

# The effect of sodium bicarbonate administration on renal function: A systematic review and meta-analysis of clinical trials

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## Research Article

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## Abstract

## Background

Metabolic acidosis is a prevalent condition in patients with chronic kidney disease (CKD). Although sodium bicarbonate is extensively used for management of metabolic acidosis, its efficacy has not been summarized in previous review studies.

## Objective

To conduct a systematic review and meta-analysis to estimate the overall effects of sodium bicarbonate on indices of renal function in patients with CKD.

## Methods

A systematic literature search was carried out through the Medline, Web of Science and Scopus databases, up to July 2020. Studies that reported the effects of oral sodium bicarbonate administration on renal function were included. Blood urea nitrogen (BUN), serum creatinine, glomerular filtration rate (GFR), and creatinine clearance were defined as renal function indices. A random-effects model was used to calculate the overall effect and reported as weighted mean difference (WMD).

## Results

Thirteen studies were included in this systematic review and meta-analysis. A beneficial effect of sodium bicarbonate was observed on BUN (WMD: - 8.63 mg/dL; 95% CI: -11.08, -6.19), serum creatinine (WMD: -0.19 mg/dL; 95% CI: -0.36, -0.02), GFR (WMD: 0.75 ml/min/1.73 m<sup>2</sup>; 95% CI: 0.14, 1.35), and creatinine clearance (WMD: 4.82 mL/min; 95% CI: 2.68, 6.96). There was no between study heterogeneity for all renal function indices. Also, no publication bias was observed in this study.

## Conclusion

This systematic review and meta-analysis showed that sodium bicarbonate supplementation could increase GFR and creatinine clearance and decrease BUN and creatinine. Therefore, sodium bicarbonate therapy may be efficacious in ameliorating the progression of CKD.

## Introduction

Chronic kidney disease (CKD) is a progressive condition that gradually induces serious health complications, including hyperlipidemia, cardiovascular and bone disease, and electrolyte disturbance (1). For industrialized and developing countries, CKD is a dangerous condition due to the wide-scale consumption of animal and fruit-based acids; where such acid-inducing diets can cause metabolic acidosis and exacerbate CKD (2). These acid loads provoke endothelin and aldosterone production and induce fibrosis, progressive decline in kidney function and adverse cardiovascular effects (3, 4). However, these effects may be reversed by alkali supplementation; indeed, the National Kidney Foundation advocates alkali therapy in acidotic patients.

Sodium bicarbonate is a major component of alkali therapy (5), where previous studies have shown that there is an inverse association between sodium bicarbonate administration and acidosis (6, 7). Also, sodium bicarbonate therapy has a significant increasing effect on serum bicarbonate level (8), thereby conferring a beneficial effect on the bicarbonate buffer system (9). Nevertheless, the efficacy of sodium bicarbonate therapy for CKD patients without significant acidosis in order to delay CKD progression remains unclear. Several studies assessed the effect of sodium bicarbonate therapy on indices of renal function (10); however, no systematic review and meta-analysis has evaluated published data regarding the efficacy of sodium bicarbonate in slowing down CKD progression. Also, the overall effect of sodium bicarbonate administration on indices of renal function is unclear. Therefore, the aim of the present study was to summarize the effect of sodium bicarbonate intake on kidney function in patients with CKD.

## Results

As illustrated in **Figure 1**, we identified 1534 records (613 from the Medline, 521 from the Web of Science, and 400 from the Scopus) through literature searches. After removing duplicate reports, 1217 studies were screened against inclusion and exclusion criteria. Subsequently, 1167 reports were excluded because they were animal studies (n=139), editorial letter (n=8), review/systematic review studies (n=23), or not relevant (n=997). Fifty remaining studies were scrutinized in detail, and 37 articles were excluded because of: 1) using intravenous sodium bicarbonate,

2) co-supplementation of sodium bicarbonate with vitamin C, 3) using vegetables and fruits as an intervention in control group, 4) not reporting relevant data, or 5) enrolling subjects with acute kidney injury. Finally, 13 studies met all inclusion and exclusion criteria were included in this systematic review and meta-analysis (3, 4, 11-21)

