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ORIGINAL ARTICLE

Effects of veverimer on serum bicarbonate and physical function in diabetic patients with chronic kidney disease and metabolic acidosis: subgroup analysis from a randomized, controlled trial

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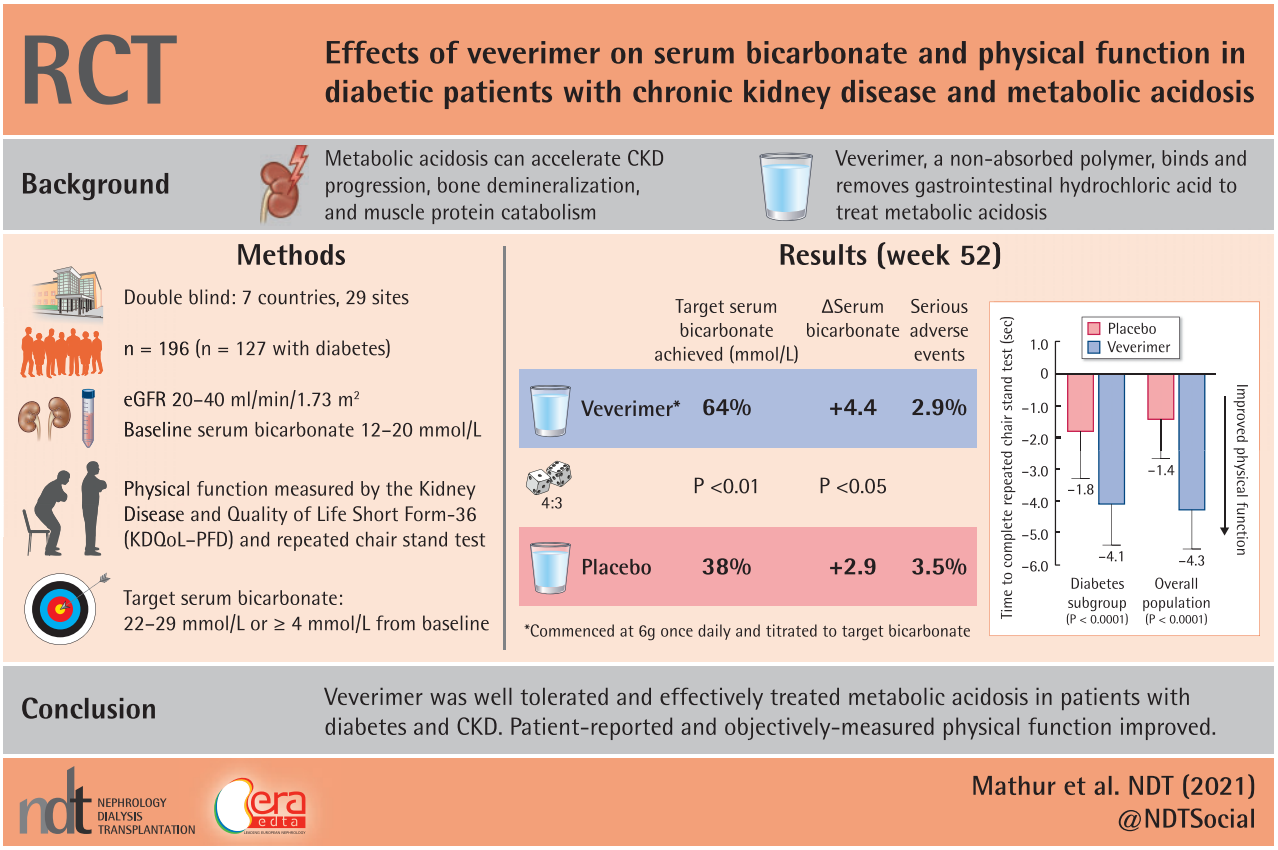
GRAPHICAL ABSTRACT



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ABSTRACT

Background. Metabolic acidosis is a complication of chronic kidney disease (CKD) that increases risk of CKD progression, and causes bone demineralization and muscle protein catabolism. Patients with diabetes are prone to metabolic acidosis and functional limitations that decrease quality of life. Veverimer, an investigational, non-absorbed polymer that binds and removes gastrointestinal hydrochloric acid, is being developed as treatment for metabolic acidosis. This *post hoc* subgroup analysis evaluated effects of veverimer on metabolic acidosis and physical function among patients with diabetes.

