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Effect of Sodium Bicarbonate in Kidney Transplant Recipients With Chronic Metabolic Acidosis

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Background. Metabolic acidosis (MA) is a common complication after kidney transplantation and regarded to increase mortality, graft failure, and bone fractures. Here, we conducted a retrospective cohort study to analyze the effect of sodium bicarbonate on those events. **Methods.** All kidney transplant recipients of the German health insurance Allgemeine Ortskrankenkasse (AOK) were selected, who received their transplantation between 2007 and 2015. Three groups were formed: (1) control group (no acidosis, n = 3602), (2) acidosis group (encoded acidosis, n = 370), and (3) treatment group (encoded therapy, n = 769). The study endpoints were mortality, death-censored graft failure, and bone fractures. **Results.** The prevalence of MA in the first year after transplantation was 46.2%. The 5-year patient and graft survival were 89.8% and 89.3% in the control group, 90% and 90.8% in the acidosis group, and 87.5% and 81.6% in the treatment group, respectively. The rate of bone fractures did not differ between the groups. Neither log-rank tests nor multivariable Cox regression analyses could detect a negative impact of MA on mortality (hazard ratio [HR] 0.94; confidence interval [CI] 0.67–1.30), graft failure (HR1.18; CI 0.82–1.72), or the incidence of bone fractures (HR1.19; CI 0.92–1.55). Treatment with sodium bicarbonate was associated with an increased risk of graft failure (HR1.52; CI 1.03–2.25), whereas mortality (HR0.86; CI 0.59–1.26) and the incidence of bone fractures (HR1.16; CI 0.86–1.56) were not altered. **Conclusions.** MA is common after kidney transplantation but not associated with an increased frequency of death, graft failure, or bone fractures. Conversely, sodium bicarbonate therapy increased the incidence of graft failure.

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INTRODUCTION

Metabolic acidosis (MA) is a common problem of patients with advanced chronic kidney disease (CKD). It is estimated that one-third of the patients with stage 4 CKD suffer from MA.[1,2] Several studies have shown that kidney transplant recipients are especially prone to develop MA. In those, the prevalence of MA reaches from 15% in CKD stage 2 to 70% in stage 4.[3–7] These differences are due to additional causal factors like the immunosuppressive medication in the renal transplant setting.

Several large observational studies found an association of reduced serum bicarbonate concentrations with increased mortality and progressive GFR decline in patients with CKD[8–12] and after kidney transplantation.[7] Several small prospective randomized trials could validate this finding and suggested that a therapy with sodium bicarbonate can slow down the GFR decline and initiation of renal replacement therapy in patients with CKD.[13–15] Furthermore, MA has shown to have a harmful influence on bone metabolism of patients with CKD. Already in the 1960s, Lemann et al[16] could show that experimentally induced MA in healthy adults results in bone

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demineralization and net calcium loss.[16] Although the negative influences of this metabolic disorder on bone metabolism were later confirmed by further studies[17–20] and MA has shown to correlate with low bone density,[21] up to now there is no evidence that an alkalinizing therapy prevents bone fractures in patients with CKD.

Although MA is an easily and inexpensively modifiable risk factor, there are no studies evaluating the relevance of bicarbonate supplementation in kidney transplant recipients and, consequently, there are no specific recommendations for the treatment of MA in kidney transplant recipients in the actual KDIGO guidelines.[22]

The aim of this study was to investigate whether bicarbonate therapy has a beneficial influence on mortality, graft failure, and bone fractures of kidney transplant recipients with MA. To achieve sufficient statistical power to answer this question, we retrospectively analyzed health insurance data of Germany's largest statutory health insurance organization, the AOK.

MATERIALS AND METHODS

The study was conducted as a retrospective cohort study utilizing health insurance data of the AOK. During the years 2007–2015, about 24 million persons were insured on average per year. The data set comprises basic demographic data (age, gender, date of death), data from ambulatory care, and data from hospital claims. Hospital claims data include date of admission, date of discharge, diagnoses according to ICD-10 (International Classification of Diseases 10th version), procedures according to OPS (the German version of the International Classification of Procedures in Medicine), and date of procedure. Ambulatory care data contain ICD-10-coded diagnoses. Primary care drug prescriptions were analyzed with the German version of the Anatomical Therapeutic Chemical (ATC) classification system.

Our Institutional Review Board approved the analyses and waived the requirement for informed consent since we only used deidentified data. The humans involved in this study were treated in a manner in accordance with the Declaration of Helsinki and Declaration of Istanbul. Ethical approval for this study was exempted by the Ethics committee of the Christian-Albrechts University Kiel (D 436/17).