Characteristics of the included studies are presented in **Table 1**. Participants were from Hong Kong, Israel, Thailand, Chinese, Brazil, Italy, South Korea, England, Thailand, and the USA. All studies enrolled both genders. Participants in all studies were pre-dialysis patients, except for two studies that recruited peritoneal dialysis patients (1, 7). The mean age ranged from 54 to 72 years old. The design of three studies was pre-post (3, 5, 6) and the remaining studies were parallel randomized clinical trials. Five studies administered an increasing dose of sodium bicarbonate (3,4,8,12,13) and the remaining trials used a fixed dose.

Table 1: Characteristics and details of included studies

First author (publication year)	Country	Sample size (male/female)	Participants	Age (y)	Reported data	Design	Duration (week)	Dose of intervention	Comparison	Results	score
Szeto (2003)	Hong Kong	60 (35/25)	PD	55	GFR	Parallel	52 weeks	0.9 g thrice daily	Placebo	No significant effect	High
Ori (2015)	Israel	13 (12/1)	Pre-dialysis	65	Serum Creatinine, GFR Urea	Before after	4 weeks	1 to 3 gr	-----	No significant effect	Low
de Brito-Ashurst (2009)	England	134 (68/66)	Pre-dialysis	54	Creatinine clearance	Parallel	52 weeks	1.82 g+-0.8	Standard care	Significant reduction in loss of creatinine clearance	High
Disthabanchong (2010)	Thailand	41 (21/20)	Pre-dialysis	70	GFR Serum Creatinine	Before after	10 weeks	increasing dose	-----	Significant reduction in serum creatinine and increase in GFR	High
Liu (2017)	Chinese	40 (20/20)	PD	56	Creatinine clearance	Parallel	104weeks	1.0 g/day	Placebo	No significant effect	High
Rizzetto (2017)	Brazil	31 (21/10)	Pre-dialysis	59	Serum Creatinine Bun Creatinine clearance	Before After	60 weeks	1.0 mmol/kg	-----	Significant reduction in BUN	Low
Di Iorio (2019)	Italy	740 (458/282)	Pre-dialysis	68	Creatinine clearance	Parallel	154 weeks	Increasing dose	Standard care	Significant reduction in loss of creatinine clearance	High
Jeong (2014)	South Korea	80 (47/33)	Pre-dialysis	55	GFR, Serum Creatinine BUN	Parallel	52 weeks	Increasing dose	Standard care	Significant increase in GFR	High
The BiCARB study group (2020)	England	300 (214/86)	Pre-dialysis	70	GFR Serum Creatinine	Parallel	104 weeks	Increasing dose	Placebo	No significant effect	High
Kittiskulnam (2020)	Thailand	42 (24/18)	Pre-dialysis	61	Serum Creatinine GFR	Parallel	17 weeks	Increasing dose	Standard care	Significant reduction in loss of in GFR	High
Melamed (2020)	US	224 (102/122)	Pre-dialysis	61	GFR	Parallel	104 weeks	0.4 mEq/kg	Placebo	No significant effect	High
Raphael (2020)	US	74 (72/2)	Pre-dialysis	72	Bun Creatinine clearance GFR	Parallel	26 weeks	0.5 meq/kg	Placebo	Significant reduction in BUN	High
Raphael (2020)	US	194 (9131/63)	Pre-dialysis	67	GFR Creatinine clearance	Parallel	28 weeks	0.8 meq/kg	Placebo	No significant effect	High

BUN: Blood urea nitrogen, GFR: Glomerular filtration rate, PD: Peritoneal dialysis

The results of quality scores allocation showed that all studies were high-quality, except for two studies that received low scores (5,6).

### Meta-analysis

Four studies reported the effect of sodium bicarbonate on BUN (4-6, 9). In comparison with control treatment, BUN was significantly decreased (WMD: - 8.63 mg/dL; 95% CI: -11.08, -6.19) after sodium bicarbonate administration (**Figure 2**). No significant heterogeneity was observed

between studies ( $I^2=0.0\%$ ,  $p=0.447$ ).