Methods. This was a Phase 3, multicenter, randomized, blinded, placebo-controlled trial in 196 patients with CKD (estimated glomerular filtration rate 20–40 mL/min/1.73 m^2) and metabolic acidosis who were treated for up to 1 year with veverimer or placebo.

Results. At Week 52, veverimer-treated patients with diabetes ($n = 70$), had a significantly greater increase in mean serum bicarbonate than the placebo group ($n = 57$) (4.4 versus 2.9 mmol/L, $P < 0.05$). Patient-reported limitations of physical function on the Kidney Disease and Quality of Life-Physical Function Domain (e.g. walking several blocks and climbing a flight of stairs) improved significantly in the veverimer versus placebo group (+12.5 versus +0.3, respectively, $P < 0.001$) as did objective physical performance on the repeated chair stand test ($P < 0.0001$).

Conclusions. Few interventions for patients with diabetes and CKD have successfully improved quality of life or physical functioning. Our study demonstrated that veverimer effectively treated metabolic acidosis in patients with diabetes and CKD, and significantly improved how these patients felt and functioned.

Keywords: chronic kidney disease, diabetes mellitus, metabolic acidosis, serum bicarbonate, veverimer

INTRODUCTION

Acid produced daily through metabolism and diet is initially neutralized through titration and reduction of serum bicarbonate, which must ultimately be excreted to maintain normal acid–base homeostasis. Normally functioning kidneys maintain this homeostasis through acid excretion and regeneration of new bicarbonate to replace the titrated bicarbonate and thereby restore serum bicarbonate to normal. Patients with chronic kidney disease (CKD) develop metabolic acidosis due to acid retention from impaired kidney acid excretion due in part to reduced kidney ammoniagenesis [1]. Reduced renin–aldosterone–angiotensin II system activity and reduced responsiveness to aldosterone (Type IV renal tubular acidosis) further contribute to metabolic acidosis in patients with diabetes [2]. Metabolic acidosis increases the risk of CKD progression and causes bone demineralization, muscle protein catabolism and loss of muscle mass [3]. Acidemia directly stimulates glutamine extraction from blood by several fold [4] and increases proximal tubule glutamine catabolism—a process that generates new bicarbonate, which is transported into the blood and ammonia, which is excreted into the urine [5]. The increased need for glutamine to support maximal renal ammoniagenesis is met, in part, by metabolic acidosis-induced skeletal muscle protein catabolism [4]. While skeletal muscle protein catabolism facilitates acid excretion, bones facilitate acid buffering. Bone is a large repository of carbonate and phosphate, which when released into the blood can serve as an acid buffer [6].

KEY LEARNING POINTS

What is already known about this subject?

- Metabolic acidosis is a common complication of chronic kidney disease (CKD) and can accelerate CKD progression, bone demineralization and muscle protein catabolism;
- patients with diabetes are prone to metabolic acidosis and functional limitations; and
- few interventions for patients with diabetes and CKD have successfully improved quality of life or physical functioning.

What this study adds?

- Veverimer effectively treated metabolic acidosis in patients with diabetes and CKD; and
- veverimer significantly improved how patients with diabetes and CKD felt and functioned.

What impact this may have on practice or policy?

- This study shows that treatment of metabolic acidosis is among the very few clinical interventions other than kidney replacement therapy that improves how patients with CKD feel and function. As a result, clinicians might more aggressively look for and treat metabolic acidosis in patients with CKD, a complication that is highly under-treated presently; and
- improved physical function from treating metabolic acidosis holds promise to allow patients with CKD to better perform activities of daily living and increase their employability, a recognition that might encourage policy makers to incentivize treatment of metabolic acidosis.

Metabolic acidosis induces direct dissolution of bone and activation of osteoclasts, which break down bone leading to release of carbonate and phosphate from the skeleton, reducing bone density and strength [6]. In patients with CKD and metabolic acidosis the bone histology is predominantly osteomalacia and it is not reversible with calcitriol treatment [7]. In patients with CKD, both low bone mineral density and annual percent decline in bone mineral density have been shown to be significant predictors of incident fractures [8].

