

Sodium bicarbonate to improve physical function in patients over 60 years with advanced chronic kidney disease: the BiCARB RCT

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Declared competing interests of authors: Peter T Donnan is a member of the New Drugs Committee of the Scottish Medicines Consortium and has received recent grants from Gilead Sciences, Inc. (Foster City, CA, USA) and Shire Pharmaceuticals Ltd (Basingstoke, UK). Alison Avenell works in the Health Services Research Unit, which is core funded by the Chief Scientific Office of the Scottish Government Health and Social Care Directorate. Paul McNamee works in the Health Economics Research Unit, which is core funded by the Chief Scientist Office of the Scottish Government Health and Social Care Directorate. Huey Chong works in the Health Economics Research Unit, which is core funded by the Chief Scientist Office of the Scottish Government Health and Social Care Directorate.

Published June 2020

DOI: 10.3310/hta24270

Scientific summary

The BiCARB RCT

Health Technology Assessment 2020; Vol. 24: No. 27

DOI: 10.3310/hta24270

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Chronic kidney disease becomes increasingly common with advancing age, with approximately 2% of the population aged ≥ 70 years suffering from advanced (glomerular filtration rate category 4 or 5) chronic kidney disease. Advanced chronic kidney disease is often accompanied by metabolic acidosis because of the inability of the kidneys to excrete sufficient excess acid. Acidosis has been associated with a range of adverse health outcomes in patients with chronic kidney disease, including worse cardiovascular health, weaker bones, weaker muscles and more rapid progression of kidney disease. As a result, oral sodium bicarbonate has been used for decades to counteract metabolic acidosis. Few trials have tested whether or not sodium bicarbonate is effective at countering these adverse outcomes. Sodium bicarbonate also carries risks of gastrointestinal side effects and is awkward for patients to take, and there are concerns that the sodium content might increase blood pressure or fluid overload. These issues are of particular relevance for older people, who make up the majority of people in the UK with advanced kidney disease and who are most likely to suffer side effects because of coexisting multimorbidity and polypharmacy.

Objectives

The primary objective of the BiCARB trial was to determine whether or not oral bicarbonate therapy improves physical function compared with placebo in older people with chronic kidney disease and mild acidosis.

The secondary objectives were to:

- determine whether or not oral bicarbonate therapy improves health-related quality of life compared with placebo
- compare the impact of oral bicarbonate therapy with that of placebo on biochemical markers of chronic kidney disease
- assess whether or not use of oral bicarbonate therapy is associated with an excess of adverse events compared with placebo
- estimate the cost-effectiveness of using oral bicarbonate therapy compared with placebo
- assess the effect of oral bicarbonate therapy compared with placebo on bone turnover and vascular health, as assessed by biochemical markers.

Methods

The study was a parallel-group, double-blind, placebo-controlled randomised trial. Participants were recruited from nephrology and geriatric medicine outpatient departments in UK hospitals. Participants were eligible for inclusion if they were aged ≥ 60 years with advanced chronic kidney disease (glomerular filtration rate category 4 or 5, not on dialysis) with a serum bicarbonate concentration of < 22 mmol/l. Participants were excluded if they were currently taking bicarbonate, had a diagnosis of renal tubular acidosis, were taking bisphosphonate drugs, were on or would soon start renal replacement therapy, were terminally ill, could not give written informed consent, had uncontrolled hypertension or decompensated chronic heart failure, were participating in another clinical trial or were allergic to sodium bicarbonate tablets or lactose (used as an excipient in the tablets). Eligible participants were randomised 1 : 1 to oral sodium bicarbonate tablets or identical matching placebo tablets using a web-based randomisation system to conceal allocation. Dosing started at 500 mg three times per day and was increased to 1 g three times per day if the serum bicarbonate concentration was < 22 mmol/l at the 3-month visit.

Outcomes were collected at baseline and 3, 6, 12 and 24 months. The primary outcome was the between-group difference in the Short Physical Performance Battery score (a measure of lower limb strength and balance that predicts future disability, need for care and death) at 12 months, adjusted for baseline values. The initial sample size calculation estimated that 380 participants were required to detect a 1-point difference between groups in the Short Physical Performance Battery score at 12 months with 90% power, assuming a standard deviation of 2.6, an alpha of 0.05 and a dropout rate of 10% every 6 months. Sample size re-estimation prior to closing recruitment indicated that 300 participants would have 87% power to detect the 1-point difference in the Short Physical Performance Battery score after adjusting for baseline values. Secondary outcome measures included generic (EuroQoL-5 Dimensions, three-level version) and disease-specific (Kidney Disease Quality of Life) health-related quality of life questionnaires; anthropometry (weight, mid-arm muscle circumference, triceps skinfold thickness, mid-thigh circumference); physical performance (6-minute walk speed, grip strength); renal function measured using creatinine, cystatin C and the urinary albumin-to-creatinine ratio; markers of bone turnover and mineral metabolism (serum calcium, serum phosphate, bone-specific alkaline phosphatase, tartrate-resistant acid phosphatase 5b, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D); vascular health (blood pressure, B-type natriuretic peptide and serum cholesterol); and other relevant biochemical markers, including haemoglobin, thyroid-stimulating hormone and serum albumin. All adverse events were recorded, including commencement of renal replacement therapy. Falls were recorded prospectively using a self-completed falls diary. For the health economic analysis, information on health and social care use was collected at each follow-up visit and was combined with quality of life measures to derive the incremental cost per quality-adjusted life-year.

