SUPPLEMENTARY MATERIAL

Table S1. Electronic search strategy

Database	Search terms
Medline	1. exp Kidney Failure, Chronic/ or exp Renal Insufficiency/ or exp Renal Insufficiency, Chronic/ 2. exp Proteinuria/ or exp Albuminuria/ or microalbuminuria.tw. 3. 1 or 2 4. exp Bicarbonates/ or exp Sodium Bicarbonate/ or exp Alkalies/ or alkali therapy.tw. or alkalinisation.tw. 5. exp Acidosis/ or exp Acid-Base Imbalance/ or metabolic acidosis.tw. 6. 4 or 5 7. exp Clinical Trial/ or exp Controlled Clinical Trial/ or exp Randomized Controlled Trials/ 8. 3 and 6 and 7
Embase	1. exp chronic kidney disease/ or exp chronic kidney failure/ 2. exp albuminuria/ or exp proteinuria/ or exp microalbuminuria/ 3. 1 or 2 4. exp bicarbonate blood level/ or exp bicarbonate/ or exp alkalinization/ or exp alkalinizing agent/ or Sodium Bicarbonate.tw. or alkali therapy.tw. 5. exp acidosis/ or exp metabolic acidosis/ or exp "disorders of acid base balance"/ 6. 4 or 5 7. exp controlled clinical trial/ or exp clinical trial/ or exp controlled study/ or exp randomized controlled trial/ 8. 3 and 6 and 7
CENTRAL	1. exp Kidney Failure, Chronic/ or exp Renal Insufficiency/ or exp Renal Insufficiency, Chronic/ or exp Kidney Transplantation/ or Renal Dialysis/ or exp Renal Replacement Therapy/ 2. exp Proteinuria/ or exp Albuminuria/ or microalbuminuria.tw. 3. 1 or 2 4. exp Bicarbonates/ or exp Sodium Bicarbonate/ or exp Alkalies/ or alkali therapy.tw. or alkalinisation.tw. 5. exp Acidosis/ or exp Acid-Base Imbalance/ or metabolic acidosis.tw. 6. 4 or 5 7. 3 and 6

Table S2. GRADE assessment of certainty of evidence

Table outlining the certainty of the evidence according to the GRADE assessment tool.

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence	Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With Intervention		Risk with Control	Risk difference with Intervention
RCTs comparing bicarbonate therapy to placebo or no medication in delaying CKD progression											
Change in Kidney Function (follow up: median 12 months; assessed with: eGFR change / CrCl change)											
2405 (14 RCTs)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	-	-	-	-	**SMD 0.26 SD higher** (0.13 higher to 0.40 higher)
Change in eGFR (follow up: median 12 months; assessed with: change in eGFR)											
1505 (11 RCTs)	serious [a]	serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	-	-	-	-	**WMD 2.63 mL/min/1.73 higher** (0.70 higher to 4.55 higher)
Change in creatinine clearance (follow up: median 12 months; assessed with: change CrCl)											
1074 (3 RCTs)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	-	-	-	-	**WMD 5.77 mL/min/1.73 higher** (3.56 higher to 7.99 higher)
Change in serum creatinine (follow up: median 12 months; assessed with: serum creatinine)											

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence	Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With Intervention		Risk with Control	Risk difference with Intervention
732 (6 RCTs)	serious [a]	serious [b]	not serious	very serious [c]	none	⨁◯ ◯ ◯ VERY LOW	-	-	-	-	**WMD 0.2 µmol/L lower** (0.46 lower to 0.06 lower)
progression to kidney failure (follow up: median 12 months; assessed with: number of events initiation of RRT)											
2371 (14 RCTs)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯ ◯ LOW	154/1095 (14.2%)	81/1201 (6.7%)	**RR 0.53** (0.32 to 0.89)	140 per 1,000	**67 fewer per 1,000** (97 fewer to 16 fewer)
Rapid decline of kidney function (follow up: median 12 months; assessed with: number of events with decrease in eGFR >3mL/min/1.73 per year)											
1481 (7 RCTs)	serious [a]	serious [b]	not serious	not serious	none	⨁⨁◯ ◯ LOW	156/705 (22.1%)	50/714 (7.0%)	**RR 0.32** (0.20 to 0.52)	221 per 1,000	**150 fewer per 1,000** (177 fewer to 106 fewer)
Change in proteinuria (follow up: median 12 months; assessed with: urinary protein estimation)											
854 (6 RCTs)	serious [a]	not serious	not serious	very serious [c]	none	⨁◯ ◯ ◯ VERY LOW	-	-	-	-	**SMD 0.09 SD lower** (0.27 lower to 0.09 higher)
Change in serum bicarbonate bicarbonate (follow up: median 12 months; assessed with: serum bicarbonate)											

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence	Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With Intervention		Risk with Control	Risk difference with Intervention
2103 (13 RCTs)	serious [a]	serious [b]	not serious	serious [c]	none	⨁◯ ◯ ◯ VERY LOW	-	-	-	-	**WMD 2.59 mmol/L higher** (1.51 higher to 3.66 higher)
Change in systolic blood pressure (follow up: median 12 months; assessed with: systolic blood pressure)											
2250 (12 RCTs)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯ ◯ LOW	-	-	-	-	**WMD 0.57 mmHg lower** (2.32 lower to 1.18 higher)
Change in diastolic blood pressure (follow up: median 12 months; assessed with: change in DBP mmHg)											
2098 (10 RCTs)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯ ◯ LOW	-	-	-	-	**WMD 0.88 mmHg higher** (0.61 lower to 2.38 higher)
Worse blood pressure (follow up: median 12 months; assessed with: number of events)											
1383 (5 RCTs)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯ ◯ LOW	53/249 (21.3%)	75/339 (22.1%)	**RR 1.36** (1.05 to 1.77)	213 per 1,000	**77 more per 1,000** (11 more to 164 more)
Peripheral oedema (follow up: median 12 months; assessed with: number of events)											

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence	Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With Intervention		Risk with Control	Risk difference with Intervention
818 (6 RCTs)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	92/355 (25.9%)	109/445 (24.5%)	**RR 1.16** (0.90 to 1.50)	259 per 1,000	**132 more per 1,000** (16 more to 303 more)
Change in weight (follow up: median 12 months; assessed with: weight in kg)											
1662 (8 RCTs)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	-	-	-	-	**WMD 0.11 kg lower** (0.93 lower to 0.70 higher)
Admission with heart failure (follow up: median 12 months; assessed with: number of events)											
708 (5 RCT)	serious [a]	not serious	not serious	very serious [e]	none	⨁◯◯◯ VERY LOW	3/310 (1.0%)	5/394 (1.3%)	**RR 1.19** (0.30 to 4.67)	52 per 1,000	**2 more per 1,000** (7 fewer to 36 more)
Mortality (follow up: median 12 months; assessed with: number of deaths)											
1974 (9 RCT)	serious [a]	not serious	not serious	very serious [e]	none	⨁◯◯◯ VERY LOW	38/902 (4.2%)	30/1011 (3.0%)	**RR 0.81** (0.39 to 1.68)	33 per 1,000	**8 fewer per 1,000** (26 fewer to 29 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unclear or high risk of bias
b. High heterogeneity
c. Wide confidence interval

Table S3. Individual study bias assessment

Table outlining sources of bias for individual studies included in our meta-analysis.

Study	Year	Random sequence generation	Allocation concealment	Bliding of participants	Blinding of investigators	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other bias
Mathur	2006	Unclear	Unclear	Low	High	Unclear	Low	Unclear	Low
de Brito-Ashurst	2009	Low	Low	High	High	Low	Low	Low	Low
Disthabanchong	2010	Unclear	Unclear	High	High	Unclear	Low	Unclear	Low
Mahajan	2010	Low	Unclear	Low	Low	Low	Low	Unclear	Low
Jeong	2014	Unclear	Unclear	High	High	Unclear	Low	Unclear	Low
Bellasi	2016	Unclear	Unclear	High	High	Unclear	Low	Low	Low
Yan	2017	Unclear	Unclear	Low	High	Unclear	Low	Unclear	Low
Dubey	2018	Low	Low	High	High	Low	Low	Unclear	Low
Alva	2019	Unclear	Unclear	High	High	High	Low	Unclear	Low
Di Iorio	2019	Unclear	High	High	High	High	Low	Low	Low
Goraya	2020	Low	High	High	High	High	Low	Low	Low
Witham	2020	Low	Low	Low	Low	Low	High	High	Low
Melamed	2020	Low	Low	Low	Low	Low	High	Unclear	Low
Raphael	2020	Low	Low	Low	Low	Unclear	Low	Unclear	Low
Raphael	2020	Low	Low	Low	Low	Unclear	Low	Unclear	Low

Figure S1. Subgroup analysis of the effect of bicarbonate therapy on change in kidney function 1: according to the use of placebo or no study medication in the control arm.

Forest plot showing subgroup analysis according to the use of placebo or no study medication on the effect of bicarbonate therapy on the change in kidney function. Interaction p-value 0.22.

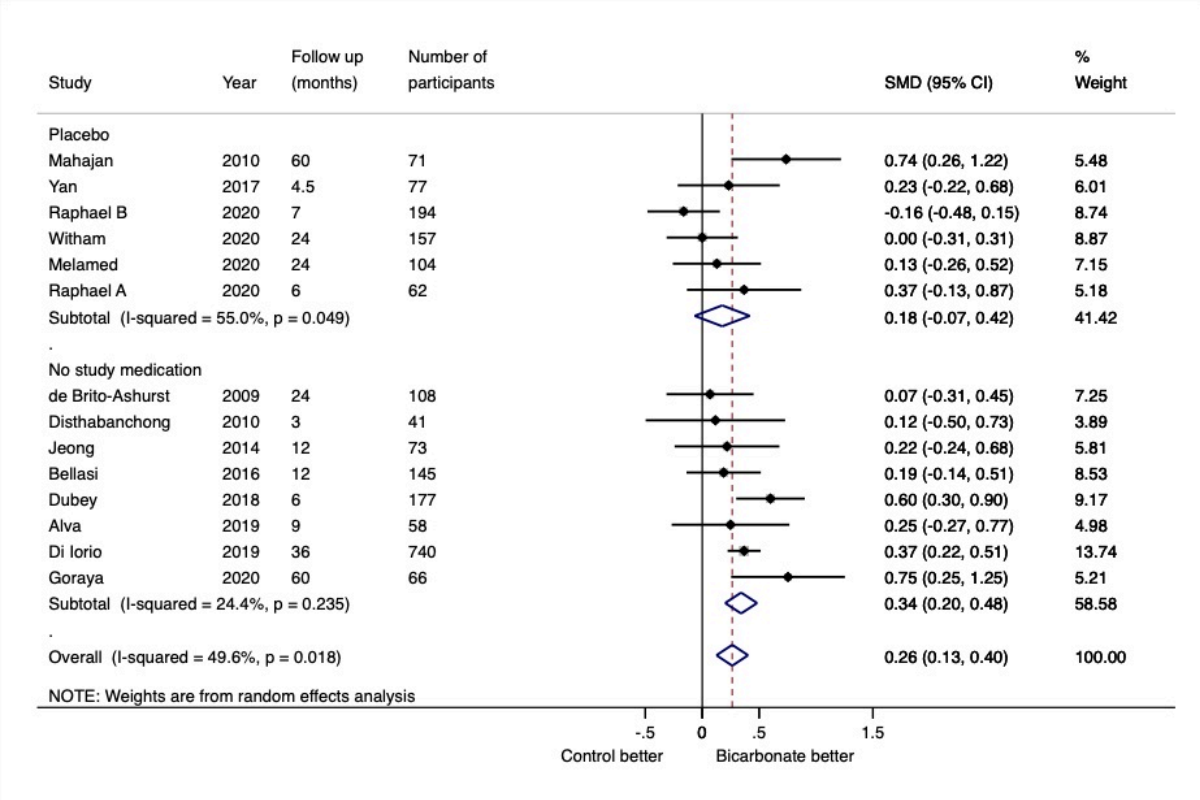

Figure S2. Subgroup analysis of the effect of bicarbonate therapy on the change in kidney function 2: according to follow-up time.

Forest plot showing subgroup analysis according to follow up time less or more than 12 months on the effect of bicarbonate therapy on the change in kidney function. Interaction p-value 0.45.

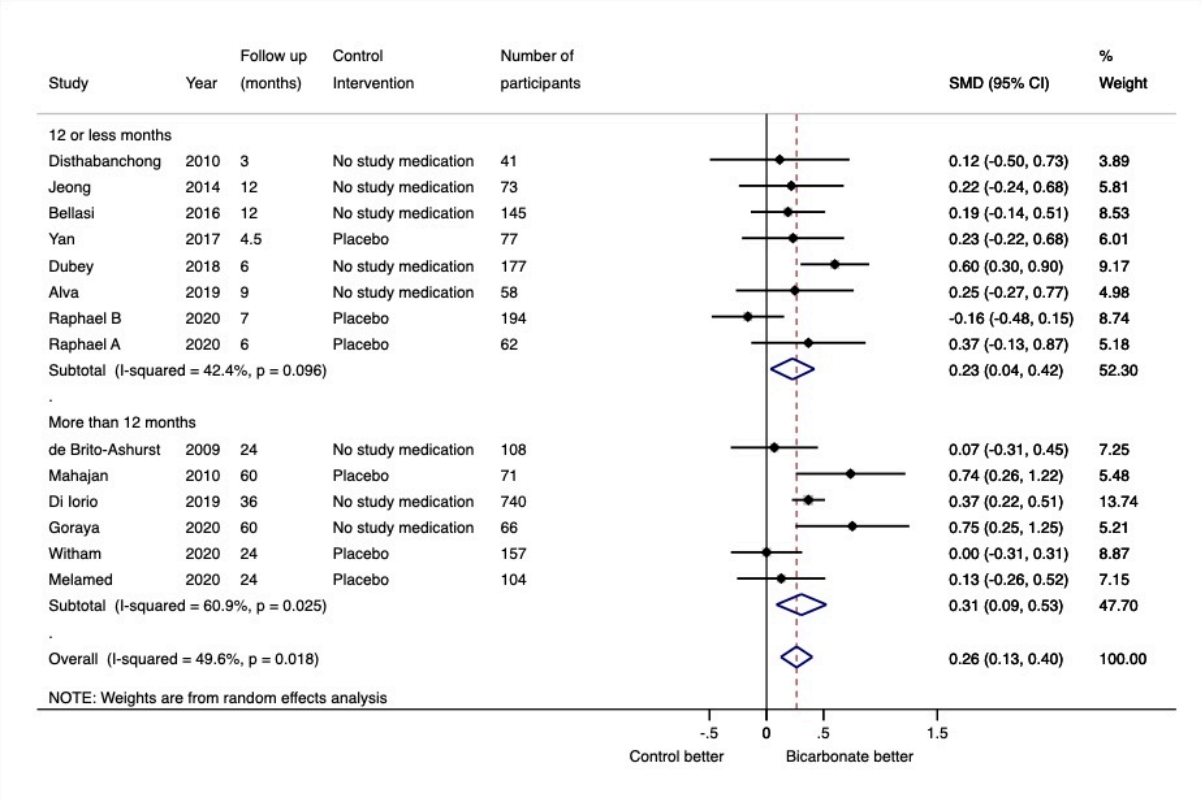

Figure S3. Subgroup analysis of the effect of bicarbonate therapy on the change in kidney function 3: according to trial quality.