Definition of Cohorts

Figure 1 gives a graphical representation of the study design. In the first step, kidney transplant recipients were identified by the OPS codes for living kidney transplantation (5-555.0) or deceased kidney transplantation (5-555.1) during the time period January 1, 2007 to March 31, 2015. Because certain covariates were analyzed within the year before transplantation, analysis was restricted to kidney transplant cases with at least 1 year of continuous insurance prior to transplantation, resulting in n = 6637 cases. Furthermore, information from the first year after transplantation was utilized for allocation of patients to the study groups. Therefore, patients who died during the first year after transplantation (n = 309) or changed their health insurance (n = 85) were excluded from the analysis. Patients were allocated to 3 study groups: first the control group (n = 3602), which is made up of kidney transplant recipients with neither an encoded MA (ICD-10 code: E 87.2) nor a prescription for bicarbonate. Second, the untreated acidosis group (n = 370), built up by transplant recipients with an acidosis diagnosis in each quarter of the first year after transplantation, but without a prescription for bicarbonate. Third, the treatment group (n = 769), which consists of patients with a documented prescription in each quarter of the first year after kidney transplantation. Of those, 94,3% (n = 725) had also an encoded acidosis diagnosis in at least quarter. Thus, a total of 4741 cases were included in the primary analysis. Patients with periods of three or less quarters with the diagnosis of acidosis (n = 309) or prescriptions

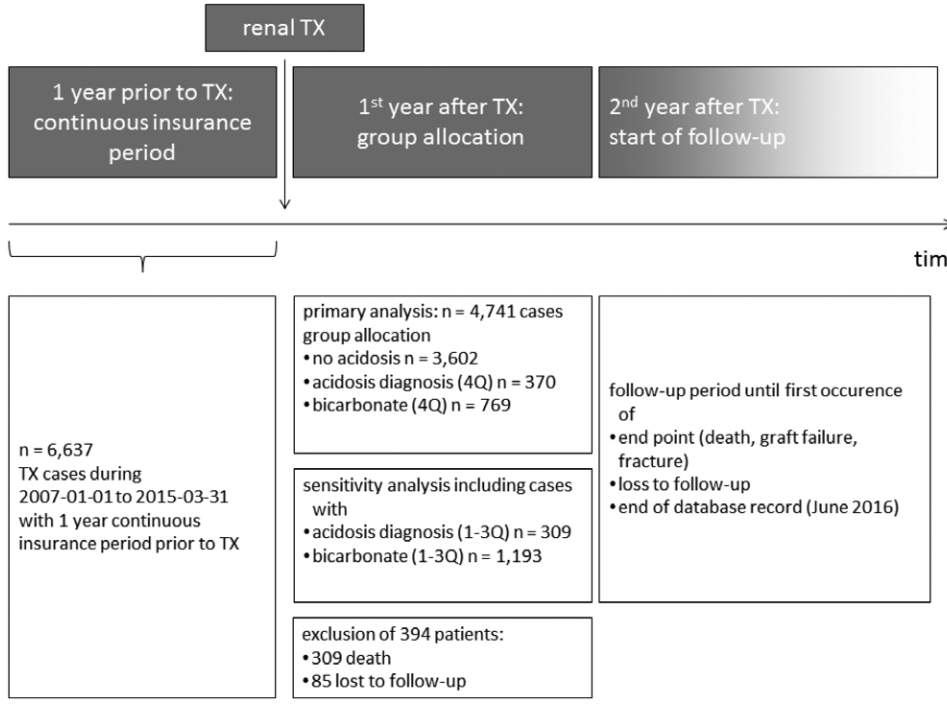

FIGURE 1. Study design and cohort attrition.

of bicarbonate (n = 1193) were excluded from the primary analysis. However, these patients were included in the sensitivity analyses.

Study Outcomes

Follow up started 1 year after transplantation and ended when the restrictive outcome occured, the patient was lost to follow-up, or at the end of database records (June 30, 2016). The predefined endpoints of this study were (1) all-cause mortality, (2) graft failure censored for death, and (3) diagnosis of bone fracture. Graft failure was assumed in case a dialysis therapy was reinitiated (detected by the presence of OPS codes 8-853, 8-854, 8-855, 8-857, or billing of dialysis costs in ambulatory data) or a second kidney transplantation was performed (OPS 5-555). Bone fractures were identified by a set of ICD-10 codes (for detailed information see **Table S1, SDC**, http://links.lww.com/TXD/A214). Cases lost to follow-up (because of a change of insurance status) were censored at the last observation. The temporal unit chosen for survival analysis was calendar quarters.

