovenous hemodiafiltration; NA, not available; CUP, cuprophane; CA, cellulose acetate; PMMA, polymethylmethacrylate; PS, polysulfone; PAN, polyacrylonitrile.

*This study was not designed to assess the impact of dialytic technique on mortality or renal recovery. Data provided by investigators. End of follow-up was at ICU discharge.
gree of publication bias (Fig 1). Inspection of RRs for mortality in individual studies showed no correlation with year of publication, country of origin, study method (retrospective versus prospective), or CRRT technique (arteriovenous versus venovenous, hemofiltration versus hemodiafiltration). However, as a group, effect sizes of RCTs were more homogeneous than nonrandomized studies.

We first analyzed the six RCTs to evaluate the primary end point. The Q statistic suggested no significant heterogeneity across studies ($P = 0.09$). The fixed-effect RR (mortality) was 0.96 (95% CI, 0.85 to 1.08; $P = 0.50$), indicating no significant difference between IHD and CRRT (Fig 2). Because of the borderline significance of the Q statistic, we repeated this analysis using a random-effects model, which did not change the results: RR (mortality) 0.97 (95% CI, 0.82 to 1.15; $P = 0.74$).

Limiting the analysis to studies in which the CRRT arm underwent only hemofiltration, only hemodiafiltration, or either hemodiafiltration or hemofiltration did not change our results: RRs (mortality) were 0.97 (95% CI, 0.70 to 1.33), 1.06 (95% CI, 0.82 to 1.37), and 1.00 (95% CI, 0.82 to 1.22), respectively. Restricting analysis to the three RCTs that enrolled patients in 1996 or later did not affect these results: RR (mortality) was 0.95 (95% CI, 0.76 to 1.19; $P = 0.68$). Performing formal tests for interaction using meta-regression did not show a significant relationship between these variables (type of CRRT or publication year) and the effect of dialytic modality on mortality. Finally, excluding the RCT in which substantial baseline differences were observed between treatment groups$^{31}$ did not change the pooled RR (mortality): 1.05 (95% CI, 0.91 to 1.20; $P = 0.53$), but a test for interaction was positive ($P \leq 0.01$), confirming the subjective impression that results obtained in this trial were significantly different from those in the other included studies.

The Q statistic for the sensitivity analysis in which all 18 studies were combined indicated substantial heterogeneity ($P = 0.0001$). The random-effect RR (mortality) for this model was 1.00 (95% CI, 0.88 to 1.14; $P = 0.99$). Including only the 12 nonrandomized trials did not appre-

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**Table 2. Study Characteristics of Nonrandomized Controlled Trials**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Publication Year</th>
<th>Country of Origin</th>
<th>IHD No.</th>
<th>IHD APACHE II</th>
<th>CRRT No.</th>
<th>CRRT APACHE II</th>
<th>CRRT Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mauritz et al$^{27}$</td>
<td>1986</td>
<td>Germany</td>
<td>22</td>
<td>NA</td>
<td>36</td>
<td>NA</td>
<td>0.75</td>
</tr>
<tr>
<td>Paganini$^{26}$</td>
<td>1988</td>
<td>US</td>
<td>47</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>0.82</td>
</tr>
<tr>
<td>Bastien et al$^{28}$</td>
<td>1991</td>
<td>France</td>
<td>32</td>
<td>19.8</td>
<td>34</td>
<td>22.5</td>
<td>0.50</td>
</tr>
<tr>
<td>McDonald and Mehta$^{30}$</td>
<td>1991</td>
<td>US</td>
<td>10</td>
<td>NA</td>
<td>22</td>
<td>NA</td>
<td>0.77*</td>
</tr>
<tr>
<td>Kierdorf$^{32}$</td>
<td>1991</td>
<td>Switzerland</td>
<td>73</td>
<td>NA</td>
<td>73</td>
<td>NA</td>
<td>0.78</td>
</tr>
<tr>
<td>Kruczynski et al$^{29}$</td>
<td>1993</td>
<td>Canada</td>
<td>23</td>
<td>28</td>
<td>12</td>
<td>26.2</td>
<td>0.25</td>
</tr>
<tr>
<td>van-Bommel et al$^{36}$</td>
<td>1995</td>
<td>The Netherlands</td>
<td>34</td>
<td>22.2</td>
<td>60</td>
<td>26.5</td>
<td>0.57</td>
</tr>
<tr>
<td>Neveu et al$^{34}$</td>
<td>1996</td>
<td>France</td>
<td>141</td>
<td>NA</td>
<td>28</td>
<td>NA</td>
<td>0.89</td>
</tr>
<tr>
<td>Rialp et al$^{31}$</td>
<td>1996</td>
<td>Spain</td>
<td>21</td>
<td>23.3</td>
<td>43</td>
<td>24.5</td>
<td>0.76</td>
</tr>
<tr>
<td>Bellomo et al$^{38}$</td>
<td>1999</td>
<td>Australia</td>
<td>47</td>
<td>25.7</td>
<td>47</td>
<td>29.4</td>
<td>0.53</td>
</tr>
<tr>
<td>Swartz et al$^{39}$</td>
<td>1999</td>
<td>US</td>
<td>137</td>
<td>NA</td>
<td>90</td>
<td>NA</td>
<td>0.68</td>
</tr>
<tr>
<td>Ji et al$^{24}$</td>
<td>2002</td>
<td>China</td>
<td>92</td>
<td>13.2</td>
<td>101</td>
<td>21.0</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.