Forest plot showing subgroup analysis according to trial quality on the effect of bicarbonate therapy on the change in kidney function. Interaction p-value 0.03.

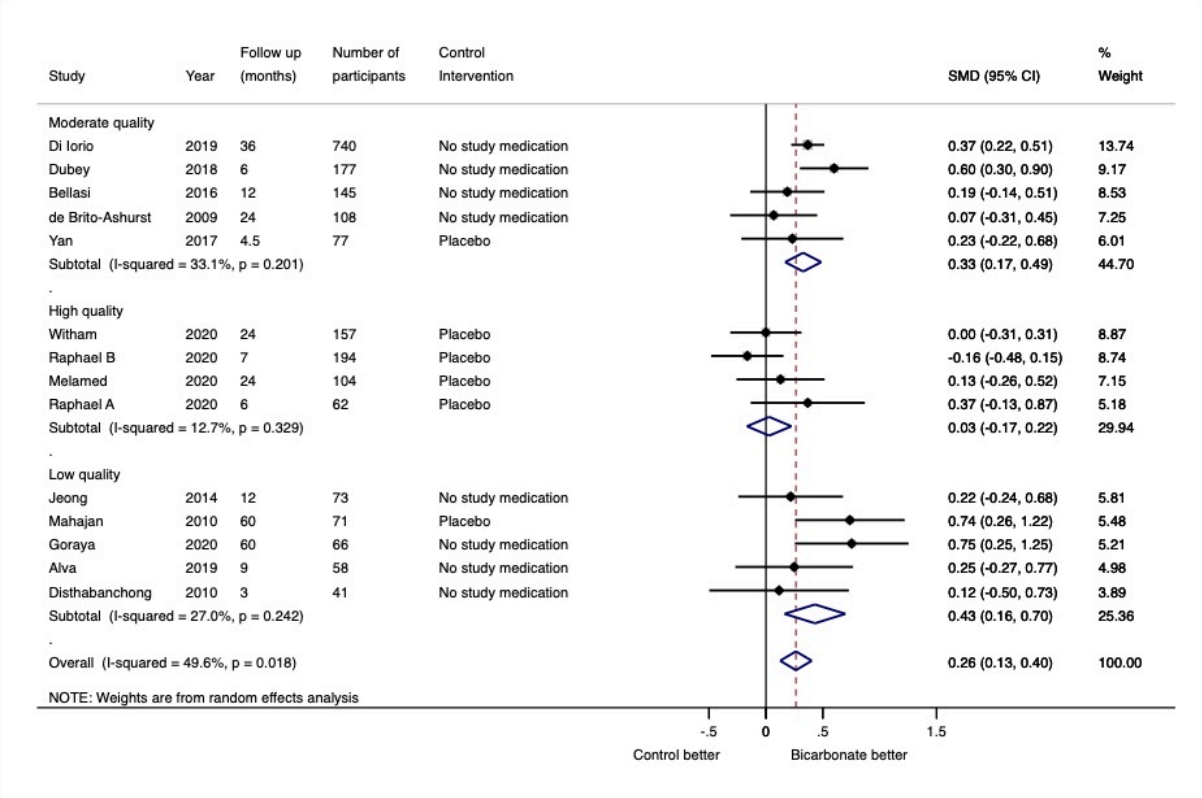

Figure S4. Cumulative metanalysis of the effect of bicarbonate therapy on the change in kidney function

Forest plot showing cumulative effect over time of bicarbonate therapy on the change in kidney function (measured by eGFR or CrCl)

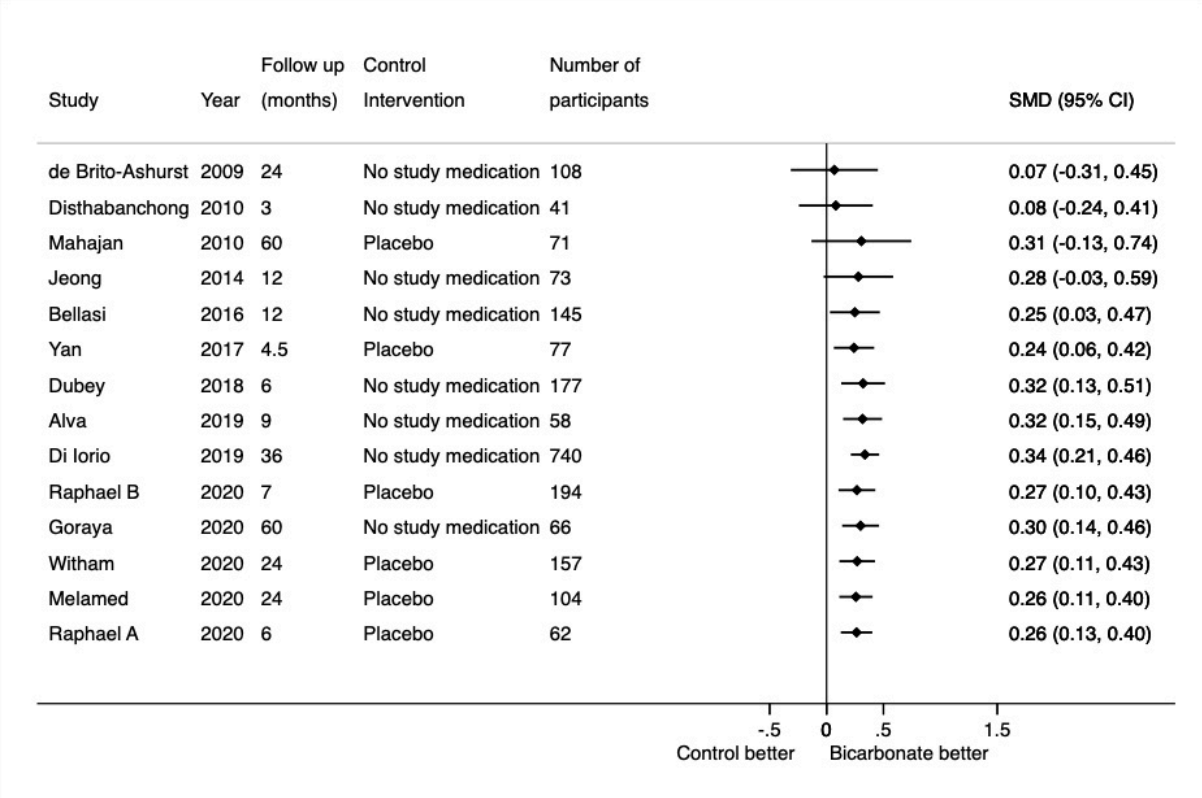

Figure S5. Effect of bicarbonate therapy on change in eGFR

Forest plot showing the effect of bicarbonate therapy on change in eGFR (mL/min/1.73 m2) from baseline to last measurement

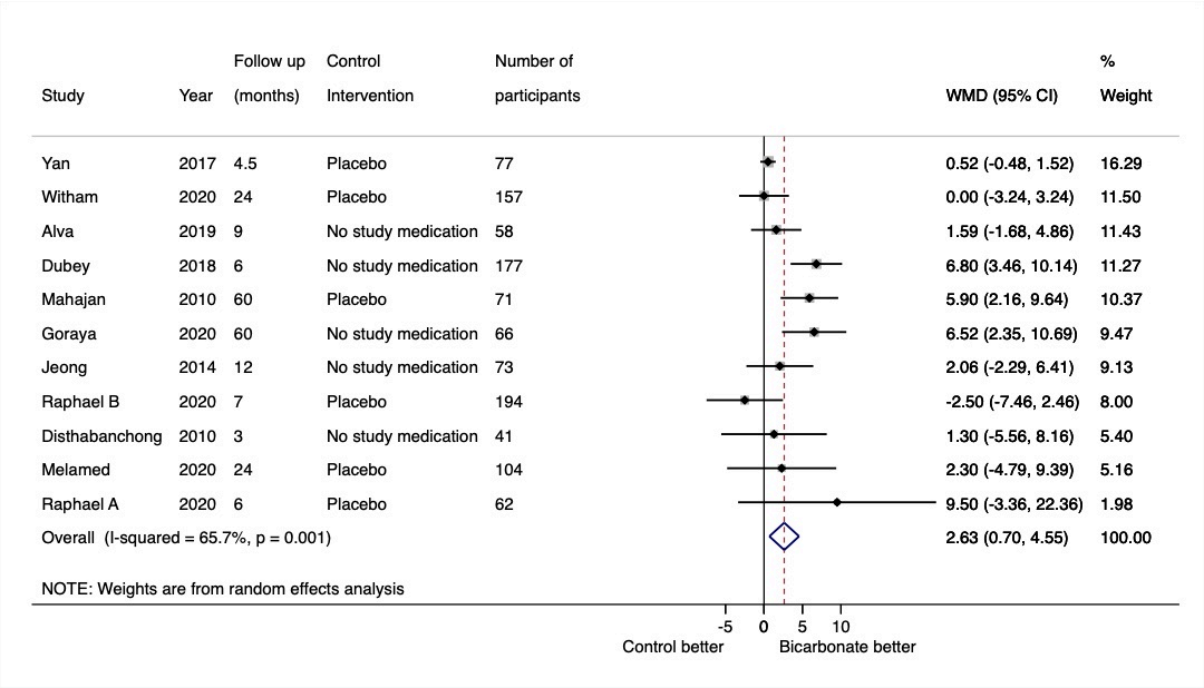

Figure S6. Effect of bicarbonate therapy on change in creatinine clearance

Forest plot showing the effect of bicarbonate therapy on change in creatinine clearance from baseline to last measurement

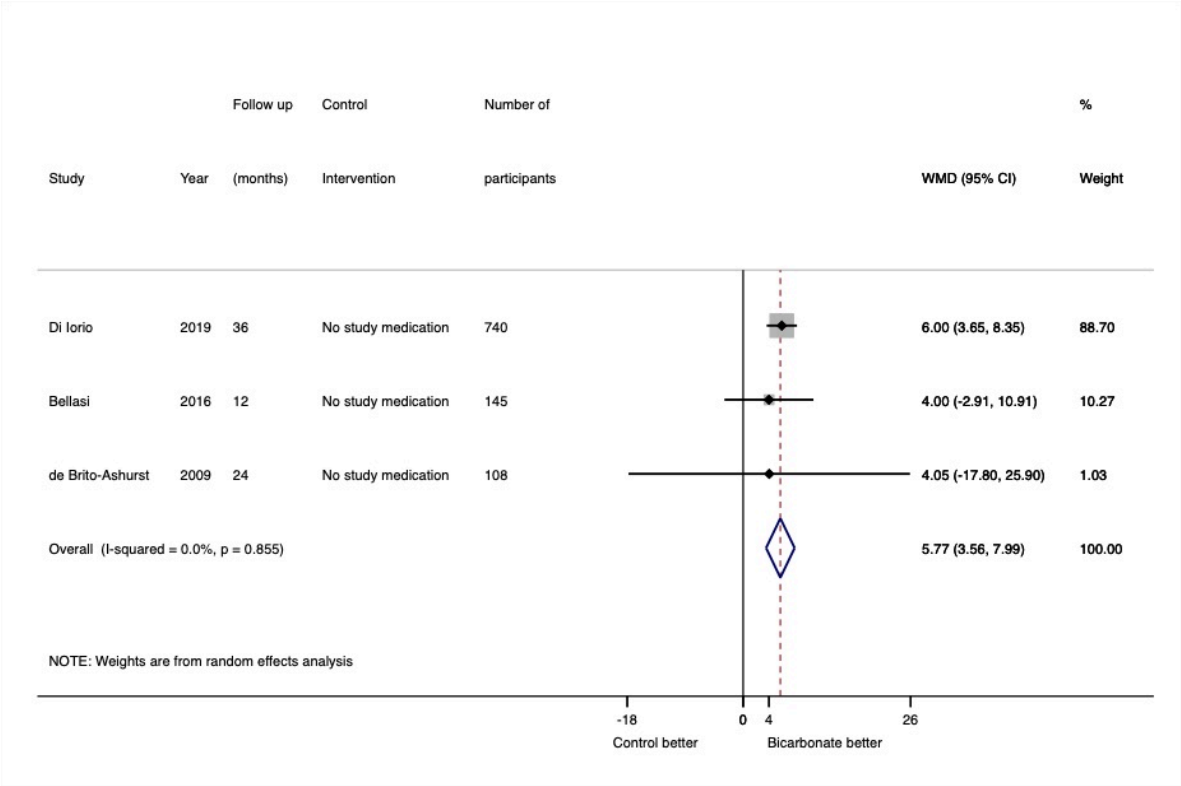

Figure S7. Subgroup analysis of the effect of bicarbonate therapy on eGFR (mL/min/1.73m2)1: according to the use of placebo or no study medication in the control arm.

Forest plot showing subgroup analysis according to the use of placebo or no study medication on the effect of bicarbonate therapy on the change in eGFR. Interaction p-value 0.04.

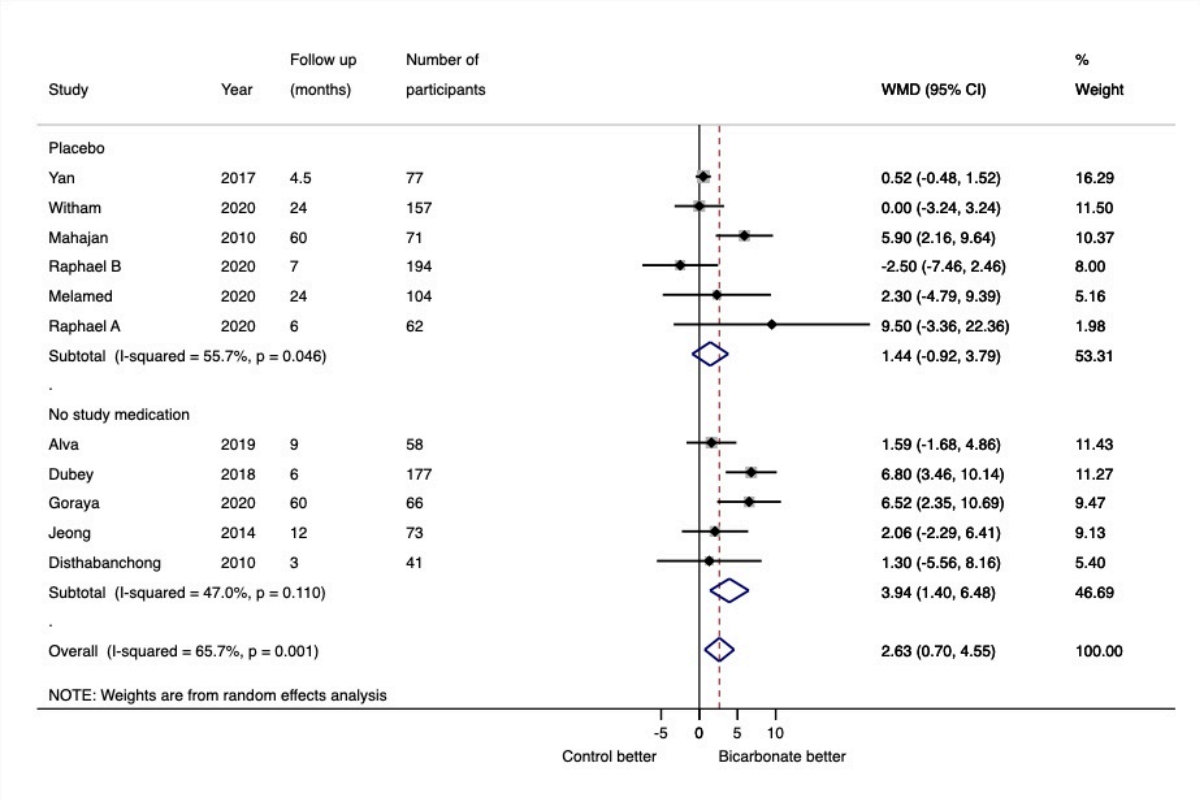

Figure S8. Subgroup analysis of the effect of bicarbonate therapy on eGFR (mL/min/1.73m2)2: according to follow-up time.

