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Longitudinal Analysis of Quality of Life, Clinical, Radiographic, Echocardiographic, and Laboratory Variables in Dogs with Myxomatous Mitral Valve Disease Receiving Pimobendan or Benazepril: The QUEST Study

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Background: Myxomatous mitral valve disease (MMVD) is an important cause of morbidity and mortality in dogs.

Objectives: To compare, throughout the period of follow-up of dogs that had not yet reached the primary endpoint, the longitudinal effects of pimobendan versus benazepril hydrochloride treatment on quality-of-life (QoL) variables, concomitant congestive heart failure (CHF) treatment, and other outcome variables in dogs suffering from CHF secondary to MMVD.

Animals: A total of 260 dogs in CHF because of MMVD.

Methods: A prospective single-blinded study with dogs randomized to receive pimobendan (0.4–0.6 mg/kg/day) or benazepril hydrochloride (0.25–1.0 mg/kg/day). Differences in outcome variables and time to intensification of CHF treatment were compared.

Results: A total of 124 dogs were randomized to pimobendan and 128 to benazepril. No difference was found between groups in QoL variables during the trial. Time from inclusion to 1st intensification of CHF treatment was longer in the pimobendan group (pimobendan 98 days, IQR 30–276 days versus benazepril 59 days, IQR 11–121 days; $P = .0005$). Postinclusion, dogs in the pimobendan group had smaller heart size based on VHS score ($P = .013$) and left ventricular diastolic ($P = .035$) and systolic ($P = .0044$) dimensions, higher body temperature ($P = .030$), serum sodium ($P = .0027$), and total protein ($P = .0003$) concentrations, and packed cell volume ($P = .030$). Incidence of arrhythmias was similar in treatment groups.

Conclusions and Clinical Importance: Pimobendan versus benazepril resulted in similar QoL during the study, but conferred increased time before intensification of CHF treatment. Pimobendan treatment resulted in smaller heart size, higher body temperature, and less retention of free water.

Key words: Canine; Mitral regurgitation; Mortality; Therapy.

Myxomatous mitral valve disease (MMVD) is common and continues to be an important cause of morbidity and mortality in older small breed dogs.[1–3] We and others have demonstrated that treatment can prolong the survival of dogs with congestive heart failure (CHF) secondary to this condition.[4,5] The ideal treatment should both lengthen life and allow the dog to enjoy a good quality of life

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Abbreviations:

ACE-I	angiotensin-converting enzyme inhibitor
ACVIM	American College of Veterinary Internal Medicine
AF	atrial fibrillation
AUC	area under curve
BPM	beats per minute
BW	body weight
CHF	congestive heart failure
FS	fractional shortening
HF	heart failure
IQR	interquartile range
K	potassium
LA/Ao	left atrial to aortic root ratio
LVIDd inc	percentage increase in LVIDd from expected values
LVIDd	left ventricular internal diameter in diastole
LVIDs inc	percentage increase in LVIDs from expected values
LVIDs	left ventricular internal diameter in systole
MMVD	myxomatous mitral valve disease
Na	sodium
NYHA	New York Heart Association
PCV	packed cell volume
PE	pulmonary edema
QoL	quality of life
SVPC	supraventricular premature complex
TPC	total protein concentration
VHS	vertebral heart scale
VPC	ventricular premature complex

(QoL). Quality of life and survival will be closely linked in veterinary patients where owners are more likely to opt for the euthanasia of their pet when they consider the pet's QoL to be intolerable. When asked, the majority of owners indicate that they would prioritize QoL of their pet over its survival time.[6] Clinicians will modify medication to optimize the QoL of the patients they are treating.

There are problems in attempting to compare QoL between groups. Quality of life and clinical heart failure scores are inherently subjective. The ability of survival studies to demonstrate differences between groups of patients is further impaired by different rates of dropout in treatment groups.[7–10] If a dog has reached the primary endpoint of a study, or has been withdrawn for other reasons, and continuation in the study is no longer possible, it can no longer contribute data to longitudinal analyses. This results in missing data, and studies have differed in how they deal with this problem. Many studies use the approach of either "last observation carried forward" or "worst observation carried forward," but this approach tends to make the treatment with the higher dropout rate appear worse.

