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**EXCLUSIVE**

# Q / Is bicarbonate therapy effective in preventing CKD progression?

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## EVIDENCE-BASED ANSWER

A / **YES.** Long-term sodium bicarbonate therapy slightly slows the loss of renal function in patients with chronic kidney disease (CKD) and may moderately reduce progression to end-stage renal disease (strength of recommendation [SOR]: **B,** meta-analyses of lower-quality randomized controlled trials [RCTs]). Therapy duration of 1 year or less may not be beneficial (SOR: **C,** secondary analyses in meta-analyses).

## Evidence summary

### Bicarbonate therapy demonstrates benefit in 2 meta-analyses

Two recent meta-analyses evaluated studies of bicarbonate therapy in patients with CKD, and both found benefit.[1,2]

A 2020 meta-analysis included 15 RCTs (N = 2445) of adults (mean age, 61 years; range, 40.5-73.9 years) with CKD.[1] Most trials enrolled patients with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m²; however, 1 study (N = 80) enrolled patients who had an eGFR of 60 to 90 mL/min/1.73 m² and albuminuria, and another (N = 74) enrolled patients with an eGFR of 15 to 89 mL/min/1.73 m². Four studies included patients with normal baseline bicarbonate levels, while the rest enrolled patients with metabolic acidosis. The primary outcome was CKD progression at study conclusion, which ranged from 3 to 60 months (median, 12 months).

Compared to placebo or no therapy, sodium bicarbonate (variously dosed) resulted in a small reduction in the rate of loss of kidney function (defined by eGFR or creatinine clearance) from baseline to trial completion (14 trials, N = 2073; standardized mean difference [SMD] = 0.26; 95% CI, 0.13-0.40; P = .018; I² = 50%).[1] Sodium bicarbonate therapy also resulted in a moderate reduction in the risk of end-stage renal disease (7 trials, N = 1526; risk ratio [RR] = 0.53; 95% CI, 0.30-0.89; P = .011; I² = 69%; number needed to treat [NNT] = 14).[1] There was no difference in hospitalizations for heart failure, risk of worsening blood pressure, or all-cause mortality between the sodium bicarbonate and control groups.

Subgroup analysis by follow-up time found a significant preservation of eGFR only in studies with follow-up > 12 months (4 trials, N = 392; weighted mean difference = 3.71 mL/min/1.73 m²; 95% CI, 0.18-7.24; P = .042; I² = 63%).[1] Duration of therapy did not affect initiation of dialysis. Another subgroup analysis found that low- and moderate-quality studies were more likely than high-quality studies to find a change in the primary outcome. Overall, there was significant heterogeneity among the trials (control intervention, follow-up duration, methods of assessment of kidney function, dosage of sodium bicarbonate), as well as underrepresentation of female, pediatric, and elderly patients.

Another meta-analysis, published in 2019 by a different research group, analyzed 7 RCTs (N = 815) that comprised a subset of those in the newer analysis.[2] The 2019 analysis similarly found that, compared to placebo or usual care, oral bicarbonate therapy resulted in statistically significantly higher eGFRs

at 3 to 60 months' follow-up (mean difference = 3.1 mL/min/1.73 m$^2$; 95% CI, 1.3-4.9).[2] The authors noted that the protective effect on eGFR was not seen in studies reporting outcomes at 1 year. Progression to end-stage renal disease or initiation of dialysis were not used as outcomes.

### Significant outcomes seen in 1 large study

The largest study (N = 740) included in the 2020 meta-analysis (and discussed separately due to its size and duration) was a multicenter, unblinded, pragmatic trial investigating bicarbonate therapy in CKD.[3] Patients were adults (mean age, 67.8 years) with CKD stages 3 to 5 and metabolic acidosis (serum bicarbonate level of 18-24 mmol/L); mean serum creatinine was 2.3 mg/dL, and mean serum bicarbonate was 21.5 mmol/L. Patients with severe heart failure or uncontrolled hypertension were excluded.

Researchers randomized patients to oral sodium bicarbonate (titrated to a target serum concentration of 24-28 mmol/L) or standard care for a median duration of 30 months. The primary endpoint was time to doubling of serum creatinine, and secondary endpoints included all-cause mortality, time to initiation of dialysis, hospitalization rate, and hospital length of stay.

Patients treated with bicarbonate therapy had a 64% lower risk of doubling their serum creatinine compared to those treated with standard care (hazard ratio [HR] = 0.36; 95% CI, 0.22-0.58; $P < .001$; NNT = 9.6).[3] Bicarbonate therapy also significantly reduced the risk of dialysis (HR = 0.5; 95% CI, 0.31-0.81; $P = .005$; NNT = 19); all-cause mortality (HR = 0.43; 95% CI, 0.22-0.87; $P = .01$; NNT = 27); hospitalization rates (34.6% vs 14.2% by end of study in standard care and bicarbonate groups, respectively; $P < .001$); and hospital length of stay (1160 total d/y vs 400 total d/y; $P < .0001$).[3] Inspection of Kaplan Meier curves shows outcomes beginning to diverge after 1 to 2 years of treatment. This trial was limited by the lack of blinding, placebo control, and standardization of care protocols.

### Recommendations from others

The National Kidney Foundation's 2012 Kidney Disease Outcomes Quality Initiative guidelines for the management of CKD recommend oral bicarbonate therapy for patients with CKD and serum bicarbonate concentrations < 22 mmol/L.[4] The guidelines state that serum bicarbonate levels < 22 mmol/L correlate with an increased risk of CKD progression and death, whereas high bicarbonate levels (> 32 mmol/L) correlate with increased risk of death independent of level of kidney function. These guidelines cite small studies of alkali therapy slowing progression of CKD, although it was noted that the evidence base was not strong.

### Editor's takeaway

The evidence shows a small but consistent effect of bicarbonate therapy on CKD progression. For patients with CKD stages 3 to 5 and metabolic acidosis (defined by serum bicarbonate levels < 22 mmol/L), the use of supplemental oral sodium bicarbonate, which is inexpensive and safe, can delay or prevent progression of serious disease. **JFP**

> **Compared to placebo or no therapy, sodium bicarbonate (variously dosed) resulted in a small reduction in the rate of loss of kidney function.**

### References

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