

Standard Article

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A Double-blind, Placebo-controlled, Multicenter, Prospective, Randomized Study of Beraprost Sodium Treatment for Cats with Chronic Kidney Disease

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Background: Chronic kidney disease (CKD) is a common progressive and irreversible disease in cats. The efficacy and safety of beraprost sodium (BPS) in cats with CKD have not been evaluated.

Hypothesis/Objectives: To evaluate the efficacy and safety of BPS in the treatment of cats with CKD, as compared to placebo.

Animals: Seventy-four client-owned cats with naturally occurring CKD.

Methods: Double-blind, placebo-controlled, multicenter, prospective, randomized trial. The cats received BPS (55 µg/cat) or a placebo PO q12 h for 180 days. The primary endpoint was prospectively defined as a change in the serum creatinine (sCr), serum phosphorus-to-calcium ratio or urine specific gravity (USG).

Results: The sCr increased significantly ($P = 0.0030$) in the placebo group (mean \pm SD: 2.8 ± 0.7 to 3.2 ± 1.3 mg/dL) but not in the BPS group (2.4 ± 0.7 to 2.5 ± 0.7 mg/dL). The difference between the groups at day 180 was significant (0.8 mg/dL, 95% CI: 0.2 to 1.3 mg/dL, $P = 0.0071$). The serum phosphorus-to-calcium ratio was significantly ($P = 0.0037$) increased in the placebo group (0.46 ± 0.10 to 0.52 ± 0.21 mg/dL) but not in the BPS group (0.50 ± 0.08 to 0.51 ± 0.11 mg/dL). There was no significant change in the USG in either group. An adverse event judged as being treatment-related included vomiting that occurred in 1 case in the placebo group. No clinically relevant change was observed in the CBC and other blood chemistry tests.

Conclusions and Clinical Importance: Beraprost sodium treatment was well tolerated and safe in cats with CKD. BPS inhibited the reduction in renal filtration function as measured by sCr increase.

Key words: Creatinine; Hypoxia; Prostacyclin; Renoprotective effect.

Introduction

Chronic kidney disease (CKD) is a progressive and irreversible disease defined as functional or structural kidney damage for 3 months or longer. In veterinary medicine, CKD is a common disease in older cats that impacts their quality of life (QoL) and longevity.¹

Despite its high prevalence, the underlying etiology of CKD in cats has not been clarified. Most cats with CKD have histopathological findings characterized by chronic tubulointerstitial inflammation and fibrosis,^{2–4}

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Place where the work was conducted: Japan.

Previous presentations of the material: None.

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Abbreviations:

ACE	angiotensin-converting enzyme
ANOVA	analysis of variance
ARB	angiotensin receptor blocker
BPS	beraprost sodium
BUN	blood urea nitrogen
CBC	complete blood cell count
CKD	chronic kidney disease
IRIS	International Renal Interest Society
QoL	quality of life
UPC	urine protein-to-creatinine
USG	urine specific gravity

and that among lesions, renal fibrosis correlates best with renal function, regardless of the primary disease.^{2,4} These observations suggest that renal fibrosis itself or the cause of renal fibrosis can affect renal function, regardless of etiology. Renal fibrosis is mediated by multiple factors, such as proteinuria, inflammation, hyperphosphatemia, and hypoxia.⁵ Among these mediators, there is increasing evidence for the involvement of chronic hypoxia both in renal fibrosis and in the progression of CKD.^{6–8} Furthermore, recent research suggested that renal hypoxia might be related to the prognosis of CKD also in cats.⁹ Therefore, targeting the renal hypoxia is hypothesized to provide a novel approach for treating CKD in cats, regardless of the primary disease.

Vascular endothelial cells primarily produce prostacyclin, a vasodilator and platelet aggregation inhibitor that has a key role in maintaining cardiovascular homeostasis.¹⁰ Prostacyclin also contributes to the

maintenance of renal vasculature homeostasis.^{11,12} Beraprost sodium (BPS) is an orally available prostacyclin analog that is used in humans to treat pulmonary arterial hypertension¹³ and atherosclerosis obliterans.¹⁴ BPS has a renoprotective effect in animal models of CKD.^{15–22} For instance, BPS inhibits the expression of inflammatory factors (notably monocyte chemoattractant protein-1), inhibited apoptosis of renal microvascular endothelial and tubular epithelial cells, and inhibited tubulointerstitial fibrosis.^{17,18,20} Furthermore, BPS treatment improved the time to doubling of serum creatinine (sCr) and survival rates in 2 rat models of CKD.¹⁹ BPS improves renal hypoxia in a rat model of glomerulonephritis²² and is efficacious in humans with CKD.²³ The efficacy and safety of BPS as a treatment for cats with naturally occurring CKD have not previously been evaluated. The objective of this study was therefore to evaluate the efficacy and safety of BPS in cats with naturally occurring CKD.

Materials and Methods

This study was a double-blind, placebo-controlled, multicenter, prospective, randomized clinical trial. It was conducted at 22 veterinary clinics in Japan and was performed in accordance with Good Clinical Practice guidelines. The protocol was prepared in consultation with veterinary experts in CKD and the Japanese regulatory agency, the National Veterinary Assay Laboratory. Before enrollment, all owners provided written informed consent.

Inclusion Criteria

Cats of all ages, breeds, and sexes with clinically stable CKD were eligible for inclusion. The criteria had to be met: sCr \geq 1.6 mg/dL, urine specific gravity (USG) $<$ 1.035, urine protein-to-creatinine (UPC) ratio $<$ 1.5, and serum T4 concentration 0.9–3.8 μ g/dL. By reference to the International Renal Interest Society (IRIS) staging guidelines, which defines CKD stage 2 as sCr of 1.6 mg/dL or higher, the cutoff of 1.6 mg/dL or higher sCr was adopted for the CKD diagnosis in this study. As stated above, the CKD diagnosis was reconfirmed by the USG $<$ 1.035, as well as sustained increase in the sCr and low USG for at least 1 month before inclusion into the study. To confirm the stability of CKD, sCr and USG were measured at 14 days and again at 7 days before enrollment. The enrollment flow is shown in Figure 1.

Exclusion Criteria

Cats were excluded if they were pregnant or had any clinical signs including the following: acute kidney injury; chronic heart failure (New York Heart Association Class II, III, or IV); diabetes mellitus; hyperadrenocorticism; urinary tract infection; leukemia virus infection; immunodeficiency virus infection; infectious peritonitis; malignant neoplasm; hepatic disease; or bleeding disorders. Cats receiving frequent and regular subcutaneous fluid therapy were also excluded.

Treatment

Cats entering the trial were randomly assigned, in chronological order, to receive BPS or placebo in a 1:1 ratio. The owner administered the BPS tablets at a dosage of 55 μ g/cat PO q12 h after

feeding. To maintain blinding of the investigators and the cat owners, BPS and placebo were indistinguishable, small, white tablets. The placebo tablets were similar in composition, except that BPS was replaced by lactose. To evaluate the compliance rate, the number of tablets administered was recorded daily by the cat owners.

Concomitant Treatments

Cardiotonic agents, diuretics, blood products, prostaglandin preparation, iodinated contrast agents, corticosteroids, and nonsteroidal anti-inflammatory drugs were withdrawn at least 2 weeks before the start of the study. Antihypertensive drugs and oral absorbents were permitted, but any change in dose and dosage was restricted. The administration period of these drugs before the start of the study was recorded. Renal-specific diets were also permitted, but any change in diet during the study was restricted. The type of diet fed within 1 month before the start of the study was recorded. Any concomitant treatment was recorded. Subcutaneous fluid therapy was permitted if needed. However, the clinical or laboratory evaluation data were excluded from the efficacy analysis if the cat had received subcutaneous fluid therapy within 7 days before the visit.

