

STUDY PROTOCOL

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Effect of oral sodium bicarbonate supplementation on progression of chronic kidney disease in patients with chronic metabolic acidosis: study protocol for a randomized controlled trial (SoBic-Study)

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Abstract

Background: Overt chronic metabolic acidosis in patients with chronic kidney disease develops after a drop of glomerular filtration rate to less than approximately 25 mL/min/1.73 m². The pathogenic mechanism seems to be a lack of tubular bicarbonate production, which in healthy individuals neutralizes the acid net production. As shown in several animal and human studies the acidotic milieu alters bone and vitamin D metabolism, induces muscle wasting, and impairs albumin synthesis, aside from a direct alteration of renal tissue by increasing angiotensin II, aldosteron and endothelin kidney levels. Subsequent studies testing various therapeutic approaches in very selected study populations showed that oral supplementation of the lacking bicarbonate halts progression of decline of renal function. However, due to methodological limitations of these studies further investigations are of urgent need to ensure the validity of this therapeutic concept.

Methods/Design: The SoBic-study is a single-center, randomized, controlled, open-label clinical phase IV study performed at the nephrological outpatient service of the Medical University of Vienna. Two-hundred patients classified to CKD stage 3 or 4 with two separate measurements of HCO₃⁻ of <21 mmol/L will be 1:1 randomized to either receive a high dose of oral sodium bicarbonate with a serum target HCO₃⁻ level of 24 ± 1 mmol/L or receive a rescue therapy of sodium bicarbonate with a serum target level of 20 ± 1 mmol/L. The follow up will be for two years. The primary outcome is the effect of sodium bicarbonate supplementation on renal function measured by means of estimated glomerular filtration rates (4-variable-MDRD-equation) after two years. Secondary outcomes are change in markers of bone metabolism between groups, death rates between groups, and the number of subjects proceeding to renal replacement therapy across groups. Adverse events, such as worsening of arterial hypertension due to the additional sodium consumption, will be accurately monitored.

Discussion: We hypothesize that sufficiently balanced acid–base homeostasis leads to a reduction of decline of renal function in patients with chronic kidney disease. The concept of an exogenous bicarbonate supplementation to substitute the lacking endogenous bicarbonate has existed for a long time, but has never been investigated sufficiently to state clear treatment guidelines.

Trial registration: EUDRACT Number: 2012-001824-36

Keywords: Metabolic acidosis, Chronic kidney disease, Kidney injury, Sodium bicarbonate, Acid–base balance, Acid retention, Acidotic, Progression

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Background

Chronic kidney disease (CKD) occurs in approximately one in ten persons worldwide and represents not only a medical challenge but also a great socioeconomic burden. Major efforts have been made to investigate treatment options aiming to slow progression to end-stage renal disease (ESRD) and, subsequently, to reduce mortality in kidney patients. A renin-angiotensin system blockade with either angiotensin-I-converting enzyme inhibitors or angiotensin-II-receptor antagonists slows the progression of decline in renal function [1-5]. However, further therapeutic interventions have not shown any benefits [6-10]. The comprehensive summary by Fink *et al.* underscores the lack of evidence-based treatment concepts in CKD and even calls screening and monitoring for early-stage CKD into question [11].

Overt chronic metabolic acidosis in CKD patients develops after a drop in glomerular filtration rate (GFR) to less than approximately 25 mL/min/1.73 m². The pathogenic mechanism seems to be a lack of tubular bicarbonate production, which in healthy individuals neutralizes the acid net production. As shown in several animal and human studies the acidotic milieu alters bone and vitamin D metabolism [12], induces muscle wasting [13], and impairs albumin synthesis [14], in addition to other detrimental effects [15,16]. Experiments in rats suggest that even in the earlier stages of CKD with serum bicarbonate levels within normal limits, increased per-nephron acidification occurs to obviate overt metabolic acidosis [17]. Investigations to elucidate the contribution to the progression of CKD itself have provided contradictory results [18-20]. However, there is evidence that the alternative complement system is activated by increased tubular ammonia production [21] and that endothelin, angiotensin II and aldosterone kidney concentrations are increased as a direct result of distal nephron acidification [17,20,22]. Taken together, these alterations induce tubulointerstitial scarring in the long term.