*Among patients undergoing only one dialytic modality.
ciably change the RR (mortality): 1.00 (95% CI, 0.92 to 1.08; \( P = 0.94 \)) or Q statistic (Fig 3).

**Fail-safe N:** mortality. We estimated how large a sample size would be required for a single new or undetected trial to make the pooled RR (mortality) for RCTs significantly greater than 1. We assumed that such a study would find a substantial benefit of CRRT (RR for IHD of 1.2) and have a mortality rate of 48% in the IHD group, similar to that observed in the two most recent RCTs. Using a fixed-effects model, the required N was 1,250, producing a pooled RR (mortality) of 1.09 (95% CI, 1.00 to 1.20; \( P = 0.049 \)). To explore the effect of varying mortality rate, we repeated this analysis assuming that 72% of patients in the IHD arm would die and leaving the RR for mortality associated with IHD at 1.2. The necessary N decreased to 720 in this scenario: pooled RR (mortality) = 1.09 (95% CI, 1.00 to 1.18; \( P = 0.046 \)). However, both these estimates probably underestimate the required sample size because the heterogeneity introduced by such a positive trial suggests that a random-effects model should be used.

![Fig 2. RR for death for IHD: primary analysis (randomized trials).](image)

![Fig 3. RR for death for IHD: sensitivity analysis (nonrandomized trials).](image)
Only one RCT had an RR (mortality) greater than 1 for IHD.\textsuperscript{33} We determined that the currently available literature would require the addition of six trials with identical N (113) and effect sizes (RR = 1.13) to make the pooled RR (mortality) significantly greater than 1.

**Meta-analysis (renal recovery).** Complete data on renal recovery were available from four RCTs. There was no heterogeneity of effect for either renal death or dialysis dependence (Q = 0.79; $P = 0.85$ and $Q = 2.6; P = 0.46$, respectively). RR (renal death) from these studies was 1.02 (95% CI, 0.89 to 1.17; $P = 0.78$; Fig 4), and RR (dialysis dependence) was 1.19 (95% CI, 0.62 to 2.27; $P = 0.60$; Fig 5).

Excluding the trial that was not designed to collect renal outcomes\textsuperscript{40} did not change these results. Conversely, excluding the RCT in which substantial baseline differences were observed between treatment groups\textsuperscript{21} increased the RR (dialysis dependence) associated with IHD to 1.66 (95% CI, 0.78 to 3.52; $P = 0.19$), although the RR (renal death) was essentially unaffected (1.07; 95% CI, 0.90 to 1.28). Only one nonrandomized trial reported data on renal recovery\textsuperscript{36}; thus, further sensitivity analysis was not performed.