Outcomes

The primary endpoints were prospectively defined as changes in the sCr, serum phosphorus-to-calcium ratio, or USG from the baseline values. The secondary endpoints were defined as blood urine nitrogen (BUN), changes in body weight, UPC ratio, clinical activity score (ie, physical activity, appetite, and dehydration), QoL assessment by the owners, and impression of the treatment by the attending veterinarians according to the prospectively defined 5-level evaluation scales.

Schedule of Events

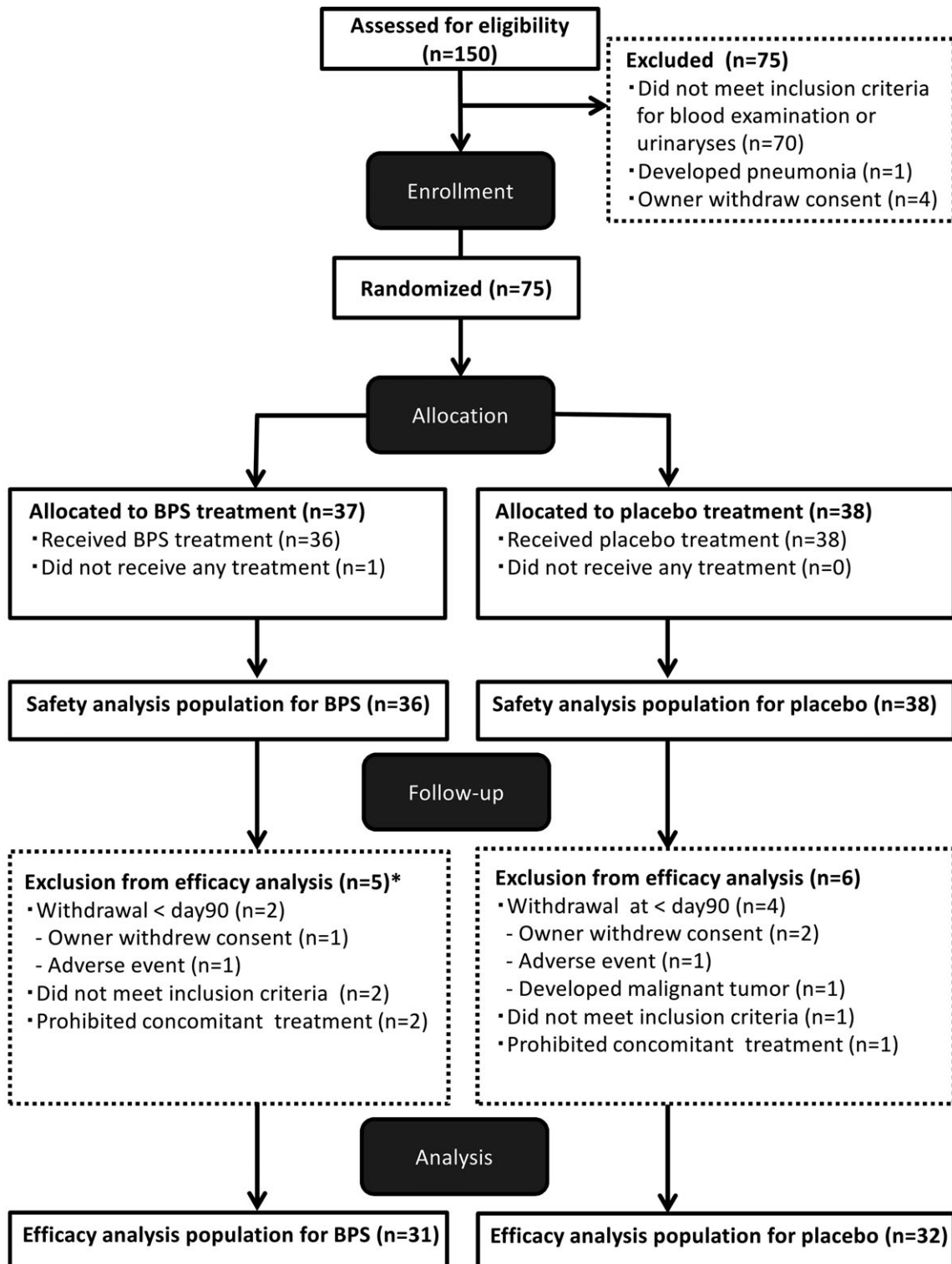
Cats were treated for 180 days. Day 0 was the day on which the cat first received BPS or placebo. Clinical and laboratory evaluations were scheduled for days 0, 30, 60, 90, 120, 150 and 180.

Blood Examination

Blood samples were collected around a set time of the day for each cat. The concentrations of fasted sCr, BUN, phosphorus, and calcium were measured to evaluate the efficacy of treatment. To evaluate drug safety, a complete blood cell count (CBC) and the concentrations of serum total protein, albumin, globulin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, glucose, and electrolytes (ie, Na, K, Cl, and Ca) were measured. Immediately after collection, the CBC was obtained on-site and other blood specimens were refrigerated and sent to IDEXX Laboratories Inc.

Urinalyses

Urine samples were collected from spontaneous urination on days 0, 30, 60, 90, 120, 150 and 180. Immediately after collection, USG was measured on-site by a refractometer. For the measurement of the UPC ratio, the urine samples were immediately refrigerated and sent to IDEXX Laboratories Inc. Microscopic examination and dipstick testing were used to screen for hematuria and urinary tract infection. If hematuria or urinary tract infection was detected, the data from urinalysis on that day were excluded from the efficacy analysis.



*one cat was excluded for two reasons: withdrawal at <day 90 and prohibited concomitant treatment.

Fig 1. Participant flow. BPS, beraprost sodium.

Clinical Examination

After taking a history from the owners, the clinical sign score (ie, physical activity, appetite, and dehydration) were recorded on days

0, 30, 60, 90, 120, 150 and 180, based on the scoring system shown in Table 1. At each examination, the body weight was recorded. Blood pressure was not measured, because clinics did not routinely use reliable methods at the time of the study.

Table 1. Clinical sign scoring system.

Variable	Score	Description
Physical activity	0	Active
	1	Normal
	2	Mildly lethargic
	3	Moderately lethargic
	4	Severely lethargic
Appetite	0	Increased
	1	Normal
	2	Decreased (3/4 normal)
	3	Decreased (1/2 normal), eat nothing at least once a week
Dehydration	4	Eat nothing at least 2 days per week
	0	Normal
	1	5% dehydration (mild decreased skin turgor, dry mucosa)
	2	7–8% dehydration (markedly decreased skin turgor; CRT, 2–3 s; mild sunken eyes; cold limbs)
	3	10–12% (severely decreased skin turgor; CRT, over 3 s; markedly sunken eyes; shock; spasm; cold skin)
	4	12–15% (shock, moribundity)

CRT, capillary refill time.

Quality-of-Life Assessment and Impression of the Treatment

The changes in QoL in comparison with the baseline (ie, “much improved” “improved” “minimally improved” “no change” or “worse”) were recorded by the owner on days 30, 60, 90, 120, 150 and 180. A subjective impression of the treatment was also recorded by the attending veterinarian on days 30, 60, 90, 120, 150 and 180.