The results of several retrospective studies conducted in different types of populations showed clear associations between acid-base imbalance and increased mortality [23,24]. Above all is the recently published analysis of the CKD registry of the Cleveland Clinic health care provider in 41,749 patients with CKD stage III and IV (estimated (e) GFR of 60 to 15 mL/min/1.73 m², measured by the Chronic Kidney Disease Epidemiology Collaboration equation). Adjusted for several covariates the all-cause mortality for subjects with a low serum bicarbonate level (<23 mmol/L) is 23% higher than for those with a level within the normal range (23 to 32 mmol/L) [25].

The first prospective studies in closely selected study populations [26] using various therapeutic interventions [27] and endpoints revealed beneficial effects. In particular, de

Brito-Ashurst *et al.* showed that sodium bicarbonate supplementation in patients with CKD stage IV slows the decline in renal function, although the study comprised some serious methodological limitations [28].

In line with the aforementioned studies we assume that a sufficiently balanced acid-base status leads to a reduction in the decline of renal function in patients with CKD. Bicarbonate is necessary to counterbalance acid net production arising from protein metabolism and acid-rich diets. Thus, the intervention of exogenous bicarbonate supplementation to substitute the lacking endogenous bicarbonate would appear to be rational. This simple concept has existed for a long time, but has never been investigated sufficiently to state clear treatment guidelines for physicians. Furthermore, including patients with both moderate and severe grades of renal impairment represents a novel and comprehensive approach. Thus, conclusions drawn by results of this study are directly applicable to routine care and treatment guidelines.

Methods/Design

Trial design

The SoBic study is a single-center, randomized, controlled, stratified, open-label clinical phase IV study and will be performed at the Nephrological outpatient service of the Medical University of Vienna. From the beginning of October 2013, 200 subjects with CKD stage III and IV and chronic metabolic acidosis will be randomized to either receive a high dose of oral sodium bicarbonate with a serum target HCO₃⁻ level of 24 ± 1 mmol/L or receive a rescue therapy of sodium bicarbonate, if necessary, with a serum target level of 20 ± 1 mmol/L. The follow up period will be 2 years. The ethics committee of the Medical University of Vienna and the Austrian Competent Authority approved the study. The study is registered at the European Union Drug Regulating Authority (EUDRACT Number: 2012-001824-36; <https://www.clinicaltrialsregister.eu>) and will be conducted in accordance with the current version of the Declaration of Helsinki [29]. All study subjects will be appropriately insured and are required to give written informed consent before any study action is taken. Data will be stored in the ClinCase version 2.6.0.33 clinical trial system (Quadratex Data Solutions Ltd, London, United Kingdom. Data structure design is developed by the science support work group of AKIM (Allgemeines Krankenhaus Informations Management) at the Center of Medical Statistics, Informatics and Intelligent Systems. The software provides advanced data management and data preparation tools for statistic evaluation. The web-based electronic case report forms allow efficient user handling and thus, error avoidance. In accordance with the Good Clinical Practice (GCP) guidelines an independent person will periodically perform data monitoring [30].

The study will be reported as suggested by the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines [31].

Participants

The study population will comprise incident and prevalent patients with CKD from the outpatient service of a tertiary care facility. Patients classified as having CKD stage III or IV, and two separate measurements of HCO_3^- of <21 mmol/L (at least 1 day apart) will be included in the study. Patients fulfilling the inclusion criteria, who are already receiving alkali treatment, can be included after a wash-out phase of 4 weeks. The inclusion criteria are age over 18 years, renal function (measured by eGFR calculated by the four-variable Modification of Diet in Renal Disease (MDRD) study equation) between 60 and 15 mL/min/1.73 m², venous serum HCO_3^- of <21 mmol/L on two consecutive measurements (at least 1 day apart), and for the patient to be in a stable clinical condition. Patients with malignant disease or within 5 years of successful treatment of malignant disease (except dermal malignancies and carcinoma *in situ* of the cervix declared to be cured), and patients with morbid obesity (body mass index >40 kg/m²), chronic inflammation (C reactive protein >10 mg/dL) or taking immunosuppressive therapy of any kind, poorly controlled blood pressure ($>150/90$ mmHg despite the use of four agents), overt congestive heart failure, or known peanut or soy allergy, will be excluded from the study.