Heart disease and heart failure are known to lead to changes in clinical, laboratory, radiographic, and echocardiographic variables. Monitoring these variables in dogs undergoing treatment for heart failure is a common practice and recommended in the ACVIM consensus statement.[11] The comparative effects of angiotensin-converting enzyme inhibitors (ACEI) and pimobendan on some of these variables have not been described, and for others they have only been described for periods of 6 months or less.[9,10]

We previously have reported results from the QUEST study showing that pimobendan treatment was associated with improved survival when compared with benazepril treatment.[5] However, we have not reported the results with respect to the secondary outcome variables of QoL or described comparisons between groups for the clinical data acquired longitudinally. The aims of this study were to compare the longitudinal effects of pimobendan treatment on QoL indices, concomitant treatment, and clinical, laboratory, echocardiographic, and radiographic variables with those of a positive control (benazepril hydrochloride) in dogs diagnosed with CHF secondary to MMVD.

Materials and Methods

We previously have described in detail the materials and methods of this study.[5] Pertinent details are repeated here.

Dogs

Client-owned dogs were recruited at 28 centers in Europe, Canada, and Australia. The study terminated on 31 October 2006.

Enrollment Criteria

Inclusion Criteria. Dogs were eligible for inclusion in the study provided the owner had given informed consent. To be eligible for inclusion at the time of the 1st examination, the dog must have been >5 years of age, weighed between 5 and 20 kg, had a characteristic heart murmur of moderate to high intensity with maximal intensity over the mitral area, had echocardiographic evidence of advanced MMVD defined as characteristic valvular lesions of the mitral valve apparatus (leaflet thickening, valve prolapse), demonstrated mitral regurgitation on color Doppler echocardiography, had echocardiographic evidence of moderate to severe left atrial, left ventricular enlargement, or both (ie, left atrial to aortic root [LA/Ao] ratio >1.5[12] and left ventricular internal diameter in diastole [LVIDd] values above normal reference range[13]), and demonstrated current or prior radiographic evidence of pulmonary edema and cardiomegaly (ie, vertebral heart scale [VHS] >10.5).[14] Clinical signs of decompensated CHF must have been present at the time of the 1st examination or have previously been resolved with treatment (that must have included furosemide) that was still being administered and in the opinion of the attending clinician necessary to prevent the return of clinical signs.

Exclusion Criteria. Dogs were excluded from the study if they had a clinically relevant cardiac disease (congenital or acquired) other than mitral regurgitation secondary to MMVD, had another relevant systemic disease, or had evidence of other clinically relevant organ dysfunction.

Study Design

Randomization and Allocation. This was a prospective multicenter, single-blinded, positive-controlled study.

Investigators, study monitors, and the sponsor remained blinded for the duration of the study. Unblinding occurred only after completion of the study and data entry.

Blinding. In each center, the blinding of the investigator was ensured by the use of a dispenser. At inclusion and before each visit, the owner was instructed to discuss test treatments with the dispenser only. Drugs were dispensed by the dispenser in opaque boxes to prevent inadvertent disclosure of the treatment group to the investigator.

Test Treatments. The pimobendan group received pimobendan[a] PO at a dosage of 0.4–0.6 mg/kg/day. The calculated daily dose was divided into 2 and adjusted to a suitable number of 1.25 or 2.5 mg capsules. Owners were instructed to administer the drug in the morning and evening, approximately 12 hours apart, and approximately 1 hour before feeding.

The benazepril group received benazepril hydrochloride[b] PO at a dosage of 0.25–0.5 mg/kg once a day. In keeping with the manufacturer's recommendations, at the discretion of the investigator, the benazepril dose could be doubled. This involved the investigator instructing the dispenser, "If the dog is receiving benazepril, please double the dose," thus ensuring the investigator remained blinded as to treatment allocation of the case. The time of such a request was recorded and regarded as an intended intensification of treatment. The dosage was adjusted to a suitable number of 5 mg tablets.

Concomitant Treatments. Standard concomitant treatment for heart failure (such as diuretics and digoxin) was permitted throughout the trial with the following restrictions: open label use of pimobendan, benazepril, or any other ACE-I was precluded as was the use of phenylalkylamine calcium channel antagonists, xanthines, or angiotensin II receptor antagonists. In cases where dogs were already receiving an ACE-I or pimobendan treatment at inclusion, these drugs were discontinued immediately before allocation to either of the 2 test treatments. Dosages of concomitant treatments could be modified, if needed, throughout the study. The time and nature of any change in concomitant treatment were recorded.