Statistical Analyses

All cats receiving the test treatment were included in the safety analysis (ie, safety analysis population). Cats treated for <90 days and cats with substantial protocol deviations were excluded from the efficacy analysis (ie, the efficacy analysis population). Statistical analyses were performed using StatView 5.0 or JMP 11.^a A value of $P < 0.05$ indicated significance, except for analyses of primary outcomes. The P values in the primary outcomes were adjusted for multiplicity using the Bonferroni method. We set 3 primary outcomes; thus, $P < 0.017$ indicated significance.

The changes from baseline (ie, day 0) to the end of the study (ie, day 180) in the sCr, serum phosphorus-to-calcium ratio, serum phosphorus, serum calcium, USG, BUN, body weight, and UPC ratio during the study period were evaluated by repeated-measures analysis of variance (ANOVA). To compare differences between groups at day 180, Welch’s test was used. Absolute changes in the sCr from baseline to the end of the study within each subgroup were analyzed using the Wilcoxon signed-rank test. Differences between the groups were analyzed by 2-way repeated-measures ANOVA. Before applying parametric statistics, the normality of distribution was assessed using the Shapiro-Wilk test. To compare the total period of time that the renal-specific diet was fed to each of the 2 groups before the start of the trial, the Mann–Whitney U -test was used.

A multiple regression analysis was conducted with the change in the sCr from the baseline as the objective variable. Explanatory variables were BPS administration, initial sCr, sex, angiotensin-

converting enzyme (ACE) inhibitor administration, and renal-specific diet. In addition, a similar multiple regression analysis was performed using the IRIS stage in place of the initial sCr value as one of the explanatory variables. To compare the percentage of change in the sCr from the baseline to the end of the study between the BPS group and the placebo group, the Welch test was used. The changes in the clinical sign score (ie, physical activity, appetite, and dehydration) from the baseline to the end of the study were compared by the Friedman test, and the difference in clinical signs between the BPS group and the placebo group was compared by the Mann–Whitney U -test. The differences in QoL assessment and clinical global impression between the BPS group and the placebo group were compared by the Mann–Whitney U -test.

Results

Animals

One hundred and fifty cats were screened, and 75 cats were recruited and randomly allocated to the BPS group or the placebo group; of these, 74 cats received the test or placebo treatment (Fig. 1). Eleven cats were excluded from the efficacy analysis because they did not receive the test treatment for 90 days (2 cats in the BPS group, 4 cats in the placebo group) or they had serious protocol deviations (4 cats in the BPS group [1 cat in this group had also been excluded because it was withdrawn at <90 days] and 2 cats in the placebo group). The 63 cats that were finally included in the efficacy analysis population consisted of 2 intact male cats, 29 neutered male cats, 4 intact female cats, and 28 neutered female cats, with an average age of 13.8 years (range: 4.6–20 years) and an average body weight of 4.3 kg (range: 2.1–9.2 kg). The baseline characteristics in the efficacy analysis population were distributed homogeneously between groups (Table 2). Baseline sCr and BUN were slightly lower in BPS group but this was not statistically significant. The BPS group consisted of 31 cats (1 intact male cat, 15 neutered male cats, 2 intact female cats, and 13 neutered female cats) with an average age of 14.1 years (range: 6.7–19.3 years) and an average body weight of 4.4 kg (range: 2.1–9.2 kg). The placebo group consisted of 32 cats (1 intact male cat, 14 neutered male cats, 2 intact female cats, and 15 neutered female cats) with an average age of 13.4 years (range: 4.6–20 years) and an average body weight of 4.2 kg (range: 2.24–6.75 kg). Approximately 60–80% of cats were classified as IRIS stage 2: 24 (77%) of 31 cats and 19 (59%) of 32 cats in the BPS group and the placebo group, respectively. The remaining cats were classified as IRIS stage 3. The mean administration rate of pills was 91% (range: 73–100%) in the BPS group and 94% (range: 39–100%) in the placebo group.

Concomitant Treatments

An equal number of cats in both groups were receiving concomitant treatment with ACE inhibitor treatment in 10 (32%) of 31 cats in the BPS group and 10 (31%) of 32 cats in the placebo group; subcutaneous

Table 2. Baseline characteristics at inclusion.

Variable	BPS (n = 31)				Placebo (n = 32)			
	Mean	Min–Max	No.	%	Mean	Min–Max	No.	%
General characteristics								
Age (years)	14.1	6.7–19.3			13.4	4.6–20		
Body weight (kg)	4.4	2.1–9.2			4.2	2.2–6.8		
Sex								
Female—intact			2	6.5			2	6.3
Female—neutered			13	41.9			15	46.9
Male—intact			1	3.2			1	3.1
Male—neutered			15	48.4			14	43.8
IRIS staging								
Stage 2			24	77.4			19	59.4
Stage 3			7	22.6			13	40.6
			No. (%) greater than or less than reference range^a				No. (%) greater than or less than reference range^a	
Serum biochemistry								
sCr (mg/dL)	2.4	1.6–4.1	61.3%	>	2.8	1.8–4.3	87.5%	>
BUN (mg/dL)	40.5	24–73	61.3%	>	46.0	22–70	81.3%	>
Albumin (g/dL)	3.0	2.2–3.6	6.5%	<	3.0	2.3–3.9	12.5%	<
Globulin (g/dL)	4.5	3.1–5.8	22.6%	>	4.3	3.1–7.1	12.5%	>
ALT (U/L)	77.2	37–234	9.7%	>	51.0	20.0–107.0	12.5%	<
AST (U/L)	34.5	16–73	29.0%	>	28.5	14.0–87.0	18.8%	>
							6.3%	<
ALP (U/L)	27.8	13–49	0%		27.9	13.0–94.0	0%	
Sodium (mEq/L)	152.5	146–158	0%		152.3	148–157	0%	
Potassium (mEq/L)	4.4	3.2–5.3	0%		4.4	3.5–6.3	6.3%	>
Calcium (mg/dL)	9.7	8.8–12.2	3.2%	>	9.7	8.3–11.8	6.3%	>
Phosphorus (mg/dL)	4.8	3.8–7.5	3.2%	>	4.4	2.8–6.2	0%	
CBC								
RBC ($\times 10^6/\mu\text{L}$)	7.3	3.3–10.7	3.2%	>	7.5	5.3–10.9	9.7%	>
			19.4%	<			19.4%	<
Hemoglobin (g/L)	11.7	6–15.7	3.2%	>	11.9	8–17.1	9.7%	>
			12.9%	<			16.1%	<
Hematocrit (%)	35.6	19.4–52.5	12.9%	>	35.5	22.2–51	6.5%	>
			25.8%	<			19.4%	<
WBC ($\times 10^3/\mu\text{L}$)	9.8	3.5–15.1	6.5%	<	9.2	3.7–15.3	3.2%	<
Platelet ($\times 10^4/\mu\text{L}$)	28.0	0.4–46.3	6.9%	<	31.6	11.2–72.8	14.3%	<
							3.6%	>
Urine biochemistry								
Specific gravity	1.016	1.007–1.033	59.3%	<	1.017	1.002–1.030	34.8%	<
UPC ratio	0.07	0–0.58	0%		0.16	0–1.23	4.2%	>
Borderline proteinuric (0.2–0.4)			2	6.5			5	15.6
Proteinuric (>0.4)			2	6.5			2	6.3
Clinical signs								
Lethargy			8	25.8			7	21.9
Decreased appetite			7	22.6			9	28.1
Dehydration			12	38.7			18	58.1

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BPS, beraprost sodium; BUN, blood urea nitrogen; IRIS, International Renal Interest Society; RBC, red blood count; UPC, urine protein-to-creatinine; WBC, white blood cell count.