Insulin normally inhibits muscle protein degradation but patients with CKD and metabolic acidosis have reduced sensitivity to the suppression of protein catabolism by insulin [9]. These defects may change body tissue composition analogous to fasting and/or low energy intake that overlap with alterations in insulin sensitivity that occur with aging [9]. As such, metabolic acidosis in patients with diabetes and CKD may contribute to the premature functional decline observed clinically in these patients. Data from a nationally representative sample of community-dwelling US adults found that in patients ≥60 years with diabetes, 32% of women and 15% of men reported an inability to walk a quarter of a mile, climb stairs or do housework compared with 14% of women and 8% of men without diabetes [10]. The effect of treating metabolic acidosis on physical function in patients with diabetes and CKD has not been reported previously.

Veverimer is a non-absorbed orally administered polymer drug that selectively binds protons and chloride in the gastrointestinal tract and thereby removes hydrochloric (HCl) acid via fecal excretion. The veverimer molecule has free amines that first bind protons, becoming positively charged, and then binds chloride, the most abundant anion in the gastrointestinal tract. The selective chloride binding is a function of the highly cross-linked structure of veverimer that prevents all but the smallest gastrointestinal tract anion (chloride) from binding [11]. The removal of HCl from the gastrointestinal tract is the equivalent of a net gain of bicarbonate in the blood because chloride secretion into the stomach is accompanied by generation of bicarbonate, which is transported into the blood. Veverimer is not an ion-exchange resin and thus does not introduce unwanted cations such as sodium or potassium. In a prior study of patients with CKD and metabolic acidosis conducted in an inpatient research unit, veverimer significantly increased serum bicarbonate within 24 h of treatment initiation, with increases in serum bicarbonate of 3–4 mmol/L after 2 weeks of treatment [12].

MATERIALS AND METHODS

Methods for this study have been previously reported [13] and are briefly summarized below.

Study design

This was a multicenter, randomized, blinded, placebo-controlled 40-week extension study of our 12-week parent study [14] conducted at 29 sites in 7 countries (TRCA-301E NCT03390842). The study protocol was approved by each site's institutional review board or ethic committee and appropriate regulatory authorities. Each patient gave his or her written informed consent prior to participation in the trial. Patients who continued from the parent study into the extension study did so with no gap in their study treatment and they continued the same blinded treatment they had received in the parent study. Following enrollment, scheduled visits were conducted at Weeks 14, 16, 20, 24, 28, 34, 40, 46 and 52 (Supplementary data, Figure S1).

Patients

Patients with CKD [estimated glomerular filtration rate (eGFR) 20–40 mL/min/1.73 m^2] and metabolic acidosis (serum bicarbonate 12–20 mmol/L) were enrolled into the parent study and randomized 4:3 to veverimer (TRC101) or placebo by an interactive web-based response system. Eligibility was based on three qualifying bicarbonate values and two qualifying screening eGFR values not different by >20% and in the range of 20–40 mL/min/1.73 m^2. Hemoglobin A1c at screening was required to be ≤9.0%. Eligibility for the extension study required completion of the 12-week parent study. Patients were excluded from participation if they: had a serum bicarbonate concentration low enough to need emergency intervention or had an assessment for an acute acidotic process; required dialysis for acute kidney injury or worsening CKD during the parent study; planned kidney replacement therapy within 6 months; had clinically significant diabetic gastroparesis, bariatric surgery, bowel obstruction, swallowing disorders, severe gastrointestinal disorders, inflammatory bowel disease, major gastrointestinal surgery or active gastric or duodenal ulcers or both.

Procedures

The starting study drug dose in the parent study was 6 g of veverimer once daily (two packets per day) or placebo once daily (two packets per day). Both were administered orally as a suspension in 60 mL of water. The study drug dose was algorithmically titrated by the interactive response technology system in the range of 0–9 g/day (or equivalent number of placebo packets) to a target serum bicarbonate concentration of 22–29 mmol/L based on bicarbonate measurement at each visit. Venous blood gases were also assessed at each visit. Background use of oral alkali supplements was permitted at a stable dose in the parent study and continued into the extension study. To avoid the long-term sodium or potassium load with oral alkali treatment in the extension study, the alkali dose was discontinued once the serum bicarbonate increased to ≥22 mmol/L. There were no protocol-specified dietary restrictions. Dietary counseling was provided to patients in accordance with dietary recommendations for patients with CKD [e.g. Kidney Disease Improving Global Outcome (KDIGO) 2012 [15]]. Bicarbonate measurements were made using a calibrated iSTAT Handheld Blood Analyzer (Abbott Point of Care, Princeton, NJ, USA). All other clinical laboratory measurements were done by a central laboratory. Management of glycemic control was at the discretion of the investigator.