Covariates

All cases in the 3 study groups were characterized by demographic data (sex and age at transplantation), the type of transplantation (living or deceased kidney donation), and whether the transplantation case was the first renal transplant in a patient. In order to characterize overall health care utilization, we determined the number of hospital days, the number of different ICD-10 diagnoses, and the number of different ATC codes within the first year after kidney transplant. Comorbidities of patients were analyzed as defined by Elixhauser et al[23] with translation into ICD-10 codes adopted from Quan et al[24] supplemented by further comorbidities with potential relevance for the end points of this study, such as hyperlipidemia, coronary artery disease, cystic kidney disease, glomerular diseases, thyrotoxicosis (hyperthyroidism), bone fractures, and osteoporosis (**Table S2, SDC**, http://links.lww.com/TXD/A214). Patients' specific medication was assessed by prescriptions for a set of ATC-codes or—in the case of bicarbonate therapy, which is poorly detectable via the ATC system—a set of product names (**Table S3, SDC**, http://links.lww.com/TXD/A214). Comorbidities and medication were also analyzed within the first year after kidney transplantation.

Statistical Analysis

Chi-squared test was used to compare categorical variables between the study groups and Mann-Whitney *U* test was used for numeric variables. *P* values <0.05 were regarded as significant. We applied survival time methods for time-to-event data. Kaplan-Meier curves were calculated for survival data, with log-rank tests for survival differences. Three different multivariate Cox regression models were used to stepwise adjust for potential confounders. At first, only the study group variable (patients without acidosis, with untreated acidosis, or with bicarbonate therapy) was included. Second, basic covariates were additionally included (age, sex, deceased vs living donation, initial transplantation, general health care utilization within first year after transplant assessed by hospital days, number of ICD diagnoses, and number of ATC codes). Third, the fully adjusted model included all basic covariates and all other covariates that were significant in univariate Cox regression models (Elixhauser comorbidities, other comorbidities, and medication variables). For each end point, the preferred model was chosen based on the lowest value for the Akaike information criterion. The proportional hazards assumption was evaluated by graphical inspection of the scaled Schoenfeld residuals on functions of time and tested for a nonzero slope with the cox.zph method.[25] All analysis were performed with RStudio version 1.1.383 (RStudio, Inc., Boston, MA) utilizing R base and packages survival, dplyr, foreign, and xlsx.[26–31]

RESULTS

Prevalence of MA in Kidney Transplant Recipients

The prevalence of MA recorded by an encoded acidosis diagnosis was 18.7% in the first, 15.1% in the second, 14.2% in the third, and 14.1% in the fourth quarter after transplantation. Thereafter, MA was constantly prevalent in about 13% of the kidney transplant recipients (Figure 2). Regarding also patients receiving bicarbonate therapy as suffering from MA, the prevalence was 35.1% in the first, 31.4% in the second, 29.6% in the third, and 28.3% in the fourth quarter after transplantation (Figure 2). Taking both groups into account, prevalence of MA was 46.2% within the first year after transplantation.

Baseline Characteristics

Table 1 and Table S4 (**SDC**, http://links.lww.com/TXD/A214) compare the baseline characteristics and comorbidities of the control and untreated acidosis group and the untreated acidosis and treatment group, respectively. Mean age at transplantation was significantly higher (49.1 vs 51.4, $P<0.01$) in the untreated acidosis group than in the control group. Furthermore, several comorbidities occurred more frequently in these patients such as hyperlipidemia (59.5% vs 45.8%, $P<0.001$) complicated hypertension (76.5% vs 65.1%, $P<0.001$), or deficiency anemias (23.8% vs 13.4%, $P<0.001$). Of the medication variables analyzed, only hypnotics and anxiolytics (9.2% vs 12.7%, $P<0.05$) were more frequently prescribed in patients with untreated acidosis.

In the treatment group, the proportion of male patients was significantly higher than in the untreated acidosis group (59.2% vs 76.1%, $P<0.001$; Table 1, columns on the right), whereas less patients received a living kidney donation (13.9% vs 23.5%, $P<0.001$). Several comorbidities occurred less frequently in patients treated with bicarbonate than in the untreated acidosis group, such as hyperlipidemia (47.2% vs 59.5%, $P<0.001$), uncomplicated hypertension (85.4% vs 91.4%, $P<0.01$), hypothyroidism (13.7% vs 20.8%, $P<0.01$), deficiency anemias (17.6% vs 23.8%, $P<0.05$), and depression (14.8% vs 19.7%, $P<0.05$). Several drugs were more frequently prescribed in the bicarbonate group than in the untreated acidosis group, especially calcineurin inhibitors, phosphate binders, and antihypertensive drugs (calcium antagonists, RAAS inhibitors, loop or thiazide diuretics, and other antihypertensives).

