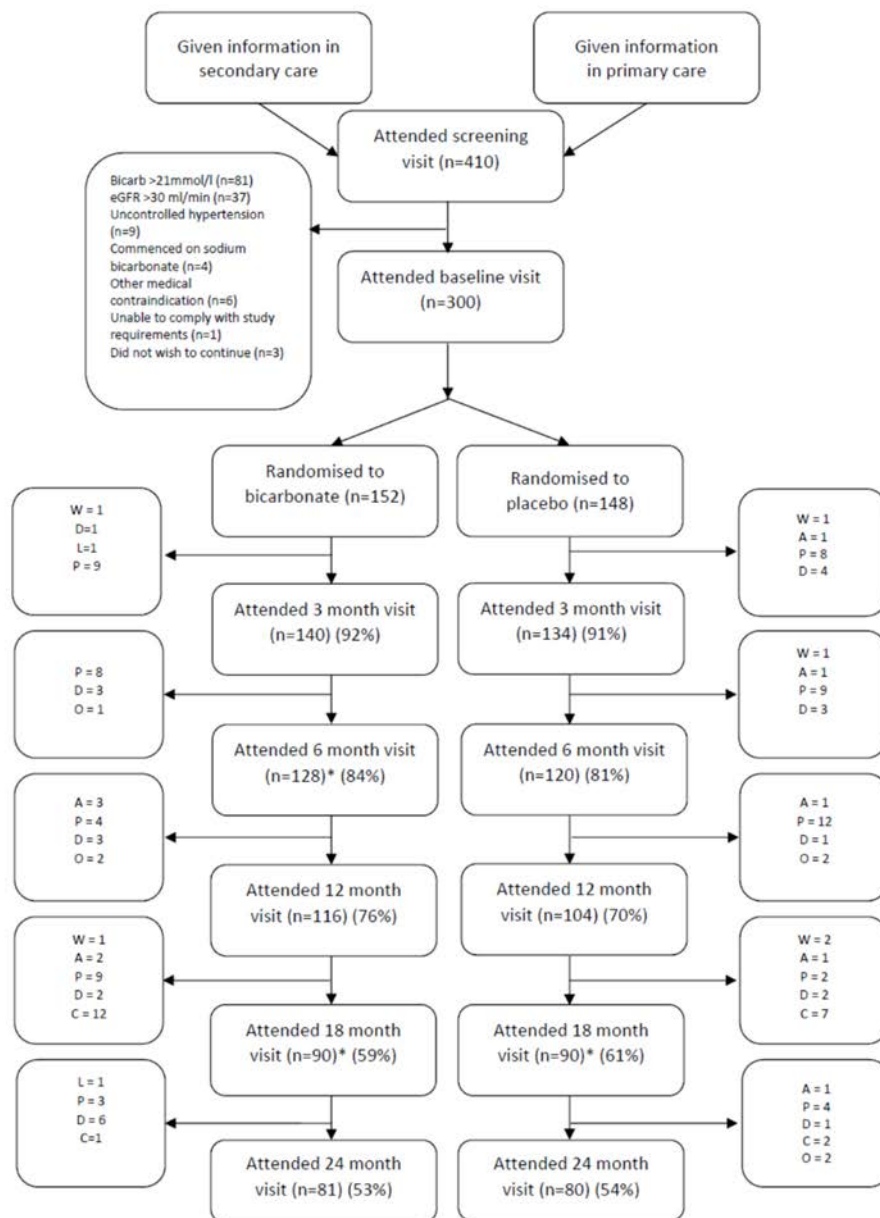


## Participant flow



(\*some did not attend visit but had not dropped out)

W = withdrawn by investigator. P = participant chose with withdraw. A = withdrew due to adverse event. D = Died. L = lost to follow up. C = early study completion due to truncated follow up. O = other.

### Baseline characteristics

		Sodium bicarbonate (n=152)	Placebo (n=148)
Mean age (years) (SD)		73.9 (7.6)	74.0 (6.6)
Age 60-69 (%)		57 (37.5)	35 (23.6)
Age 70-79 (%)		53 (34.9)	81 (54.7)
Age 80 and over (%)		42 (27.6)	32 (21.6)
Female sex (%)		42 (27.6)	44 (29.7)
Ethnicity	White	144 (94.7)	143 (96.6)
	East Asian	0 (0)	1 (0.7)
	Black	1 (0.7)	0 (0)
	South Asian	4 (2.6)	2 (1.4)
	Hispanic	1 (0.7)	0 (0)
	Other	2 (1.3)	2 (1.4)
Cause of renal dysfunction	Hypertension	37 (24.3)	40 (27.0)
	Diabetes mellitus	23 (15.1)	23 (15.5)
	Glomerulonephritis	9 (5.9)	11 (7.4)
	Polycystic kidney disease	11 (7.2)	9 (6.1)
	Vascular disease	19 (12.5)	21 (14.2)
	Other	52 (34.2)	63 (42.6)
	Not known	31 (20.4)	22 (14.9)
Cardiovascular comorbidity	Hypertension	135 (88.8)	129 (87.2)
	Diabetes mellitus	54 (35.5)	47 (31.8)
	Ischaemic heart disease	26 (17.1)	31 (20.9)
	Stroke	16 (10.5)	12 (8.1)
	Heart failure	19 (12.5)	5 (3.4)
	Peripheral vascular disease	14 (9.2)	10 (6.8)
Previous fragility fracture (%)		2 (1.3)	5 (3.4)
Mean number of medications (SD)		8.2 (3.7)	7.9 (3.3)
Medication use:	ACEi/ARB	105 (69.1)	91 (61.5)
	Phosphate binder	32 (21.1)	28 (18.9)