Forest plot showing subgroup analysis according to follow up time less or more than 12 months on the effect of bicarbonate therapy on the change in eGFR. Interaction p-value 0.03

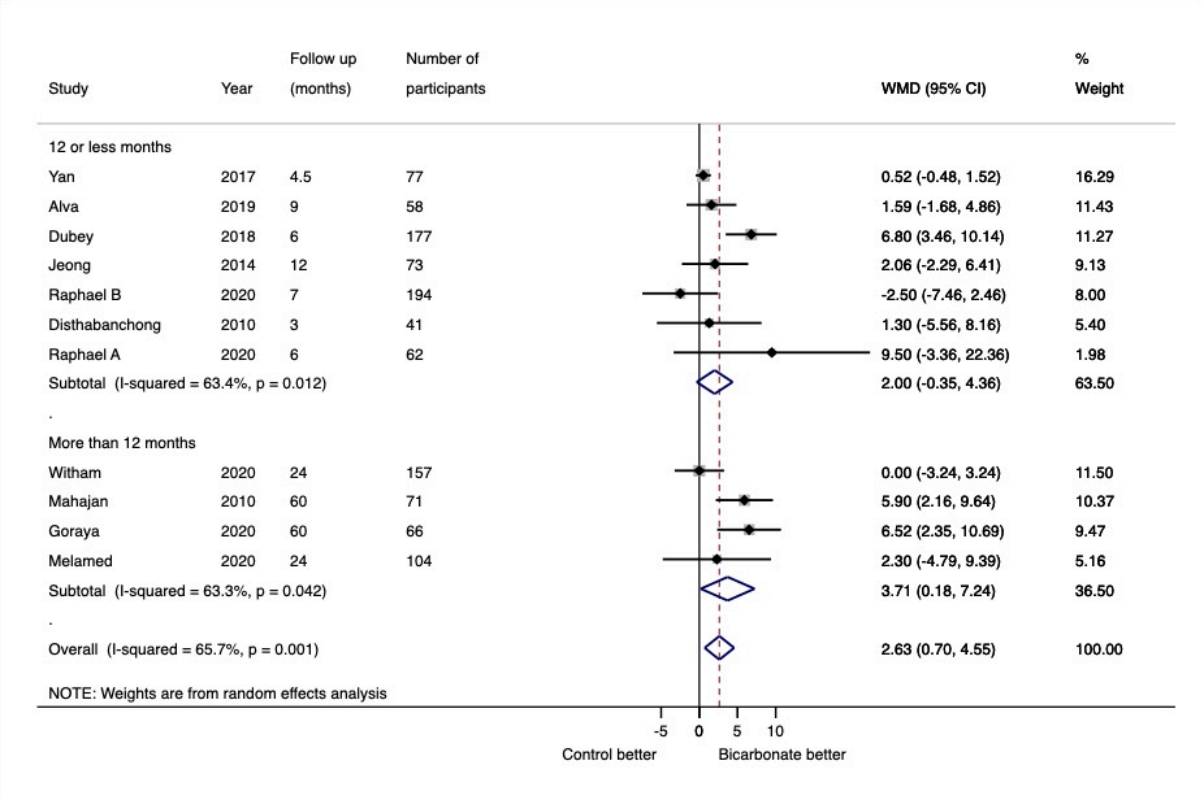

Figure S9. Subgroup analysis of the effect of bicarbonate therapy on eGFR (mL/min/1.73m2)3: according to trial quality.

Forest plot showing subgroup analysis according to trial quality on the effect of bicarbonate therapy on the change in eGFR. Interaction p-value 0.19

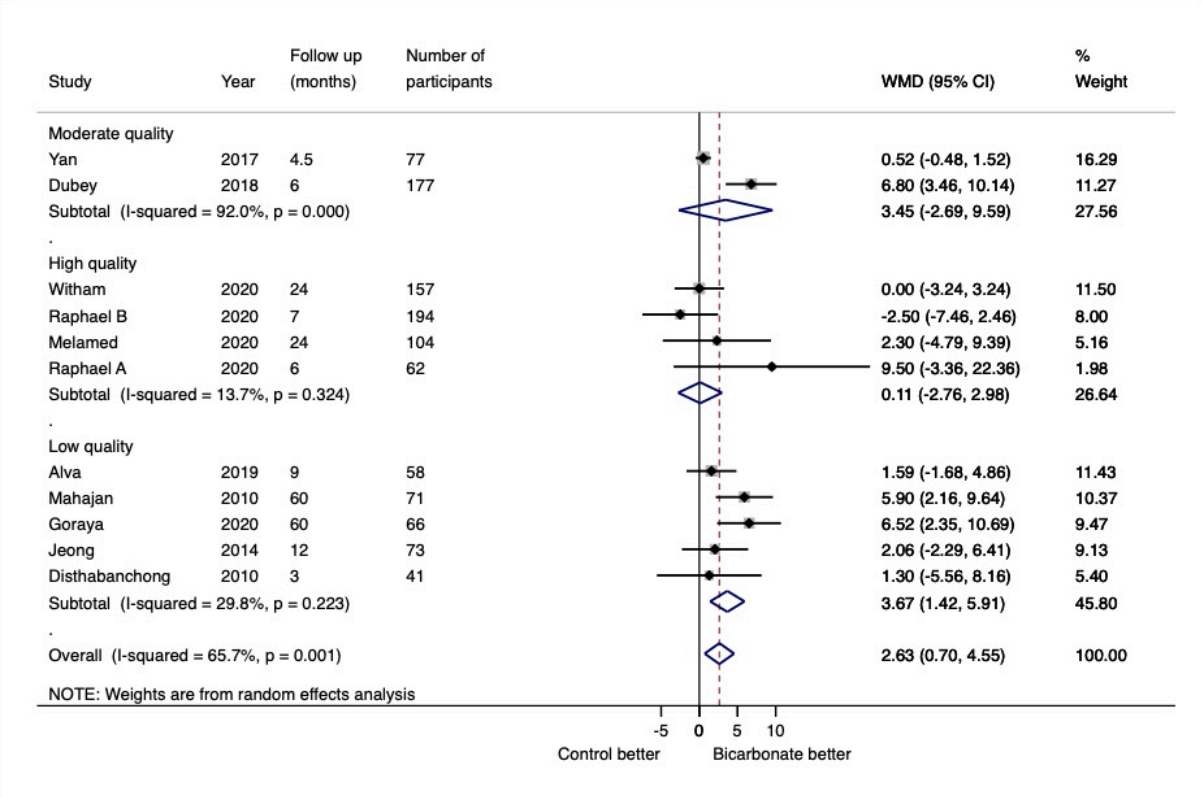

Figure S10. Effect of bicarbonate therapy on change in serum creatinine

Forest plot showing the effect of bicarbonate therapy on change in serum creatinine (mg/dL) from baseline to last measurement

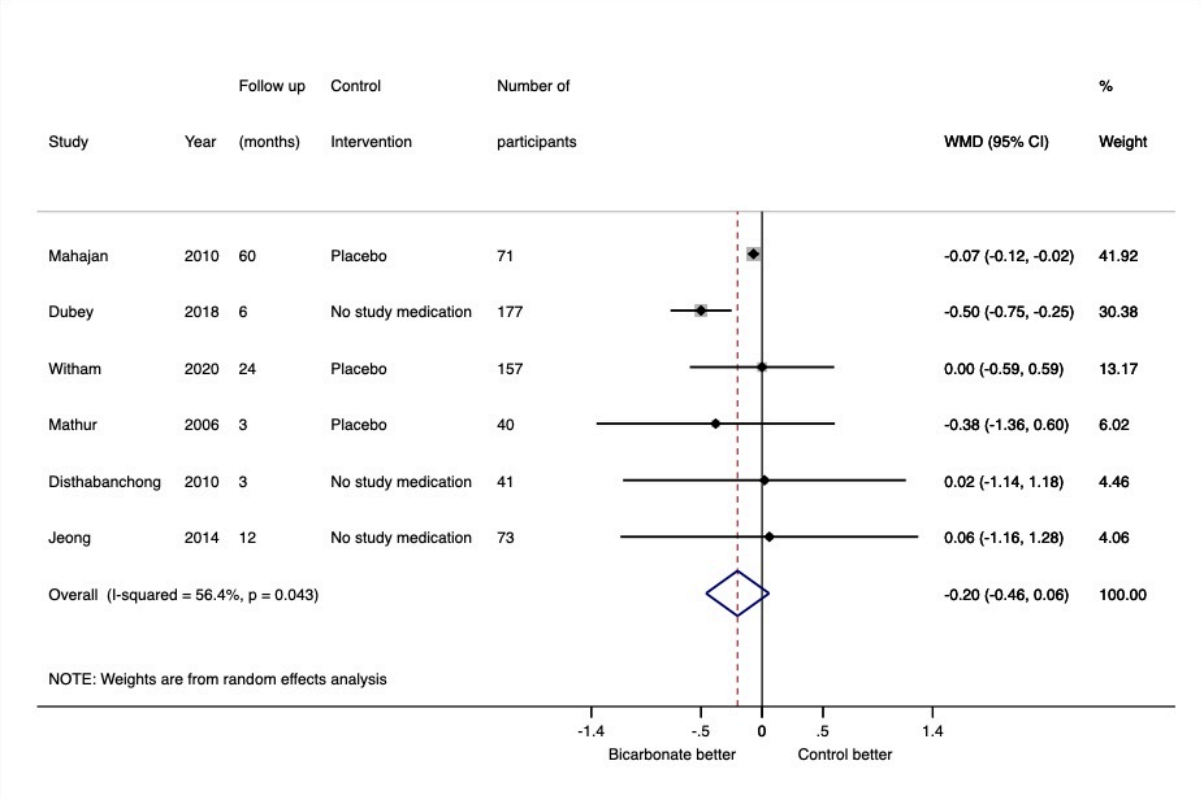

Figure S11. Subgroup analysis of the effect of bicarbonate therapy on progression to kidney failure 1: according to the use of placebo or no study medication in the control arm.

Forest plot showing subgroup analysis according to the use of placebo or no study medication on the effect of bicarbonate therapy on progression to kidney failure. Interaction p-value 0.04.

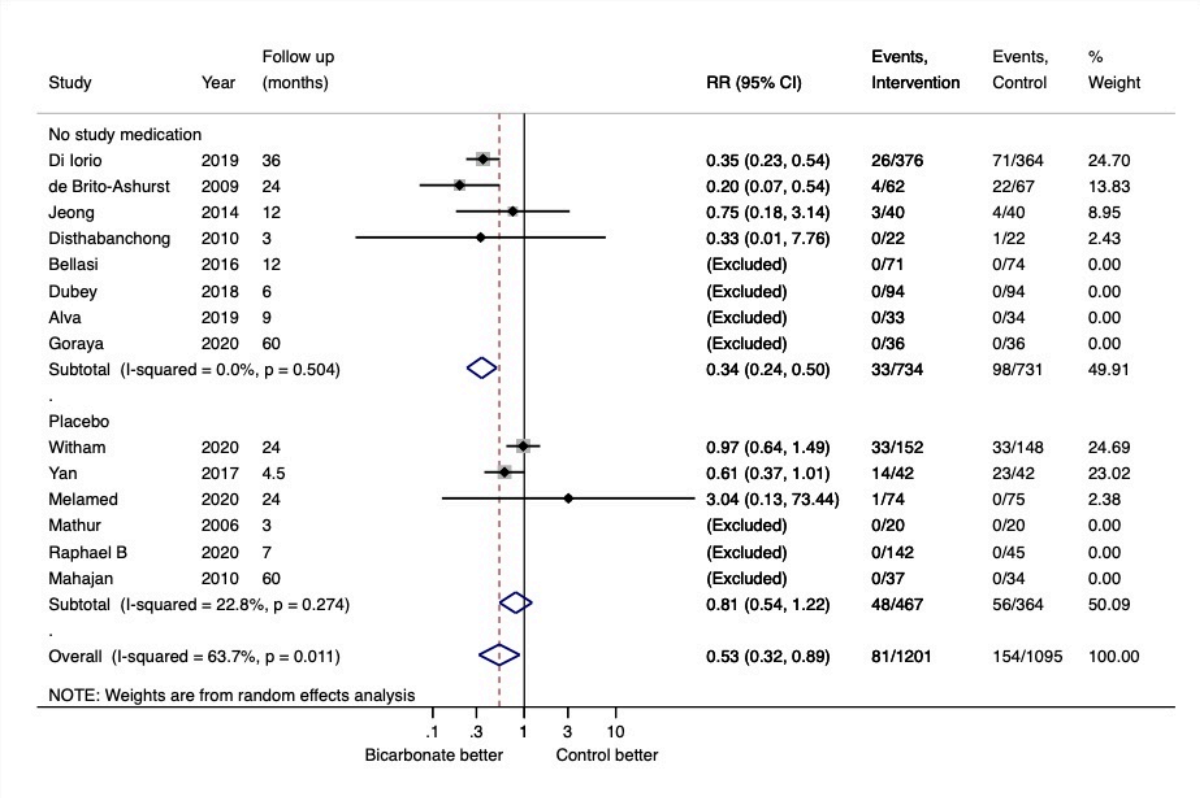

Figure S12. Subgroup analysis of the effect of bicarbonate therapy on the progression to kidney failure 2: according to follow-up time.

Forest plot showing subgroup analysis according to follow up time less or more than 12 months on the effect of bicarbonate therapy on the progression to kidney failure. Interaction p-value 0.73.