**Fail-safe N: renal recovery.** As with RR (mortality), the addition of either one very large or several intermediate RCTs would be required to make RR (renal death) statistically significant in favor of either therapy. However, the addition of one trial with 190 participants and an effect size equivalent to that observed by Sandy et al\textsuperscript{37} would establish a significantly greater incidence of dialysis dependence among survivors who underwent IHD (RR, 1.52; 95% CI, 1.01 to 2.29; $P = 0.047$). This shows that renal recovery is the pooled outcome most likely to be affected by data from future studies.

**Adjustment for Differences in Illness Severity**

APACHE II scores for both arms were available from 11 trials (Tables 1 and 2); 4 of these trials were RCTs. We performed meta-regression to adjust for differences in baseline APACHE II scores, which tended to be higher in the CRRT groups. This was performed as a form of sensitivity analysis that favored CRRT.

Using meta-analysis, pooled RR (mortality) from the 11 studies was 1.02 (95% CI, 0.88 to 1.18; $P = 0.78$). Meta-regression yielded an adjusted RR (mortality) of 1.18 (95% CI, 0.91 to 1.53; $P = 0.20$). When this analysis was repeated on only the 4 RCTs for which APACHE II data were available, pooled RR (mortality) by meta-analysis was 0.88 (95% CI, 0.73 to 1.07; $P = 0.11$), and meta-regression found an adjusted RR (mortality) of 0.96 (95% CI, 0.81 to 1.14; $P = 0.66$).

**DISCUSSION**

This meta-analysis of six RCTs included more than 600 patients treated in four countries.
found no significant difference in mortality rate for critically ill patients with ARF treated with IHD compared with those who underwent CRRT. This result was unchanged by the inclusion of nonrandomized trials or by controlling for baseline differences in illness severity using meta-regression and was consistent in sensitivity analyses that stratified by CRRT technique and treatment era.

Given the high mortality rates associated with continuous therapies (illness acuity notwithstanding), concern has been raised that CRRT may be harmful, rather than beneficial.39 Our results show no evidence of adverse outcomes associated with CRRT, an important finding given that many patients with ARF are treated with continuous rather than intermittent therapies.

Patients assigned to CRRT appeared to be more severely ill in most nonrandomized investigations and in one RCT. These differences may reflect physician bias in favor of continuous therapies despite a lack of evidence to support this belief. Unfortunately, APACHE II scores were the best available marker of illness severity in most studies, although limitations of this index in ARF are well described.43 Nonetheless, adjusting for baseline differences in APACHE II scores did not significantly change our results.

For renal recovery, neither the incidence of renal death nor the likelihood of dialysis dependence among survivors was significantly different between modalities. This component of the analysis included 401 patients in four RCTs. Renal recovery is important clinically because it enables patients to discontinue dialysis therapy, a treatment associated with significant impairment in health-related quality of life.44-46 Moreover, chronic dialysis therapy is expensive, costing on average US $69,751/y.47 Because the majority of this cost is from outpatient dialysis treatments, greater rates of renal recovery might save significant resources. In addition, even mild chronic renal insufficiency is associated with adverse patient outcomes and high health care costs, suggesting that the relative incidence of any sustained renal impairment is potentially relevant.48

Although we did not find a significant association between renal recovery and dialytic modality, the estimate for RR (dialysis dependence) was the most likely of the three outcome measures to be affected by the inclusion of new studies. Because available data are insufficient to draw firm conclusions, it is important for future studies to explore the impact of dialytic modality on renal recovery from ARF in both the short and long term.

For methods, we followed published recommendations for conducting and reporting systematic reviews.49,50 We included all available studies in our meta-analysis, including those published only in the “grey literature” (unpublished or not
Inclusion criteria, dialytic techniques, and patient populations varied among RCTs in our meta-analysis. However, there was no statistical evidence of heterogeneity in the RR for mortality by dialytic modality. Nonetheless, we took the conservative approach of using random-effects models and performing multiple sensitivity analyses to assess the impact of individual trials, different CRRT techniques, baseline comorbidity, and era in which patients were enrolled. Results obtained were similar in all analyses, supporting the conclusion that dialytic modality used in ARF does not affect rates of death or renal recovery.