The Kidney Disease and Quality of Life Short Form-36, question 3-Physical Function Domain (KDQoL-PFD) and standardized repeated chair stand test were administered at baseline and Weeks 12, 40 and 52. The KDQoL-PFD (Supplementary

data, Figure S2) was forward and backward translated, linguistically validated (including clinician's review) and culturally adapted. The paper questionnaires, consisting of 10 questions, were completed by patients by themselves, while at the study site. Patients responded to the question: 'The following items are about activities you might do during a typical day. Does your health now limit you in the activities? If so, how much?' Answer choices were 'yes, limited a lot', 'yes, limited a little' and 'no, not limited at all'.

The five-repetition chair stand test, a component of the Short Physical Performance Battery, was administered by study site personnel using a verbatim written script (in the patient's spoken language) to instruct patients during the test. The time for a patient to complete five repeated sit–stands with arms folded across the chest from an armless chair was measured with a stopwatch.

The primary endpoint for the extension study was the long-term safety based on the incidence of adverse events (AEs), serious AEs (SAEs) and AEs leading to withdrawal. Secondary endpoints (analyzed in pre-specified rank order) compared veverimer versus placebo at Week 52: achieving a ≥ 4 mmol/L increase from baseline in serum bicarbonate or a serum bicarbonate in the normal range (22–29 mmol/L); the change from baseline in serum bicarbonate to Week 52; the change from baseline to the Week 52 visit in total KDQoL-PFD score; and the change from baseline to the Week 52 visit in the time to complete the repeated chair stand test. Baseline serum bicarbonate was determined in the parent study as the mean of the serum bicarbonate values from Screening 1, Screening 2 and Day 1 (pre-dose) visits. Baseline values of total KDQoL-PFD score and repeated chair stand test were the measurements taken at the Day 1 (pre-dose) visit in the parent study.

AEs were identified by several methods. Patients were questioned at every study visit about any adverse effects they had experienced. Additionally, investigators were required to report any AEs revealed from physical examination, laboratory tests, electrocardiogram findings and other assessments.

The study patients were required to return all used and unused packets of the study drug at each visit. The compliance was calculated based on the returned empty packets and expected usage.

Statistical methods

The safety analysis set was defined as all patients who received any amount of study drug (veverimer or placebo) in the extension study and was used for assessments of safety. A modified intention-to-treat analysis set, defined as all randomly assigned patients who had both baseline and at least one post-baseline serum bicarbonate value in the parent study and at least one serum bicarbonate value after the Week 12 visit in the extension study, was used for evaluation of efficacy (secondary endpoints), based on planned treatment assignment. To control family-wise error rate, hypothesis testing for the four durability-of-effect (secondary) endpoints was pre-specified to be done sequentially, with subsequent tests only being done when all previous tests were statistically significant at the two-sided 0.05 level: responder analysis at Week 52 using the Fisher's exact test; change from baseline to Week 52 in serum bicarbonate using a mixed model for repeated measurements; change from baseline to Week 52 in the total KDQoL-PFD score using a rank-based analysis of covariance (ANCOVA) model; and change from baseline to Week 52 in the duration of the repeated chair stand test using a rank-based ANCOVA model.

RESULTS

Of the 196 patients enrolled in the extension study, 127 had a history of diabetes (70 in the veverimer group and 57 in the placebo group). In the veverimer and placebo groups, respectively, 97.3% (111/114) and 90.0% (74/82) of patients completed the study (Supplementary data, Figure S3). The mean daily dose in the veverimer group was 7.9 (1.8) g/day. Dosing compliance, defined as >80% of the prescribed doses taken, was 100% and 99% in the veverimer and placebo groups, respectively.

Baseline characteristics within the diabetes subgroup and the overall study population, including demographics, serum bicarbonate, eGFR and the urine albumin to creatinine ratio (ACR) were generally balanced across treatment groups (Table 1). Among patients with diabetes, the mean age was 63.2 years and the mean serum bicarbonate was 17.3 mmol/L; 10.2% were on background oral alkali. Most patients with diabetes were on anti-diabetic drug treatments (90% in the veverimer group and 80% in the placebo group), most commonly sulfonylurea drugs, insulin and metformin (Table 1). No patients received phosphate binders during the study.