With respect to concomitant medication, various drugs are known to induce metabolic acidosis [32]. However, most relevant with regard to the planned study are the phosphate binder sevelamer hydrochloride and potassium-sparing diuretics. Other agents known to neutralize metabolic acidosis, such as calcium citrate, sodium citrate and calcium carbonate are not allowed.

Laboratory measurements

Serum creatinine will be determined by means of the Jaffe method (reference range <1.2 mg/dL, mg/dL $\times 88.4 = \mu\text{mol/L}$). Bicarbonate measurements will be performed in venous blood samples and determined by an ABL 700 Copenhagen Blood Gas Analyzer (Radiometer Copenhagen, Copenhagen, Denmark). Markers of bone metabolism (bone alkaline phosphatase, osteocalcin, C-telopeptide pyridinoline crosslinks of type I collagen, procollagen type I N-propeptide) will be measured as detailed in Cejka *et al.* [33]. All laboratory measurements, including urinalyses, will be performed in an ISO 9001–2008 certified and ISO 15189-accredited clinical laboratory at the Medical University Vienna [<http://www.kimcl.at>].

Randomization and study visits

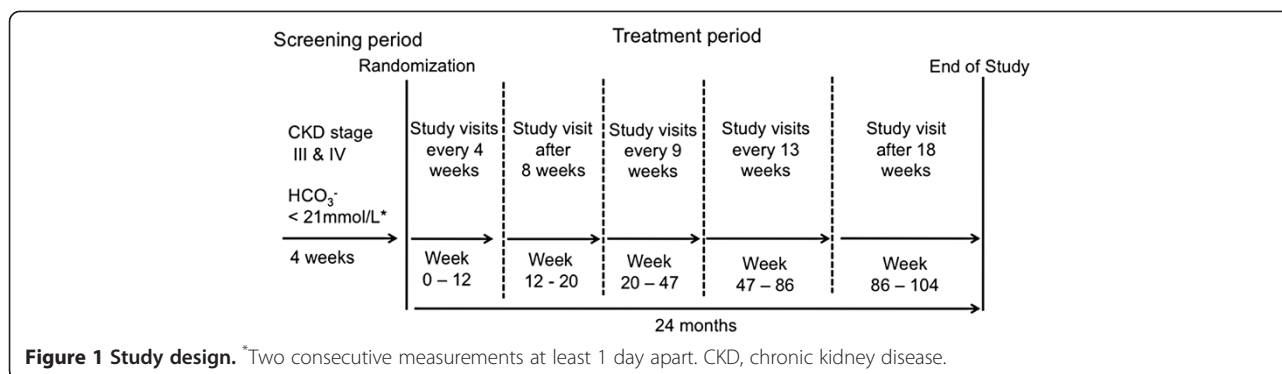
Subjects will attend the clinic for a regular visit and blood draw. After a careful review of their medical history

patients who fulfill the inclusion criteria will be contacted and informed about the study protocol. Patients who agree to participate in the study will be invited to a further blood work-up to ensure that metabolic acidosis is chronic rather than a one-time imbalance of the acid–base status. After obtaining written informed consent (day 0) each patient will be randomized 1:1 either to the treatment group or the control group (Figure 1). Subjects will be stratified for age >60 years and ≤ 60 years [34], presence of diabetes mellitus (yes/no) [35], severe chronic metabolic acidosis (serum $\text{HCO}_3^- <18$ mmol/L) versus moderate metabolic acidosis (serum $\text{HCO}_3^- \geq 18$ mmol/L), and for previous alkali treatment (yes/no). Previous alkali treatment is defined as being continued for longer than 6 months ($>25\%$ of the treatment period of the planned study) and serum $\text{HCO}_3^- \geq 20$ mmol/L on more than 75% of measurements. Stratified randomization will be carried out using the web-based randomizer program provided by the Medical University of Vienna [<https://www.meduniwien.ac.at/randomizer/web/login.php>]. We use the minimization method with a preferred treatment probability of 0.9, and a combination depth of 2.0, to guarantee that treatment allocation is balanced in all levels of the stratification factors, as well as in all pairwise combinations of stratification factors. After randomization, subjects will receive either the high dose of sodium bicarbonate or, if necessary, a low-dose rescue therapy with sodium bicarbonate.