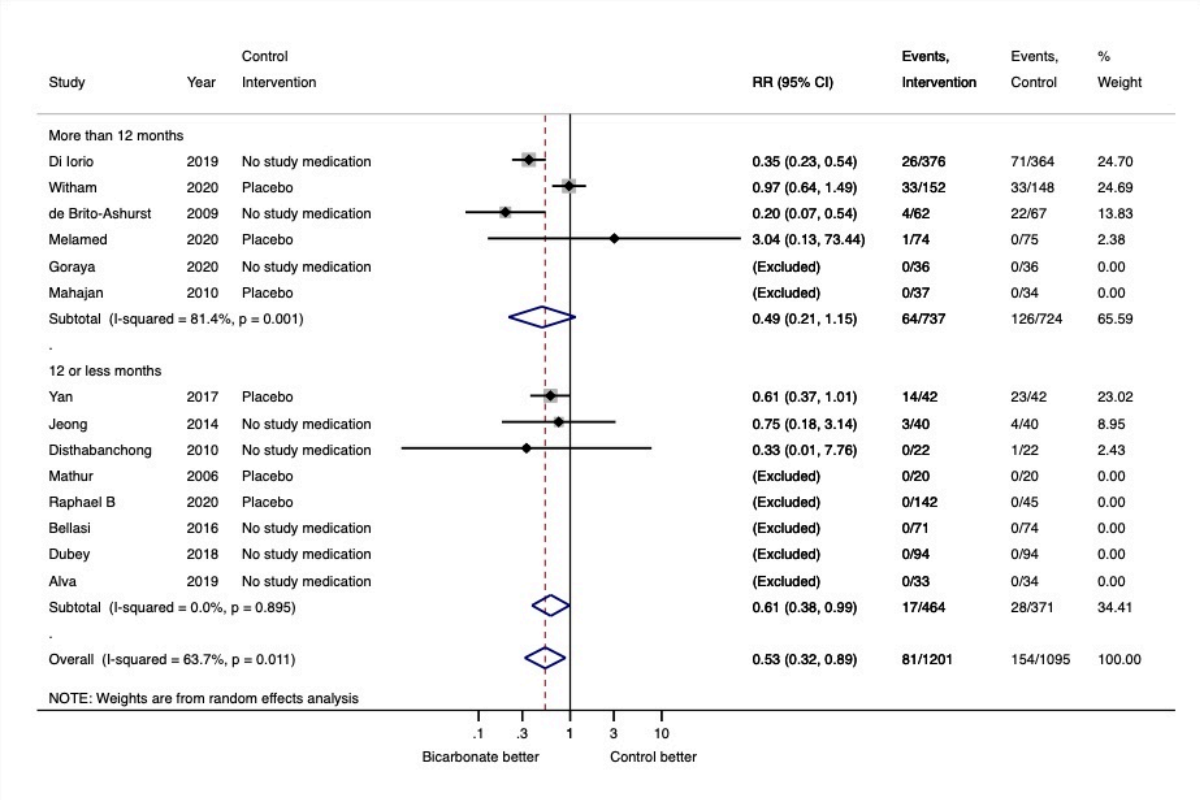

Figure S13. Subgroup analysis of the effect of bicarbonate therapy on the progression to kidney failure 3: according to trial quality.

Forest plot showing subgroup analysis according to trial quality on the effect of bicarbonate therapy on the progression to kidney failure. Interaction p-value 0.24.

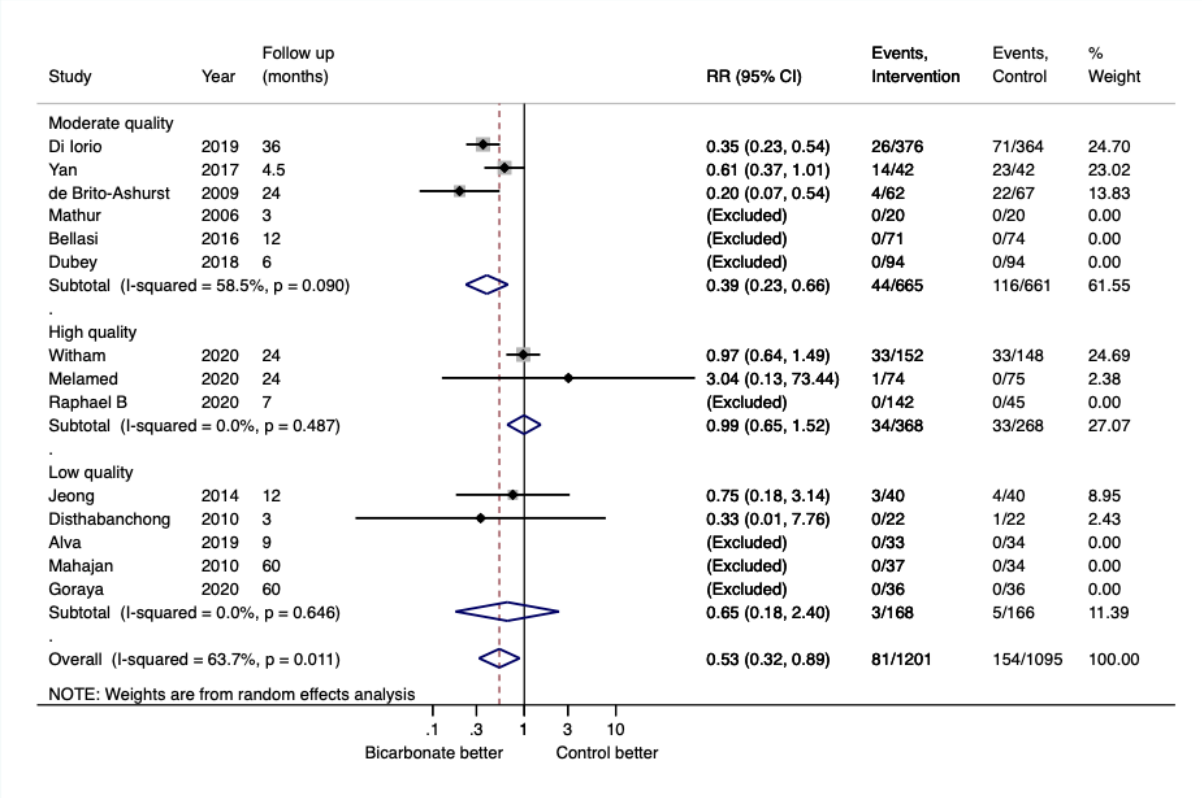

Figure S14. Effect of bicarbonate therapy on rapid decline in kidney function

Forest plot showing the effect of bicarbonate therapy on change in rapid decline in kidney function

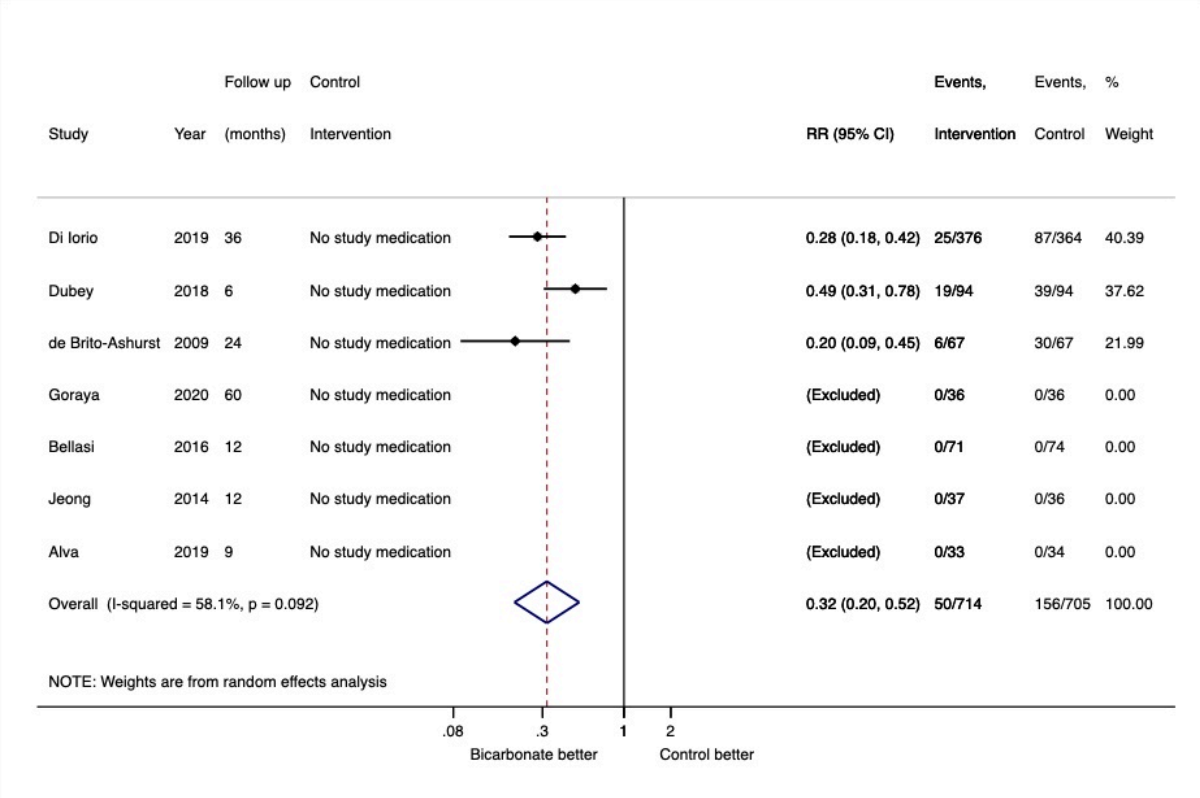

Figure S15. Effect of bicarbonate therapy on change in proteinuria

Forest plot showing the effect of bicarbonate therapy on change in proteinuria from baseline to last measurement

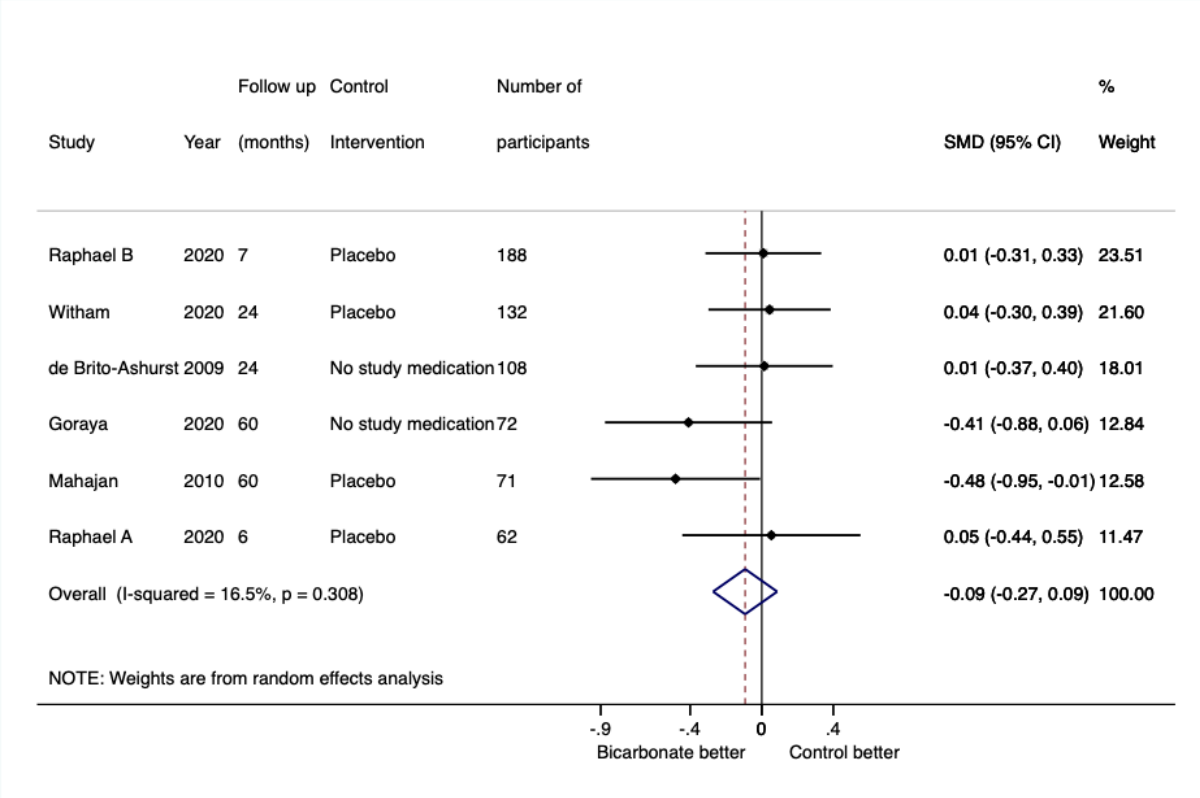

Figure S16. Effect of bicarbonate therapy on change in serum bicarbonate

Forest plot showing the effect of bicarbonate therapy on change in serum bicarbonate (mmol/L) from baseline to last measurement

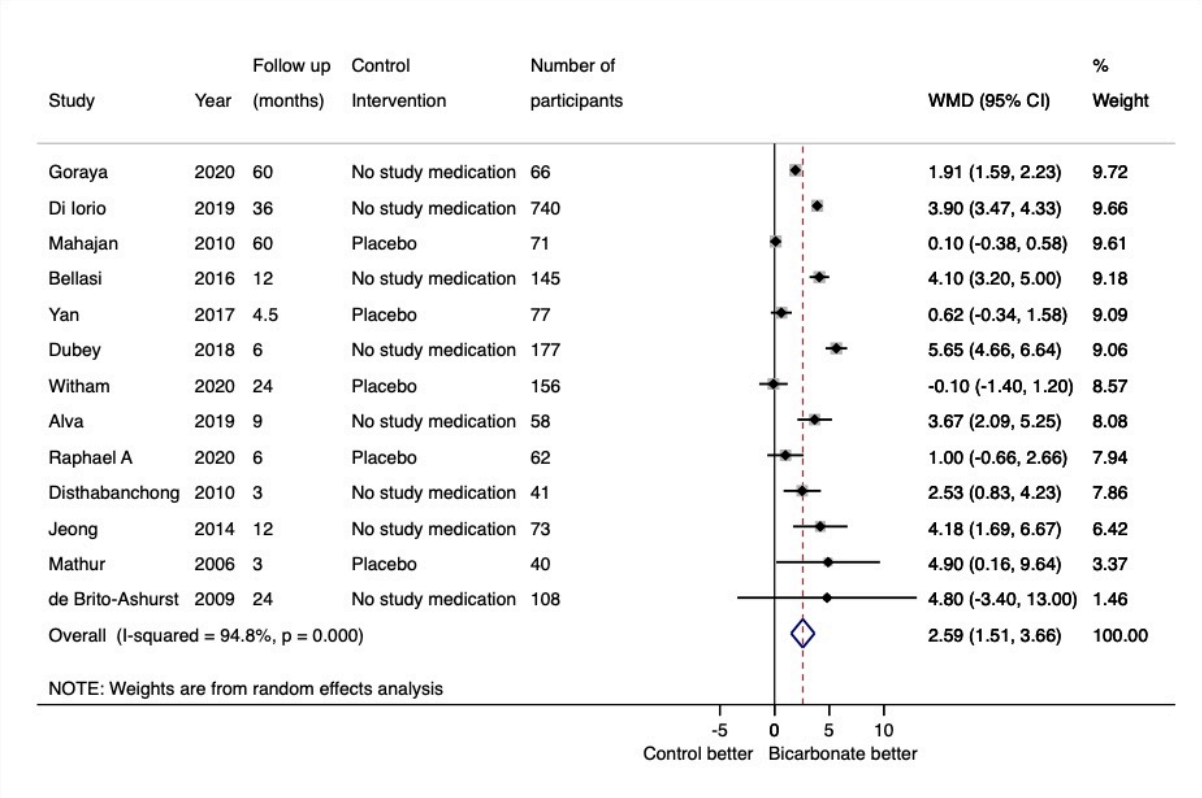

Figure S17. Subgroup analysis of the effect of bicarbonate therapy on serum bicarbonate (mmol/L)1: according to the use of placebo or no study medication in the control arm.