	Activated vitamin D	77 (50.7)	73 (49.3)
	Erythropoietin	89 (58.6)	106 (71.6)
	Iron	60 (39.5)	51 (34.5)
Mean eGFR (mL/min/1.73m <sup>2</sup> ) (SD)		19.7 (6.5)	18.2 (6.4)
CKD category 5 (%)		72 (47.4)	69 (46.6)
Mean serum bicarbonate (mmol/L) (SD)		20.6 (2.6)	20.1 (2.5)
Mean haemoglobin (g/L) (SD)		115 (14)	117 (17)
Mean serum potassium (mmol/L) (SD)		4.9 (0.5)	4.9 (0.5)
Mean Short physical performance battery (SD)		8.0 (2.4)	8.1 (2.2)
Mean six-minute walk distance (m) (SD)		304 (134)	317 (133)
Mean handgrip strength (kg) (SD)	Males	26.6 (8.8)	28.0 (7.6)
	Females	15.4 (4.8)	15.8 (4.4)
Mean body mass index (kg/m <sup>2</sup> ) (SD)		28.9 (4.5)	28.3 (4.6)
Mean mid-arm muscle circumference (cm) (SD)		24.9 (3.6)	24.8 (4.0)
Mean triceps skinfold thickness (mm) (SD)		16 (8)	17 (9)
Mean mid-thigh circumference (cm) (SD)		47.4 (7.0)	46.8 (7.0)
Mean EQ-5D-3L (SD)		0.73 (0.22)	0.74 (0.24)
Mean EQ-5D thermometer (SD)		69 (19)	71 (19)
Mean KDQoL scores	SF36 PCS (SD)	36 (11)	36 (11)
	SF36 MCS (SD)	53 (11)	53 (9)
	Burden (SD)	75 (26)	75 (25)
	Symptoms (SD)	79 (14)	81 (12)
	Effects (SD)	86 (14)	87 (15)
Mean office systolic blood pressure (mmHg) (SD)		143 (18)	143 (18)
Mean office diastolic blood pressure (mmHg) (SD)		75 (11)	73 (10)

Dosing and adherence:

		<i>Bicarbonate group</i>	<i>Placebo group</i>
Dose at 3 months	500mg 3x/day (%)	82 (58.6)	45 (33.6)
	1000mg 3x/day (%)	46 (32.9)	83 (61.9)
	Not dispensed (%)	12 (8.6)	6 (4.5)
Overall % Adherence (SD)		72.8 (35.2)	73.4 (39.6)
Adherence <=80% (%)		76 (50.0)	73 (49.3)

## Outcome measures

Primary outcome – Short Physical Performance Battery (SPPB) at 12 months

	Bicarbonate group	Placebo group	Adjusted treatment effect* (95% CI)	p
Baseline SPPB (SD)	8.0 (2.4)	8.1 (2.2)	-0.4 (-0.9 to 0.1)	0.15
12 month SPPB (SD)	8.3 (2.5)	8.8 (2.2)		

\*adjusted for baseline SPPB, age, sex and CKD category (4 vs 5).

## Secondary outcomes

(between-group repeated measures analyses, adjusted for baseline values, age, sex and CKD stage, exc for creatinine, eGFR and cystatin C, where adjustment for CKD stage was not performed)