Schedule of Events. Before inclusion, the case history of each dog was ascertained and any previous documentation of the case was reviewed (eg, radiographs, laboratory results). The dogs then underwent physical examination, electrocardiography (ECG), echocardiography, thoracic radiography, and routine hematology and blood biochemistry with a minimal database consisting of packed cell volume (PCV) and plasma total protein concentration (TPC), and serum creatinine, potassium, and sodium concentrations.

Scheduled reexaminations were at day 7, day 28, and 3 months after inclusion. Thereafter, the dogs were scheduled for reexamination every 3 months. On every visit, the following occurred: a case history was obtained including recording the type and dose of each medication the dog was receiving, a complete physical examination was performed, an ECG was recorded, and blood was taken to measure PCV, TPC, and serum creatinine, sodium, and potassium concentrations. Echocardiography and thoracic radiographic examinations were scheduled every 6 months after inclusion.

Clinical Evaluation. At inclusion, canine characteristics were recorded. The time since onset of clinical signs and the duration, type, and efficacy of any pretreatment were recorded. At each examination, body weight and rectal temperature were measured.

Quality of Life and Respiratory Variables. After history taking and clinical examination, the following variables were scored according to the system outlined in Table 1: appetite, demeanor, exercise tolerance, respiratory effort, coughing, and nocturnal dyspnea.

Heart Rate and ECG. The resting heart rate was measured during the physical examination. A 3-minute ECG recording was performed with the dogs lying in right lateral recumbency. Each dog's cardiac rhythm was classified as showing sinus rhythm, extrasystoles (ventricular or supraventricular or both), or atrial fibrillation (AF).

Table 1. Scoring protocol for clinical variables.

Variable	Score	Clinical Correlate
Exercise tolerance	1 (Very good)	Dog moved around with ease, was able to fully exercise
	2 (Good)	Dog moved around with ease, was not able to fully exercise; ability to run was reduced
	3 (Moderate)	Dog was less active than normal, moved around a few times per day, avoided long walks
	4 (Poor)	Dog was inactive and would only get up to eat, drink, or urinate
Demeanor	1	Alert, responsive
	2	Mildly depressed
	3	Moderately depressed
	4	Minimally responsive
	5	Unresponsive
Appetite	1	Increased
	2	Normal
	3	Decreased (2/3 normal)
	4	Markedly decreased (<2/3 normal)
Respiratory effort	1	Normal
	2	Mildly increased rate or effort
	3	Moderately labored
	4	Severe respiratory distress
Coughing	1	None
	2	Occasional (a few times a week)
	3	Frequent (a few times a day)
	4	Persistent (frequently during the day)
Nocturnal dyspnea	1	None
	2	Dog coughed from time to time during the night, but no other clinical signs of dyspnea or restlessness were present
	3	Dog coughed consistently; increased respiratory effort or restlessness during the night
Pulmonary edema	1	None
	2	Mild interstitial opacity
	3	Moderate interstitial opacity
	4	Alveolar pattern, severe consolidation
Modified NYHA heart failure score[16]	I	Asymptomatic dogs with murmur, but no cardiac enlargement
	II	Asymptomatic dogs with murmur and cardiac enlargement, but no pulmonary edema or congestion
	III	Slightly or moderately symptomatic dogs (dyspnea), increased heart rate and disappearance of sinus arrhythmia) with murmurs, cardiac enlargement, and interstitial pulmonary edema
	IV	Severely symptomatic dogs with murmurs, cardiac enlargement, and alveolar pulmonary edema

NYHA, New York Heart Association.

Echocardiography. Echocardiography was used to confirm the diagnosis of MMVD before inclusion and, thereafter to monitor disease progression. The following measurements were recorded:

the LA/Ao ratio obtained from the right parasternal short axis 2-dimensional (2D) view as previously described.[12] The LVIDd and left ventricular internal diameter in systole (LVIDs) were measured from the M-mode echocardiogram, which was obtained from the right parasternal short-axis 2D view.[15] M-mode values were used to derive the percent increase in LVIDd (LVIDd inc) and LVIDs (LVIDs inc) as follows: % increase = [100 × (observed dimension − expected normal dimension)/expected normal dimension] and the fractional shortening (FS). Expected normal dimensions based on body weight (BW) were calculated as previously described.[13]

Thoracic Radiography. Thoracic radiography was used to confirm the presence of cardiomegaly and pulmonary edema, to exclude concurrent disease at inclusion into the study, and to measure cardiac dimensions. Right lateral and dorsoventral projections were used to evaluate the thorax. Cardiomegaly was assessed with the VHS method[14] and pulmonary edema if present was scored (Table 1).

