In this issue of *JASN*, Tumlin et al. report results of a revolutionary phase 2 multicenter, randomized clinical trial comparing 72 h of continuous venovenous hemofiltration (CVVH) with and without a bioartificial kidney (referred to as a renal tubule assist device [RAD]) in the management of severe acute kidney injury. Fifty-eight patients were randomly assigned: 40 to CVVH (RAD) and 18 to CVVH alone. Multiple outcomes were evaluated, including the standard metric for clinical trials in critical care with 28-d survival as the primary outcome. All-cause mortality at 90 and 180 d, time to recovery of kidney function, time to intensive care unit and hospital discharge, and safety parameters were also examined. Mortality rates at 28 and 180 d were marginally lower among patients who were randomly assigned to CVVH + RAD.

One could easily criticize aspects of the design, implementation, and analysis of the trial and its reporting. First, there was no documentation of the expected effect size, except in the context of the investigators' estimated improvement (stratified as $<10$, $10$ to $23.3$, and $>23.3$%) that would guide the conduct of subsequent trials. Regardless, the study was hopelessly underpowered. If one were to consider a comparison of two strategies directed toward the management of severe acute kidney injury in the intensive care unit and estimate the 28-d mortality in CVVH-treated patients as the midpoint of the range cited by the authors (60%), the sample size required to detect a reasonable and clinically meaningful reduction in mortality (10% absolute, 16.7% relative) would be 768 with 80% power or 1028 with the 90% power typically recommended for substantive interventions. Corresponding sample sizes would be 188 and 252 with a larger, arguably unrealistic effect estimate (20% absolute, 33% relative). Of note, these sample size estimates do not account for loss to follow-up or dropout. We previously highlighted the pitfalls of conducting underpowered clinical trials, even when results are conventionally significant.

Second, only 10 of 40 patients who were randomly assigned to CVVH + RAD completed the planned 72 h of therapy. The rationale for discontinuing the RAD intervention for clinical improvement or deterioration was not provided.

Third, the primary result (28-d mortality in 13 [33%] of 39 CVVH + RAD versus 11 [61%] of 18 CVVH alone-treated patients) was not statistically significant and failed to consider the patient who was assigned to CVVH + RAD and died before RAD therapy was instituted; that is, the comparison was performed in an as-treated rather than an as-randomized “intention-to-treat” sample.

Fourth, at least seven outcomes were assessed (death at three discrete time points, recovery of kidney function at two discrete time points, and time to death and time to recovery of kidney function) without consideration of the statistical implications of multiple comparisons. Moreover, the authors failed to offer a compelling hypothesis for why a nonsignificant effect in the short term might be expected to produce a significant benefit in the longer term, particularly when the intervention lasted at most 72 h. Finally, numerous nonprespecified subgroup analyses were conducted; for example, with and without sepsis or with higher and lower APACHE II and SOFA scores.

Despite these limitations, the investigators should be commended for having extraordinary vision, courage, and creativity to invent and legitimatley test a bioartificial renal device. Although conventional dialysis technologies have been developed and refined with the primary goal of enhancing the clearance of metabolic waste, hazardous electrolytes, and excess extracellular fluid, they have failed to address many, if not most, of the broad-ranging functions of the kidney, as the authors articulate. Although some investigators have questioned whether critically ill patients die with or from acute kidney injury, epidemiologic evidence strongly suggests that patients with acute kidney injury experience an excess of death directly attributable to the kidney injury itself, although it seems unlikely that azotemia, hyperkalemia, hypervolemia, or other dialysis-remediable abnormalities are culpable. Indeed, one might look toward the dialysis versus transplantation experience in ESRD as an informative analog.

The provision of dialysis itself, although sustaining life, fails to restore health to the majority of patients who have ESRD. Patients who have ESRD and receive a kidney transplant enjoy markedly prolonged survival and enhanced health-related quality of life relative to patients who remain on dialysis, despite the multiplicity of assaults on

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**Toward the Promise of Renal Replacement Therapy**

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**In this issue of *JASN*, Tumlin et al. report results of a revolutionary phase 2 multicenter, randomized clinical trial comparing 72 h of continuous venovenous hemofiltration (CVVH) with and without a bioartificial kidney (referred to as a renal tubule assist device [RAD]) in the management of severe acute kidney injury. Fifty-eight patients were randomly assigned: 40 to CVVH + RAD and 18 to CVVH alone. Multiple outcomes were evaluated, including the standard metric for clinical trials in critical care with 28-d survival as the primary outcome. All-cause mortality at 90 and 180 d, time to recovery of kidney function, time to intensive care unit and hospital discharge, and safety parameters were also examined. Mortality rates at 28 and 180 d were marginally lower among patients who were randomly assigned to CVVH + RAD.**

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the transplanted kidney and its recipient: ischemia reperfusion injury, low nephron mass of the allograft, and immunosuppressive therapies that result in impaired kidney function, insulin resistance, dyslipidemia, osteoporosis, and increased risk of opportunistic infections and malignancy. It should be no surprise, then, that an analogous approach in acute kidney injury—that is, dialysis or hemofiltration to remove water-soluble metabolic wastes, salt, and water—might not achieve resounding or complete biologic success.

The incidence of acute kidney injury requiring dialysis is rising, and although large population-based studies suggested that outcomes may have improved marginally in the past 15 yr, rates of death and nonrecovery remain unacceptably high.7–9 Altering our approach to the modality or dosage of dialysis or hemofiltration has yielded inconsistent and conflicting results.10–14 While we anxiously await the results of the Veterans Affairs– and National Institutes of Health–sponsored Acute Renal Failure Trial Network (ATN) study,15 a comparison of intensive versus less intensive hemodialysis or hemofiltration in severe acute kidney injury, additional attempts at restoring some of the vital (noninert) aspects of kidney function to critically ill patients needs encouragement. Regardless of whether this particular iteration of the bioartificial kidney ultimately achieves success in clinical trials, this effort represents a landmark event in the history of nephrology. The authors should be celebrated for their efforts.

DISCLOSURES
None.

REFERENCES

See related article, “Efficacy and Safety of Renal Tubule Cell Therapy for Acute Renal Failure,” on pages 1034–1040.

The Appearance of Brief Communications in JASN

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With this issue of JASN, we introduce a new feature for original manuscripts, the Brief Communication. These articles are short, about 1500 words, and written in letter format followed by concise methods and no more than four figures; some of the dataset may be submitted supplemental to the manuscript. For a while we have felt such an outlet might stimulate the submission of interesting or novel findings where an expanded story will have to follow from subsequent work. Will our reviewers be able to adapt to evaluating less than is expected for a full-length manuscript? It remains to be seen. The editors expect a good story well supported by controlled data and some insight into mechanism. This is a tall order for authors in the limited space available for such letters, but other well-regarded journals attract such submissions. So far, we have declined a number of offerings, and with this issue start with two manuscripts surviving review and much revision. We hope this new feature will be used wisely and add value to the wonderful content already in our pages. Details for submitting Brief Communications can be found in the instructions to authors. Submissions should be labeled as such.

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