Among patients with diabetes, a significantly greater percentage of patients in the veverimer group at Week 52 had a $\geq$4 mmol/L increase, or normalization, in serum bicarbonate than the placebo group (64% versus 38%, $P < 0.01$; Figure 1A), and patients in the veverimer group had a significantly greater least squares mean increase from baseline in serum bicarbonate than the placebo group [4.4 (0.4) versus 2.9 (0.5) mmol/L, $P < 0.05$] (Figure 1B). These findings were nearly identical to those observed in the overall study population (Figure 1).

In the diabetes subgroup, patient-reported limitations of physical function on the KDQoL-PFD, which measured daily activities such as walking several blocks and climbing a flight of stairs, improved significantly in the veverimer group versus the placebo group (+12.5 versus +0.3 points, respectively, $P < 0.001$; Figure 2A) as did objectively measured physical performance on the repeated chair stand test at Week 52 ($P < 0.0001$; Figure 2B). These findings were nearly identical to those observed in the overall study population (Figure 2). Formal testing of interaction by diabetes showed that there was no significant effect of the presence or absence of diabetes on the effect of veverimer on improvement in either measure of physical function (rank-based ANCOVA, $P \geq 0.6$).

Examination of the individual items of the KDQoL-PFD in the overall study population revealed that patients in the veverimer group reported significant improvements in all items related to walking, climbing a flight of stairs and bending/kneeling/stopping compared with patients in the placebo group [13]. These activities require lower body strength and use muscle groups that are also needed to perform the repeated chair stand test.

Table 1. Baseline demographic and clinical characteristics

Parameter	Overall population		Diabetes subgroup	
	Veverimer ($n = 114$)	Placebo ($n = 82$)	Veverimer ($n = 70$)	Placebo ($n = 57$)
Age, mean (SD), years	62.9 (12.1)	61.7 (11.9)	64.7 (11.7)	61.4 (10.7)
Sex, male, *n* (%)	68 (60)	51 (62)	43 (61)	35 (61)
Race, White, *n* (%)	113 (99)	79 (96)	69 (99)	54 (95)
Region, *n* (%)				
Europe	108 (95)	71 (87)	66 (93)	47 (82)
USA	6 (5)	11 (13)	5 (7)	10 (18)
SBP, mean (SD), mmHg	135.9 (8.9)	136.5 (9.0)	136.7 (9.4)	136.6 (9.5)
Selected medical history, *n* (%)				
Congestive heart failure	34 (30)	28 (34)	21 (30)	15 (26)
Hypertension	110 (96)	79 (96)	68 (97)	55 (96)
Left ventricular hypertrophy	56 (49)	35 (43)	36 (51)	17 (30)
Diabetes	70 (61)	57 (70)	70 (100)	57 (100)
Myocardial infarction	17 (15)	10 (12)	12 (17)	6 (11)
Stroke	8 (7)	8 (10)	4 (6)	6 (11)
Laboratory values, mean (SD)				
Serum bicarbonate, mmol/L	17.2 (1.4)	17.1 (1.5)	17.2 (1.4)	17.3 (1.6)
≤18 mmol/L, *n* (%)	77 (68)	59 (72)	48 (69)	38 (67)
>18 mmol/L, *n* (%)	37 (32)	23 (28)	22 (31)	19 (33)
eGFR, mL/min/1.73 m^2	29.4 (6.4)	27.9 (5.4)	29.1 (6.4)	27.8 (5.7)
Serum potassium, mmol/L	4.9 (0.6)	4.9 (0.6)	4.8 (0.6)	4.9 (0.5)
Hemoglobin A1c, mean (SD), %	6.1 (0.9)	6.2 (1.1)	6.5 (1.0)	6.5 (1.1)
Serum creatinine, mg/dL	2.2 (0.5)	2.3 (0.6)	2.2 (0.5)	2.3 (0.6)
ACR, geometric mean (95% CI), mg/g	209 (147–297)	305 (207–449)	258 (152–436)	434 (257–734)
ACR > 300 mg/g, *n* (%)	50 (47)	49 (65)	35 (52)	37 (69)
Hemoglobin, mean (SD), g/dL	12.6 (1.8)	12.6 (1.7)	12.5 (1.9)	12.6 (1.8)
Concomitant medications, *n* (%)	$n = 112$	$n = 81$	$n = 69$	$n = 56$
ACE inhibitor or ARB	75 (67)	66 (82)	47 (68)	48 (86)
β-Blocker	52 (46)	45 (56)	33 (48)	29 (52)
Calcium channel blocker	64 (57)	48 (59)	37 (54)	30 (54)
Diuretic	66 (58)	51 (63)	44 (64)	31 (55)
Lipid modifying drug	48 (43)	39 (48)	32 (46)	24 (43)
Sodium bicarbonate	11 (10)	5 (6)	8 (12)	5 (9)
Drugs for diabetes[a]	62 (55)	45 (56)	62 (90)	45 (80)
Insulin	19 (17)	12 (15)	19 (28)	12 (21)
Metformin	8 (7)	16 (20)	8 (12)	16 (29)
Sulfonylurea	38 (34)	25 (31)	38 (55)	25 (45)
Physical functioning, mean (SD)				
KDQoL-PFD total score	52.6 (22.4)	55.7 (26.2)	51.1 (20.6)	52.9 (26.8)
Repeated chair stand (s)	21.7 (16.9)	21.0 (17.1)	22.1 (16.6)	20.1 (16.9)

