RENAL FAILURE
2022, VOL. 44, NO. 1, 106–115
https://doi.org/10.1080/0886022X.2021.2023023

Taylor & Francis
Taylor & Francis Group

CLINICAL STUDY

OPEN ACCESS Check for updates

Effects of oral alkali drug therapy on clinical outcomes in pre-dialysis chronic kidney disease patients: a systematic review and meta-analysis

Honghong Shi[a], Xiaole Su[a], Bingjuan Yan[a], Chunfang Li[a,b] and Lihua Wang[a]

[a]Division of Nephrology, The Second Hospital of Shanxi Medical University, Taiyuan, China; [b]Division of Nephrology, Shanxi Cardiovascular Hospital, Taiyuan, China

ABSTRACT

Background: Metabolic acidosis accelerates the progression of chronic kidney disease (CKD) and increases the mortality rate. Whether oral alkali drug therapy benefits pre-dialysis CKD patients is controversial. We performed a meta-analysis of the effects of oral alkali drug therapy on major clinical outcomes in pre-dialysis CKD patients.

Methods: We systematically searched MEDLINE using the Ovid, EMBASE, and Cochrane Library databases without language restriction. We included all eligible clinical studies that involved pre-dialysis CKD adults and compared those who received oral alkali drug therapy with controls.

Results: A total of 18 eligible studies, including 14 randomized controlled trials and 4 cohort studies reported in 19 publications with 3695 participants, were included. Oral alkali drug therapy led to a 55% reduction in renal failure events (relative risk [RR]: 0.45; 95% confidence interval [CI]: 0.25–0.82), a rate of decline in the estimated glomerular filtration rate (eGFR) of 2.59 mL/min/1.73 m^2 per year (95% CI, 0.88–4.31). There was no significant effect on decline in eGFR events (RR: 0.34; 95% CI: 0.09–1.23), proteinuria (standardized mean difference: −0.32; 95% CI: −1.08 to 0.43), all-cause mortality events (RR: 0.90; 95% CI: 0.40–2.02) and cardiovascular (CV) events (RR: 1.03; 95% CI: 0.32–3.37) compared with the control groups.

Conclusion: Based on the available and low-to-moderate certainty evidence, oral alkali drug therapy might potentially reduce the risk of kidney failure events, but no benefit in reducing all-cause mortality events, CV events, decline in eGFR and porteninuria.

ARTICLE HISTORY
Received 22 June 2021
Revised 20 December 2021
Accepted 20 December 2021

KEYWORDS
Oral alkali drug therapy; pre-dialysis chronic kidney disease; meta-analysis; renal outcomes; all-cause mortality; cardiovascular events

Introduction

Metabolic acidosis (MA), a common complication of chronic kidney disease (CKD) caused by failure to balance the daily acid load, causes kidney damage, leading to protein-energy consumption, chronic inflammation, endocrine disorders, and the aggravation of metabolic osteopathy [1]. MA is associated with adverse outcomes in CKD patients, including the progression of CKD, all-cause mortality, and cardiovascular (CV) events [2,3].

Oral bicarbonate supplementation is commonly used to correct MA and improve the prognosis of CKD patients. According to the 2020 KDIGO guidelines for glomerulonephritis, MA should be treated with supplementation with oral sodium bicarbonate if the serum bicarbonate level is < 22 mmol/L [4]. However, it remains unclear whether treatment of MA based on oral alkali supplementation would translate into improved clinical outcomes, including delaying the progression of MA and decreasing the risks of all-cause mortality and CV events. In the UBI study, treatment of MA with sodium bicarbonate in patients with stage 3–5 CKD was safe and reduced the risks of CKD progression and all-cause mortality [5]. However, other studies did not confirm the benefits of alkali supplementation in terms of delaying CKD progression and improving survival. Randomized controlled trials (RCTs) showed no significant effects of oral alkali supplementation on renal outcomes and mortality [6,7]. In a cohort study of 386 CKD patients, compared with those who did not receive bicarbonate supplementation, the risk of ischemic heart disease was significantly lower in patients who received bicarbonate supplementation [8]. In a multi-center RCT, no differences were found in CV events between the sodium bicarbonate group and the placebo group [6]. Therefore, the association between

CONTACT Lihua Wang lihuawang236@126.com The Second Hospital of Shanxi Medical University, No.382, Wuyi Road, Taiyuan, Shanxi, China.
Supplemental data for this article can be accessed here.

oral alkali drug supplementation and clinical outcomes in pre-dialysis CKD patients is unclear.

In this systematic review, we summarized all available clinical study data to evaluate the benefits of oral alkali drug therapy regarding kidney outcomes, all-cause mortality, and CV events in pre-dialysis CKD patients.

Materials and methods

Data sources and search strategy

We performed this systematic review according to a pre-specified protocol [9] registered in the International Prospective Register of Systematic Reviews (CRD42018111030), and the reporting was in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines. A comprehensive search was conducted using the following databases: MEDLINE by Ovid (1946 to February 2020), EMBASE (1966 to February 2020), and Cochrane Central Register of Controlled Trials (no date restriction), with relevant keywords and medical subject headings that included various spellings of 'CKD', 'RCT', 'Cohort Studies', and 'Oral Alkali Therapy' (the terms 'Sodium Bicarbonate', 'Alkali', (see item S1). Studies were considered without any language restriction. To ensure a comprehensive literature search, we also screened reference lists from included articles. The ClinicalTrials.gov website was searched for ongoing but unpublished trials in this field.