^aReference ranges were derived from IDEXX Laboratories Inc.

fluid therapy in 4 (13%) cats in the BPS group and 5 (16%) cats in the placebo group; and an oral absorbent for 2 (7%) cats in the BPS group and 1 (3%) cat in the placebo group. The medication protocol of all concomitant treatments remained unchanged throughout the study period. The mean administration periods of ACE inhibitor therapy before the start of the study were 219

(range: 63–760) days in the BPS group and 132 (range: 57–132) days in the placebo group. An oral absorbent was administered for 81 and 600 days in BPS group and 93 days in placebo group before the start of the study. An equivalent number of cats were fed a renal-specific diet in both groups: 17 (55%) of 31 cats in the BPS group and 15 (47%) of 32 cats in the placebo

group. The type of diet was not changed for any cat from the 1-month period before the study to the end of the study. The mean time periods before the study initiation in which a renal-specific diet was fed to the BPS group and the placebo group were 542 ± 827 and 368 ± 709 days, respectively. The difference between the 2 groups was not statistically significant ($P = 0.0679$).

Primary Outcomes

The sCr increased statistically significantly ($P = 0.0030$) in the placebo group (mean \pm SD: 2.8 ± 0.7 to 3.2 ± 1.3 mg/dL; Fig. 2A) but not ($P = 0.92$) in the BPS group (mean \pm SD: 2.4 ± 0.7 to 2.5 ± 0.7 mg/dL). The difference between the groups at day 180 was significant (0.8 mg/dL, 95% CI: 0.2 to 1.3, $P = 0.0071$). The serum phosphorus-to-calcium ratio was significantly increased ($P = 0.0037$) in the placebo group (mean \pm SD: 0.46 ± 0.10 to 0.52 ± 0.21 ; Fig. 2B), but not ($P = 0.30$) in the BPS group (mean \pm SD: 0.50 ± 0.08 to 0.51 ± 0.11), and the difference between the groups at day 180 was not statistically significant (0.008, 95% CI: -0.080 to 0.096 , $P = 0.85$). In the USG, there was no statistically significant change in either group (mean \pm SD 1.016 ± 0.006 to 1.017 ± 0.008 in the BPS group; 1.017 ± 0.007 to 1.015 ± 0.008 in the placebo group; Fig. 2C).

Secondary Outcomes

Laboratory Examination

As with the sCr, the BUN was statistically significantly ($P < 0.001$) increased in the placebo group (mean \pm SD: 46.0 ± 11.9 to 57.4 ± 24.4 mg/dL; Fig. 3A), but not ($P = 0.94$) in the BPS group (mean \pm SD: 40.5 ± 13.2 to 43.1 ± 16.1 mg/dL); there was a significant difference between the groups at day 180 (14.3 mg/dL, 95% CI: 3.4 to 25.2 mg/dL, $P = 0.015$). No significant change occurred in the UPC ratio, in either group (mean \pm SD: 0.1 ± 0.2 to 0.1 ± 0.4 in the BPS group; 0.2 ± 0.3 to 0.3 ± 0.5 in the placebo group; Fig. 3B). Body weight was significantly decreased ($P < 0.001$) in the placebo group (mean \pm SD: 4.19 ± 1.07 to 4.02 ± 1.13 kg; Fig. 3C), but not ($P = 0.37$) in the BPS group (mean \pm SD: 4.38 ± 1.58 to 4.22 ± 1.27 kg). The difference between the groups at day 180 was not statistically significant ($P = 0.52$).

Clinical Examination

The physical activity score was significantly worse in the placebo group ($P = 0.035$; Fig. 3D) than in the BPS group ($P = 0.12$). At day 0, a similar percentage of cats showed lethargy in the BPS group (27%) and in the placebo group (23%). At day 180, fewer cats in the BPS group (14%) showed lethargy than in the placebo group (31%). The appetite score significantly improved in the BPS group ($P = 0.0099$; Fig. 3E). No significant change in the appetite score was observed in the placebo group ($P = 0.62$), although there was a statistically

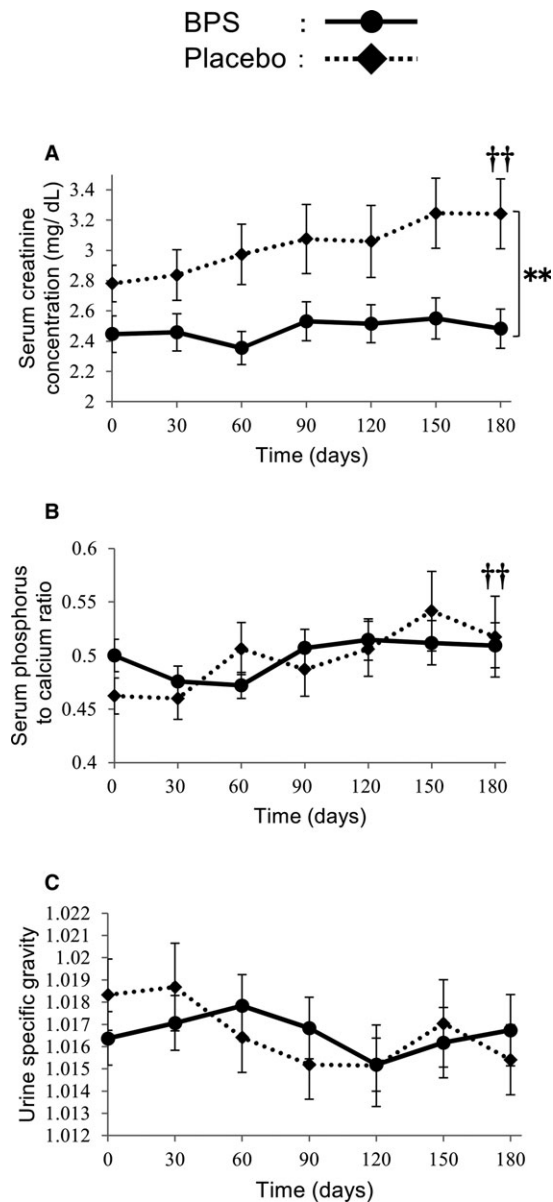


Fig 2. Changes in the primary outcomes from baseline values in the efficacy analysis population. Data are shown as mean \pm SE. ** $P < 0.01$ in comparison between the BPS group and the placebo group at day 180. †† $P < 0.01$ in comparison of posttreatment with baseline values within each group. P values have been adjusted for multiplicity by the Bonferroni method. BPS, beraprost sodium.

significant difference between the groups on day 180 ($P = 0.0064$). At day 0, a similar percentage of cats had dysorexia (23% in the BPS group and 29% in the placebo group), whereas at day 180, a smaller percentage of cats in the BPS group (7%) had dysorexia than in the placebo group (31%). The dehydration score did not change significantly in either group, although a statistically significant difference was seen between the BPS and placebo group on day 180 ($P = 0.025$; Fig. 3F).