[a]Data are shown for most commonly used diabetic drugs. ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; SBP, systolic blood pressure; SD, standard deviation.

In the overall population, long-term treatment with veverimer was well tolerated, with a safety profile that was not different from placebo [13]. Two patients died and both were in the placebo group. Fewer patients in the veverimer group than in the placebo group discontinued treatment prematurely (3% versus 10%, respectively), and no patient in the veverimer group discontinued due to an AE. SAEs occurred in 2% of patients in the veverimer group and 5% of patients in the placebo group; no SAE was considered by the investigator as related to the study drug. The only AE with a between-group difference of >5% was headache, which was more common in the placebo group [13]. Renal system AEs, which included only events related to worsening kidney function (other than one event of proteinuria), were reported for 8% of patients in the veverimer group and 15% in the placebo group. An increase in serum bicarbonate to >30 mmol/L occurred in only one patient (in the veverimer group) and this increase occurred in the context of over-diuresis. There was little change in hemoglobin A1c during the study in either group. Veverimer showed no apparent off-target effects including on other electrolytes, lipids, vital signs or electrocardiogram intervals [13].

Among patients with diabetes, AEs, SAEs and treatment-related AEs were reported with similar frequency in the veverimer and placebo groups (Table 2); there was one death (in the placebo group).

DISCUSSION

In this multicenter, randomized, blinded, placebo-controlled study of up to 52 weeks in patients with CKD and metabolic acidosis, veverimer, a novel non-absorbed HCl binder, was effective in treating metabolic acidosis and improving both

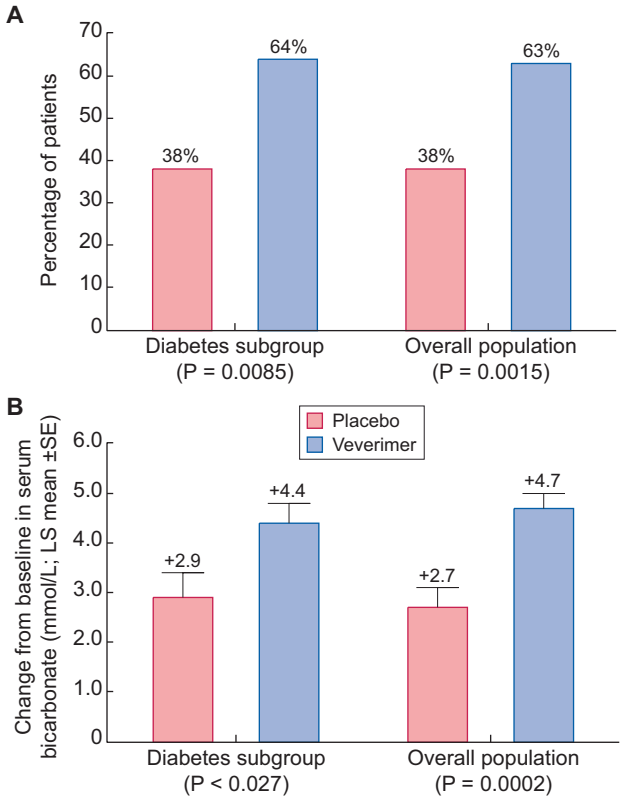

FIGURE 1: Veverimer effects on serum bicarbonate. (**A**) Percent of patients achieving an increase in serum bicarbonate of ≥4 mmol/L or serum bicarbonate in the normal range (22–29 mmol/L) at Week 52. (**B**) Serum bicarbonate change from baseline to Week 52. LS, least squares; SE, standard error.