Study selection and outcome estimation

We included data from RCTs and cohort studies in which oral alkali drug therapy was provided to adults with pre-dialysis CKD (participants who were pregnant, had malignancies or acute illnesses, or had a follow-up time of less than 3 months were excluded) and comparisons were made with subjects receiving the usual therapy.

Pre-defined outcomes that contained analyzable data were extracted as follows. A renal failure event was defined as a more than 50% decline in estimated glomerular filtration rate (eGFR) from baseline during follow-up, doubling of serum creatinine, or progression to end-stage renal disease (ESRD) [10]. Decline in eGFR was defined as a decrease of eGFR >3 mL/min/1.73 m^2 per year [11]. The rate of change in eGFR per year and changes in urinary protein or urinary albumin during follow-up, including urinary protein excretion, urinary albumin excretion, and the urinary albumin/creatinine ratio, were recorded. Additionally, the incidences of all-cause mortality events and CV events, defined as a composite, including fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, coronary artery revascularization, CV disease, and CV death, were recorded.

Data extraction and quality assessment

Two independent reviewers (H.S. and X.S.) extracted data and assessed their quality according to the pre-specified protocol. Disagreements were resolved by a third reviewer (L.W.). Data from all eligible studies were extracted into a spreadsheet. The data sought included the characteristics of the studies (study type, randomization method, follow-up time, withdrawals/dropouts), baseline patient characteristics (age, sex, baseline eGFR), intake of alkali drug supplementation, and outcome events.

We used the Cochrane Collaboration risk-of-bias tool [12] to assess all potential sources of bias for the included RCTs. Trials were assessed as being at low or high risk of bias or subject to other risks or some concerns, and the overall risk of bias generally corresponded to the worst risk of bias in any of the domains. However, if a study was judged to be subject to some concerns about the risk of bias for multiple domains, it might be judged as being at high risk of bias overall. In addition, the quality of the RCTs was assessed using the Jadad scale [13]. We used the Newcastle-Ottawa Scale (NOS) to assess the quality of cohort studies in terms of selection of cohorts, comparability of cohorts, and assessments of outcomes [14].

Data synthesis and statistical analyses

When dichotomous outcome data from individual studies were analyzed, relative risks (RRs) and their 95% confidence intervals (CIs) were calculated. If the RR for an individual study was unavailable in the original article, the RR and 95% CI were calculated from event numbers extracted from each study before data pooling. In calculating the RR values, we used the total number of patients randomized in each group as the denominator. Continuous outcome data from individual trials were analyzed using differences in means (MDs) with 95% CIs to pool eGFR data, whereas the standardized mean differences (SMDs) with 95% CIs were used to pool proteinuria or albuminuria data. When continuous outcome data were analyzed, the difference in the mean change between values at baseline and the end of treatment was used. If data on changes between baseline and end-of-treatment values were not

available in the studies, we calculated them using correlations estimated from other included studies that had a similar follow-up period and reported their results in considerable detail according to the imputed formulation and its related interpretations in the Cochrane Handbook [15].

Because of the poor stability of the Der Simonian-Laird procedure for small numbers of studies, we used the empirical Bayes procedure to estimate all outcomes [16,17]. We also used the Der Simonian-Laird random effects model and restricted maximum likelihood approach to assess summary effects as part of sensitivity analyses [18,19]. Considering the inevitable heterogeneity among studies, subgroup and sensitivity analyses were performed. Subgroup analyses were performed based on a pre-specified protocol according to the study type, baseline serum bicarbonate, baseline eGFR, mean age, follow-up time, and sample size. In addition, we performed sensitivity analyses using different random-effects estimation methods, excluding studies with a sample size <50, those with a follow-up of < 12 months, and studies of low quality (Jadad score <3, NOS score <5★). Heterogeneity among studies was evaluated using the I^2 or τ^2 statistic. Stata version 15.0 (StataCorp LP, College Station, TX) was used for statistical analysis, and a two-sided p-value < 0.05 was considered indicative of significance.

Results

Overview of included trials

The literature search yielded 9284 potentially relevant records, of which the full texts of 185 publications were reviewed (Figure 1). After screening and eligibility assessment, 14 RCTs [5–7,20–32] and 4 cohort studies [8,29,33,34] reported in 19 publications with 3695 individuals were included in this systematic review and meta-analysis. Baseline and key characteristics of the enrolled studies are presented in Supplementary Table S1 and Table S2. The median follow-up time was 19.5 months. Individuals were enrolled at an average age of 55.78 years, and male participants accounted for 59.55% of the total. The average eGFR of participants was 31.51 mL/min/1.73 m^2. A total of 2 oral alkali drug therapies were studied, including those featuring sodium bicarbonate in 17 studies, veverimer in 1 study,.

The Jadad score for each included RCT is presented in Supplementary Table S1. Eleven trials had a Jadad score of 3–5, and the others scored less than 3. Of all RCTs, 78.57% were associated with a low risk of bias arising from the randomization process, and all studies had a low risk of bias due to deviations from intended interventions, due to missing outcome data, associated with measurements of outcomes, and associated with selection of the reported results. In terms of overall bias, 78.57% of the