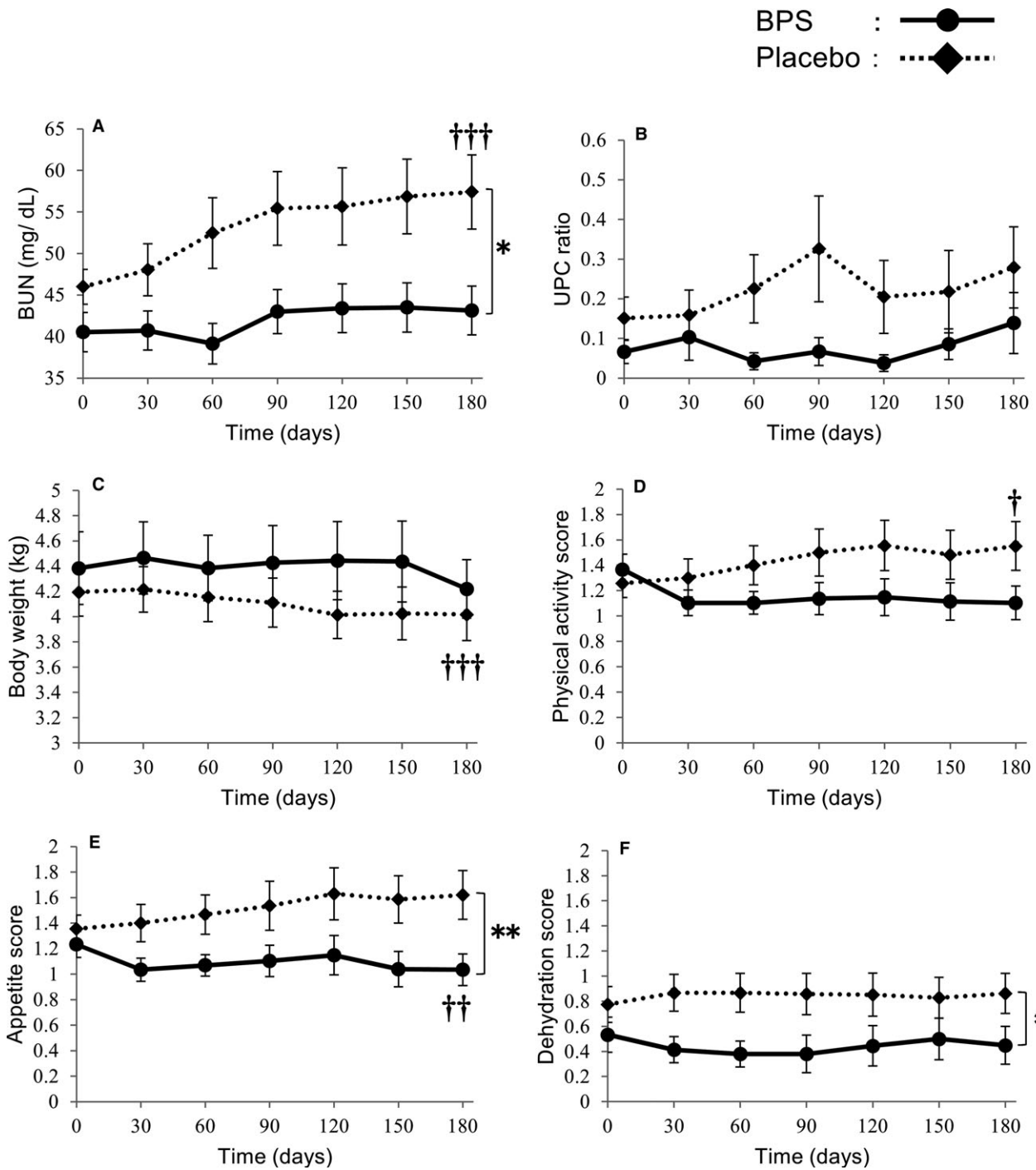


Fig 3. Changes in the secondary outcomes from baseline values in the efficacy analysis population. Data are shown as mean ± SE. **P* < 0.05 and ***P* < 0.01 in comparison between the BPS group and the placebo group at day 180. †*P* < 0.05, ††*P* < 0.01, and †††*P* < 0.001 in comparison of posttreatment with baseline within each group. BUN, blood urea nitrogen; UPC, urine protein-to-creatinine.

Quality-of-Life Assessment and Impression of the Treatment

In the QoL assessment, the total proportion of “much improved” “improved” and “minimally improved” answers was statistically higher in the BPS

group than in the placebo group (*P* = 0.0054, *P* = 0.0015, *P* < 0.001, *P* < 0.001, *P* < 0.001, and *P* < 0.001 on days 30, 60, 90, 120, 150 and 180, respectively; Fig. 4A,B). In the assessment of the impression of the treatment, the total proportion of “much improved” “improved” and “minimally improved”

answers was statistically significantly higher in the BPS group than in the placebo group ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$ and $P < 0.001$ on days 30, 60, 90, 120, 150 and 180, respectively; Fig. 4C,D).

Post hoc Analysis

A statistically significant increase in serum phosphorus ($P = 0.0012$) was observed in the placebo group (mean \pm SD: 4.4 ± 0.8 to 5.1 ± 1.9 mg/dL), but not

($P = 0.21$) in the BPS group (mean \pm SD: 4.8 ± 0.8 to 4.9 ± 1.1 mg/dL). The difference between groups at day 180 was also not statistically significant (0.2 mg/dL, 95% CI: -0.7 to 1.0 mg/dL, $P = 0.69$). Neither group showed statistically significant changes in the serum calcium.

The mean percentage of change in the sCr from baseline was $19 \pm 34\%$ (mean \pm SD) in the placebo group and $1 \pm 15\%$ (mean \pm SD) in the BPS group. The difference between the groups at day 180 was significant