A previous publication constitutes a complete review of the literature available at that time, but limited information was available on renal outcomes. In addition, meta-analysis was not performed, in part because of the low number of randomized trials available to the investigators.

Although a recently published meta-analysis attempted to address this topic, its primary outcome was based on combined results of randomized and nonrandomized trials, and several apparently relevant randomized investigations were not included. In addition, most of its sensitivity analyses were based on an unvalidated instrument that was administered by the study's investigators to assess data quality and illness severity. Unfortunately, these analyses are unlikely to adjust appropriately for differences between studies. Finally, it is likely that including all available investigations would have substantially changed the results. Thus, we disagree with the investigators' conclusions that available data suggest a survival advantage associated with CRRT.

There are several potential limitations of our study. Because the study populations included in our meta-analysis were relatively unselected, our conclusions may not apply to subsets of patients, such as those with increased intracranial pressure or severe hypotension, in whom CRRT might be more efficacious.

Our systematic review could be criticized on the grounds that the majority of included studies have not been published in peer-reviewed journals. Such a criticism would imply that unpublished work may be of lesser quality or might be less likely to find a difference between treatments. We believe this assertion would be unfounded. The most likely reason that many of these studies have not been published is precisely because they failed to find a significant difference between modalities, exemplifying the well-known phenomenon of publication bias. In addition, poor-quality literature is known to exaggerate effect sizes compared with more rigorous studies; it therefore is difficult to attribute that we did not find a mortality difference between treatments to the inclusion of unpublished trials.

Although limitations of meta-analysis have been well described, we attempted to minimize bias through rigorous methods. As with all meta-analyses, despite the multiple sensitivity analyses performed, it is conceivable that differences in patient or study characteristics between studies influenced our results. Although our study does not eliminate the possibility that dialytic modality confers a survival advantage, it shows that the magnitude of such a benefit (if it exists) is exceedingly small in patients without severe hypotension. We believe that consideration of unpublished studies appropriately strengthens this position.

Because we found no difference in mortality for patients with ARF who were treated with IHD or CRRT, one could conclude that most patients should be treated with the less expensive form of treatment. Most reports suggest that CRRT is at least twice as expensive as IHD, increasing treatment costs by US $150 to $450 per day (depending on the form of CRRT considered). However, treatment of all patients with IHD on this basis may be incorrect from both clinical and economic standpoints because it does not consider potential downstream outcomes, such as those attributable to costs of chronic dialysis therapy.

Future trials aimed at showing a mortality benefit in unselected patients should be undertaken with caution because our data suggest that the required N for such a study would be very high. Nonetheless, multicenter investigations of this issue could be performed successfully, as with other common interventions in critical illness, even those laden with perceived ethical issues, such as blood transfusion. The design of new studies evaluating the impact of dialytic modality in ARF would need to account for contamination (caused by treatment...
crossover), illness severity (by stratification), and variations in dialytic technique, dialysis membrane, and dose (perhaps by a detailed protocol). Lessons learned from the conduct of previous trials could be used to develop inclusion criteria that would minimize ethical concerns and produce a suitably homogeneous patient population. Finally, because the mortality rate of critically ill individuals remains elevated long after leaving the ICU, outcomes should be assessed at hospital discharge, or perhaps even later. Until information from such a trial is available, a systematic review such as this may constitute the best evidence possible.

In summary, we found no difference in mortality between CRRT or intermittent renal replacement therapy for critically ill patients with ARF. Although we did not find a difference in the frequency of renal recovery between treatments, this outcome has been less extensively studied. However, even a slight difference in renal recovery between therapies might significantly influence the overall cost-effectiveness of each dialytic modality. As such, future investigations should collect detailed information on long-term costs and the relative likelihood of renal recovery associated with dialysis modality.

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