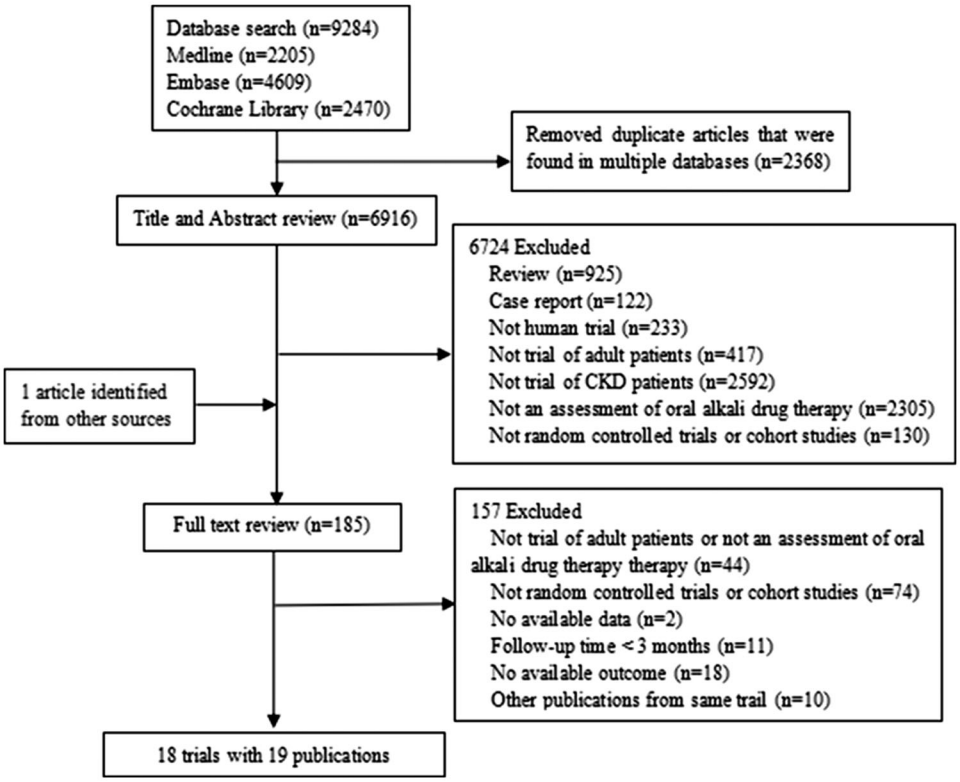

Figure 1. PRISMA flow chart for the included studies.

research trials were assessed as at low risk, and 21.43% as subject to some concerns (Supplementary Table S3).

As shown in Supplementary Tables S1 and S4, all included cohort studies were considered of high quality (with scores of 7★–8★) according to the NOS checklist.

Effects of oral alkali drug therapy on renal outcomes

Nine RCTs with 1833 participants reported 250 renal failure events. Compared with the control group, oral alkali drug therapy was associated with a 55% reduction in the risk of renal failure events (RR: 0.45; 95% CI: 0.25–0.82), with significant heterogeneity across studies ($I^2 = 67.8\%$, $p = 0.005$; Figure 2). No significant heterogeneity was observed in any subgroup analysis (Table 1).

Data regarding the effects of oral alkali drug therapy on decline in eGFR events were available from three RCTs that included 404 individuals and 123 events. Overall, there was no significant effect of oral alkali drug therapy on decline in eGFR events (RR: 0.34; 95% CI: 0.09–1.23) compared with the control group. Moderate heterogeneity across these trials (I^2 =54.1%, $p = 0.113$; Figure 2) was found.

Thirtine RCTs and three cohort studies with 2746 participants provided data on differences in the rate of change in eGFR. Compared with the control group, oral alkali drug therapy slowed the rate of eGFR decline by 2.59 mL/min/1.73 m^2 per year (95% CI: 0.88–4.31), with significant heterogeneity observed ($I^2 = 97.6\%$, $p < 0.001$; Figure 3). Subgroup analyses showed that effect sizes were greater in studies that enrolled patients baseline serum bicarbonate < 20.95 mmol/L, baseline eGFR 30-59 mL/min/1.73 m^2, age < 55 years ($p < 0.001$; Supplementary Table S5).

Data on the effects of oral alkali drug therapy on proteinuria or albuminuria were available in only five studies (four RCTs and one cohort study) with 591 participants, and no significant effect was found (SMD: −0.32; 95% CI: −1.08 to 0.43). I^2 statistics (88.2%, $p < 0.001$; Figure 4) indicated significant heterogeneity across studies. Subgroup analyses did not reveal heterogeneity regarding pre-specified characteristics (Supplementary Table S5).

Effects of oral alkali drug therapy on all-cause mortality and CV events

Seven RCTs involving 1709 individuals reported 127 all-cause mortality events. There was no significant effect of oral alkali drug therapy on the risk of all-cause mortality compared with the control groups (RR: 0.90; 95% CI: 0.40–2.02). Significant heterogeneity was noted across the included trials ($I^2 = 54.7\%$, $p = 0.05$; Figure 5). No significant heterogeneity was found for all-cause mortality in the subgroup analyses (Supplementary Table S5).