Survival Analysis

At 5 years after transplantation, survival rate was 89.8% in the control group, 90.0% in patients with untreated acidosis, and 87.5% in patients treated with bicarbonate. The corresponding Kaplan-Meier curves are depicted in Figure 3A. There were no significant differences between the groups in log-rank tests.

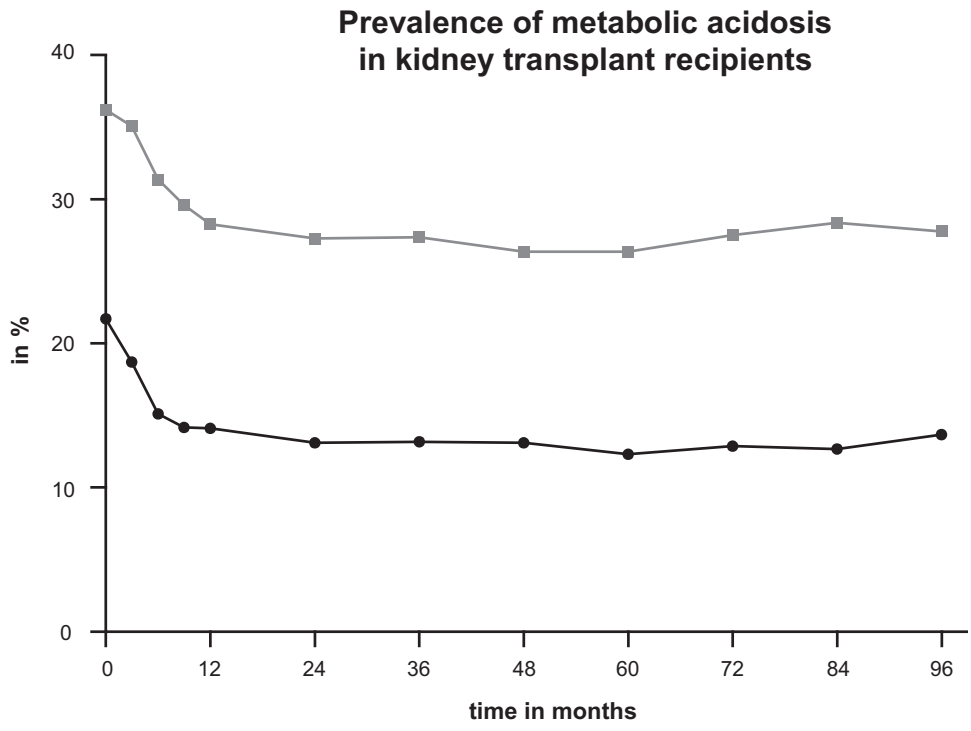

FIGURE 2. Prevalence of MA. Black line with dots: prevalence of MA based on encoded acidosis diagnosis. Gray line with quadrates: prevalence of MA based on acidosis diagnosis and prescription of bicarbonate therapy. MA, metabolic acidosis.

Death-censored graft survival did not differ significantly between kidney transplant recipients without acidosis (89.3% at 5 y) and those with acidosis (90.8%; see Kaplan-Meier curve in Figure 3B). However, the bicarbonate treatment group displayed a significantly lower rate of graft survival (81.6% at 5 y) in comparison to the untreated acidosis group ($P<0.01$, Figure 3B). Of the patients in the treatment group, 51.1% (n = 393) received <3 g sodium bicarbonate per day, 37.3% (n = 287) 3–6g, and 10.4% (n = 80) >6 g per day. There was no dose-effect relationship concerning the increased rate of death-censored graft failure.

Bone fractures occurred in ~20% of all kidney transplant recipients after 5 years. The rate of bone fractures did not differ between the 3 groups (Figure 3C).