Analyses were prespecified in statistical analysis plans and conducted in accordance with intention-to-treat principles. The primary outcome (between-group difference in the Short Physical Performance Battery at 12 months) was analysed using linear mixed models, adjusted for baseline measurements, minimisation variables (age, sex and stage of chronic kidney disease) and a random effect variable for recruitment site. Preplanned subgroup analyses were conducted for age, sex, baseline chronic kidney disease stage, baseline bicarbonate level, baseline Short Physical Performance Battery score and high versus low adherence. Secondary outcomes were analysed using repeated-measures models, adjusted for baseline values and minimisation variables as above. Time-to-event analyses (time to death, time to commencement of renal replacement therapy) were conducted using Cox proportional hazards models, adjusted for minimisation variables as above. For all analyses, a two-sided p -value of < 0.05 was taken as significant, with no adjustment for multiple testing. For the health economic analysis, a cost-utility analysis was undertaken that involved estimation of the incremental costs and incremental effects, measured using quality-adjusted life-years, based on responses to the EuroQoL-5 Dimensions, three-level version, instrument. Estimation was performed using generalised linear regression modelling, with adjustment for skewed data and for baseline differences in cost, EuroQoL-5 Dimensions, three-level version, score and other patient characteristics (age, sex, chronic kidney disease stage). Non-parametric bootstrap methods were used for calculating confidence intervals around cost and quality-adjusted life-year differences. Cost-effectiveness acceptability curves were employed to show the probability that bicarbonate therapy was cost-effective for different values of willingness to pay per additional quality-adjusted life-year.

Results

We randomised 300 participants from 27 UK nephrology and geriatric medicine outpatient centres between May 2013 and February 2017. In total, 152 were allocated to bicarbonate and 148 were allocated to placebo. The mean age of participants was 74 years and 86 (29%) were female. The Short Physical Performance Battery score at baseline was 8.0 and 8.1 points in the bicarbonate and placebo arms, respectively, denoting substantially impaired physical performance. Adherence to study medication was 73% in both groups. A total of 116 (76%) and 104 (70%) participants were assessed at the 12-month visit in the bicarbonate and placebo groups, respectively. The mean dose of bicarbonate prescribed was 1.88 g per day, with a mean dose of 1.39 g per day ingested. The serum bicarbonate concentration was, on average, 1.1 mmol/l higher in the bicarbonate group than in the placebo group over the whole course of the trial.

No significant treatment effect was evident for the primary outcome of the between-group difference in the Short Physical Performance Battery score at 12 months (−0.4 points, 95% confidence interval −0.9 to 0.1 points; $p = 0.15$). Very similar results were found in sensitivity analyses using multiple imputation of missing data. Subgroup analyses showed no significant difference in treatment effect based on age (< 75 vs. ≥ 75 years), sex, baseline chronic kidney disease category (4 vs. 5), baseline bicarbonate level (< 18 vs. ≥ 18 mmol/l) or baseline Short Physical Performance Battery score (< 10 vs. ≥ 10 points). Participants with adherence above and below the prespecified 80% threshold showed similar treatment effects according to the Short Physical Performance Battery score at 12 months (adherence > 80%: −0.6 points, 95% confidence interval −1.3 to 0.1 points; adherence $\leq 80\%$: 0.0 points, 95% confidence interval −0.7 to 0.7 points). These results excluded the minimum clinically important improvement for the Short Physical Performance Battery (of 1 point) with a high degree of confidence.

No significant treatment benefit was seen for any of the secondary outcomes, including quality of life, anthropometry, N-terminal pro-B-type natriuretic peptide and markers of bone turnover and mineral metabolism. Of particular note is that there was no significant treatment effect on estimated glomerular filtration rate (repeated-measures treatment effect 0.6 ml/minute/1.73 m², 95% confidence interval −0.8 to 2.0 ml/minute/1.73 m²; $p = 0.39$). Measures of physical performance were worse in the bicarbonate arm than in the placebo arm when considered across all visits: Short Physical Performance Battery treatment effect −0.6 points (95% confidence interval −1.0 to −0.1 points; $p = 0.02$); 6-minute walk treatment effect −33 m (95% confidence interval −62 to −4 m; $p = 0.02$); and handgrip strength −1.5 kg (95% confidence interval −2.8 to −0.2 kg; $p = 0.03$). Blood pressure was no higher in the bicarbonate arm than in the placebo arm: repeated-measures treatment effect for systolic blood pressure 0 mmHg (95% confidence interval −4 to 3 mmHg; $p = 0.93$) and repeated-measures treatment effect for diastolic blood pressure −1 mmHg (95% confidence interval −3 to 1 mmHg; $p = 0.16$).