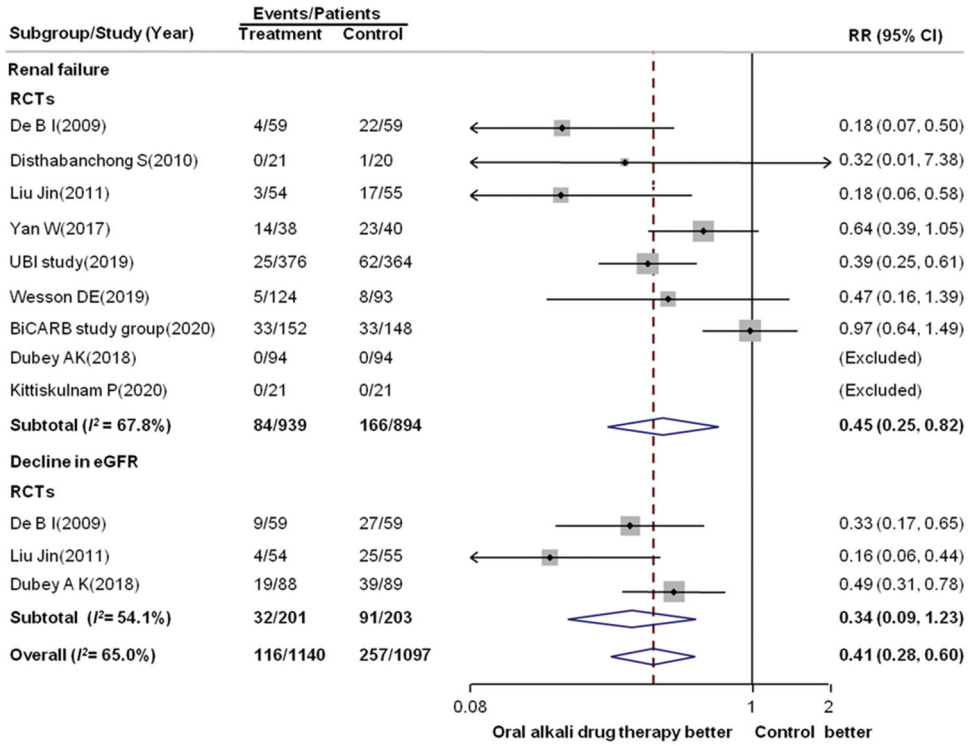

Figure 2. Forest plot for renal failure events and decline in eGFR events. Renal failure was defined as a more than 50% decline in eGFR from baseline during follow-up, doubling of serum creatinine or ESRD. CI: confidence interval; RR: relative risk.

Table 1. Subgroup analysis of renal failure events.

Subgroup	No. of trials	*n*	RR (95% CI)	*p* for RR	I^2	*p* for heterogeneity test [a]
Study type						
RCT	–	–	–	–	–	–
Cohort study	–	–	–	–	–	
Baseline serum bicarbonate						
< 20.58	6	1010	0.45 (0.24, 0.86)	0.016	73.9%	0.07
≥ 20.58	3	823	0.39 (0.25, 0.60)	<0.001	0.0%	
Baseline eGFR (mL/min/1.73 m^2)						
30–59	3	970	0.39 (0.25, 0.61)	<0.001	–	0.08
15–29	6	863	0.45 (0.24, 0.83)	0.01	67.8%	
Mean age (years)						
<55	4	493	0.30 (0.11, 0.86)	0.02	76.9%	0.34
≥55	5	1340	0.57 (0.30, 1.09)	0.09	66.9%	
Follow-up time (months)						
< 24	5	566	0.60 (0.38, 0.94)	0.02	0%	0.55
≥ 24	4	1267	0.38 (0.17, 0.83)	0.01	83.2%	
Sample size						
< 127	4	270	0.38 (0.13, 1.10)	0.08	56.0%	0.52
≥ 127	5	1563	0.46 (0.23, 0.93)	0.03	79.0%	

Note. a *p* value calculated by χ^2 statistics was shown. CI: confidence interval; n: number of patients; RCT: randomized parallel-group controlled trial; RR: relative risk.

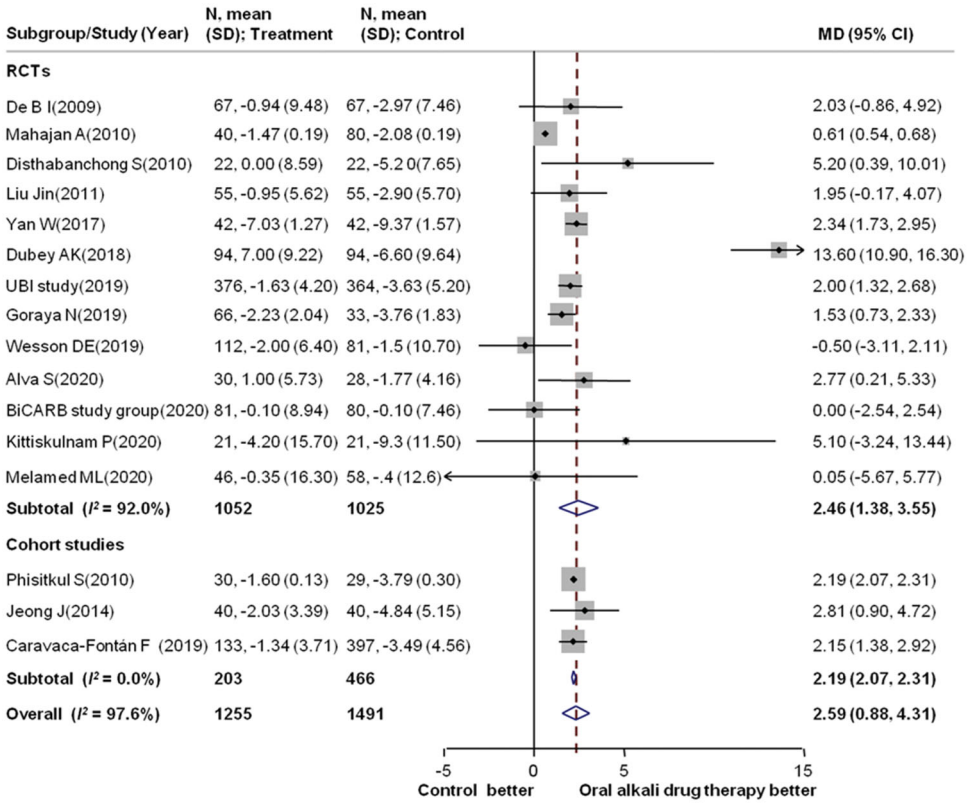

Figure 3. Forest plot for rate of change in estimated glomerular filtration rate (eGFR). CI: confidence interval; MD: mean difference; SD: standard deviation.