The effect of sodium bicarbonate administration on serum creatinine was reported in six studies (3-6, 12, 13). We observed a significant reduction in serum creatinine (WMD: -0.19 mg/dL; 95% CI: -0.36, -0.02) after sodium bicarbonate supplementation compared with control treatment (**Figure 3**). There was no significant heterogeneity between studies ( $I^2= 10.0\%$ ,  $p = 0.353$ ).

As illustrated in **Figure 4**, five clinical trials (2, 6-9) reported that sodium bicarbonate had a beneficial effect on creatinine clearance compared with control treatment (WMD: 4.82 mL/min; 95% CI: 2.68, 6.96). We do not find any significant heterogeneity between studies ( $I^2=50.5\%$ ,  $P=0.089$ ).

The forest plot from nine trials (1,3,4,5,9,10,11,12,13) of GFR response to sodium bicarbonate supplementation is shown in **Figure 5**. GFR was significantly increased following sodium bicarbonate administration in comparison with control treatment (WMD: 0.75 ml/min/1.73 m<sup>2</sup>; 95% CI: 0.14, 1.35). There was no significant heterogeneity between studies ( $I^2=14.6\%$ ,  $P=0.308$ ).

We did not find any evidence of publication bias for BUN (Begg's  $P=0.497$ , Eggers's  $P=0.491$ ), serum creatinine (Begg's  $P=0.573$ , Eggers's  $P=0.353$ ), creatinine clearance (Begg's  $P=0.573$ , Eggers's  $P=0.378$ ), and GFR (Begg's  $P=0.297$ , Eggers's  $P=0.524$ ).

The results of the sensitivity analysis showed that, in the case of GFR, results were insignificant when the Jeong et al. study was eliminated (WMD: 0.402 ml/min/1.73 m<sup>2</sup>; 95% CI: -0.187, 0.991). A similar finding was observed for serum creatinine after omitting the Rizzetto et al. study (WMD: -0.053 mg/dL; 95% CI: -0.297, 0.190). In the case of BUN and creatinine clearance, the omission of any study did not significantly alter the results.

## Discussion

The results of the present systematic review and meta-analysis indicated that sodium bicarbonate could significantly increase GFR and creatinine clearance and decrease BUN and serum creatinine. These changes can decrease the risk of ESRD, consequently reducing the mortality of patients (17).

Our findings were in line with some related review studies; for instance, a previous systematic review reported that alkali therapy is associated with an improvement in kidney function, which may cause a long-term benefit in slowing the progression of CKD (22). Another review study suggested that oral alkali supplementation or a reduction in dietary acid intake may slow the rate of kidney function decline and potentially reduce the risk of ESKD in patients with CKD and metabolic acidosis (23).

The results of sensitivity analysis revealed that excluding the Rizzetto et al. study (14) attenuated beneficial effect of sodium bicarbonate on serum creatinine. This study showed a significant reduction in serum creatinine after sodium bicarbonate administration, however, the reported confidence interval for changes in serum creatinine was very short in this study compared with other included studies. Therefore, the weight of this study was high in our analysis and omitting it resulted in a notable change in overall effect size. For GFR, we found that excluding the Jeong et al study (12) attenuated observed effect of sodium bicarbonate. All included studies enrolled subjects at a certain stage of CKD, except for the Jeong et al study, which included participants with CKD4 and CKD5. Therefore, the design of this study was different from other included publications.

There are several putative mechanisms for the effect of acidosis on the CKD progression including ammonia-induced activation of the alternative complement system, overproduction of endothelin-1, angiotensin II, aldosterone and proinflammatory cytokines, and induction of tubulointerstitial fibrosis (24, 25). It was observed that serum bicarbonate levels below the normal range increased QRS duration and arterial pressure (23). Intravenous sodium bicarbonate treatment increases plasma bicarbonate, adjusts excess hydrogen ion concentrations, raises blood pH, and reverses the clinical manifestations of acidosis (26). Alkaline oral treatment can reduce acidosis and thus reduce the progression of CKD and its complications, including protein catabolism, chronic inflammation, insulin resistance, and growth hormone (27).