Each study visit consists of a fasting blood draw (last food intake including the study medication should be at least 8 hours before) and urinalysis, measurement of vital signs, and assessment of changes in concomitant medication and adverse events (Table 1). At the beginning of the study a physical examination will be done and body weight and height will be assessed. Study visits will be performed at weeks 4, 8, 12, 20, 29, 38, 47, 60, 73, 86, and 104.

Intervention

The initial and the maintenance dose for the intervention group will be determined based on the baseline HCO_3^- level and the levels measured during follow up visits. Based on pilot data we expect the daily dose for the intervention group to vary between two and six capsules of Nephrotrans[®] 840 mg (1,680 to 5,040 mg sodium bicarbonate per day). In the case of HCO_3^- lower than 19 mmol/L at the baseline visit, or during follow up, subjects randomized to the control group will receive rescue therapy. We expect the daily dose to be zero to three capsules of Nephrotrans[®] 840 mg (0 to 2,520 mg sodium bicarbonate per day) for the control group. After each study visit the study drug can be down- and up-titrated according to the actual HCO_3^- level and the respective target value, as pre-specified at randomization, by means of the suggested treatment algorithm (Table 2A and B). However, due to intra-individual differences in



drug response the algorithm is not obligatory and might be modified if necessary to reach the target HCO_3^- level for respective subjects.

Outcome parameters

The primary outcome is renal function and will be measured by means of eGFR, calculated according to the 4-variable-MDRD Study equation [36].

Secondary outcomes are death, and the need for renal replacement therapy (RRT) (patients with renal transplantation, hemodialysis, peritoneal dialysis, and subjects who are in need of RRT, but personally elect not to start it). The need for RRT will be clinically evaluated, including monitoring of uremic symptoms (nausea and/or vomiting, fatigue, deterioration in nutritional status and significant weight loss, neuropathy, encephalopathy, or psychic disturbances), blood and fluid disturbances (volume overload, malignant hypertension, anemia, bleeding diathesis, pleuritis and/or pericarditis), and significant electrolyte imbalances. A further secondary outcome is the percent change in markers of bone metabolism (bone alkaline phosphatase, osteocalcin, c-telopeptide pyridinoline crosslinks of type I collagen, and procollagen type I N-propeptide) across groups.

Sample size

Assuming equal baseline levels of eGFR between the two study groups, a clinically relevant difference of 5 ml in eGFR after 2 years, and an estimated standard deviation of 12 ml for the change in eGFR after 2 years (pilot data, Figure 2), an independent sample *t*-test with a sample size of 2×100 patients will give 80% power to reach statistical significance at a two-sided significance level of 5%.

Statistical methods

The intention-to-treat population will be used for statistical analysis. The primary analysis focuses on the estimated treatment effect at 2 years (difference between the two groups in eGFR after two years), which will be provided as the point estimate at the expected difference, 95% confidence interval and *P*-value. Mortality of

patients or other reasons for dropout will be addressed by jointly modeling longitudinal eGFR and time to death using an appropriate joint model for longitudinal and time-to-event outcome [37]. In the longitudinal part of this model, a linear mixed model will be used with the repeated eGFR measurements as outcome values, and including as fixed factors treatment group, all stratification criteria (age, diabetes, severity of acidosis, previous alkali treatment), the eGFR baseline value and time since start of treatment, and a random intercept. An interaction effect (product term) of the treatment group and the time since start of treatment will also be included. Graphical diagnostic tools (residual plots) will be used to confirm the adequacy of model assumptions. A secondary outcome is time to death, compared between the treatment groups, which will also be estimated by the joint modeling approach. The time up to the point of need of RRT will be compared between the two treatment groups, accounting for death as a competing risk, by modeling the cumulative incidence function [38], including treatment group and the covariates age, diabetes, severity of acidosis and baseline eGFR. Percent change (from baseline to week 20 and baseline to week 104, respectively) in markers of bone metabolism will be analyzed by analysis of covariance, to adjust for sex, age, change in renal function, and baseline values of the bone markers. The incidence of serious adverse events will be reported and compared between groups using the chi-squared test. Baseline parameters (etiology of CKD, relevant medical disease, age, gender, concomitant medication, blood pressure, number of antihypertensive medications, and laboratory measurements) will be analyzed descriptively for the interventional and control group, respectively. SAS (Version 9.3, SAS Institute Inc., Cary, NC, USA, 2011) will be used for data management and analysis, and R 2.12.2/package JM [37] will be used for the main outcome analysis.