Data for CV events were available from three RCTs and one cohort studie that included 1098 participants and 160 events. There was no significant difference in the risk of CV events between treatment and control groups (RR: 1.03; 95% CI: 0.32–3.37), with significant heterogeneity observed among trials (I^2 = 65.1%, p = 0.057; Figure 5). Subgroup analyses revealed no heterogeneity for CV events (Supplementary Table S5).

Sensitivity analysis

The results did not change after the exclusion of studies with a follow-up duration of < 12 months, with a sample size < 50, or assessed as low quality, or when

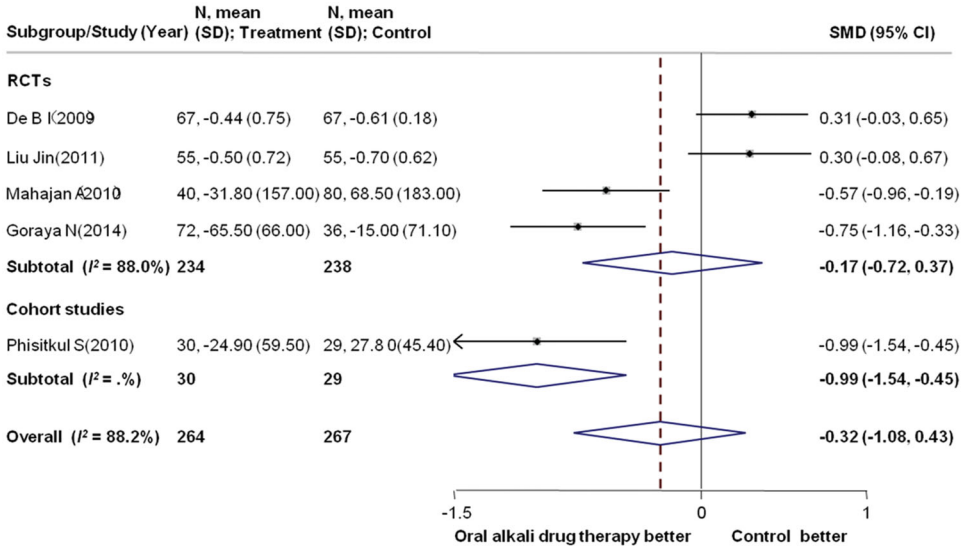

Figure 4. Forest plot for the change in proteinuria or albuminuria. CI: confidence interval; SD: standard deviation; SMD: standard mean difference.

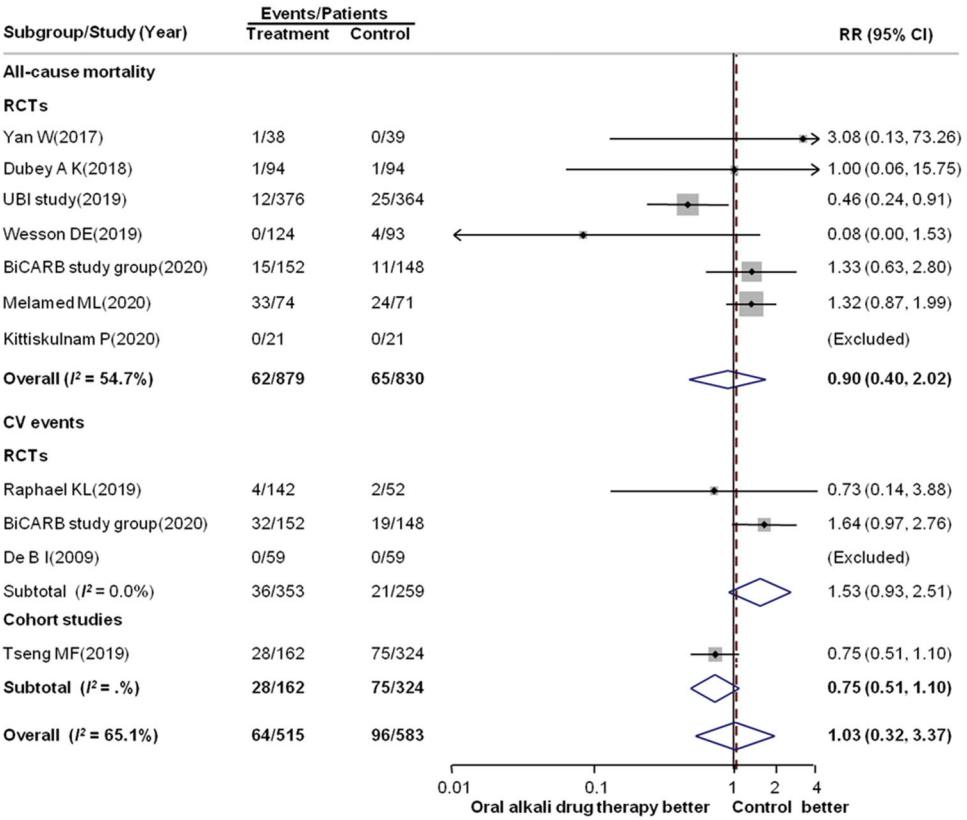

Figure 5. Forest plot for all-cause mortality and cardiovascular events. Cardiovascular events were defined as a composite, including fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, coronary artery revascularization, cardiovascular disease and cardiovascular death. CI: confidence interval; N: number of trials; RR: relative risk.

different random-effects estimation methods were used (Supplementary Table S6).