Although sodium bicarbonate is a very effective drug in patients with CKD, it interacts with some of the most ubiquitous medications, such as captopril, iron compounds, multivitamins, chloroquine, corticosteroids, mesalamine, rosuvastatin, sotalol, and dabigatran (28). These interactions are caused by various mechanisms, such as reduction/increases in absorption, bioavailability, serum concentration, and the effect of the medications (29). Therefore, drug-drug interaction should be considered in these cases. In the present review, the medications received by patients were not reported and drug-drug interaction was not considered, and thus, we could not include such information in our study. Future studies should consider possible interactions and contraindications between sodium bicarbonate and other prescribed medications in patients with CKD (29).

There is a concern regarding sodium content of the sodium bicarbonate (27% of sodium bicarbonate is sodium) and its potential deleterious effect of blood pressure. A clinical trial showed that acute loading of high dose (300 mg/kg) sodium bicarbonate could increase diastolic blood

pressure among athletes (30). Although high dose sodium bicarbonate may be harmful, low/moderate dose sodium bicarbonate elicited no significant effect on blood pressure in hypertensive men. Additionally, compared with NaCl, sodium bicarbonate has been shown capable of decreasing blood pressure (31). Therefore, it seems that using sodium bicarbonate in high-doses may not be safe or advisable for patients with CKD.

This meta-analysis has some limitations and strengths. One of the limitations was using different doses of sodium bicarbonate (some studies used a fixed dose and other studies used an increasing dose). Therefore, we could not draw a firm conclusion regarding intervention dose. Another limitation was that no intervention was performed on hemodialysis patients and there was no information regarding these patients. However, a strength of this meta-analysis was that between-study heterogeneity was low among the studies; thereby allowing us to assert veracity in the reliability of our results. Also, most of the included studies were long-term interventions, and therefore, we were able to report the long-term effect of sodium bicarbonate effect on renal function.

In conclusion, this systematic review and meta-analysis showed that sodium bicarbonate supplementation could elicit significant increases GFR and creatinine clearance and decrease BUN and creatinine. Therefore, sodium bicarbonate therapy may be regarded as efficacious in ameliorating the progression of CKD.

## Methods

### Search strategy

This systematic and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. A systematic literature search was carried out through the Medline ([www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)), Web of Science and Scopus ([www.scopus.com](http://www.scopus.com)) databases until July 2020. The following terms were used in the electronic search to identify studies, with no restrictions: ("sodium bicarbonate" OR "NaHCO<sub>3</sub>") AND ("GFR" OR "glomerular filtration rate" OR "BUN" OR "blood urea nitrogen" OR "urea" OR "creatinine" OR "creatinine clearance"). In addition, the reference lists of all eligible articles were reviewed to find more relevant studies lost in the initial search.

### Eligibility criteria

We included relevant articles if they: 1) examined the effects of oral supplementation sodium bicarbonate on GFR, creatinine, creatinine clearance, serum urea, or BUN; 2) provided sufficient information regarding baseline and endpoint serum levels of GFR, creatinine, creatinine clearance, or BUN; and 3) enrolled patients with CKD. No time and language limitation were applied. We excluded articles if they: 1) reported duplicate data, 2) were animal-based, reviews, letters, editorial articles, or case reports, 3) co-supplemented sodium bicarbonate with other agents, 4) used other medications in the control group. In instances of multiple publications that reported the same or overlapping data, the most recent, with the largest sample size, were included.

### Quality assessment

The quality of selected articles was evaluated by two authors (M.T and M.H.R) using the Cochrane risk of bias tool (32). It was based on seven criteria including sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential threats to validity. Therefore, articles were scored as high risk, low risk, or unclear.