Discussion

In 1931 Lyon *et al.* described for the first time the simple approach of compensating metabolic acid excess in a

Table 1 Visit and assessment schedule

	Screening period (4 weeks)							Treatment period (0 to 24 months)					
	Day 0		Week 4	Week 8	Week 12	Week 20	Week 29	Week 38	Week 47	Week 60	Week 73	Week 86	Week 104
			(± 2 days)	(± 2 days)	(± 2 days)	(± 5 days)	(± 5 days)	(± 5 days)	(± 5 days)	(± 10 days)	(± 10 days)	(± 10 days)	(± 10 days)
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13
Informed consent		x											
Inclusion/exclusion criteria	x	x											
Randomization		x											
Medical history		x											x
Concomitant medication		x	x	x	x	x	x	x	x	x	x	x	x
Physical examination		x											x
Body weight and height		x											x
Vital signs (BP, PR)		x	x	x	x	x	x	x	x	x	x	x	x
Laboratory test	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory test: bone markers		x				x							x
Biobank sample		x				x			x		x		x
Urinalysis	x	x	x	x	x	x	x	x	x	x	x	x	x
24-hour urine collection	x ^a	x ^a	x			x			x				x
Urine pregnancy test ^b		x	x	x	x	x	x	x	x	x	x	x	x
Adverse events			x	x	x	x	x	x	x	x	x	x	

^aTo be performed either at screening visit 1 or screening visit 2, prior to randomization; ^bfor females of childbearing age only. BP, blood pressure; PR, pulse rate.

Table 2 Study drug up- and down-titration

(A) Baseline treatment algorithm	Daily sodium bicarbonate (Nephrotrans® 840 mg) dosage	
	Investigational group	Control group
Mean HCO ₃ of two measurements		
<18 mmol/L	5,040 mg (2 capsules TID)	2,520 mg (1 capsule TID)
18 to 19 mmol/L	4,200 mg (2 capsules BID, 1 capsule QD)	1,680 mg (1 capsule BID)
19.1 to 20.0 mmol/L	2,520 mg (1 capsule TID)	Monitor
>20 mmol/L	1,680 mg (1 capsule BID)	
(B) Follow-up visit treatment algorithm	Investigational group and control group	
Difference to target HCO ₃ level		
-1 mmol/L	Add 1,680 mg to the previous daily dosage (+1 capsule BID)	
-2 mmol/L	Add 3,360 mg to the previous daily dosage (+2 capsules BID)	
≤ -3 mmol/L	Add 5,040 mg to the previous daily dosage (+2 capsules TID)	
+1 mmol/L	Subduct 1,680 mg from the previous daily dosage (-2 capsules)	
+2 mmol/L	Subduct 3,360 mg from the previous daily dosage (-4 capsules)	
≥ +3 mmol/L	Subduct 5,040 mg from the previous daily dosage (-6 capsules)	

QD, every day; BID, twice daily; TID, trice daily.

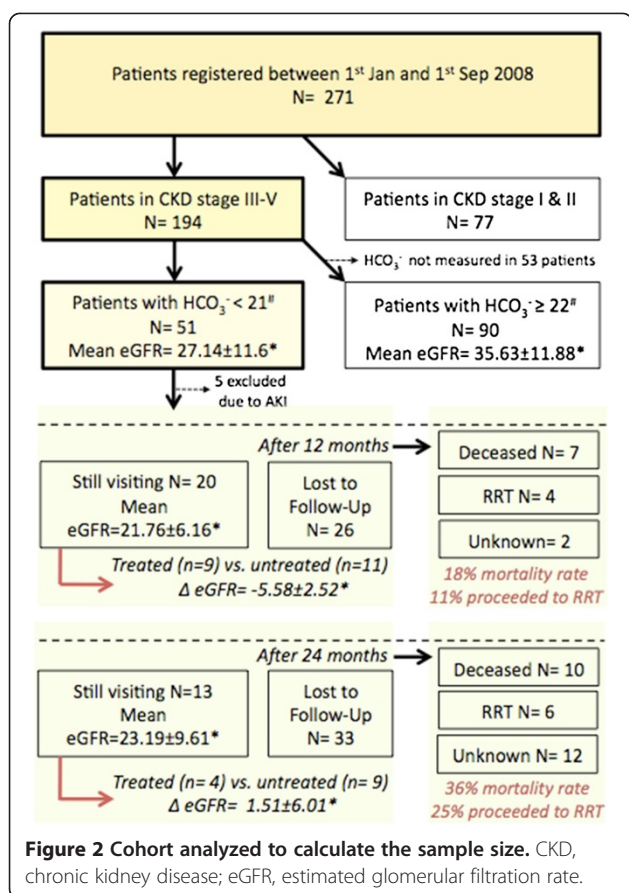
series of 17 patients with chronic nephritis by providing an alkaline diet or substituting alkaline salts [39]. In 2012 the question of whether or not systematic treatment of metabolic acidosis in CKD is indicated is still to be addressed by the scientific community, due to the paucity of acceptable evidence [40-42].