Cox Regression Analysis

In order to account for differences between groups in the presence of risk factors and possible confounders, we performed several multivariable Cox regression analyses for each end point as described in the Materials and Methods section. In the fully adjusted multivariable Cox models, HRs for the group of patients with untreated acidosis versus patients without acidosis were not significantly different for any of the endpoints studied: death, death-censored graft failure, or bone fractures (Table 2, upper part, model III). Hence, untreated acidosis was not associated with an increased risk for any of the end points studied. For the group of patients with bicarbonate therapy when compared with untreated acidosis patients, HRs for death and fractures were not significantly different. However, the HR for graft failure was increased in the bicarbonate treatment group and remained significantly different from one even in the fully adjusted model (HR = 1.52, CI 1.03–2.25, $P < 0.05$; Table 2, lower part). Sensitivity analyses including patients with <4 quarters of acidosis diagnoses or bicarbonate therapy yielded similar results.

DISCUSSION

This study, which is to the best of our knowledge the first, analyzing the effect of a bicarbonate therapy in the renal transplant setting, has 3 major findings. First, prior studies showing a high prevalence of MA after kidney transplantation could be confirmed. Second, MA showed no association with increased mortality, graft failure, or bone fractures in our cohort and, third, bicarbonate supplementation was associated with an increased rate of death-censored graft failure.

The current KDIGO guideline defines MA as serum bicarbonate <22 mEq/L. However, because of the fact that impaired renal acid excretion can be found in patients with serum bicarbonate >22mEq/L[32,33] and data shown by Goraya et al[34] suggested that CKD patients with serum bicarbonate >22mEq/L might also benefit from oral bicarbonate, MA is inconsistently defined in the literature. Accordingly, the recorded prevalence varies between 12% (serum bicarbonate <21 mEq/L) and 58.1% (serum bicarbonate <24 mEq/L) in kidney transplant recipients depending on the applied definition.[35,36] Furthermore, the frequency inversely correlates with transplant function and depends on the actual immunosuppressive treatment. Due to the latter, MA is most frequently found in the first 3 months after transplantation. Therefore, a valid estimation of the prevalence requires a representative cross section through the general population of kidney transplant recipients. Park et al[7] recently showed in a very thoroughly performed cohort study, in which the acid-base status of 2318 kidney transplant recipients was analyzed over a time period of 15 years, that the prevalence of MA (serum bicarbonate <22 mEq/L) drops from 20% in the first month

TABLE 1.

Baseline characteristics and comorbidities of the study population

Characteristics and comorbidities	Control group	Untreated acidosis group	*P* (control group vs untreated acidosis) group	Bicarbonate treatment group	*P* (untreated acidosis group vs bicarbonate treatment)
No. cases	3602	370	n.s.	769	n.s.
Age at transplantation, y (±SD)	49.1 (±15.2)	51.4 (±13.9)	<0.01	49.5 (±15.1)	n.s.
Sex (male% / female%)	59.8% / 40.2%	59.2% / 40.8%	n.s.	76.1% / 23.9%	<0.001
Living kidney donation (n, %)	773 (21.5%)	87 (23.5%)	n.s.	107 (13.9%)	<0.001
Coronary artery disease	918 (25.5%)	107 (28.9%)	n.s.	230 (29.9%)	n.s.
Hyperlipidaemia	1651 (45.8%)	220 (59.5%)	<0.001	363 (47.2%)	<0.001
Congestive heart failure[a]	636 (17.7%)	71 (19.2%)	n.s.	165 (21.5%)	n.s.
Hypertension, complicated[a]	2345 (65.1%)	283 (76.5%)	<0.001	582 (75.7%)	n.s.
Hypertension, uncomplicated[a]	3083 (85.6%)	338 (91.4%)	<0.01	657 (85.4%)	<0.01
Chronic pulmonary disease[a]	676 (18.8%)	77 (20.8%)	n.s.	139 (18.1%)	n.s.
Diabetes, complicated[a]	775 (21.5%)	94 (25.4%)	n.s.	182 (23.7%)	n.s.
Hypothyroidism[a]	580 (16.1%)	77 (20.8%)	<0.05	105 (13.7%)	<0.01
Liver disease[a]	562 (15.6%)	70 (18.9%)	n.s.	111 (14.4%)	n.s.
Fractures	251 (7.0%)	35 (9.5%)	n.s.	64 (8.3%)	n.s.
Osteoporosis	328 (9.1%)	48 (13.0%)	<0.05	86 (11.2%)	n.s.
Weight loss[a]	103 (2.9%)	13 (3.5%)	n.s.	37 (4.8%)	n.s.
Deficiency anaemias[a]	482 (13.4%)	88 (23.8%)	<0.001	135 (17.6%)	<0.05
Depression[a]	601 (16.7%)	73 (19.7%)	n.s.	114 (14.8%)	<0.05
Alcohol abuse[a]	64 (1.8%)	3 (0.8%)	n.s.	21 (2.7%)	n.s.
Tabacco abuse	267 (7.4%)	74 (9.4%)	<0.01	45 (12.2%)	n.s.
Medication					
Calcineurin inhibitors (ciclosporine, tacrolimus)	3377 (93.8%)	345 (93.2%)	n.s.	748 (97.3%)	<0.01
mTOR inhibitors (everolimus, sirolimus)	284 (7.9%)	29 (7.8%)	n.s.	65 (8.5%)	n.s.
Mycophenolate	3240 (90.0%)	333 (90.0%)	n.s.	709 (92.2%)	n.s.
Phosphate binders	338 (9.4%)	38 (10.3%)	n.s.	201 (26.1%)	<0.001
Cotrimoxazol	2560 (71.1%)	267 (72.2%)	n.s.	606 (78.8%)	<0.01
Valganciclovir	1689 (46.9%)	186 (50.3%)	n.s.	424 (55.1%)	n.s.
Calcium antagonist	2323 (64.5%)	257 (69.5%)	n.s.	581 (75.6%)	<0.05
Beta blocker	2789 (77.4%)	295 (79.7%)	n.s.	651 (84.7%)	n.s.
RAAS inhibitor	1967 (54.6%)	213 (57.6%)	n.s.	507 (65.9%)	<0.01
Thiazide diuretic	233 (6.5%)	21 (5.7%)	n.s.	46 (6.0%)	n.s.
Loop diuretic	1758 (48.8%)	172 (46.5%)	n.s.	436 (56.7%)	<0.01
Other antihypertensives	1114 (30.9%)	125 (33.8%)	n.s.	342 (44.5%)	<0.001
Osteoporosis medication	219 (6.1%)	23 (6.2%)	n.s.	64 (8.3%)	n.s.
Hypnotics and anxiolytics	330 (9.2%)	47 (12.7%)	<0.05	79 (10.3%)	n.s.
CNS active drugs	966 (26.8%)	107 (28.9%)	n.s.	186 (24.2%)	n.s.