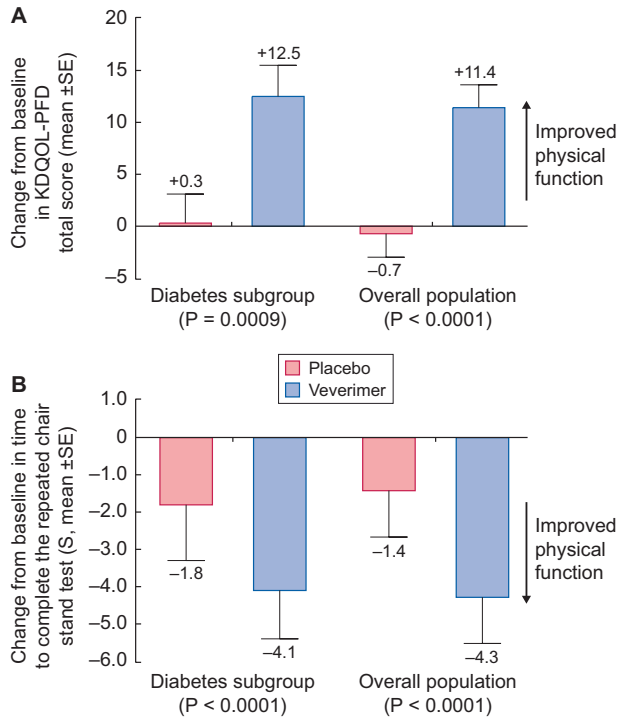

FIGURE 2: Veverimer effects on physical function. (**A**) Change from baseline in KDQoL-PFD. (**B**) Change from baseline in time to complete the repeated chair stand test. S, seconds.

Table 2. Safety summary in patients with diabetes

Type of event	Veverimer ($n = 70$)	Placebo ($n = 57$)
Deaths, *n* (%)	0	1 (1.8)
SAEs, *n* (%)	2 (2.9)	2 (3.5)
Premature discontinuation of study drug due to an AE, *n* (%)	0	1 (1.8)
Any AE, *n* (%)	93	93
Treatment-related AE, *n* (%)	20	28

Data are *n* (%) of patients. The data in this table reflect safety reporting from the subgroup of patients with diabetes who received treatment for up to 1 year in both the parent and extension studies.

patient-reported and objectively measured physical function. This *post hoc* subgroup analysis of the 127 patients with diabetes enrolled in this trial showed that the veverimer-treated group, compared with placebo, had significant improvement in serum bicarbonate and physical function, similar to improvements observed in the overall study population. Veverimer was well-tolerated and had a high treatment adherence, no treatment discontinuations due to AEs and an overall safety profile not different from placebo. While this study was not designed to evaluate CKD progression or mortality, fewer fatal events and AEs related to worsening kidney function were reported in the veverimer group than the placebo group. These findings are consistent with those of several single-center studies showing that treatment of metabolic acidosis slows CKD progression [16–18] and the observations that metabolic acidosis is associated with higher mortality [19]. Longer and larger trials are required to further evaluate these findings.

Improvement in the ability to conduct activities of daily living and to rise from a chair are important clinical and patient-centric outcomes. Loss of these abilities has important health, social and economic consequences because they can gauge whether a patient can continue to live independently. Prior studies showed that metabolic acidosis leads to bone loss and increased protein degradation; and correction of acidosis increases bone density and reduces protein degradation [20, 21]. Others have suggested that metabolic acidosis contributes to frailty, fractures and failure to thrive in patients with CKD [22, 23]. Our study provides evidence that treatment of metabolic acidosis in patients with CKD improves physical function. The observed effects on physical function in this study were both statistically and clinically significant. The observed improvement in patient-reported physical function on the KDQoL-PFD in the veverimer group (+11.4 points in the overall study population and +12.5 points in the diabetes subgroup) exceeded the minimal clinically important difference of 3–5 points for this subscale [24–26]. Similarly, the improved physical performance on the repeated chair stand test (−4.3 s in the overall population and −4.1 s in the diabetes subgroup) exceeded the 1.7 s minimally reported difference for this instrument [27]. Moreover, the chair stand time decrease of 4.3 s in the veverimer group between baseline and Week 52 was larger than the 3.4 s difference in mean expected performance between 80- to 89-year-olds and 60- to 69-year-olds (i.e. ∼20-year age difference) [28]. While this was not a mechanistic study, our findings of reduced limitations in physical functions,

particularly those related to lower extremity strength, are consistent with the expected clinical manifestations of reduced muscle protein catabolism and bone loss.