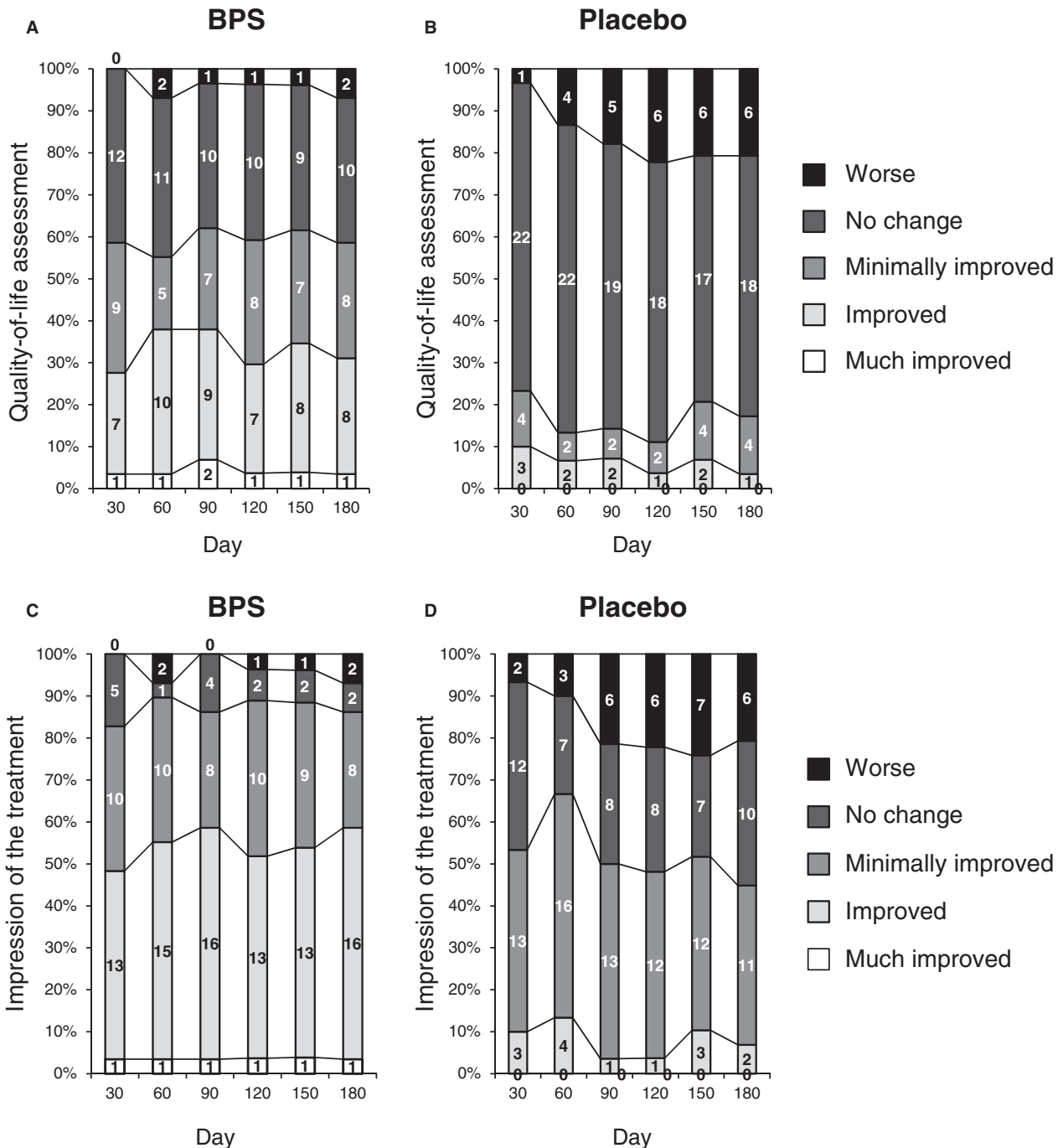


Fig 4. Changes in the quality-of-life assessment and impression of the treatment. BPS, beraprost sodium.

(18%, 95% CI: 4–32%, $P = 0.014$; Fig. 5A). The mean percentage of change in BUN, serum phosphorus-to-calcium ratio, and serum phosphorus from baseline increased in the placebo group were 23 ± 32 , 14 ± 34 , and $16 \pm 33\%$ (mean \pm SD), respectively, and suppressed in the BPS group (5 ± 20 , 3 ± 23 , and $2 \pm 24\%$ (mean \pm SD), respectively; Fig. 5B–D). Serum calcium was not changed in either group (mean \pm SD: $0 \pm 7\%$ in the BPS group; mean \pm SD: $2 \pm 6\%$ in the placebo group; Fig. 5E). At day 180, the difference between the groups was significantly observed only for BUN (18%, 95% CI: 4–32%, $P = 0.015$; Fig. 5B). The mean percentage change in USG was low in the placebo group compared to the BPS group, but the difference between groups was not significant (Fig. 5F).

The mean and median absolute changes in the sCr from baseline to day 180 were higher in the placebo group than in the BPS group and in all subgroups (ie, initial IRIS stage, sex, body weight, and age; Table 3).

Subgroup analyses have shown a statistically significant difference between the BPS group and the placebo group within each subgroup of IRIS stage 2, female, without renal-specific diet, and without ACE inhibitor administration. According to a multiple regression analysis, with the increase from the baseline of the sCr as the objective variable and the initial sCr value, sex, ACE inhibitor administration, renal-specific diet feeding, and BPS administration as the explanatory variables, the only factor that significantly influenced the inhibition of the sCr increase was BPS administration (Table 4). Similarly, another analysis that used as an explanatory factor the initial IRIS stage instead of the initial sCr value also found BPS administration to be the only factor that significantly impeded increase in the sCr.

Cats progressing to an advanced IRIS stage (ie, stage 2–3 or stage 3–4) during the study period comprised 3 (13%) of 24 cats in the BPS group and 6 (32%) of 19 cats in the placebo group with initial IRIS stage 2, and 0 (0%) of 7 cats in the BPS group and 3 (23%) of 13 cats in the placebo group with initial IRIS stage 3.

Adverse Events

The incidence of all reported adverse events in the safety analysis population comprised 16 cases (32 events) in the BPS group and 22 cases (61 events) in the placebo group. No adverse event in the BPS group was judged as being treatment-related. However, 1 adverse event in the placebo group was judged as being treatment-related: the cat vomited every 3 h after the administration of the placebo for 4 days, from the start of the study. There was no clinically relevant change in the CBC and other blood chemistry tests in either group.

Discussion

This study aimed to evaluate the efficacy and safety of BPS in the treatment of CKD in cats. In the prospectively defined primary endpoints, sCr did not

significantly increase in the BPS group, whereas it increased significantly in the placebo group. The difference between the groups was statistically significant. This suggested that BPS treatment inhibited the deterioration of renal filtration function in cats with CKD.

Previous studies revealed that the severity of renal fibrosis correlated best with markers of renal filtration function, such as the sCr concentration in cats with CKD^{2,4} and in humans.^{24,25} Renal fibrosis is mediated by multiple factors, such as proteinuria, inflammation, hyperphosphatemia, and hypoxia.⁵ Renal hypoxia exacerbates fibrosis, creating a vicious cycle of further renal hypoxia and fibrosis. In recent years, hypoxia in the tubulointerstitial region has been studied as the final common pathway of any and all primary diseases leading to end-stage kidney diseases⁶; indeed, increasingly indicates that hypoxia is a crucial in its pathogenesis.^{7,8} Beraprost sodium has endothelial protective, anti-inflammatory, vasodilatory, and antiplatelet effects.^{26,27} These effects might contribute to maintaining renal blood flow and prevent the progression of renal hypoxia. The findings of the current study suggested that BPS treatment disrupted this vicious cycle and prevented a further decline in renal function in cats with CKD by improving hypoxia via endothelial protective, anti-inflammatory, vasodilatory, and antiplatelet effects.

The primary disease in CKD cats is believed to be interstitial nephritis.² The study has shown that administration of BPS, initiated after an increase in the sCr is noted, can inhibit sCr increase in CKD cats, as observed in rat and human glomerular nephritis as the primary disease. These study results strongly suggest that BPS could be acting on a common deterioration pathway to end-stage CKD, most likely acting on tubulointerstitial hypoxia.

The dosage in this study was set at 55 μg per body. The justification for the selection of the dosage is as follows. First, in a preliminary safety evaluation test of healthy cats, we had confirmed BPS safety at 10–30 $\mu\text{g}/\text{kg}$ (or approximately 30–90 $\mu\text{g}/\text{body}$). Moreover, in a dose setting test, we had adopted the doses of 20–55 $\mu\text{g}/\text{body}$, in consideration of a generally higher incidence rate of adverse reactions among CKD cats, and the test results showed 55 $\mu\text{g}/\text{body}$ to be more effective.

Blood pressure was not measured because no validated and reliable methods for measuring the blood pressure in cats were available at the time of this study. Moreover, we estimated the 55 $\mu\text{g}/\text{body}$ dose in this study would not have acute action to reduce the blood pressure; in a study using healthy cats, we had confirmed BPS at doses up to 100 $\mu\text{g}/\text{kg}$ had no influence on the blood pressure.²⁸ Furthermore, a human study also suggests that BPS inhibits increase in the sCr without lowering the blood pressure.^{23,29} Thus, it is unlikely that reduced blood pressure might be involved in the mechanism of action of BPS.