Forest plot showing subgroup analysis according to the use of placebo or no study medication on the effect of bicarbonate therapy on change in serum bicarbonate. Interaction p-value 0.001.

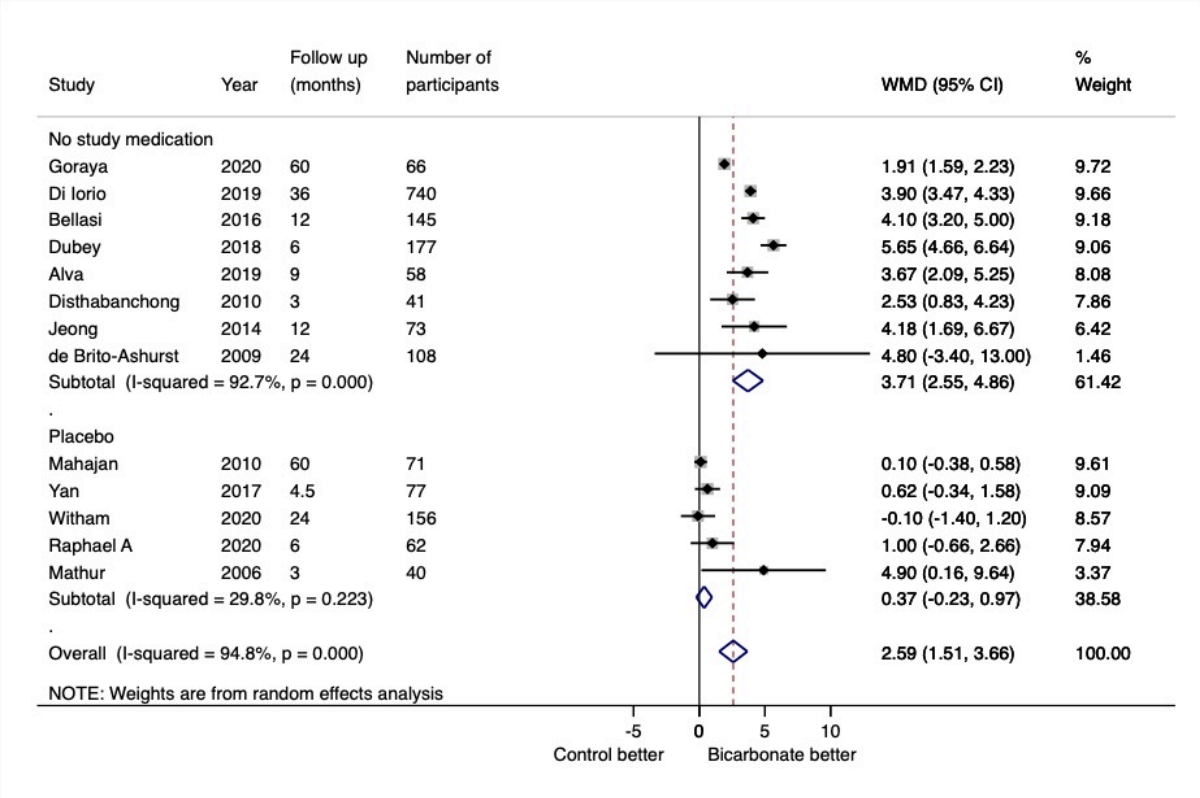

Figure S18. Subgroup analysis of the effect of bicarbonate therapy on serum bicarbonate (mmol/L) 2: according to follow-up time.

Forest plot showing subgroup analysis according to follow up time less or more than 12 months on the effect of bicarbonate therapy on change in serum bicarbonate. Interaction p-value 0.1

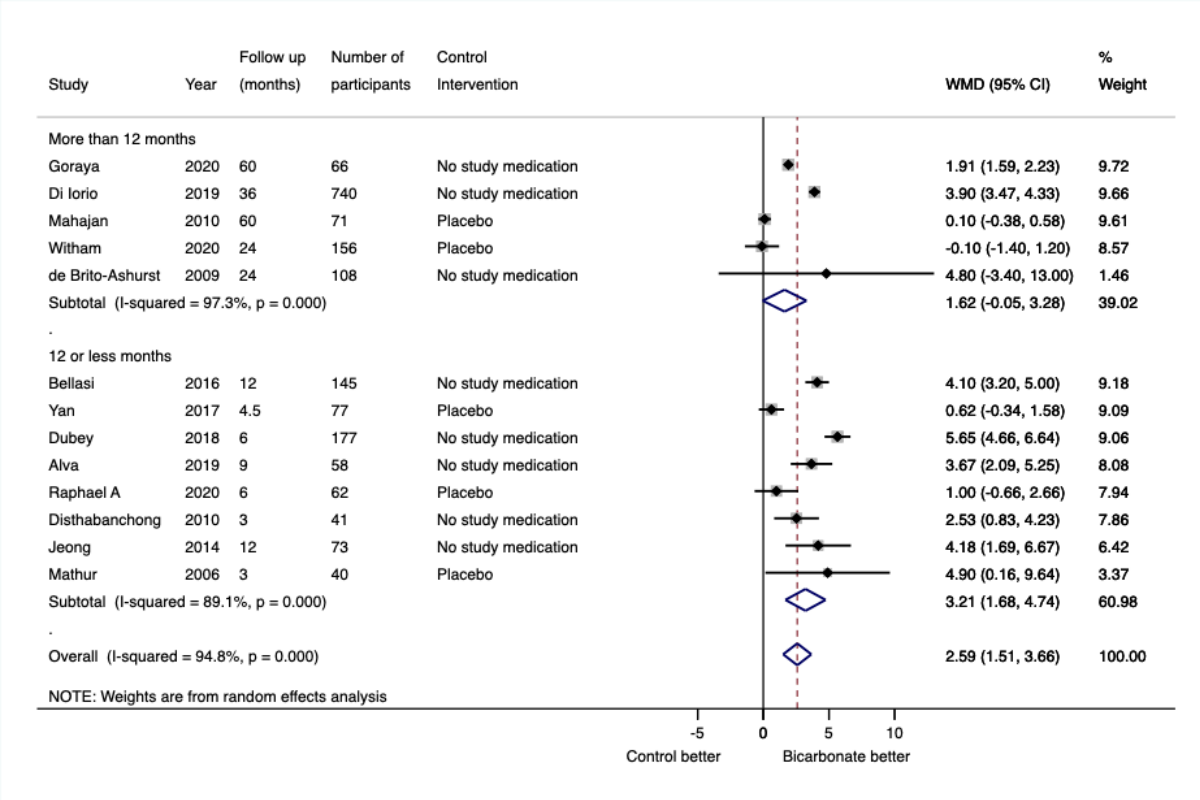

Figure S19. Subgroup analysis of the effect of bicarbonate therapy on serum bicarbonate (mmol/L) 3: according to trial quality.

Forest plot showing subgroup analysis according to trial quality on the effect of bicarbonate therapy on change in serum bicarbonate. Interaction p-value 0.58

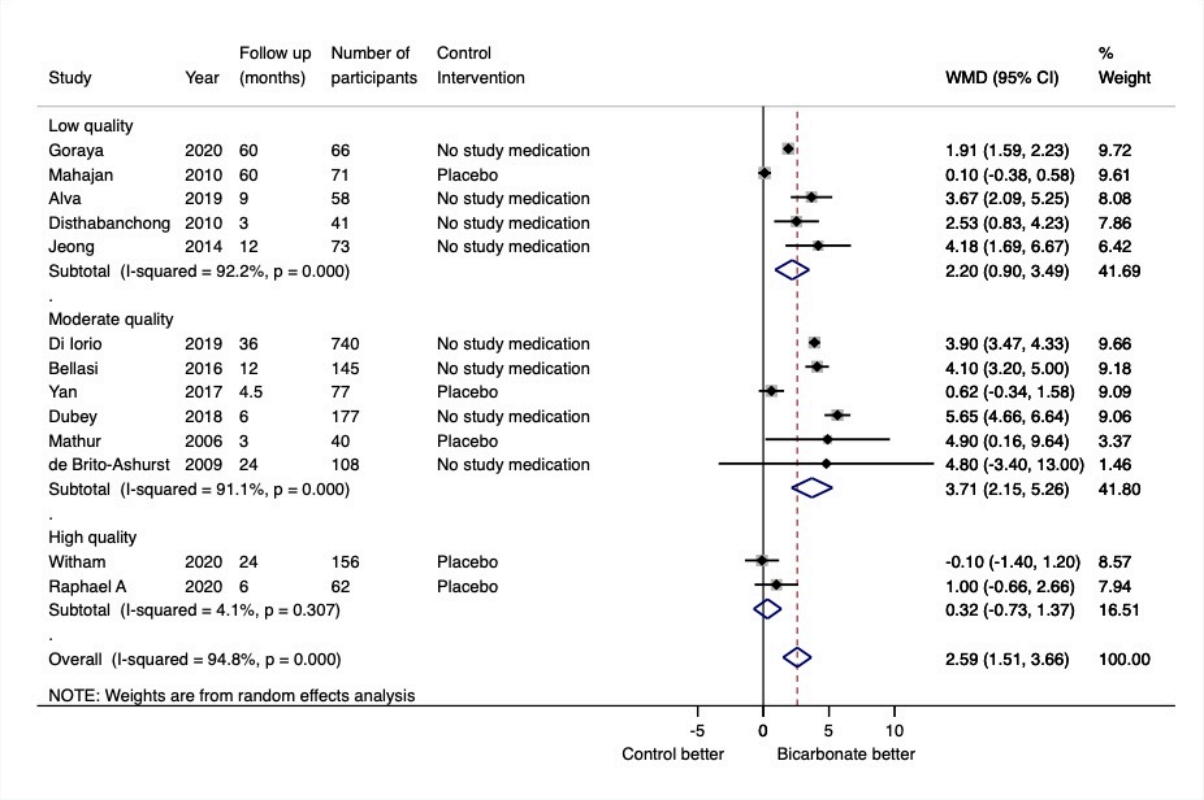

Figure S20. Effect of bicarbonate therapy on change in systolic blood pressure

Forest plot showing the effect of bicarbonate therapy on change in systolic blood pressure (mm Hg) from baseline to last measurement

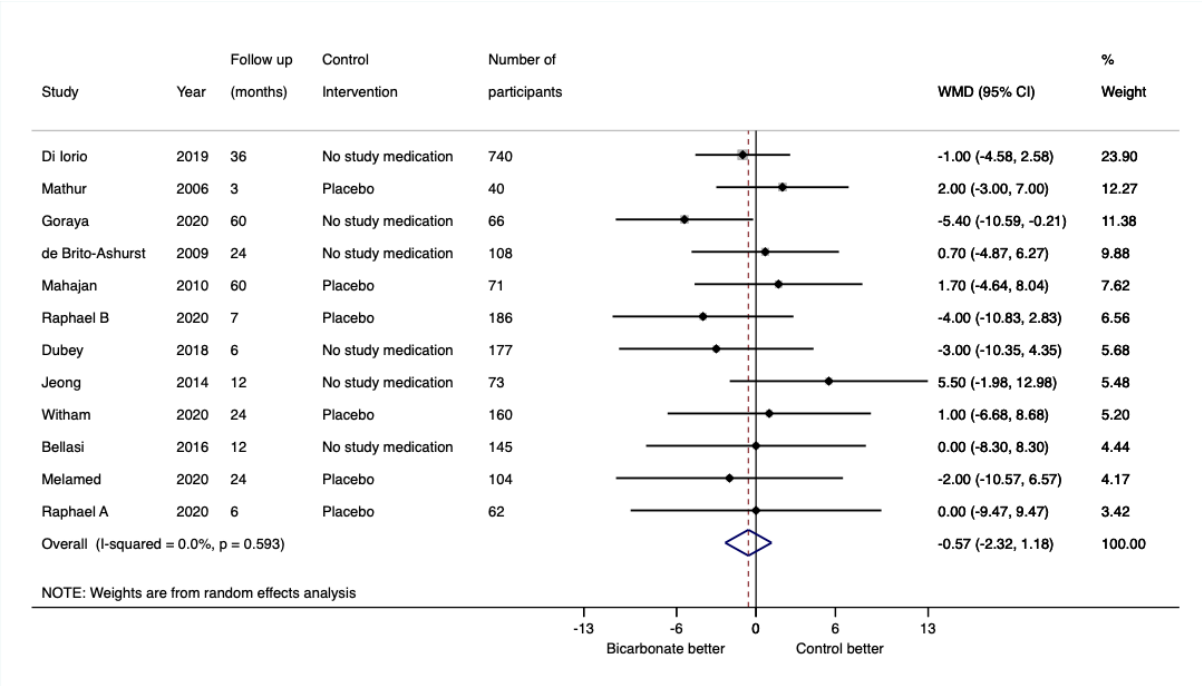

Figure S21. Effect of bicarbonate therapy on change in diastolic blood pressure

Forest plot showing the effect of bicarbonate therapy on change in diastolic blood pressure (mm Hg) from baseline to last measurement

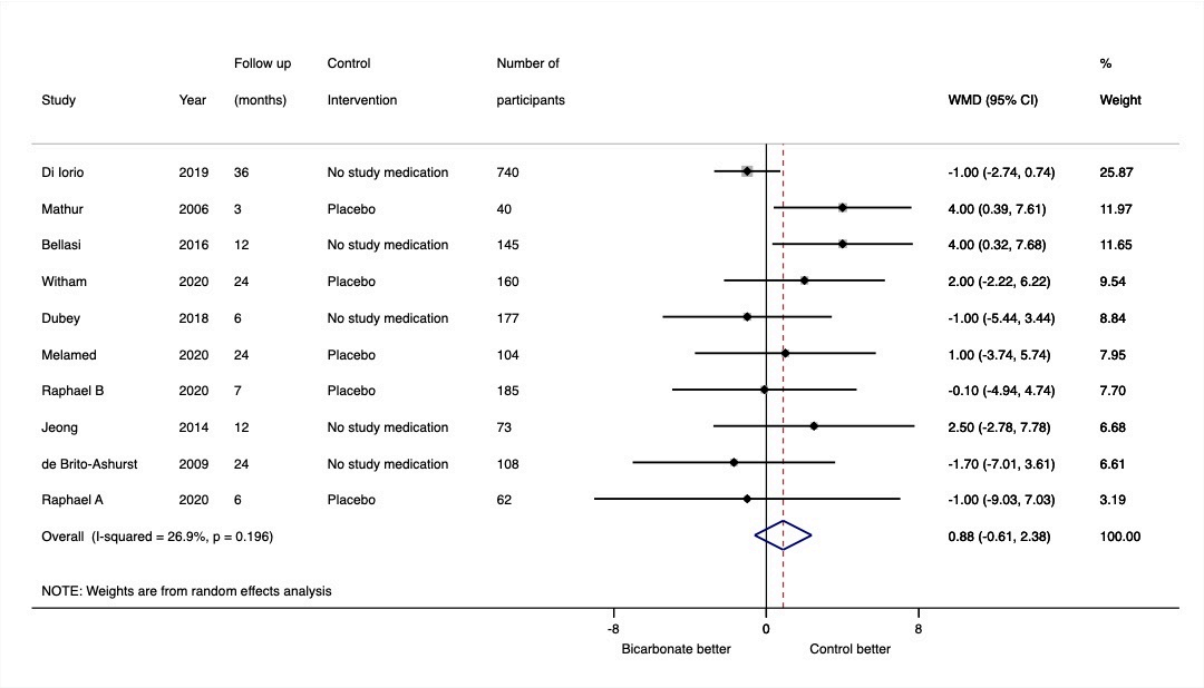

Figure S22. Effect of bicarbonate therapy on worsening of blood pressure

Forest plot showing the effect of bicarbonate therapy on worsening of blood pressure