Current strategies for treatment of metabolic acidosis in patients with CKD include decreasing metabolic acid production through increasing base-producing dietary fruits and vegetables and neutralizing accumulated acid with alkali supplements such as sodium bicarbonate. Based on evidence that chronic metabolic acidosis is associated with increased protein catabolism, muscle wasting, uremic bone disease, chronic inflammation, impaired glucose homeostasis, impaired cardiac function, progression of CKD and increased mortality, the International Nephrology Clinical Practice guidelines: KDIGO recommends treating patients with CKD whose serum bicarbonate is <22 mmol/L [15], and Kidney Disease Outcomes Quality Initiative (KDOQI) suggests that it is reasonable to maintain serum bicarbonate between 24 and 26 mmol/L [29]. However, despite these guidelines, only a minority of patients are currently treated with alkali supplements. In the US-based prospective Chronic Renal Insufficiency Cohort study, for example, only 2.7% of patients with a serum bicarbonate <22 mmol/L and CKD were receiving treatment with oral alkali [30]. Sodium bicarbonate treats metabolic acidosis by entering the systemic circulation to supply bicarbonate that neutralizes retained acid. However, there is an obligatory sodium load delivered that may be absolutely or relatively contraindicated in the many patients with CKD, especially those whose blood pressure is above target levels, have edema and/or have heart failure [31, 32]. Compared with patients without diabetes, the risk of heart failure in patients with diabetes is doubled and cardiovascular outcomes, hospitalization and prognosis are worse [33]. Thus, patients with diabetes may have greater susceptibility to adverse consequences of excess sodium intake. The current KDOQI nutrition guideline for sodium intake is <2.3 g/day [29] and the American College of Cardiology and American Heart Association target is <1.5 g/day [34]. To increase serum bicarbonate by 3–4 mmol/L with sodium bicarbonate in an 80 kg individual, for example, requires 6–8 g/day of sodium bicarbonate, which has a sodium content of 1.7–2.2 g [35]. The mechanism of action of veverimer represents an alternative strategy for the treatment of metabolic acidosis in which acid is bound and removed from the gastrointestinal tract, leading to a net increase in serum bicarbonate. Because veverimer is not an ion-exchange resin, unwanted ions such as sodium are not introduced [12].

The strengths of this study include its multicenter, randomized, blinded, placebo-controlled design, the rigor of evaluation of both serum bicarbonate and physical function endpoints, and the 1-year treatment duration. The primary limitation of the present analysis is that it was conducted *post hoc* in a subgroup of patients and therefore results should be viewed as hypothesis-generating. The subgroup findings were highly consistent with those of the overall study population, however. Racial homogeneity was another limitation. While diet data were not collected, all patients were required to undergo dietary counseling at specific time points in accordance with dietary recommendations for CKD patients and the potential confounding effects of diet was excluded based on 24-h urea urine nitrogen measurements at baseline and post-baseline timepoints [13, 14].

Management of patients with diabetes and CKD is challenging. Progression of CKD and accompanying decline in physical function have multiple ramifications on patients' lives and influence the decision to initiate dialysis. Few interventions for patients with diabetes and CKD have successfully improved patient quality or life or physical functioning. Our study suggests that veverimer is an effective treatment for metabolic acidosis in patients with diabetes and CKD. Treatment with veverimer significantly improved how these patients felt and functioned.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

V.S.M. and E.L. developed the study protocol and statistical analysis plan. V.S.M. was responsible for management of the study. E.L. did the statistical analysis. V.S.M., E.L. and D.E.W. contributed to the interpretation of the results and preparation of this manuscript.

CONFLICT OF INTEREST STATEMENT

V.S.M., E.L. and D.E.W. were paid consultants to Tricida, Inc. in connection with the development of this manuscript. V.S.M. is a member of advisory boards at Tricida listed on patents related to work for Tricida and reports stock or stock options in Tricida. V.S.M. reports additional consulting fees from Tricida, Equillium, Myovant, Rigel, Corvidia, Acuta, Frazier, Intarcia, PTC Bio and Sanifit outside the submitted work. E.L. and D.E.W. report consultancy and personal fees from Tricida, Inc.

DATA AVAILABILITY STATEMENT

The data for this study have not been made publically available.

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