A subgroup analysis of the change in the sCr from baseline, which is one of the primary endpoints of this study, suggested that within each subgroup of IRIS stage 2, female, without renal-specific diet feeding, and with ACE inhibitor administration, the sCr increase

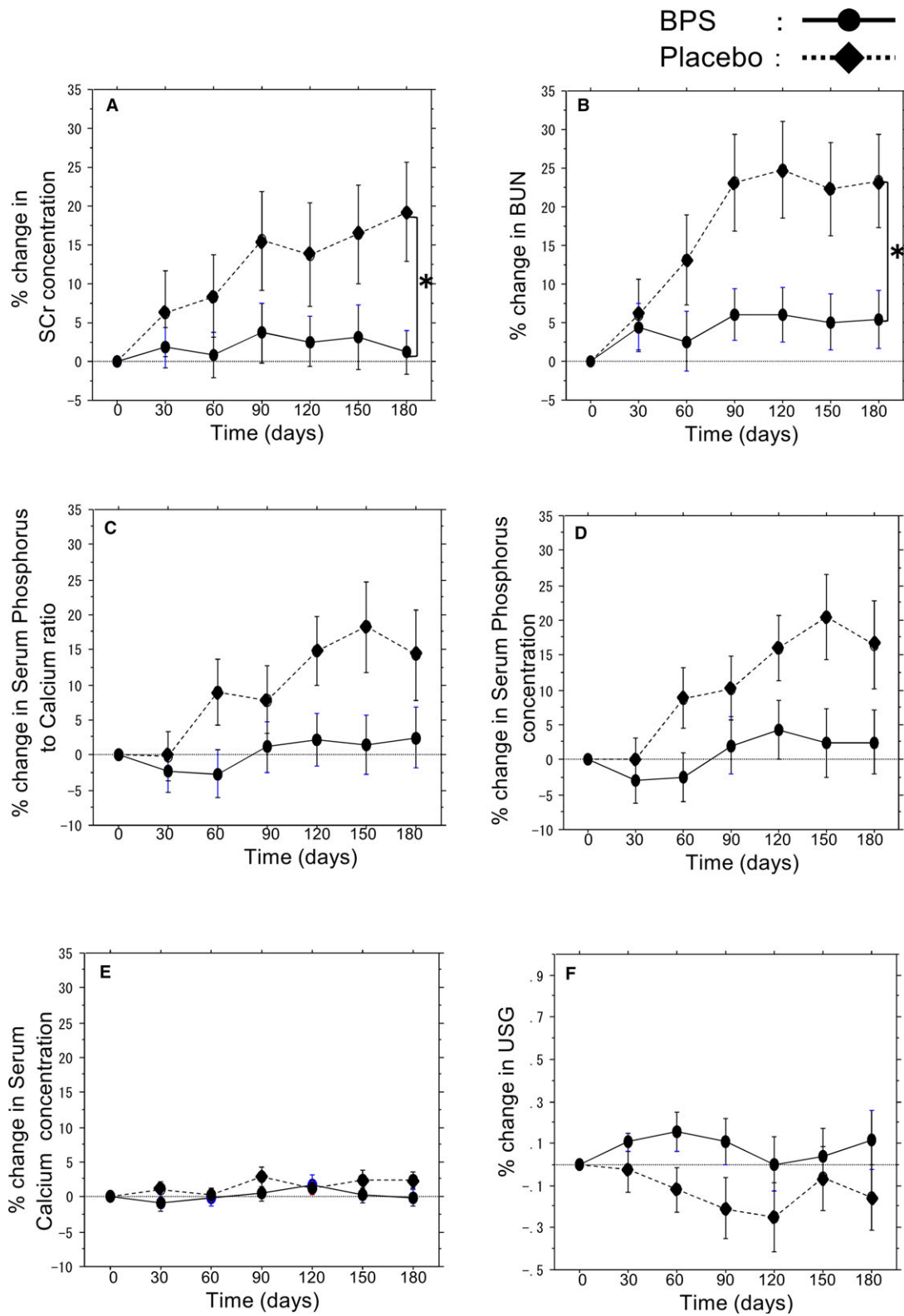


Fig 5. Changes in the SCr, serum phosphorus-to-calcium ratio, USG, BUN, serum phosphorus and calcium concentration from baseline value in the efficacy analysis population in case baseline values were set to zero. Data are shown as mean \pm SE. * $P < 0.05$ in comparison between the BPS group and the placebo group at day 180. BPS, beraprost sodium; BUN, blood urine nitrogen.

Table 3. Changes in the serum creatinine level from baseline to day 180, based on the treatment and subgroups.

	BPS											Placebo					BPS versus Placebo									
	P (Pretreatment versus Posttreatment)											P (Pretreatment versus Posttreatment)					P									
	Mean	SD	Median	Range	IQR	N	Mean	SD	Median	Range	IQR	N	Mean	SD	Median	Range	IQR	N	Mean	SD	Median	Range	IQR	N		
All Cats	+0.02	0.37	+0.05	-0.7 to +0.9	0.5	28	+0.52	0.99	+0.40	-1.7 to +2.5	1.25	28	+0.52	0.99	+0.40	-1.7 to +2.5	1.25	28	+0.0091*						0.015*	
Subgroups of cats																										
Initial IRIS stage 2	+0.09	0.34	+0.10	-0.4 to +0.9	0.45	21	+0.49	0.69	+0.40	-0.3 to +2.4	0.90	17	+0.49	0.69	+0.40	-0.3 to +2.4	0.90	17	0.01*							0.013*
Initial IRIS stage 3	-0.19	0.43	-0.30	-0.7 to +0.5	0.8	7	+0.57	1.37	+0.90	-1.7 to +2.5	2.3	11	+0.57	1.37	+0.90	-1.7 to +2.5	2.3	11	0.24							0.34
Male	+0.01	0.44	0.00	-0.7 to +0.9	0.5	15	+0.59	1.18	+0.25	-1.7 to +2.5	1.6	12	+0.59	1.18	+0.25	-1.7 to +2.5	1.6	12	0.13							0.18
Female	+0.03	0.30	+0.10	-0.4 to +0.5	0.5	13	+0.47	0.86	+0.45	-1.0 to +2.4	1.2	16	+0.47	0.86	+0.45	-1.0 to +2.4	1.2	16	0.049*							0.036*
Body weight, <4 kg	-0.10	0.29	-0.15	-0.6 to +0.3	0.50	12	+0.59	0.87	+0.50	-1.0 to +2.4	1.05	16	+0.59	0.87	+0.50	-1.0 to +2.4	1.05	16	0.016*							0.078
Body weight, ≥4 kg	+0.09	0.42	+0.10	-0.7 to +0.9	0.60	15	+0.43	1.17	+0.10	-1.7 to +2.5	1.58	12	+0.43	1.17	+0.10	-1.7 to +2.5	1.58	12	0.23							0.11
Age <14 years	+0.05	0.41	+0.05	-0.4 to +0.9	0.56	10	+0.50	1.07	+0.20	-1.7 to +2.5	1.55	13	+0.50	1.07	+0.20	-1.7 to +2.5	1.55	13	0.13							0.12
Age ≥14 years	+0.00	0.36	+0.05	-0.7 to +0.7	0.53	18	+0.51	0.98	+0.45	-1.0 to +2.4	1.36	14	+0.51	0.98	+0.45	-1.0 to +2.4	1.36	14	0.089							0.073
Concomitant treatment																										
With renal-specific diet	+0.05	0.44	-0.10	-0.6 to +0.9	0.70	15	+0.58	1.01	+0.50	-1.0 to +2.5	1.35	13	+0.58	1.01	+0.50	-1.0 to +2.5	1.35	13	0.06							0.10
Without renal-specific diet	-0.02	0.30	+0.10	-0.7 to +0.3	0.45	13	+0.47	1.00	+0.40	-1.7 to +2.4	1.3	15	+0.47	1.00	+0.40	-1.7 to +2.4	1.3	15	0.09							0.04*
With ACEI	+0.05	0.34	0.00	-0.3 to +0.7	0.50	10	+0.94	1.01	+1.00	-0.3 to +2.5	1.95	9	+0.94	1.01	+1.00	-0.3 to +2.5	1.95	9	0.023*							0.039*
Without ACEI	0.00	0.40	+0.10	-0.7 to +0.9	0.55	18	+0.32	0.94	+0.20	-1.7 to +2.4	1.1	19	+0.32	0.94	+0.20	-1.7 to +2.4	1.1	19	0.15							0.14

