through it is reasonable to experiment with AFTMs,14 this information that is based only on two P values of \( P = 0.04 \) can not yet be used to inform changes in either current concepts about patient physiology on dialysis or the statistical methods used by the renal community.

## DISCLOSURES

None.

## REFERENCES


The concentration of hydrogen ion is normally managed by several buffering and elimination systems, including the kidney. Consequently, progressive renal failure is accompanied by an increasing inability to excrete metabolites of fuel consumption, lower blood pH, and reduced plasma bicarbonate levels,1,2 but is the inverse true? Can correcting this chronic metabolic acidosis slow or prevent progressive kidney damage?

An elegant series of experiments several years ago by Mitch and colleagues3–6 found that metabolic acidosis in the rat activates the ubiquitin-proteasome pathway, leading to increased protein breakdown to amino acids, including glutamate, which is excreted by the proximal tubule as ammonium. Nath et al.7 observed even earlier that nitrogen nucleophiles such as ammonia are injurious to the kidney and stimulate chronic tubulointerstitial inflammation through a complement-mediated pathway. Both findings together suggest a deleterious multisystem mechanism contributing to progression of chronic kidney disease (CKD).

Data from studies of rats on the effects of alkali therapy in CKD have been contradictory: Some studies posit alkali therapy is protective,4,5 or neutral,8 whereas others suggest the opposite—that metabolic acidosis is protective.10,11 Investigation of this issue in humans also reveals divergent results. In an early report from 1931, Lyon and Stewart12 treated 17 patients with moderate renal failure for periods of several weeks to months with both low-acid diets and sufficient oral supplementation with sodium bicarbonate and potassium citrate to maintain an alkaline urine pH. This work advanced the notion that lightening of an acid load on the kidney stabilizes or temporarily improves renal function. Since then, there have been only limited numbers of short-term studies in small groups of humans with CKD.13–15

In this issue of *JASN*, Ashurst et al.16 make a significant contribution to this field by performing a randomized, placebo-controlled trial of oral sodium bicarbonate supplementation (approximately 21 mmol/d in divided doses) in 134 adults with stages 4 to 5 CKD (GFR 15 to 30 ml/min per 1.73 m²) and levels of serum bicarbonate between 16 and 20 mmol/L. Primary end points following intention to treat were rates of decline in creatinine clearance and development of ESRD that required dialysis. Recruited patients were a heterogeneous mix of race, gender, and cause of renal failure on typical medications used in advanced CKD, including renin-angiotensin

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blocks other antihypertensive drugs, diuretics, and calcium acetate as a phosphate binder (avoiding sevelamer hydrochloride, which induces metabolic acidosis and is now being replaced by the manufacturer with sevelamer carbonate). Exclusion criteria included malignancy, morbid obesity, overt congestive heart failure, and failure to understand or comply with the treatment.

At the end of 1 yr, 14 patients in the control group but none in the bicarbonate group came to dialysis. At the end of 2 yr, 22 patients in the control group progressed to dialysis compared with four in the intervention group (33 versus 6.5%; relative risk 0.13; 95% confidence interval 0.04 to 0.40; P < 0.001). In addition, among the patients who did not require dialysis, those in the bicarbonate treatment group had significantly lower rates of decline in creatinine clearance compared with control subjects (1.88 versus 5.93 ml/min per 1.73 m²; P < 0.0001).

A key strength of this investigation is that it is a randomized, controlled trial. There is a widely recognized paucity of randomized, controlled trials in nephrology,17 and too often our therapies are guided by imperfect observational or association studies. This important study should stimulate larger, multi-center, randomized, controlled trials to confirm or refute its impressive effect. If these effects are confirmed, then this should lead to a change in clinical practice. To date, only three classical interventions have been shown by rigorous randomized, controlled trials to be effective in retarding progression of CKD: BP lowering, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and glycemic control among patients with diabetes. It is exciting to think there may be a fourth intervention on the horizon that is relatively inexpensive to implement.

This study is also refreshing insofar as treatment of metabolic acidosis has received much less attention than treatment of several other complications of CKD such as anemia, hyperphosphatemia, and secondary hyperparathyroidism. This is almost certainly due to the lack of interest on the part of pharmaceutical companies in sponsoring clinical trials of alkali therapies are guided by imperfect observational or association studies. This important study should stimulate larger, multi-center, randomized, controlled trials to confirm or refute its impressive effect. If these effects are confirmed, then this should lead to a change in clinical practice. To date, only three classical interventions have been shown by rigorous randomized, controlled trials to be effective in retarding progression of CKD: BP lowering, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and glycemic control among patients with diabetes. It is exciting to think there may be a fourth intervention on the horizon that is relatively inexpensive to implement.

This study is also refreshing insofar as treatment of metabolic acidosis has received much less attention than treatment of several other complications of CKD such as anemia, hyperphosphatemia, and secondary hyperparathyroidism. This is almost certainly due to the lack of interest on the part of pharmaceutical companies in sponsoring clinical trials of alkali therapy. All of this is a reminder of how much our national research agenda and the focus of physician attention are determined by nonscientific considerations, particularly because there is as much rationale in pathophysiology to study the correction of acidosis as there is to pursue the amelioration of anemia. Ashurst et al. should be applauded for initiating this study and Barts and the London Charitable Foundation for being sponsors.

DISCLOSURES

None.

REFERENCES