CNS, central nervous system.
[a]Comorbidity as defined by Elixhauser et al.[23]

after transplantation to 16% in the third month after transplantation. Thereafter, ~10% of the patients continuously suffer from MA. Depending on the transplant function, the prevalence ranged between 5% and 70% (stage 1 to stage 4).[7] Of note, in these numbers, only patients with an overt MA were included. Patients with an oral bicarbonate therapy and normal serum bicarbonate were not considered. Therefore, those rates can be best compared with the proportion of patients in our study, who had an encoded but untreated acidosis. Taking only this group into account, prevalence of MA is slightly higher in our study. This little difference may be a consequence of the typical protein-rich German diet.[37] Since those who receive bicarbonate therapy principally also suffer from MA, we think those receiving oral bicarbonate should also be taken into account to determine the prevalence of MA. Doing so, the prevalence of MA is ~15% higher. Doubtless, it is a weakness of our analysis that patient's acid-base status was not directly accessible. However, the fact that the prevalence of MA was slightly higher in our study than in the study of Park et al[7] suggests that acid-base disturbances were reliably diagnosed and encoded. Furthermore, it is noteworthy that our study design excludes bias by selection, because all patients insured by the AOK were included into this study without exception.

Several large observational studies have focused on the association of MA and all-cause mortality in patients with CKD. In 2008, Kovesdy et al[38] showed for the first time an association of low serum bicarbonate (<22 mEq/L) and all-cause mortality in CKD patients. Similarly, Raphael et al[12] reported a 2.6-fold increase of all-cause mortality in CKD patients with MA based on data from NHANES III registry. On the contrary, in the MDRD cohort, low serum bicarbonate was only associated with all-cause mortality prior to adjustment for the kidney function.[10] If kidney function was included in the analysis, the association disappeared. No increased hazard for all-cause mortality was seen in the