Discussion

MA, a common complication of CKD, is associated with CKD progression and higher mortality. The benefits of oral alkali drug supplementation for renal outcome events, all-cause mortality, and CV events in pre-dialysis CKD patients are controversial. This meta-analysis of 18 studies including 3695 participants suggests that oral alkali drug therapy produces a 55% reduction in renal failure events. No significant effects were observed for

decline in eGFR, proteinuria, the risk of all-cause mortality events and CV events. The results were broadly consistent across major subgroups, as demonstrated by the sensitivity analyses. Of note, the existence of significant heterogeneity may limit the interpretation and clinical application of these results. Heterogeneity in the study included different CKD stages of patients, different baseline serum bicarbonate levels across studies, considerable variation in follow-up time, and different strategies to correct MA. Although we preformed subgroup analyses, which remains a concern for meaningful interpretation of the results.

MA is associated with the progression of CKD [35,36]. However, there are sparse data on the effects of oral alkali drug supplementation on renal function in CKD patients, with inconsistent effects reported to date. In accordance with our study, a 2012 systematic review suggested that oral alkali therapy could slow the decline of the eGFR in patients with MA [37]. A 2019 systematic review indicated that oral alkali supplementation was associated with an improvement in eGFR and a reduction in the risk of progression to ESRD [38]. However, only two studies evaluated the effect of oral alkali therapy on the incidence of ESRD. Compared with previous meta-analyses [37,38], our study included many new studies on the effects of oral alkali therapy on changes in eGFR and ESRD events. Our summary data showed smaller reduction in kidney function decline, although with significant heterogeneity between the included studies. These data should be interpreted with caution. . . Additional well- designed trials are needed to explore the effect of treatment of MA on the risk of kidney disease progression with these different types of interventions. In the Chronic Renal Insufficiency Cohort study [2], the role of serum bicarbonate level as a risk factor for renal outcomes (ESRD or 50% reduction in eGFR) was evaluated in 3939 individuals with stage 2–4 CKD. After adjusting for covariates, the risk of developing a renal endpoint was 3% lower per 1 mmol/L increase in serum bicarbonate level [2]. A retrospective study from the National Health and Nutrition Examination Survey III involving 1486 CKD patients with a median 14.2 years of follow-up demonstrated that a higher dietary acid load was independently associated with an increased risk of ESRD, and this association was more pronounced in individuals with advanced CKD than in those with mild or moderate CKD [39]. Several studies included in this meta-analysis reported that oral alkali supplementation can delay the progression of CKD in patients with MA [28,29,32,35,37]. However, Mahajan [21] found that oral alkali supplementation delayed the progression of CKD in stage 2 CKD patients without MA. Wesson and Simoni [40] demonstrated that oral alkali dietary supplementation prevented eGFR decline in the two-thirds nephrectomy rat model (a model of early-stage CKD that does not include MA) compared with control rats over a 24-week period. This implies that mechanisms other than the correction of MA are involved in the renoprotective effect of oral alkali supplementation and raises important questions regarding the potential use of oral alkali supplementation in other conditions. Several potential mechanisms may be involved, including decreasing interstitial ammonium levels and reducing complement activation; the correction of interstitial acidosis and decreasing the local production of endothelin-1 and angiotensin II; decreasing tubular H^+ secretion, which can limit tubular cast formation; activation of the cholinergic anti-inflammatory pathway and decreasing renal inflammation; or the correction of MA leading to enhanced blood glucose control [41]. The mechanisms underlying the renoprotective effect of oral alkali therapy need to be further explored. No high-quality study has assessed the effects of oral alkali therapy on CKD progression in patients with and without MA. Therefore, well-designed studies are needed. Both the BiCARB Study Group [7] and Raphael KL [28] studies failed to find a benefit of oral alkali therapy in terms of preventing an eGFR decline in CKD. In both studies, the mean age of participants was around 72.5 years, which may explain why some patients were not responsive to oral alkali therapy. The eGFR typically declines with age. It is possible that sodium bicarbonate is less effective in older patients with CKD compared to younger patients [7,28], which was consistent with the results of subgroup analyses. Further well-designed studies are needed to explore this.

In our study, there was no compelling evidence that oral alkali drug therapy was associated with a lower incidence of all-cause mortality events and CV events. The scarcity of data on all-cause mortality events (seven studies with 127 events) and CV events (four studies with 160 events) available for the meta-analysis might have introduced a risk of false-negative results because of low statistical power. Among 740 individuals with 3 years of follow-up enrolled in the UBI study, the correction of MA reduced the risk of all-cause mortality in stage 3–5 CKD (fully adjusted hazard ratio: 0.36; 95% CI: 0.18–0.74) [5]. The Large Chronic Renal Insufficiency Cohort study showed that maintenance of a serum bicarbonate level >26 mmol/L was associated with increased risks of congestive heart failure events and mortality [42]. Numerous trials showed a U-shaped relationship between serum bicarbonate and mortality in

patients with CKD [43,44]. The overall effects of alkali supplementation on all-cause mortality and CV events are uncertain. Chronic alkaline therapy for renoprotection may impact vascular calcification. In animal studies, alkali supplementation worsened arterial calcification [45,46]. Mixing sodium bicarbonate and calcium results in an insoluble precipitate, calcium carbonate ($CaCO_3$). Supplementation with sodium bicarbonate increased the levels of serum phosphorous and FGF-23, risk factors for CV events and mortality [47,48] . In addition, a high sodium retention level is a cause for concern. There are 0.0123 mmol of sodium in every 1 mg of sodium bicarbonate, and high sodium can cause hypertension, a fluid overload, and an increased risk of heart failure in CKD patients [2]. Therefore, salt restrictions should be stricter in patients taking oral sodium bicarbonate. The optimal dosage of supplementary oral alkali drugs that provides renal and cardiovascular protection and minimizes side effects is uncertain. It is important to determine the optimal serum bicarbonate level and safe dose of oral alkali drugs according to CKD stage as well as monitor the serum bicarbonate level when an oral alkali supplement is given to pre-dialysis CKD patients.