Adverse events were more frequent in the bicarbonate arm than in the placebo arm (457 vs. 400, respectively), driven in part by higher rates of gastrointestinal adverse events, but also by higher rates of cardiovascular and respiratory adverse events. Thirty-three participants commenced renal replacement therapy (dialysis or transplantation) in each group during the trial. Time to commencement of renal replacement therapy was similar in both groups (hazard ratio 1.22, 95% confidence interval 0.74 to 2.02; $p = 0.43$). There were 15 deaths in the bicarbonate group compared with 11 in the placebo group. The time to death was not significantly different between the two groups (hazard ratio 1.30, 95% confidence interval 0.60 to 2.83; $p = 0.51$). There were more falls among participants in the bicarbonate group than among participants in the placebo group (49 vs. 39, respectively); the fall rate per participant was not significantly different in the two arms: bicarbonate, 0.99 falls per year (95% confidence interval 0.61 to 1.38 falls per year); placebo, 0.72 falls per year (95% confidence interval 0.25 to 1.19 falls per year).

Health economic analysis showed higher costs and lower quality of life in the bicarbonate arm at 1 year, with additional costs of £564 (95% confidence interval £88 to £1154) and a quality-adjusted life-year difference of −0.05 (95% confidence interval −0.08 to −0.01). Similar differences were also found at 2 years' follow-up. In further analyses, the addition of the costs of renal replacement for renal replacement patients who were lost to follow-up led to a non-significant additional cost of £809 (95% confidence interval −£4125 to £5412) in the bicarbonate arm over 24 months. A series of one-way sensitivity analyses was conducted [lower generic prescribing costs, lower cost per day, lower and higher dialysis costs, use of ICECAP (Investigating Choice Experiments for the preferences of older people CAPability) values rather than EuroQoL-5 Dimensions, three-level version, values and quality-adjusted life-years]. In all sensitivity analyses, patients in the placebo group were estimated to have lower costs and a better quality of life. Excluding dialysis patients who were lost to follow-up and their renal replacement costs, the probability of sodium bicarbonate being more cost-effective than placebo was close to zero in all analyses. The inclusion of dialysis costs for patients who dropped out of the trial after commencement of dialysis led to non-significant additional costs in the bicarbonate arm, and the probability of sodium bicarbonate being more cost-effective than placebo was found to be between 15% and 20%. Placebo dominated bicarbonate under all sensitivity analyses for incremental cost-effectiveness.

Conclusions: implications for health care

The results from this pragmatic, multicentre, placebo-controlled trial suggest that, at least for older patients in chronic kidney disease category 4 or 5, 1.5–3 g per day of oral bicarbonate did not produce any health benefits and may be associated with net harms. Although other indications for the control of acidosis exist (e.g. high potassium concentrations), evidence from the current trial suggests that the additional cost, treatment burden and side effects of oral bicarbonate may not justify its routine use in older people with advanced chronic kidney disease and mild acidosis.

Suggestions for further research

Other trials of bicarbonate are in progress. Once complete, an individual participant meta-analysis should be conducted, examining the effects of bicarbonate therapy on physical function, quality of life, renal function and progression to renal replacement therapy, anthropometry, and bone and vascular health. Such a meta-analysis should also seek to pool adverse events, particularly cardiovascular events, and to identify the characteristics of those most likely to respond to bicarbonate therapy, if any.

Depending on the results of meta-analyses, it may be necessary to formally test the effectiveness of bicarbonate therapy in other groups with chronic kidney disease, for example younger patients or those with lower serum bicarbonate concentrations, in randomised controlled trials. Alternative methods to manage acidosis in advanced chronic kidney disease need to be tested, either different bicarbonate treatment strategies, such as dose titration to target, or novel methods of managing acidosis that do not rely on the use of bicarbonate.

A final, broader recommendation is that there is a need to design and execute more trials like the BiCARB trial, focusing on outcomes that are important to older patients both in the field of chronic kidney disease and, more widely, in other organ-specific fields of clinical practice.

Trial registration

This trial is registered as ISRCTN09486651 and EudraCT 2011-005271-16. The systematic review is registered as PROSPERO CRD42018112908.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 27. See the NIHR Journals Library website for further project information. Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.819

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics, Science Citation Index.

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The research reported in this issue of the journal was funded by the HTA programme as project number 10/71/01. The contractual start date was in October 2012. The draft report began editorial review in February 2019 and was accepted for publication in September 2019. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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