Heart Failure Score. The modified New York Heart Association (NYHA) score was used to score the severity of heart failure (Table 1).[16]

Endpoints. Dogs were considered to have reached the primary endpoint of the QUEST trial only when one of the following occurred: sudden cardiac death, euthanasia as a consequence of the cardiac disease, or treatment failure leading to the clinician withdrawing the dog from the trial.[5] Dogs were censored if they died or were euthanized because of noncardiac causes, were lost to follow-up, or were alive and had not reached the primary endpoint at the termination of the study.

Time from randomization to the 1st increase in dose of any treatment or the introduction of any permitted additional concomitant treatment (as outlined above) after enrollment in the study was considered as a secondary endpoint and referred to as intensification of CHF treatment. For this secondary endpoint, dogs in which no intensification of their treatment had occurred during the study were censored, which included dogs that had reached the primary endpoint without undergoing any intensification of their treatment.

Outcome Measure. The primary outcome measure of the QUEST trial was the time from randomization to withdrawal because of death or euthanasia owing to cardiac causes or treatment failure.

Secondary outcome measures included values of QoL, clinical, radiographic, echocardiographic, and laboratory variables measured over the duration of the study and time from randomization to any increase in dose of any treatment, or the introduction of any permitted additional concomitant treatment (as outlined above) after enrollment in the study.

Statistical Methods

For every dog for which any of the QoL, clinical, radiographic, echocardiographic, and laboratory variables was measured on ≥1 occasions after baseline assessment, a curve was constructed by plotting each data point on a graph with the unit of measurement on the vertical axis and time on the horizontal axis. The area under the curve averaged for the number of days between the 1st and last observation was calculated thus giving an average value for the variable that incorporated all of the observations made and was independent of the duration of time the dog remained in the study.[17] These derived variables were used as summary measures of the values of the variable over the time in study for each dog. These values then were compared between treatment groups using the Wilcoxon rank sum test.[17]

The proportions of dogs in each treatment group experiencing modifications in the dose, or addition of the drugs furosemide, spironolactone, or digoxin, or in which the investigator expressed an intention to increase the benazepril dosage, at the time of the 1st intensification of treatment, were compared using the Fisher's exact test. Furthermore, the proportion of dogs in each treatment group receiving spironolactone and the proportion of dogs in each treatment group receiving digoxin at each scheduled visit were compared using the Fisher's exact test.

A log-rank test with right censoring was used to determine whether a significant difference existed between the 2 treatment groups for the variable "time from randomization to the first increase in dosage of any treatment, or the introduction of any permitted additional concomitant treatment after enrollment in the study." The Kaplan–Meier method was used to estimate the median time to this secondary endpoint for each treatment group and plot time to event curves. In addition, univariate and multivariate Cox proportional hazards analyses with right censoring were performed to determine whether there was a significant difference between treatment groups. The hazard ratio with 95% confidence intervals was calculated.

For all analyses, a P value <.05 was considered significant. All analyses were 2-tailed. Median values and interquartile (IQR) ranges are reported. All statistical analyses were performed by an independent statistician[c] using a commercially available software program.[d]

Results

The study population (Table 2), event rate, and effect of baseline variables and treatment on the time to composite primary endpoint have been described previously.[5] Pertinent details are repeated below.

Two hundred and sixty dogs were recruited; 8 dogs were excluded from further analysis after termination of the trial, but before unblinding. Of the 252 dogs analyzed (116 males, 38 females, 37 neutered males, and 61 neutered females), the most commonly recruited breed was the CKCS (n = 82). One hundred and twenty-four dogs were randomized to the pimobendan group and 128 dogs to the benazepril group. One hundred and ninety dogs (75%) reached the primary endpoint; 62 dogs (25%) were censored. No dogs were lost to follow-up.

Effect of Treatment over Time (AUC adjusted for days in study) and Incidence of Arrhythmias

The results of the comparisons of QoL, clinical, laboratory, radiographic, and echocardiographic variables between groups over time are illustrated in Table 3. The following variables were significantly higher in the dogs receiving pimobendan: rectal temperature, serum sodium concentration, PCV, and TPC. The following variables were significantly lower in the dogs receiving pimobendan: VHS, LVIDs inc, and LVIDd inc (also LVIDd and LVIDs). There was no difference in incidence of new arrhythmias between the treatment groups (Table 4).