ACE, angiotensin-converting enzyme; BPS, beraprost sodium; IQR, interquartile range; IRIS, International Renal Interest Society; SD, standard deviation. *Significantly different from baseline.

was significantly suppressed in the BPS group than in the placebo group. On the other hand, in a multiple regression analysis of those factors that influenced this variable, BPS administration alone was extracted, whereas no other variable was found to significantly influence outcome. Therefore, further study is needed to confirm the efficacy of BPS in these subgroups.

Although the baseline sCr was slightly but not significantly lower in the BPS group than in the placebo group, the multiple regression analyses demonstrated the efficacy of BPS even after adjusting for the baseline sCr.

Before commencing this study, we set the serum phosphorus-to-calcium ratio, which was considered to be an index for serum phosphorus was set as one of the primary endpoint. However, the clinical significance of this index has not yet been fully established. Therefore, we performed a posthoc analysis of phosphate and calcium, respectively. High plasma phosphate concentrations had been reported to be a predictor of the progression of azotemia.³⁰ Our posthoc analysis showed increase in the serum phosphorus in the placebo group, whereas no such increase was observed in the BPS group. The results were similar to those of the phosphorus-to-calcium ratio, suggesting that BPS administration could impede the increase in phosphorus.

Previous studies have revealed that increased sCr concentration is one of the best predictors of prognosis in cats with CKD.^{9,31} Thus, inhibiting an increase in the sCr level might improve the prognosis of cats with CKD. BPS treatment has previously significantly improved survival in rat models of kidney disease.¹⁹ Further studies evaluating the potential effect of BPS on long-term survival in cats with CKD are therefore needed.

Clinical signs also improved in the BPS group. The appetite score significantly improved in the BPS group, but not in the placebo group. The physical activity score was significantly worse in the placebo group than in the BPS group. Most cats with CKD have dysorexia,³ however, only 7% of the BPS-treated cats had decreased appetite on day 180, whereas 31% of the placebo-treated cats had decreased appetite. Increased appetite helped to inhibit a significant decrease in body weight in the BPS group. Renal function seemed to be maintained without improvement, although BPS treatment significantly increased the appetite to a normal level. Dysorexia in cats with CKD can be caused by a stimulation of the chemoreceptor trigger zone by uremic toxins.¹ Recent reports have stated that BPS treatment decreased uremic toxins in a rat model of glomerulonephritis and in human patients.³² The increased appetite might be attributed to a decrease in the presence of uremic toxins in cats with CKD. Another explanation may involve the vasodilatory effect of BPS on the mesenteric artery. BPS has a relatively high relaxation potency in mesenteric and renal arteries as compared to other arteries.²⁷ An increase in the blood flow in the mesenteric artery may activate digestive and metabolic activity, thereby increasing appetite. Similar to the effect on appetite, fewer cats in the BPS group

Table 4. Results of multiple regression analysis of the change in the sCr level from the baseline as the objective variables. Renal-specific diet, ACEI, BPS, sex, age, and baseline sCr level were set as the explanatory variables.

	Unstandardized Coefficient	SE	Standardized Coefficient	<i>t</i>	<i>P</i>
Intercept	9.712	33.171	9.712	0.293	0.7709
Renal-specific diet	1.576	7.934	0.029	0.199	0.8434
ACEI	-8.409	8.383	-0.146	-1.003	0.3208
Beraprost	17.624	7.688	0.326	2.292	0.0263
Sex	0.039	7.455	0.001	0.005	0.9958
Age	-0.552	1.098	-0.070	-0.503	0.6174
sCr	-2.746	5.723	-0.069	-0.480	0.6335

ACE, angiotensin-converting enzyme; BPS, beraprost sodium.

(14%) than in the placebo group (31%) demonstrated lethargy on day 180. These improvements in the clinical sign score may correlate with the good evaluation in the QoL assessment by owners and in the impression of the treatment by veterinarians. In the treatment of chronic disease in particular, facilitation of the owner's engagement is important.³³ Improvement in the clinical signs and the early perception of the effect of a drug can be useful for maintaining the motivation to continue treatment and compliance.

In this study, BPS inhibited an increase in the sCr, BUN, and phosphorus-to-calcium ratio, regardless of the UPC ratio, which is the therapeutic target of an ACE inhibitor³⁴ or an angiotensin receptor blocker (ARB).³⁵ BPS has a vasodilatory effect similar to that of ACE inhibitors and ARB. Research findings indicate that the administration of 60 µg/d of BPS to human patients with CKD increases renal blood flow without affecting glomerular hyperfiltration,²³ whereas ACE inhibitors selectively dilate efferent arterioles and ameliorate hyperfiltration.³⁴ The nonsignificant change in the UPC ratio in the present study may reflect the mild effect of BPS on glomerular hypertension. These results may have also occurred simply because of the low initial UPC ratio in the present cases.

A previous study³⁴ suggested that benazepril produced a significant reduction in proteinuria in CKD cats, although the effect was largest in cats with higher UPC ratios. Thus, commencing treatment for proteinuria is recommended for cats with CKD with a UPC ratio >0.4.^{36,37} Several reports have revealed that one half to two-thirds of cats with CKD were nonproteinuric or had mild proteinuria;^{9,31,38} BPS could therefore provide a new treatment option for cats with CKD, regardless of the presence of proteinuria.

During the study period, an adverse event related to the medication occurred in only 1 cat in the placebo group in the safety analysis population. Other reported adverse events mostly involved clinical signs of CKD, which was relatively frequent in the placebo group. Among the clinical and laboratory findings, there was no clinically relevant change in the BPS group. In addition, the mean compliance rate was more than 90% in both groups. These results suggest that BPS is safe and well tolerated in the treatment of cats with CKD.

In conclusion, BPS effectively inhibited the reduction in renal filtration function as measured by sCr and

improved clinical signs in cats with CKD. In addition, adverse events were minimal and the compliance rate was high. The findings of this study indicate that BPS is an effective and safe drug for the treatment of cats with CKD.

Footnote

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Off-label Antimicrobial Declaration: The authors declare no off-label use of antimicrobials.

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