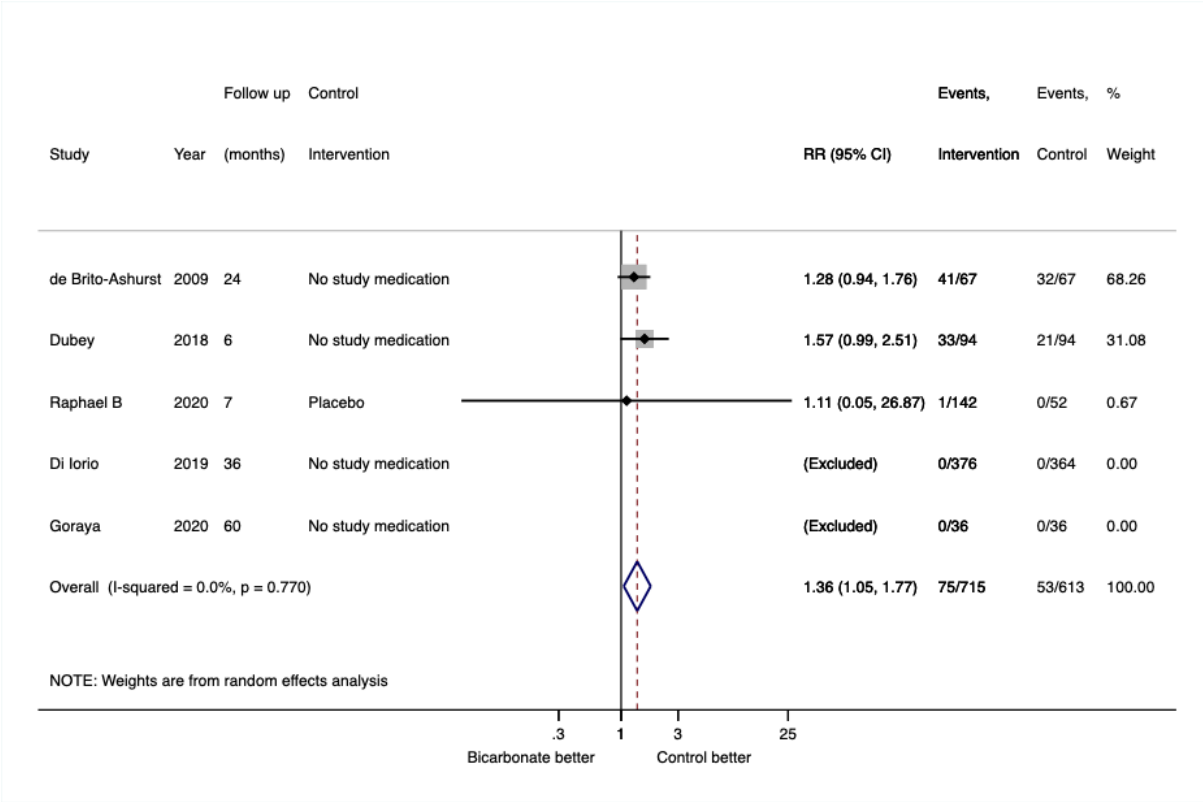

Figure S23. Effect of bicarbonate therapy on worsening of edema

Forest plot showing the effect of bicarbonate therapy on worsening of edema

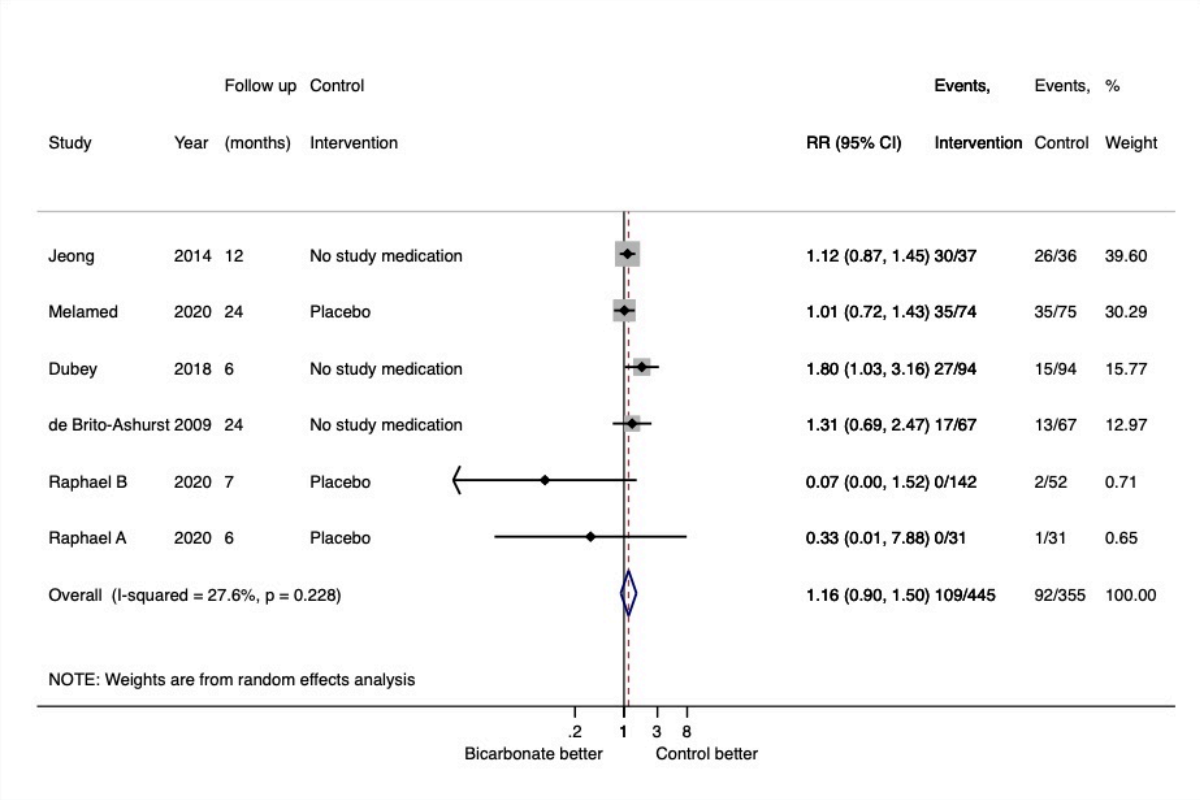

Figure S24. Effect of bicarbonate therapy on change in body weight

Forest plot showing the effect of bicarbonate therapy on change in body weight (kg) from baseline to last measurement

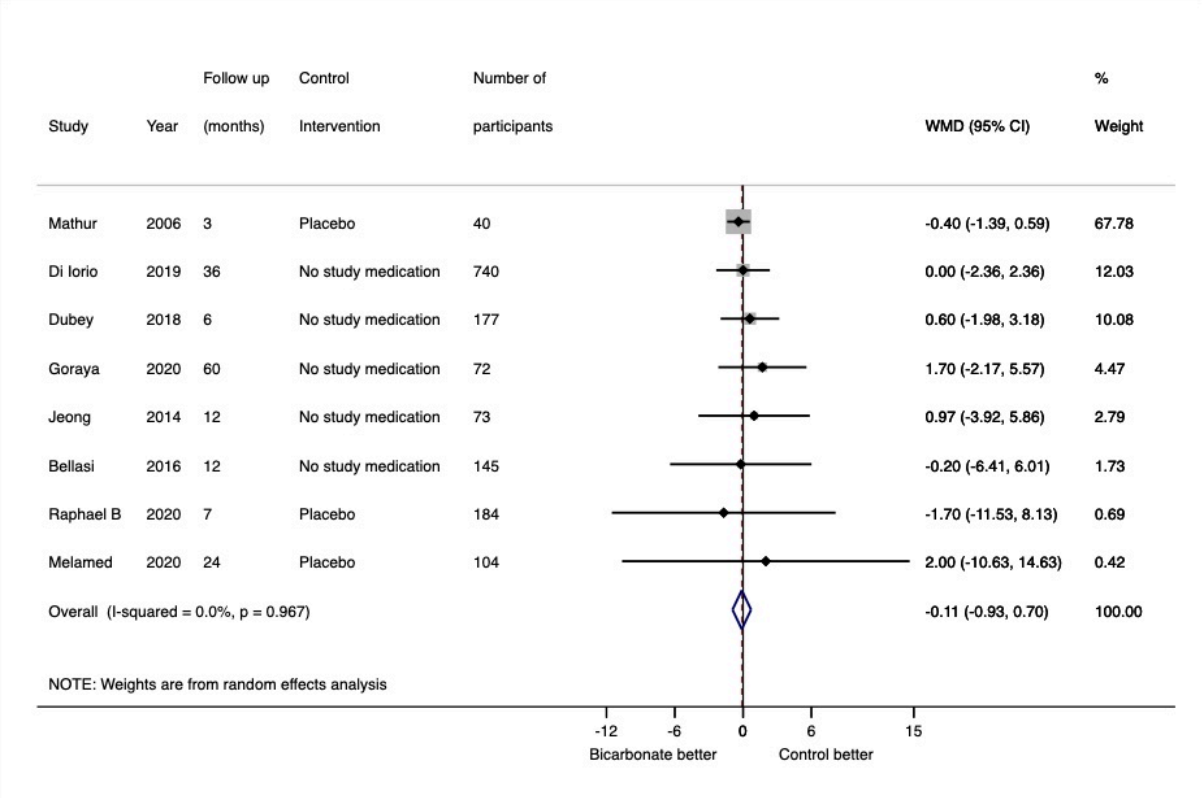

Figure S25. Effect of bicarbonate therapy on all-cause mortality

Forest plot showing the effect of bicarbonate therapy on change in all cause mortality

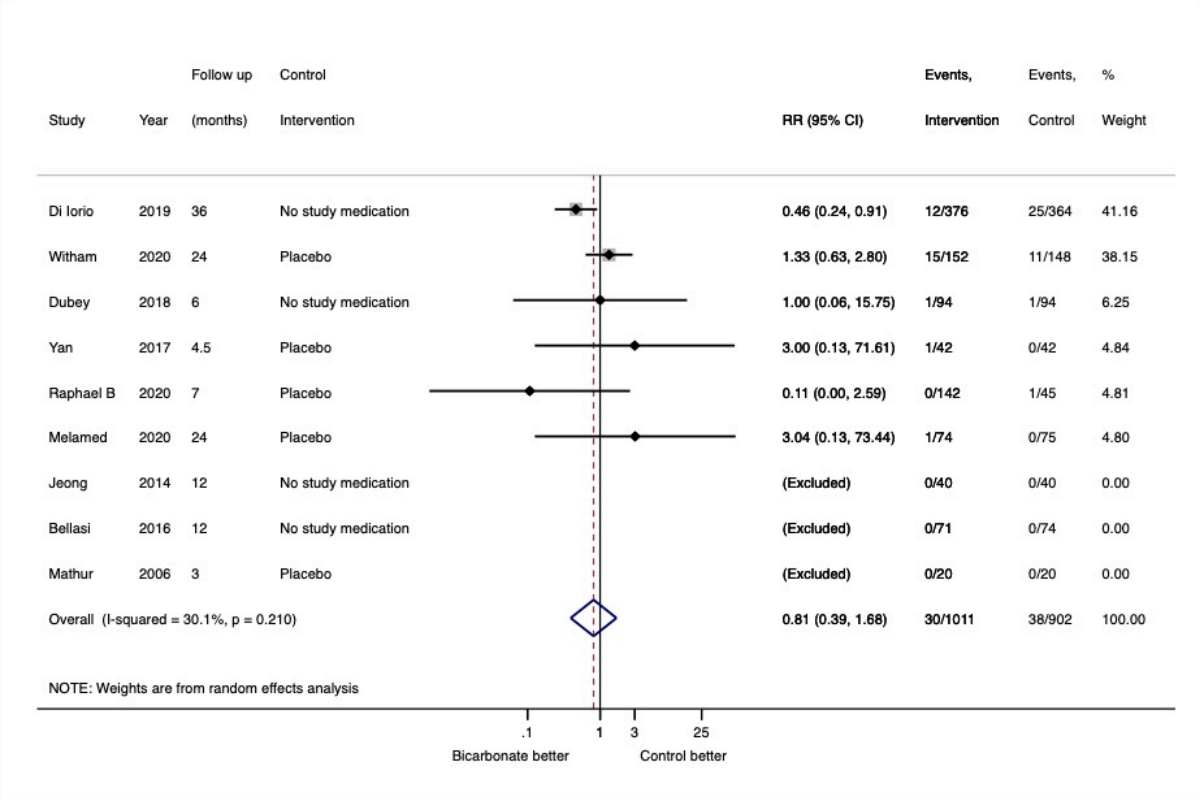

Figure S26. Effect of bicarbonate therapy on admissions for heart failure

Forest plot showing the effect of bicarbonate therapy on change in hospital admission rate for heart failure