Indeed, patients with CKD comprise a difficult study cohort in terms of sample size calculation and accurate methodological planning, due to severe comorbidities and increased mortality [25,43-47]. De Brito-Ashurst *et al.* [28] tried to show that correcting metabolic acidosis stabilizes renal function in patients with CKD stage IV. In the open-label study the control group had a significantly greater decline in creatinine clearance (5.93 mL/min) compared to the treatment group (1.88 mL/min) after 2 years. Furthermore, subjects in the treatment group presented with significantly slower progression of CKD (defined as creatinine clearance loss >3 mL/min/year) (9% versus 45% in the control group). However, critical issues concerning the study methodology are that first, rapid progression and development of ESRD are competing endpoints, and second, the way this was handled in the data analysis is unclear. They stated that 'the rate of decline of creatinine clearance was similar between the two groups up to 12 months of follow-up because of dropout of 17 patients of the control group who had rapid decline and reached ESRD between 6 and 12 months'. However, only 15 dropouts are depicted in the respective Kaplan-Meier curve (Figure three in de Brito-Ashurst *et al.* [28]) between months 6 and 12. This might be the source of confounding and can be avoided by using a more appropriate competing endpoint analysis [48]. Further, the need of that additional endpoint is questionable, because subjects with

rapid decline in renal function essentially reach ESRD at some point in time. Also, the control group was treated with 'standard care' with no further explanation whether that protocol included sodium bicarbonate supplementation. If this was not the case, the administration of placebo in the control group might have been indicated.

Mahajan *et al.* [26] recently compared the effect of sodium bicarbonate, sodium chloride and placebo on GFR in patients with early hypertensive nephropathy over 5 years. This was a randomized blinded trial in patients with CKD stage II, hypertension and albuminuria (200 to 2,000 mg/g creatinine), but normal plasma total carbon dioxide levels (equivalent to serum bicarbonate concentrations). Although the study population showed no biochemical signs of metabolic acidosis the supplementation of sodium bicarbonate was beneficial in terms of renal function: the rate of change of eGFR in the sodium bicarbonate group was -1.47 ± 0.19 compared to -2.13 ± 0.19 ($P < 0.014$) in the placebo group and -2.05 ± 0.19 mL/min/1.73 m² per year ($P < 0.029$) in the sodium chloride group. This gives good evidence that sodium bicarbonate supplementation provides positive effects on renal function on the one hand, but on the other only for that very selected cohort of patients with well-preserved renal function and albuminuria. Unfortunately, one cannot conclude that in patients with advanced renal injury and low GFR the therapeutic intervention would lead to the same outcome.

Another study, although designed to investigate the mechanism of preventing renal injury by oral sodium citrate, showed that treating metabolic acidosis in patients with CKD slows the decline of renal function (sodium citrate versus control: eGFR -1.60 ± 0.13 versus -3.79 ± 0.30 mL/min/1.73 m² per year, $P < 0.0001$) [27]. We



refrain from using this agent to treat metabolic acidosis in our study patients due to the known increased aluminum absorption in combination with sodium citrate [49].