Outcome (units)	Treatment effect (95% CI)	p
SPPB	-0.6 (-1.0 to -0.1)	0.02
EQ5D-3L	-0.04 (-0.08 to 0.00)	0.06
EQ5D thermometer	-3 (-7 to 1)	0.09
Potassium (mmol/L)	0.0 (-0.1 to 0.1)	0.80
Bicarbonate (mmol/L)	1.1 (0.6 to 1.6)	<0.001
Calcium (mmol/L)	0.02 (0.00 to 0.04)	0.11
Phosphate (mmol/L)	0.02 (-0.03 to 0.06)	0.52
Log [Bone-specific Alkaline Phosphatase (ug/L)]	0.01 (-0.11 to 0.13)	0.83
Log [TRACP-5b (IU/L)]	-0.18 (-0.43 to 0.08)	0.17
Log [Parathyroid hormone (pmol/L)]	0.03 (-0.14 to 0.19)	0.75
Log [25OHD (nmol/L)]	-0.08 (-0.23 to 0.06)	0.24
1,25OHD (pmol/L)	3 (-3 to 9)	0.30
Albumin (g/L)	0 (-1 to 1)	0.67
Haemoglobin (g/L)	-0.1 (-0.4 to 0.2)	0.48
Log [thyroid stimulating hormone (mIU/L)]	0.07 (-0.10 to 0.24)	0.39
HbA1c (mmol/mol)	1 (-1 to 4)	0.38
Total Cholesterol (mmol/L)	0.1 (-0.2 to 0.3)	0.58
Log Urinary albumin/creatinine ratio	0.32 (-0.05 to 0.70)	0.09
Creatinine (umol/L)	-8 (-28 to 13)	0.46
eGFR (by MDRD4 equation) (ml/min/1.73m <sup>2</sup> )	0.6 (-0.8 to 2.0)	0.39
Cystatin C (mg/L)	-0.01 (-0.17 to 0.14)	0.89
Weight (kg)	0.2 (-2.9 to 3.4)	0.89
Mid-arm muscle circumference (cm)	0.0 (-0.6 to 0.6)	0.99
Triceps skinfold thickness (mm)	-1 (-2 to 1)	0.34
Mid-thigh circumference (cm)	0.1 (-0.8 to 1.1)	0.80

Handgrip strength (kg)	-1.5 (-2.8 to -0.2)	0.03
Six minute walk distance (m)	-33 (-62 to -4)	0.02
KDQoL symptoms	-1 (-3 to 2)	0.67
KDQoL burden of disease	-3 (-8 to 2)	0.20
KDQoL effect of disease	-2 (-5 to 1)	0.25
KDQoL SF36 physical component score	-1 (-4 to 1)	0.23
KDQoL SF36 mental component score	-2 (-4 to 0)	0.03
Systolic blood pressure (mmHg)	0 (-4 to 3)	0.93
Diastolic blood pressure (mmHg)	1 (-1 to 3)	0.16
Log [B-type natriuretic peptide (pg/ml)]	0.13 (-0.18 to 0.44)	0.42

TRACP-5b: Tartrate-resistant acid phosphatase 5b. eGFR: estimated glomerular filtration rate. MDRD4: Modification of diet in renal disease 4 variable equation. KDQoL: Kidney disease quality of life. SPPB: Short physical performance battery. EQ5D: Euroqol 5 dimension questionnaire. HbA1c: Glycosylated haemoglobin. 25OHD: 25-hydroxyvitamin D. 1,25OHD: 1,25 dihydroxyvitamin D

Notes:

Outcomes listed in the ISRCTN description but not included in the prespecified Statistical Analysis Plan were:

Urine protein/creatinine ratio (not measured); sodium, magnesium, urea

Alkaline Phosphatase (bone-specific version was measured)

Falls, deaths and commencement of renal replacement therapy (dialysis or transplantation)

Outcome	Bicarbonate	Placebo
All cause deaths	15	11
Deaths due to end stage renal failure	3	0
Commenced renal replacement therapy	33	33
Falls	124	70
Number with at least one fall	49	39
Falls rate (per year)	0.99 (95% CI 0.61 to 1.38)	0.72 (95% CI 0.25 to 1.19)

Time to death by Cox proportional hazards model: HR 1.30, 95% CI 0.60 to 2.83; p=0.51

Time to renal replacement by Cox proportional hazards model: HR 1.22, 95% CI 0.74 to 2.02; p=0.43

### Adverse events by System Order Class

	Bicarbonate (n=152)	Placebo (n=148)
Number with at least one adverse event (%)	131 (86.1)	132 (89.1)
Number of adverse events:	457	400
<i>SOC classification – number of events:</i>		
Blood and lymphatic system disorders	5	1
Cardiac disorders	32	19
Congenital, familial and genetic disorders	0	1
Ear and labyrinth disorders	1	1
Endocrine disorders	1	2
Eye disorders	6	6
Gastrointestinal disorders	45	25
General disorders and administration site conditions	14	20
Hepatobiliary disorders	0	0
Immune system disorders	0	0
Infections and infestations	113	118
Injury, poisoning and procedural complications	41	32
Investigations	5	7
Metabolism and nutrition disorders	19	27
Musculoskeletal and connective tissue disorders	28	17
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9	16
Nervous system disorders	24	12
Psychiatric disorders	1	5
Renal and urinary disorders	23	23
Reproductive system and breast disorders	4	1
Respiratory, thoracic and mediastinal disorders	26	14
Skin and subcutaneous tissue disorders	16	11
Surgical and medical procedures	34	30
Vascular disorders	10	12



Deaths	15	11
Commenced renal replacement therapy	33	33