This study has several potential limitations. First, as a result of different abilities to regulate the acid-base balance according to CKD stage, different baseline serum bicarbonate levels across studies, the inclusion of some patients without MA at baseline, and different target serum bicarbonate levels across studies, the data do not provide insight into the safe and upper dosage limits of oral alkali supplementation or the optimal serum bicarbonate level for patients with CKD. Second, findings related to proteinuria, decline in eGFR, and all-cause mortality and CV events were based on limited studies, restricting the reliability of the results related to these outcomes. Third, the small sample size in some studies, as well as the existence of statistical heterogeneity and clinical heterogeneity, limited the reliability of our conclusions. Fourth, veverimer, a novel drug correcting MA, corrected MA by selectively binding and removing hydrochloric acid from the gastrointestinal tract, resulting in increased serum bicarbonate concentrations. However, there is only one RCT currently comparing veverimer and placebo. Futher studies including comparison between veverimer and sodium bicarbonate supplementation would be helpful to determine if there are any significant differences between the two strategies. Finally, none of the studies included patients with uncontrolled hypertension or obvious chronic heart failure. Whether oral alkali drug therapy is safe in these patients is unclear and needs to be further explored.

In summary, based on the available and low-to-moderate certainty evidence, oral alkali drug therapy might potentially reduce the risk of kidney failure events, but no benefits in reducing all-cause mortality events, CV events, decline in eGFR and porteninuria. Notably, due to significant heterogeneity among studies the findings are not the final word. Further studies are needed to confirm these results for patients with CKD.

Acknowledgements

We thank Textcheck for helping in proofreading and editing the english of the final manuscrip.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the [National Natural Science Foundation of China #1] under Grant [number 82000655]; [PRO. Run Project of Beijing Ronghe Medical Development Foundation #2] under Grant [KYS2021-03-02–11].

References

[1] Kraut JA, Madias NE. Metabolic acidosis of CKD: an update. Am J Kidney Dis. 2016;67(2):307–317.
[2] Dobre M, Yang W, Chen J, et al. Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: a report from the Chronic Renal Insufficiency Cohort (CRIC) study. Am J Kidney Dis. 2013;62(4):670–678.
[3] Menon V, Tighiouart H, Vaughn NS, et al. Serum bicarbonate and long-term outcomes in CKD. Am J Kidney Dis. 2010;56(5):907–914.
[4] Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100(4S):S1-S276.
[5] Di Iorio BR, Bellasi A, Raphael KL, et al. Treatment of metabolic acidosis with sodium bicarbonate delays progression of chronic kidney disease: the UBI study. J Nephrol. 2019;32(6):989–1001.
[6] Melamed ML, Horwitz EJ, Dobre MA, et al. Effects of sodium bicarbonate in CKD stages 3 and 4: a randomized, placebo-controlled, multicenter clinical trial. Am J Kidney Dis. 2020;75(2):225–234.
[7] BiCARB study group. Clinical and cost-effectiveness of oral sodium bicarbonate therapy for older patients with chronic kidney disease and low-grade acidosis (BiCARB): a pragmatic randomised, double-blind, placebo-controlled trial. BMC Med. 2020;18:91.

