EDITORIAL

Early to Dialyze
Healthy and Wise?

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Acute kidney injury (AKI) among hospitalized patients is common, consequential, and costly. Annually in the United States, approximately 10% of the estimated 5 million hospitalizations are complicated by AKI, with 0.4% of cases severe enough to require dialysis. Among patients with AKI requiring extracorporeal kidney support (dialysis), in-hospital mortality rates are consistently in excess of 20%, and may exceed 40% when accompanied by nonrenal organ system failure.[1-3] Acute kidney injury results in prolonged hospital stay, and is associated with marked increase in hospital costs, with attributable costs estimated to be between $5 billion and $10 billion annually.[3-5] Moreover, AKI has been linked with increased longer-term risks of chronic kidney disease (CKD), another condition associated with poor outcomes and high health care resource consumption,[6] as well as of higher risks of hypertension.[7]

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Several cleverly designed and well-conducted trials to prevent AKI or ameliorate its course have been conducted over the past several years; however, findings from these trials have been largely disappointing. Among the interventions tested were anti-inflammatory and pleiotropic drugs (corticosteroids, statins, and aspirin),[8-10] vasoactive or antiplatelet drugs aimed to improve perfusion of the kidneys (fenoldopam, clonidine, and aspirin), different fluid administration strategies (buffered crystalloid solution vs saline),[11] and electronic health records–based alerts of evolving early-stage AKI.[12] Even though off-pump coronary artery bypass graft surgery significantly reduced AKI incidence compared with on-pump coronary artery bypass graft surgery, no improvement in kidney function or in the incidence of CKD was found after 12 months of prospective follow-up.[13] Early excitement about the potential efficacy of remote ischemic preconditioning in preventing AKI[14] was later tempered by larger trials that found no such benefit.[15,16]

As reported in *JAMA*, Zarbock et al[17] report findings from a single-center trial examining the effects of early vs delayed initiation of kidney replacement therapy in the course of patients who are critically ill with AKI. Patients were eligible to be randomized once they had reached stage 2 AKI per Kidney Disease: Improving Global Outcomes (KDIGO) guidelines,[18] which is present if the serum creatinine concentration has doubled from baseline, urine output has decreased to below 0.5 mL/kg/h for at least 12 hours, or both. Eligible patients were also required to have 1 other condition from among severe sepsis, use of vasopressors or catecholamines, refractory fluid overload, or development or progression of organ dysfunction in another (nonkidney) organ. In addition, patients had to exhibit a plasma concentration of 150 ng/mL of neutrophil gelatinase–associated lipocalin (NGAL), a marker of presence and severity of AKI not currently used in routine practice.

Patients were randomized into 2 treatment groups: a group that initiated early kidney replacement therapy (early group; within 8 hours of reaching stage 2 AKI) and a group that delayed initiation of kidney replacement (delayed group; 12 hours after having reached stage 3 AKI per KDIGO criteria [serum creatinine has tripled from baseline, or urine output has decreased to below 0.3 mL/kg/h for at least 24 hours, or serum creatinine concentration of 4 mg/dL with an increase of 0.5 g/dL within 48 hours, or a combination of these outcomes]). Kidney replacement therapy involved continuous venovenous hemodiafiltration, the delivery of which was standardized and had to be strictly adhered to in both groups for at least 7 days. Patients were then followed for the primary end point of all-cause mortality at 90 days as well as several secondary end points focused on kidney outcomes, intensive care unit and hospital length of stay, and selected inflammatory biomarkers.

Of 231 patients enrolled, all 112 patients in the early group and 108 of 119 patients in the delayed group underwent kidney replacement therapy after meeting eligibility criteria (median time to initiation, 6 hours for the early group and 25.5 hours for the delayed group). Mortality after 90 days was 39.3% in the early group compared with 54.7% in the delayed group (P = .03), for an absolute risk reduction of −15.4% (95% CI, −28.1% to −2.6%). Several of the secondary end points were also significantly different between the groups, including shorter duration of kidney replacement therapy (median, 9 days for the early group vs 25 days for the delayed group), mechanical ventilation (125.5 hours for the early group vs 181 hours for the delayed group), and overall hospital length of stay (51 days for the early group vs 82 days for the delayed group). Recovery of kidney function without the need for dialysis was also more common in the early treatment group (53.6% for the early group vs 38.7% for the delayed group).

Zarbock and colleagues were appropriately reserved in their conclusions, highlighting the need for confirmatory data. Although the investigators carefully designed the intervention in a way that could be easily replicated—using widely accepted classification criteria for AKI by stage—the separation between groups (in other words, the difference between earlier and later initiation of dialysis) was modest—less than 24 hours. It is difficult to imagine how such a modest change in the dialytic intervention could yield such significant effects on multiple end points, including a 4-week difference in median hospital length of stay, let alone a 15% absolute reduction in in-hospital

mortality. Other single-center, modestly sized published trials of dialytic interventions have yielded similarly remarkable results. In 2003, Marenzi et al[19] published data from a randomized clinical trial of 114 patients undergoing coronary interventions, in which hemofiltration and saline infusion delivered before and after radiocontrast exposure were compared. Rates of all major clinical events, including the development of AKI and the provision of dialysis or hemofiltration were reduced multifold. Moreover, in-hospital mortality was 2% in the hemofiltration group vs 14% in the saline infusion group (P = .02) and corresponding 1-year mortality rates were 10% for the hemofiltration group and 30% for the saline infusion group (P = .01). At the time many clinicians thought these results were implausible; to date, no confirmatory trials have been conducted. Zarbock et al appropriately acknowledged that single-center trials and trials of relatively modest sample size often overestimate the treatment effect; underpowered trial results showing positive effects with a P value less than .05 may be more likely to represent false-positive findings, rather than true-positive results.[20] However, similarly sized trials with less strikingly positive results often go unpublished.

Whether the findings reported by Zarbock et al represent a plausible effect or not, the investigators have performed a rigorous trial and have presented their results appropriately, with responsible and conservative reporting. Two large randomized clinical trials of dialysis "dose" following AKI definitively showed no material benefit for patients given higher intensity hemofiltration, hemodiafiltration, or hemodialysis.[21,22] Although these interventions proved ineffective, the trials were resoundingly successful, in that they were definitive, and informed clinical practice. The question of the optimal timing of dialytic support in critically ill patients is one of high priority and interest. In view of the provocative findings reported by Zarbock et al, it is the responsibility of the nephrology and critical care communities to confirm or refute these findings across multiple sites in a much larger, diverse population.

ARTICLE INFORMATION

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