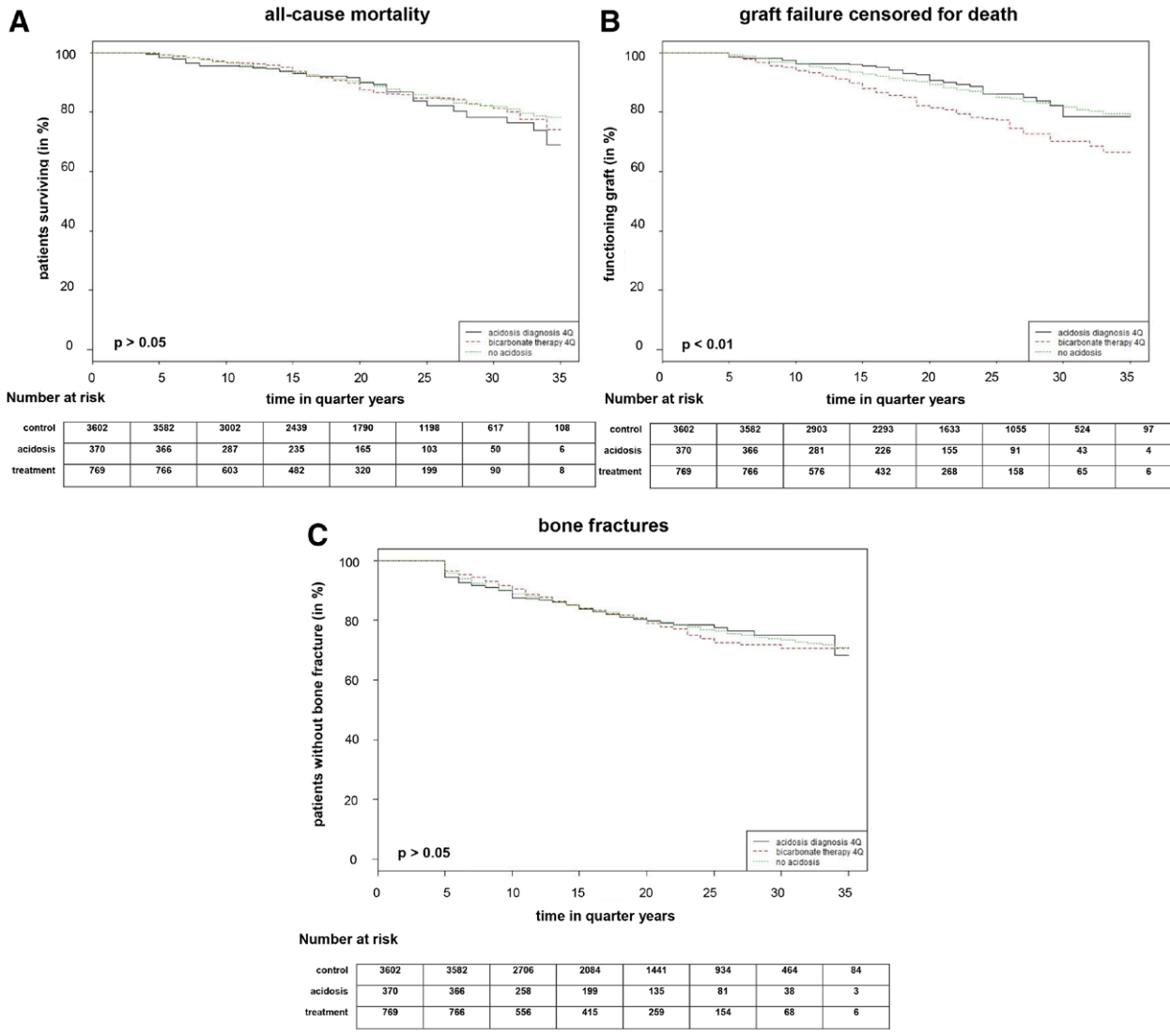

FIGURE 3. Kaplan-Meier curves for the endpoints. A, all-cause mortality; (B) graft failure censored for death; (C) bone fractures.

TABLE 2.

Multivariable Cox regression analyses of the effect of MA and acidosis therapy

	Model I		Model II		Model III	
End point	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Control group; reference: untreated acidosis group						
Death	0.85 (0.63–1.15)	>0.05	0.99 (0.73–1.35)	>0.05	0.94 (0.67–1.30)	>0.05
Death-censored graft failure	1.10 (0.77–1.56)	>0.05	1.09 (0.76–1.54)	>0.05	1.18 (0.82–1.72)	>0.05
Bone fractures	1.00 (0.78–1.29)	>0.05	1.18 (0.82–1.72)	>0.05	1.19 (0.92–1.55)	>0.05
Bicarbonate group; reference: untreated acidosis group						
Death	0.89 (0.62–1.27)	>0.05	0.85 (0.59–1.22)	>0.05	0.86 (0.59–1.26)	>0.05
Death-censored graft failure	***1.89 (1.29–2.76)***	**<0.01**	***1.54 (1.05–2.27)***	**<0.05**	***1.52 (1.03–2.25)***	**<0.05**
Bone fractures	1.02 (0.76–1.37)	>0.05	1.05 (0.78–1.42)	>0.05	1.16 (0.86–1.56)	>0.05

Significant results are highlighted in bold and italic font. Results of Cox regression models for different end points; model I: including only group variable (control group, untreated acidosis, bicarbonate treatment), model II: additionally adjusted for basic variables (age, sex, deceased vs living donation, initial transplantation, general health care utilization within first y after transplant assessed by hospital days, number of ICD diagnoses, and number of ATC codes), and model III: additionally adjusted for any variables that were significant in univariate models (including Elixhauser comorbidities, further comorbidities, and co-medication variables).