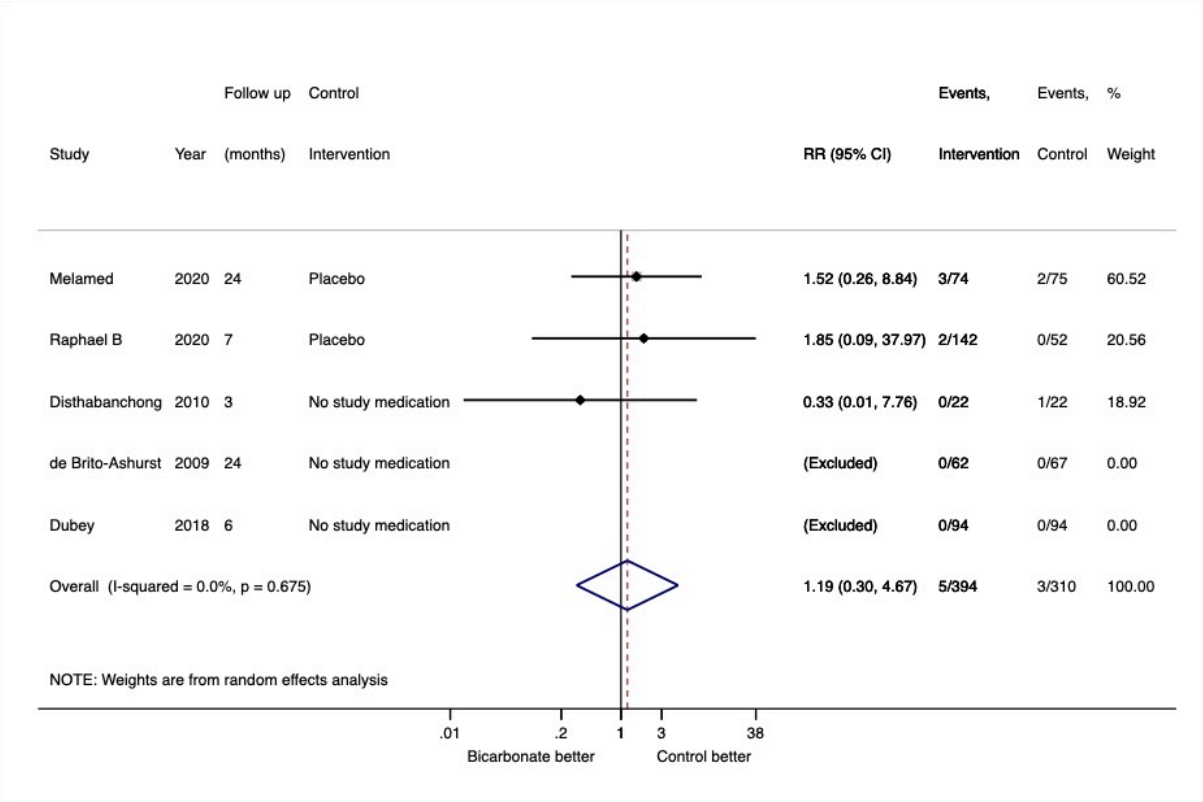

Figure S27. Funnel plot of effect of bicarbonate therapy on kidney function

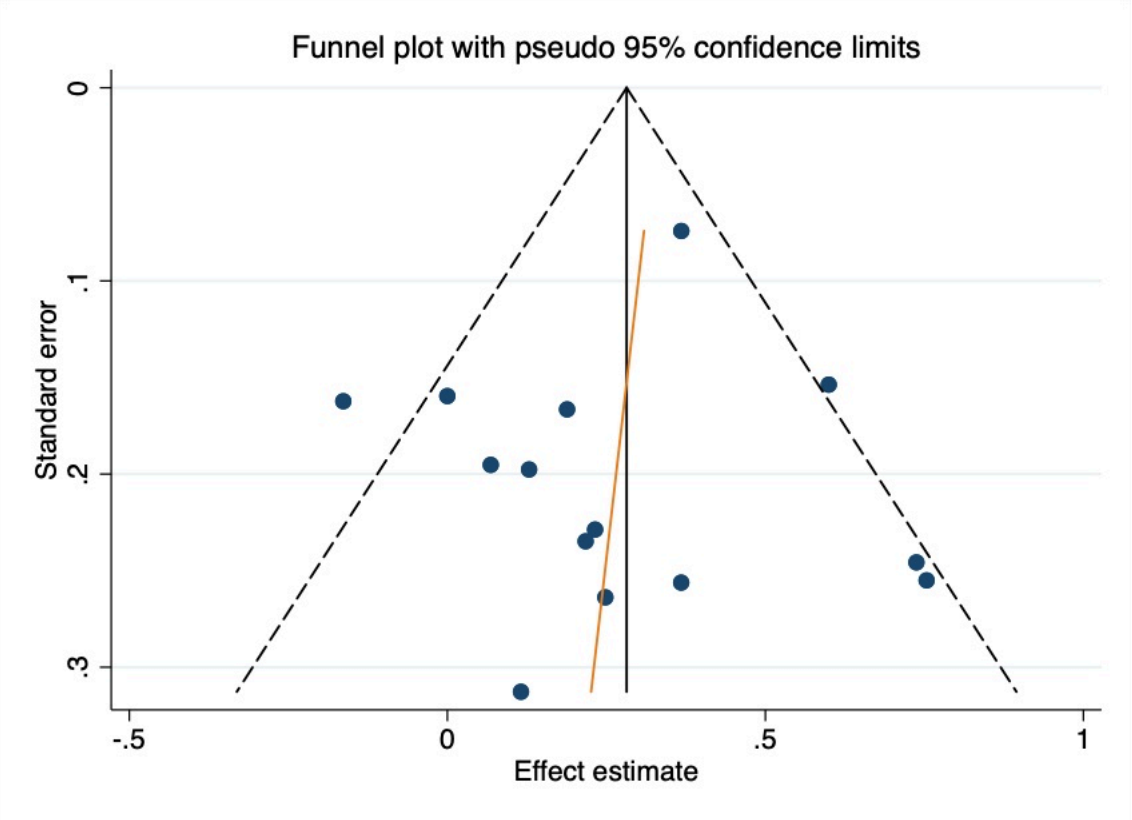

Figure S28. Funnel plot of effect of bicarbonate therapy on the progression to kidney failure

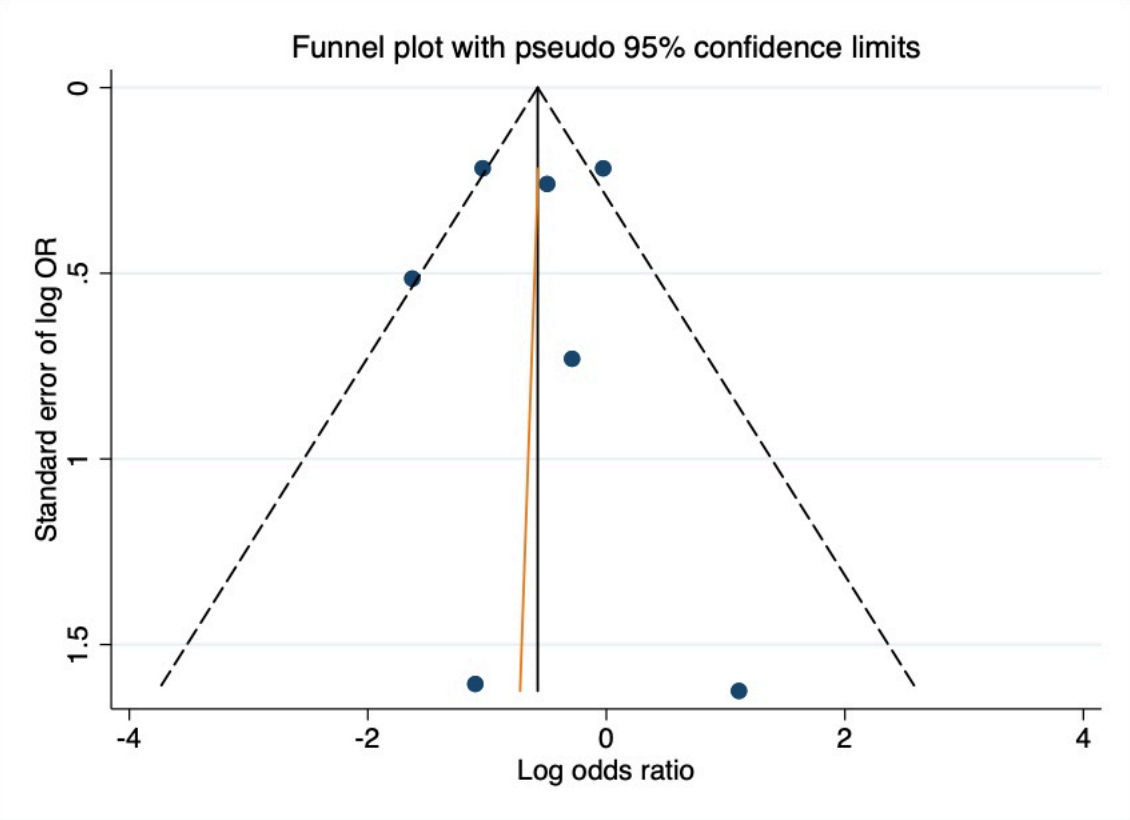

Figure S29. Funnel plot of the effect of bicarbonate therapy on eGFR (mL/min/1.73m^2)

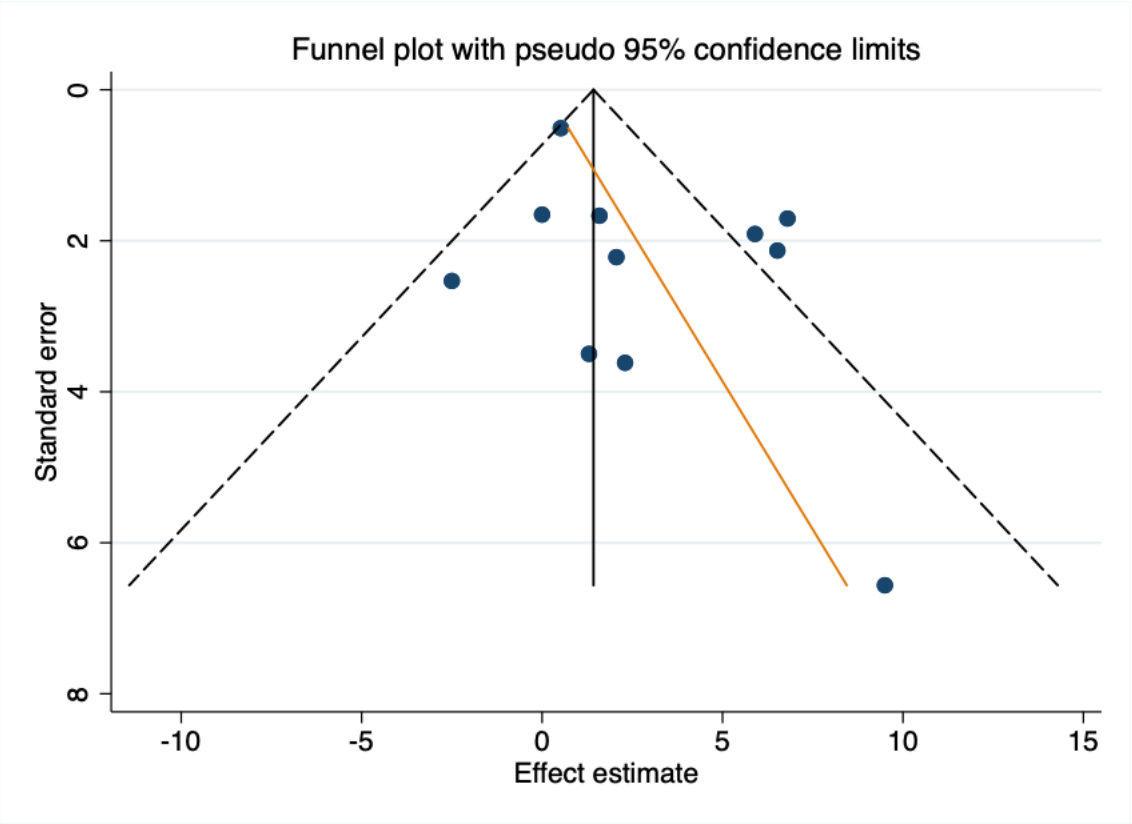

Figure S30. Funnel plot of the effect of bicarbonate therapy on serum bicarbonate

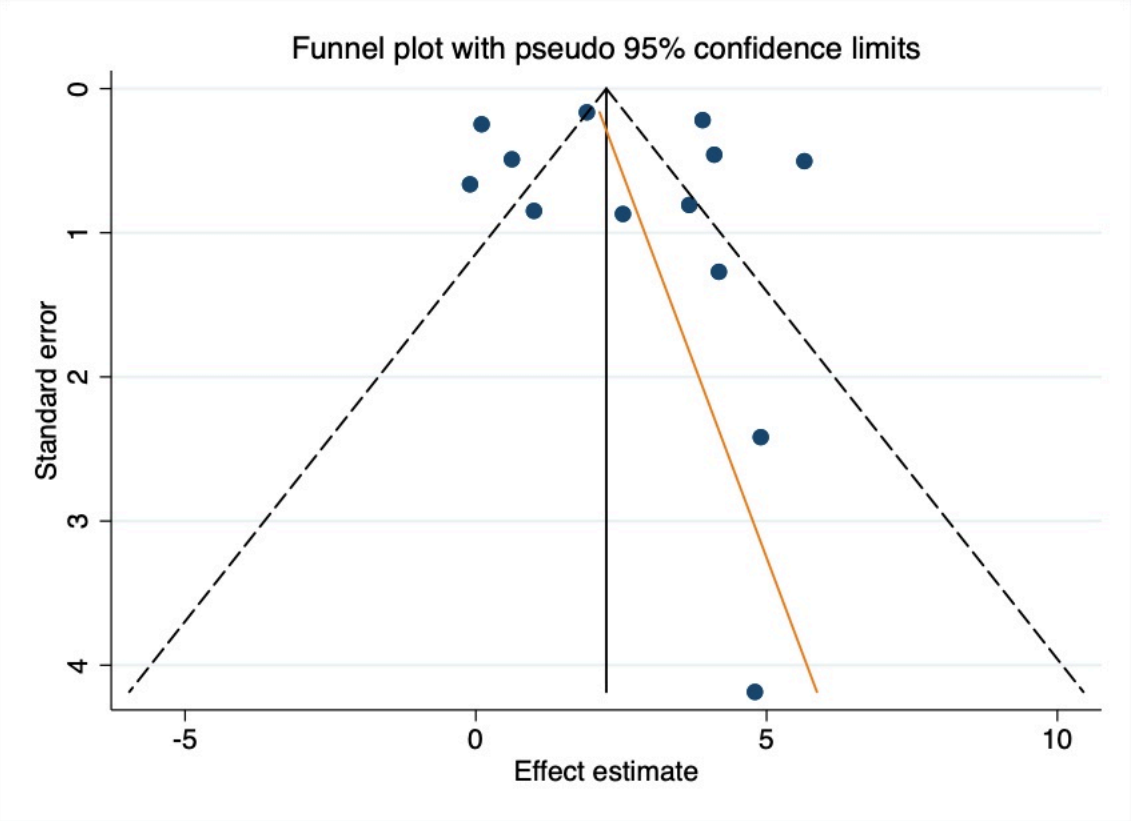

Figure S31. Funnel plot of the effect of bicarbonate therapy on weight (kg)