### Data extraction

Two independent researchers (M.T and M.H.R) extracted relevant data. A third author (F.M) discussed and resolved any controversy. We extracted the following data: first author name and publication year, country, sex-stratified sample size, comorbidities among participants, mean age, design, duration, dose of intervention and intervention in comparison group. Also, mean, standard deviation or standard error of the following outcomes were extracted when available in the groups: GFR (ml/min/1.73m<sup>2</sup>), BUN or serum urea (mg/dL), creatinine (mg/dL), and creatinine clearance (mL/min).

### Statistical analysis

The current meta-analysis was conducted using STATA software (version 11.0; Stata Corporation). To calculate effect size, the reported net changes for main outcomes including GFR, BUN or serum urea, creatinine, and creatinine clearance in each study, respectively, were used. When net change was not reported, we used mean and SD at baseline and endpoint in sodium bicarbonate and control groups. Moreover, endpoint mean and standard error (SE) or standard deviation (SD) were used when baseline means were not reported. The overall effect size was calculated using a random-effects model and reported as weighted mean difference (WMD). We converted all reported data to the acceptable units including ml/min/1.73m<sup>2</sup> for GFR, mg/dL for BUN, serum urea and creatinine, and mL/min for creatinine clearance. Between-study

heterogeneity was evaluated using the I-square ( $I^2$ ) statistic. Subgroup analysis was performed when between-study heterogeneity was high. To evaluate the possible influence of each single study on the pooled effect size, the stability of the results was checked through sensitivity analyses. Finally, Egger's regression asymmetry test and Begg's rank-correlation methods were conducted to assess the presence of publication bias. Statistical significance was accepted, *a priori*, at  $P < 0.05$ .

## Declarations

**Details of the roles of the authors (Authorship):** M.H.R and F.M design the study. M.T and F.M screened the studies and checked inclusion and exclusion criteria. M.H.R and M.T analyzed the study. E.H, C.C.T.C and M.T wrote the manuscript. M.H.R and C.C.T.C revised the manuscript.

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**Conflict of Interests:** Authors had no conflict of interests.