ATC, Anatomical Therapeutic Chemical; CI, confidence interval; HR, hazard ratio; ICD, International Classification of Diseases; MA, metabolic acidosis.

CRIC study, another large observational study including patients with CKD.[39] Up to now, only one study examined this relationship in the renal transplant setting and showed a 3.2-fold increased all-cause mortality in acidotic kidney transplant recipients.[7] In this study, we found no association between untreated MA and all-cause mortality. Similarly,

there was no association of untreated MA and death-censored graft failure. Conversely, Park et al[7] showed a 3.2-fold increased risk of death-censored graft failure for kidney transplant recipients suffering from MA after adjusting for possible confounders (eg, age, delayed graft function, eGFR). In this context, it is important to recognize that data concerning transplant function was not available for all patients and could not be integrated into the regression analyses. As MA is more frequent in kidney transplant recipients with a low transplant function, one could hypothesize that the proportion of patients with reduced transplant function is higher within the acidosis group than in the control group. Theoretically, as a diminished graft function is a risk factor itself, one would expect a higher mortality or rate of graft failure in the acidosis group. However, we did not observe such an increased risk for mortality or graft failure in the acidosis group. Therefore, it is unlikely that our study is confounded hereby. Principally, a false negative result (ie, no observed increased risk of mortality or graft failure in the acidosis group) could be the consequence of bias by misclassification. In case MA is present in a kidney transplant recipient but not diagnosed by the treating physician, this patient would be wrongly allocated to the control group. However, the comparably high prevalence of MA in our study argues against a pronounced misclassification.

Although several studies have focused on the influence of MA on bone metabolism and architecture,[20] up to now there is no evidence that MA is associated with an increased rate of bone fractures irrespective of the dialysis or transplant status. Admittedly, bone fractures showed to be a common problem after kidney transplantation, nevertheless our study suggests that MA has no critical impact on the frequency of bone fractures.

Remarkably, oral sodium bicarbonate supplementation was associated with an increased risk for death-censored graft failure in our study while MA itself showed no deleterious effect on graft survival. What could be the explanation for this unexpected finding? Pharmacokinetic studies have shown that drugs raising gastric pH influence dissolution and hydrolysis of mycophenolate mofetil (MMF) and may significantly reduce mycophenolate plasma concentration.[40,41] Although orally administered sodium bicarbonate (eg, Nephrotrans (R)) has enteric coating, it is known to have an influence on the gastric pH value.[42] Since several authors have described an association of lower MMF exposure with an increased risk for transplant rejections, this could explain our finding.[43,44] In this context, 2 smaller retrospective trials are interesting which compared the acute rejection rate of kidney transplant recipients on proton pump inhibitors with patients on the less potent antacid raniditin and failed to show an increased rejection rate in the proton pump inhibitors-treated group.[45,46] This finding could be due to the fact that the statistical power of those trials was low, the follow-up time restricted to 1 year, and the comparator group also received an antacid treatment. Although the increased risk for death-censored graft failure persisted after adjustment for several possible confounders (eg, type of kidney transplantation), we cannot definitely rule out that patients in the bicarbonate treatment group had worse transplant function than those in the untreated acidosis group. This may result in an increased risk of graft failure in the bicarbonate treatment group. However, in our opinion, this finding is of special interest, and future studies should focus on this aspect in more detail.

Although we did not observe a beneficial effect of oral sodium bicarbonate supplementation—even after controlling for a multitude of possible confounders—one has to keep in mind that the observational nature of the analysis may still be biased by unmeasured confounding. Therefore, further prospective randomized studies are needed to elucidate whether patients can profit from bicarbonate supplementation. Nevertheless, we think that it is advisable to pay special attention to the MMF plasma concentration of kidney transplant recipients treated with sodium bicarbonate, to ensure that bicarbonate treatment does not inadvertently lead to reduced MMF levels and compromised immunosuppression, which may result in untimely graft failure.

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