[8] Tseng MF, Chung CH, Hsu YJ, et al. Alkali therapy lessens risks of ischemic heart disease in CKD patients: a nationwide propensity-score-matched cohort study. Int J Clin Exp Med. 2019;5:5487–5496.
[9] Shi H, Su X, Yan B, et al. The effects of dietary alkali supplements on renal outcomes and nutritional indices in patients with chronic kidney disease. PROSPERO. 2018;CRD42018111030. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018111030.
[10] Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA. 2014;311(24):2518–2531.
[11] Naik RP, Derebail VK, Grams ME, et al. Association of sickle cell trait with chronic kidney disease and albuminuria in African Americans. JAMA. 2014;312(20):2115–2125.
[12] Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
[13] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1–12.
[14] Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Ottawa Hospital Research Institute. [cited 2017 Mar 14]. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[15] Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. version 5.1.0. Chichester (UK): The Cochrane Collaboration. 2011.
[16] Cornell JE, Mulrow CD, Localio R, et al. Random-effects meta-analysis of inconsistent effects: a time for change. Ann Intern Med. 2014;160(4):267–270.
[17] Friston KJ, Penny W, Phillips C, et al. Classical and Bayesian inference in neuroimaging: theory. Neuroimage. 2002;16(2):465–483.
[18] DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials. 2015;45(Pt A):139–145.
[19] Harville DA. Maximum likelihood approaches to variance component estimation and to related problems. J Am Stat Assoc. 1977;72(358):320–338.
[20] de Brito-Ashurst I, Varagunam M, Raftery MJ, et al. Bicarbonate supplementation slows progression of CKD and improves nutritional status. JASN. 2009;20(9):2075–2084.
[21] Mahajan A, Simoni J, Sheather SJ, et al. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. Kidney Int. 2010;78(3):303–309.
[22] Disthabanchong S, Treeruttanawanich A. Oral sodium bicarbonate improves thyroid function in predialysis chronic kidney disease. Am J Nephrol. 2010;32(6):549–556.
[23] Jin L, Lifan M. Effect of oral sodium bicarbonate on progression of chronic kidney disease. Chin JMAP. 2012;29:178–181.
[24] Yan W, Wang L, Huang T, et al. Treatment for non-thyroidal illness syndrome in advanced chronic kidney disease: a single-blind controlled study. J Nephrol. 2017;30(4):557–565.
[25] Dubey AK, Sahoo J, Vairappan B, et al. Correction of metabolic acidosis improves muscle mass and renal function in chronic kidney disease stages 3 and 4: a randomized controlled trial. Nephrol Dial Transplant. 2020;35:121–129.
[26] Goraya N, Simoni J, Jo CH, et al. Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate. Kidney Int. 2014;86(5):1031–1038.
[27] Goraya N, Munoz-Maldonado Y, Simoni J, et al. Fruit and vegetable treatment of chronic kidney disease-related metabolic acidosis reduces cardiovascular risk better than sodium bicarbonate. Am J Nephrol. 2019;49(6):438–448.
[28] Raphael KL, Greene T, Wei G, et al. Sodium bicarbonate supplementation and urinary TGF-β1 in nonacidotic diabetic kidney disease: a randomized, controlled trial. Clin J Am Soc Nephrol. 2020;15(2):200–208.
[29] Caravaca-Fontán F, Díaz-Campillejo R, Valladares J, et al. Successful correction of metabolic acidosis is difficult to achieve in chronic kidney disease. Nefrologia. 2020;40(3):328–335.
[30] Wesson DE, Mathur V, Tangri N, et al. Long-term safety and efficacy of veverimer in patients with metabolic acidosis in chronic kidney disease: a multicentre, randomised, blinded, placebo-controlled, 40-week extension. Lancet. 2019;394(10196):396–406.
[31] Alva S, Divyashree M, Kamath J, et al. A study on effect of bicarbonate supplementation on the progression of chronic kidney disease. Indian J Nephrol. 2020;30(2):91–97.
[32] Kittiskulnam P, Srijaruneruang S, Chulakadabba A, et al. Impact of serum bicarbonate levels on muscle mass and kidney function in pre-dialysis chronic kidney disease patients. Am J Nephrol. 2020;51(1):24–34.
[33] Phisitkul S, Khanna A, Simoni J, et al. Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR. Kidney Int. 2010;77(7):617–623.
[34] Jeong J, Kwon SK, Kim HY. Effect of bicarbonate supplementation on renal function and nutritional indices in predialysis advanced chronic kidney disease. Electrolyte Blood Press. 2014;12(2):80–87.
[35] Raphael KL, Wei G, Baird BC, et al. Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans. Kidney Int. 2011;79(3):356–362.
[36] Shah SN, Abramowitz M, Hostetter TH, et al. Serum bicarbonate levels and the progression of kidney disease: a cohort study. Am J Kidney Dis. 2009;54(2):270–277.
[37] Susantitaphong P, Sewaralthahab K, Balk EM, et al. Short- and long-term effects of alkali therapy in chronic kidney disease: a systematic review. Am J Nephrol. 2012;35(6):540–547.
[38] Navaneethan SD, Shao J, Buysse J, et al. Effects of treatment of metabolic acidosis in CKD: a systematic review and meta-analysis. CJASN. 2019;14(7):1011–1020.

[39] Banerjee T, Crews DC, Wesson DE, et al. High dietary acid load predicts ESRD among adults with CKD. J Am Soc Nephrol. 2015;26(7):1693–1700.
[40] Wesson DE, Simoni J. Acid retention during kidney failure induces endothelin and aldosterone production which lead to progressive GFR decline, a situation ameliorated by alkali diet. Kidney Int. 2010;78(11): 1128–1135.
[41] Mannon EC, O'Connor PM. Alkali supplementation as a therapeutic in chronic kidney disease: what mediates protection? Am J Physiol Renal Physiol. 2020; 319(6):F1090–F1104.
[42] Dobre M, Yang W, Pan Q. Persistent high serum bicarbonate and the risk of heart failure in patients with chronic kidney disease (CKD): a report from the Chronic Renal Insufficiency Cohort (CRIC) study. J Am Heart Assoc. 2015;4:e001599.
[43] Raikou VD, Kyriaki D. Mortality and low serum bicarbonate level in patients on hemodiafiltration versus peritoneal dialysis. Indian J Nephrol. 2018;28:105–112.
[44] Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD. Nephrol Dial Transplant. 2008;24(4):1232–1237.
[45] Lomashvili K, Garg P, O'Neill WC. Chemical and hormonal determinants of vascular calcification in vitro. Kidney Int. 2006;69(8):1464–1470.
[46] Mendoza FJ, Lopez I, Montes de Oca A, et al. Metabolic acidosis inhibits soft tissue calcification in uremic rats. Kidney Int. 2008;73(4):407–414.
[47] Kendrick J, Kestenbaum B, Chonchol M. Phosphate and cardiovascular disease. Adv Chronic Kidney Dis. 2011;18(2):113–119.
[48] Kendrick J, Cheung AK, Kaufman JS, et al. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. J Am Soc Nephrol. 2011; 22(10):1913–1922.