Furthermore, studies in animals and humans suggest that an acid-reduced diet may improve kidney function equally to supplementation with bicarbonate by means of tablets [50]. However, base-inducing diets predominantly include vegetables and fruits, which contain high amounts of potassium. In the long term, however, subjects with preserved renal function, who are not prone to hyperkalemia, might benefit tremendously from base-rich diets over the commonly preferred acid-inducing diet of our society [51,52].

With regard to the presented study protocol we opted for an open-label approach, predominantly because to some extent sodium bicarbonate is included in standard routine care. Withdrawing that therapeutic intervention from study subjects could be deemed unethical. Aside from ethical reasons, the dose of the study drug in the interventional group is not fixed and administering an average amount of placebo tablets to the control group is also questionable. Moreover, given the relatively narrow range of suggested optimal HCO_3^- levels and the distinct between-subject difference in response to treatment, blood levels have to be maintained regularly. Blinding of

these laboratory results would have caused a disproportionately high amount of effort and cost compared to its benefits.

With regard to the intervention itself, sodium bicarbonate supplementation represents a simple therapeutic maneuver to restore acid–base balance in CKD patients. Few adverse events are reported in combination with oral sodium bicarbonate supplementation. Abdominal bloating would appear to be innocuous as it can be avoided by dividing the daily dosage into several smaller portions.

A mentionable concern is the additional sodium consumption evoked by the study medication. For each 100 mg of sodium bicarbonate the additional sodium intake is approximately 27.4 mg. Dietary sodium intake is known to negatively influence arterial hypertension, therefore, blood pressure should be carefully monitored and if necessary, treated with antihypertensive agents. Notably, none of the studies performed in humans have noticed worsening of arterial hypertension in relation to the sodium bicarbonate supplementation. Nevertheless, this adverse event is reported for animal experiments [18]. However, former investigations suggested that the blood pressure-elevating effect is led by chloride and not by sodium. Although sodium retention and weight gain was similar across study groups an increase in arterial blood pressure could not be detected in subjects ingesting additional dietary sodium bound to an alternative anion than chloride [53–55]. In addition, there is a theoretical concern that long-term sodium bicarbonate intake may favor the development of calcium phosphate- and magnesium phosphate stones in the urinary tract, but so far this has not been observed in humans.

A single study was performed in cultured cells and uremic rats to investigate whether sodium bicarbonate supplementation affects the pathologic calcification of blood vessels. De Solis *et al.* reported that acid media prevented calcification of cultured vascular smooth muscle cells, and that uremic rats treated with sodium bicarbonate had a significantly higher aortic calcification index [56]. Given all the evidence of positive alteration by the supplementation of sodium bicarbonate, these concerns need to be kept in mind, and blood pressure will be closely monitored during the follow up period.

Taken together, previous studies, including observational and animal studies, give confidence that simply supplementing sodium bicarbonate in patients with CKD of any degree could positively alter decline in renal function. Possible adverse events are within the acceptable ratio of benefit to risk, however, adverse events will be followed closely in the study participants.

In summary, we believe that a clinical investigation to elucidate the effect of sodium bicarbonate supplementation in patients with metabolic acidosis and advanced CKD is of urgent need to develop a proper treatment

strategy for those patients. This would not only improve the prognosis for each individual patient, but also help to decrease health care expenses, as sodium bicarbonate represents a relatively cheap treatment option.

Trial status

Recruitment is planned to start in October 2013.

Abbreviations

AKIM: Allgemeines Krankenhaus informations management; CKD: Chronic kidney disease; CONSORT: Consolidated standards of reporting trials; eGFR: Estimated GFR; ESRD: End-stage renal disease; EUDRACT: European union drug regulating authority; GFR: Glomerular filtration rate; GCP: Good clinical practice; MDRD: Modification of diet in renal disease; RRT: Renal replacement therapy.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MG and GSP designed the study, wrote the study protocol and manuscript, organized the funding, and will conduct the study. GH designed the study with regard to the statistical methodology and will perform randomization and stratification procedures and will perform the statistical analysis. MF programmed the electronic case report forms and will regularly maintain the database. DC, WHH, MP and AS contributed to the planning of the study and critically revised the manuscript. All authors read and approved the final manuscript.

Authors' information

We are saddened by the sudden passing of our department head and teacher, Prof. DDr. Walter H. Hörl FRCP, whom we want to dedicate this manuscript.

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