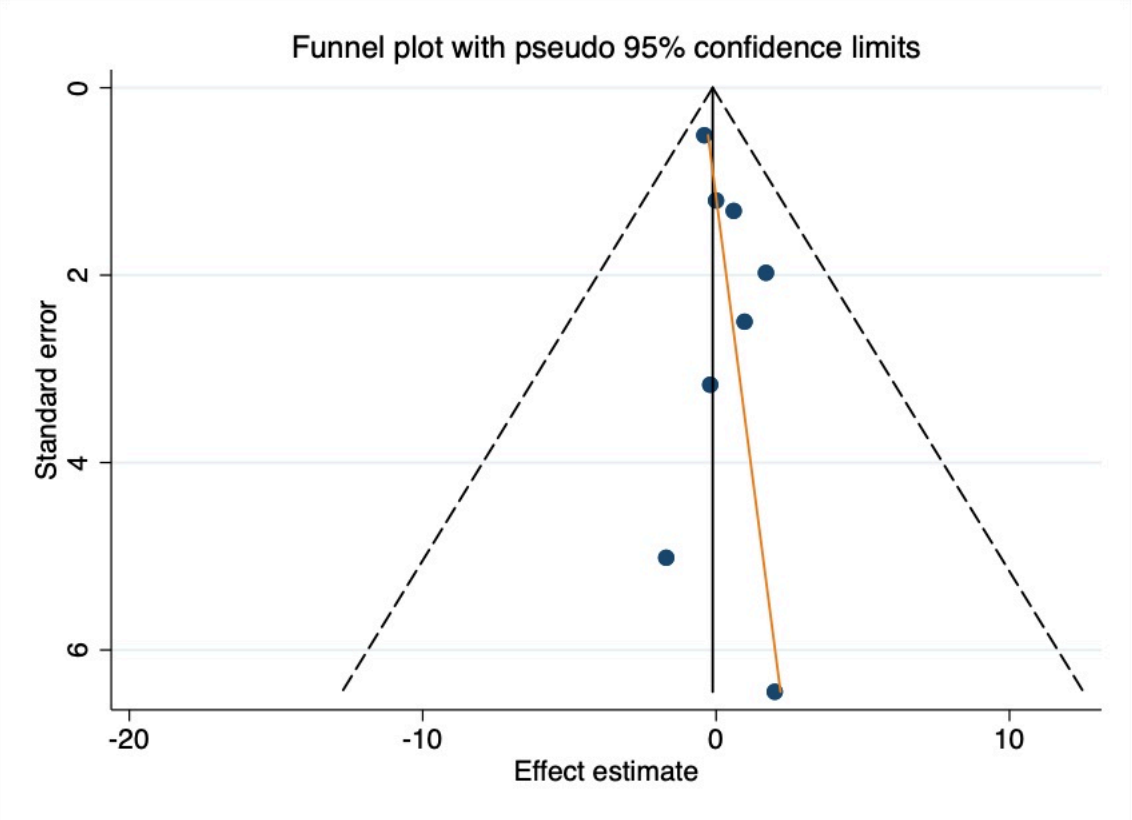

Figure S32. Funnel plot of the effect of bicarbonate therapy on systolic blood pressure

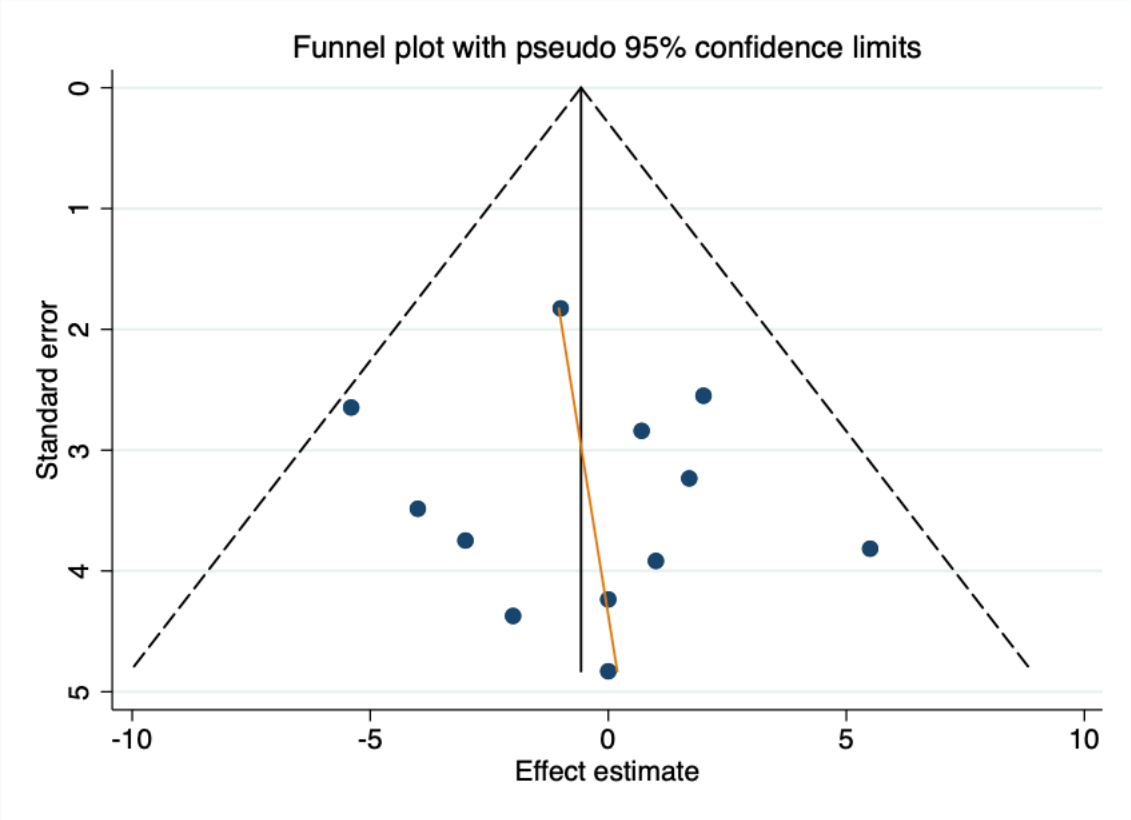

Figure S33. Funnel plot of the effect of bicarbonate therapy on diastolic blood pressure

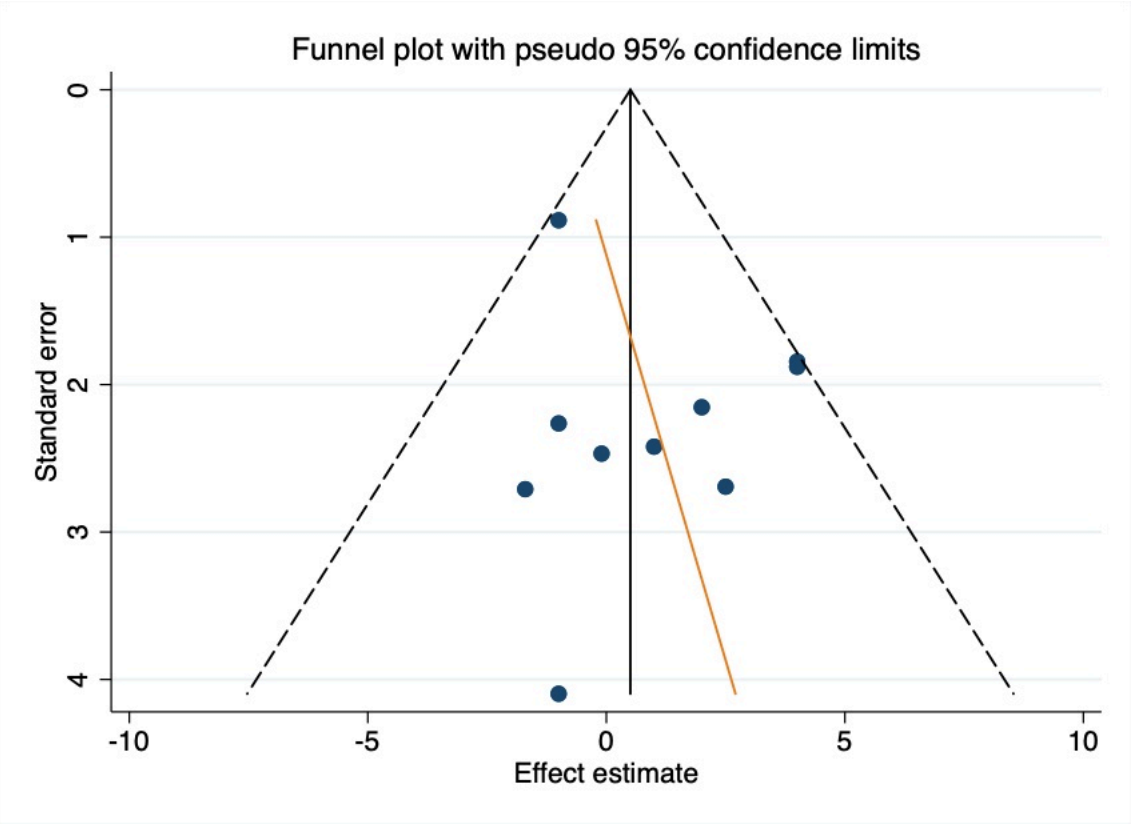

Figure S34. Subgroup analysis of the effect of bicarbonate therapy on systolic blood pressure according to trial quality.

Forest plot showing subgroup analysis according to trial quality on the effect of bicarbonate therapy on change in systolic blood pressure. Interaction p-value 0.81

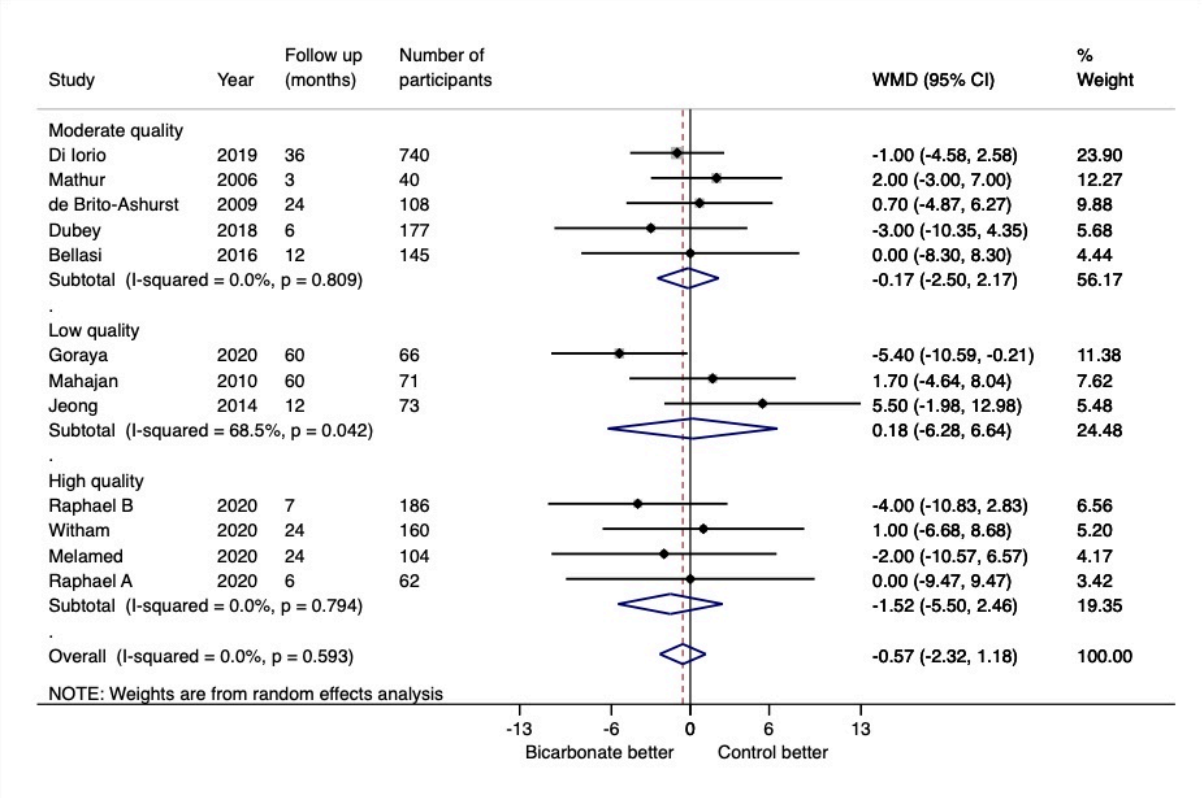

Figure S35. Subgroup analysis of the effect of bicarbonate therapy on diastolic blood pressure according to trial quality.

Forest plot showing subgroup analysis according to trial quality on the effect of bicarbonate therapy on change in diastolic blood pressure. Interaction p-value 0.75.

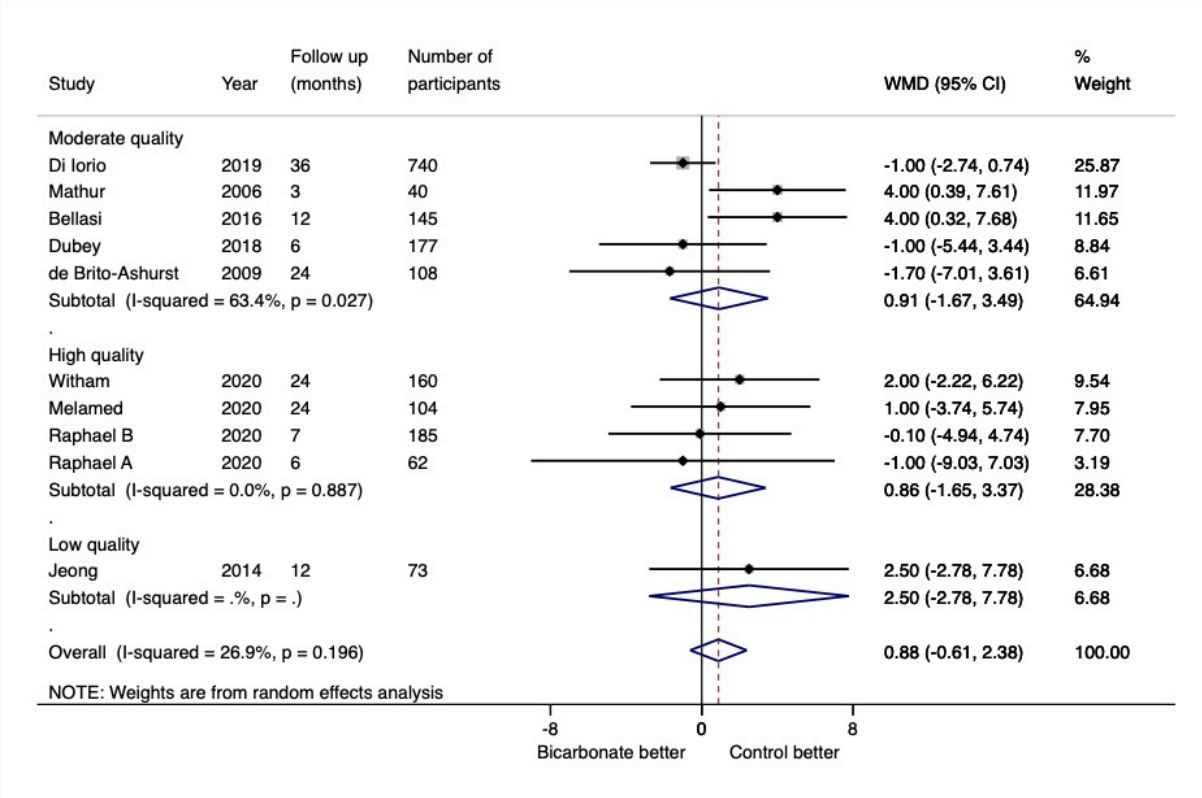

Figure S36. Subgroup analysis of the effect of bicarbonate therapy on change in weight according to trial quality.

Forest plot showing subgroup analysis according to trial quality on the effect of bicarbonate therapy on change in weight. Interaction p-value 0.37