**Data availability:** Data will be made available on request

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## Figures

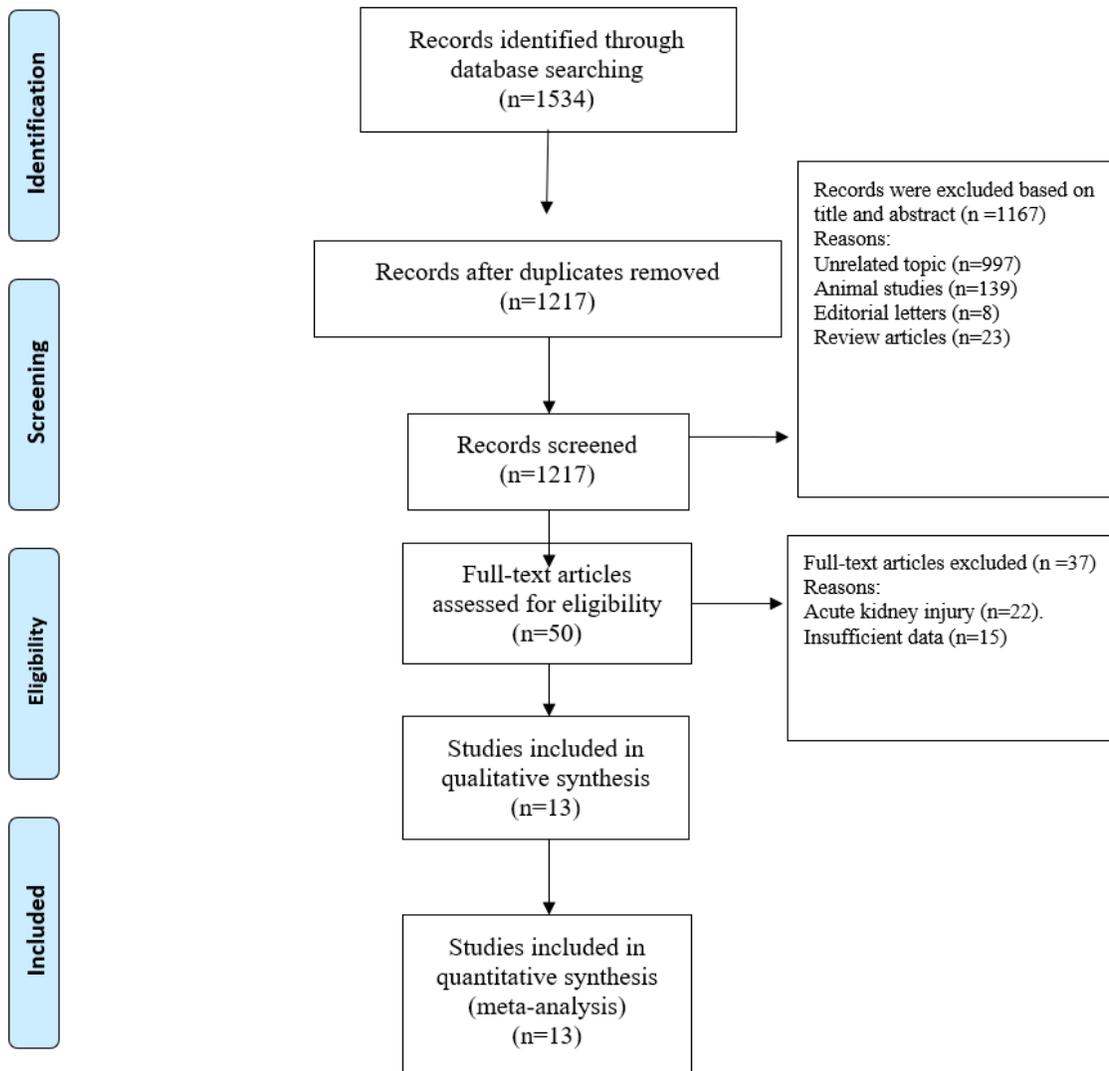


Figure 1

Flow diagram of search strategy and review process

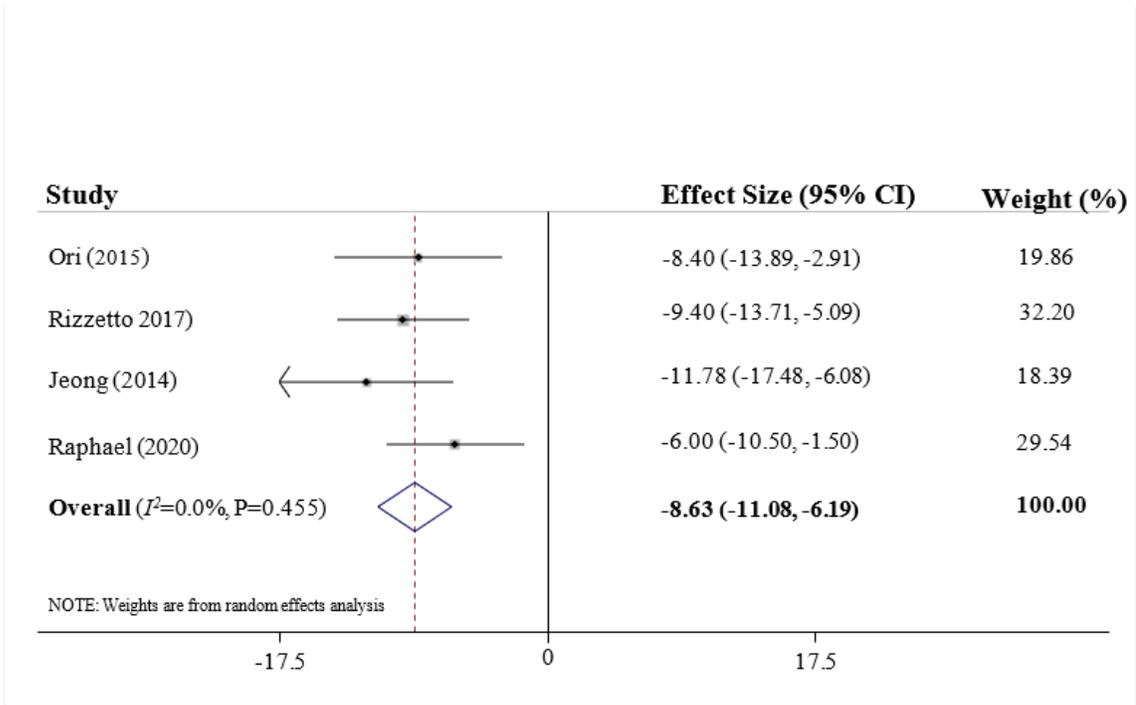


Figure 2

Meta-analysis of the effect of sodium bicarbonate on blood urea nitrogen

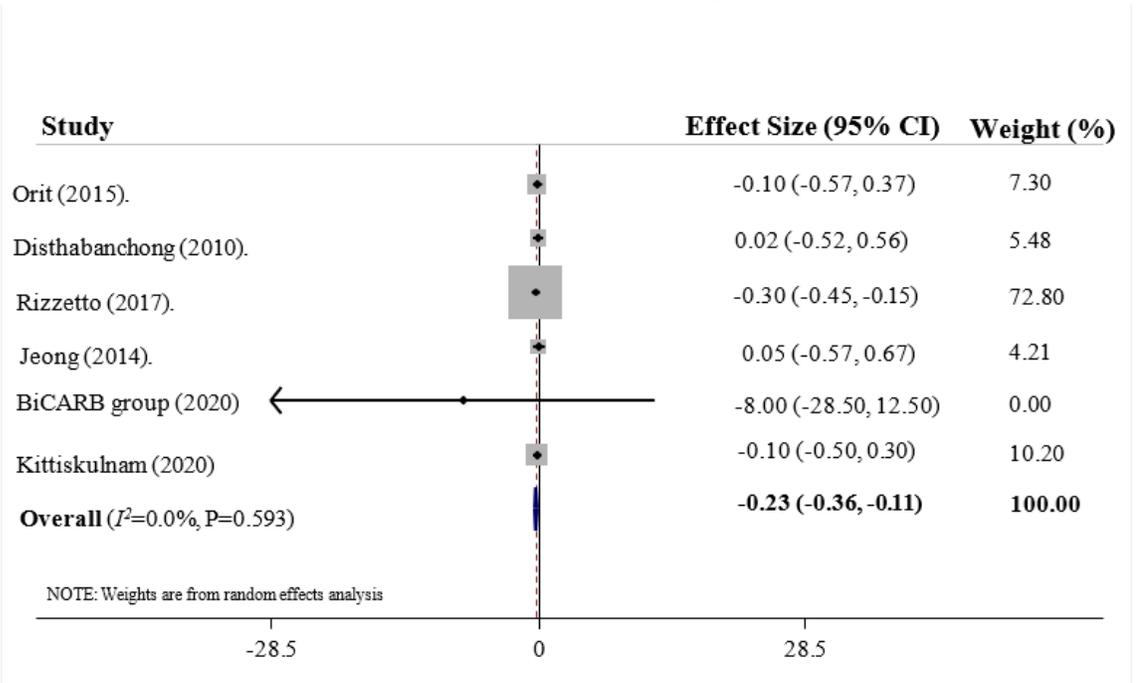
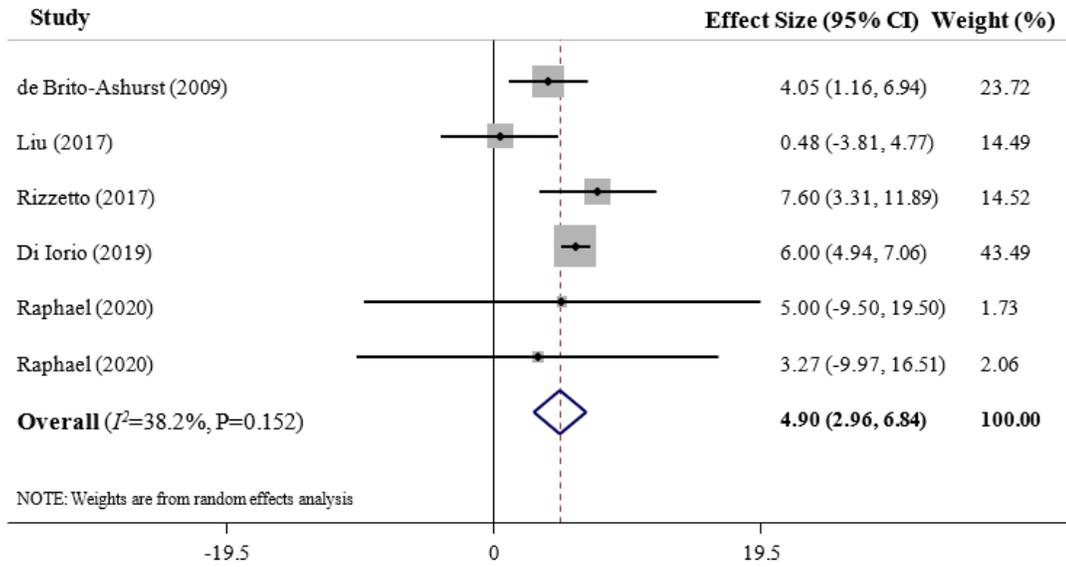
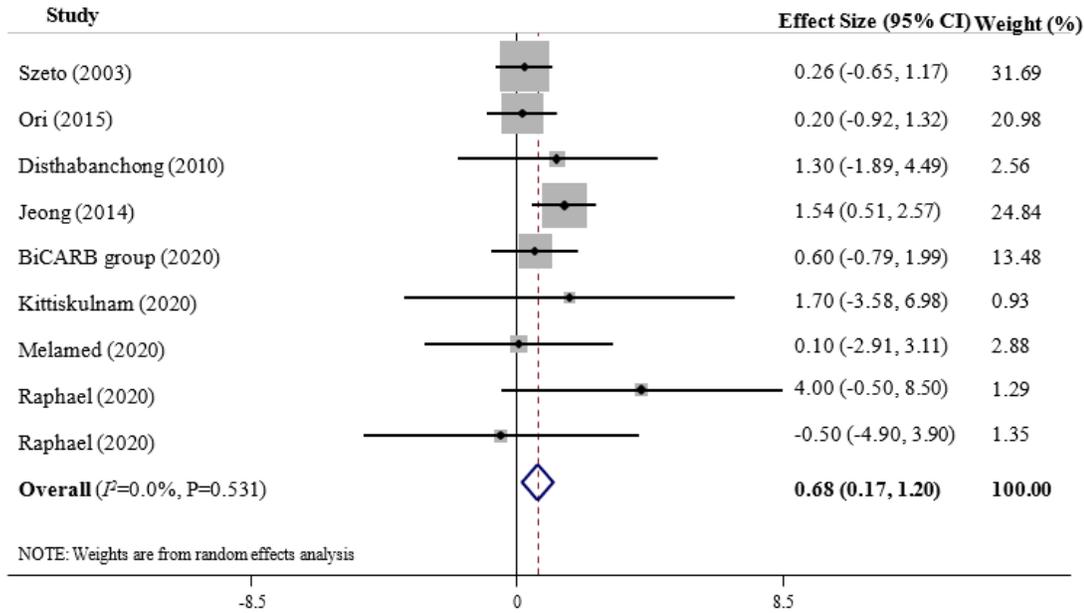


Figure 3

Meta-analysis of the effect of sodium bicarbonate on serum creatinine



**Figure 4**  
 Meta-analysis of the effect of sodium bicarbonate on creatinine clearance



**Figure 5**  
 Meta-analysis of the effect of sodium bicarbonate on Glomerular filtration rate