Effect of Treatment Group on Concurrent Treatment

The proportions of dogs and the nature of the change in treatment required at the time of modification that

Table 2. Summary of baseline characteristics in the 2 treatment groups (frequencies or medians [IQR]).

Variable	Pimobendan (N = 124)	Benazepril (N = 128)	*P* Value
Canine characteristics			
Age (years)	10.0 (8.0–11.0)	10.0 (8.0–12.0)	.06
Sex (M/F/MC/FN)	59/14/24/27	57/24/13/34	.08
Cavalier (yes/no) (%)	34/90 (27/73%)	48/80 (38/62%)	.09
Treatment			
Furosemide dose (mg/kg/day)	4.7 (3.4–6.7)	4.4 (3.0–6.4)	.18
Digoxin (yes/no)	16/108	27/101	.10
Spironolactone (yes/no)	21/103	24/104	.74
Quality of life and respiratory variables			
Appetite	2.0 (2.0–3.0)	2.0 (2.0–3.0)	.95
Demeanor	1.0 (1.0–2.0)	1.0 (1.0–2.0)	.61
Exercise tolerance	2.0 (2.0–3.0)	2.0 (2.0–3.0)	.62
Respiratory effort	2.0 (1.2–3.0)	2.0 (1.0–3.0)	.84
Cough	3.0 (2.0–3.0)	3.0 (2.0–3.0)	.32
Nocturnal coughing	2.0 (1.0–3.0)	2.0 (1.0–3.0)	.74
Physical examination			
Rectal temperature (°C)	38.5 (38.2–38.9)	38.5 (38.2–38.9)	.42
Heart rate (bpm)	144 (126–162)	148 (128–165)	.54
Body weight (kg)	9.0 (6.9–11.4)	9.5 (7.6–11.7)	.18
HF score	3.0 (3.0–3.0)	3.0 (3.0–3.0)	.97
Diagnostic imaging			
VHS score	12.5 (11.5–13.0)	12.5 (12.0–13.5)	.15
PE score	2.5 (1.0–5.0)	3.0 (1.0–5.0)	.65
LVIDs inc (%)	19.7 (4.0–37.0)	24.5 (10.7–43.4)	.08
LVIDd inc (%)	42.9 (30.0–57.6)	45.5 (33.8–58.6)	.40
FS (%)	45 (41–50)	44 (39–48)	.09
LA/Ao	2.4 (2.0–2.7)	2.3 (2.0–2.7)	.61
Laboratory variables			
Na (mmol/L)	148 (145–151)	148 (146–150)	.65
K (mmol/L)	4.4 (3.9–4.9)	4.3 (3.9–4.8)	.53
PCV (%)	45.2 (42–51)	46.0 (41–50)	.39
Creatinine (mg/dL)	1.0 (0.8–1.1)	1.0 (0.8–1.2)	.38
TPC (g/dL)	6.5 (6.0–7.0)	6.4 (6.0–7.0)	.72

IQR, interquartile range; M, male; F, female; MC, male castrated; FN, neutered female; bpm, beats per minute; HF, heart failure; VHS, vertebral heart scale; PE, pulmonary edema; LVIDs, left ventricular internal diameter in systole; LVIDs inc, percentage increase in left ventricular internal diameter in systole from expected values; LVIDd, left ventricular internal diameter in diastole; LVIDd inc, percentage increase in left ventricular internal diameter in diastole from expected values; FS, fractional shortening; LA/Ao, left atrial to aortic root ratio; K, potassium; Na, sodium; PCV, packed cell volume; TPC, total protein concentration.

were first deemed as necessary were no different in the 2 treatment groups (Table 5). Only 6 dogs (4 dogs in the benazepril group and 2 in the pimobendan group) had an intended intensification of heart failure treatment consisting only of a desire to increase the benazepril dosage. Intensifications in all other dogs for which the investigator expressed a desire to increase the benazepril dosage consisted of a change in at least 1 additional drug. A significantly greater proportion of dogs received spironolactone treatment in the benazepril group at 28 days, 3 months, and 6 months and a significantly greater proportion of dogs received digoxin treatment in the benazepril group at 3 months (Table 6).

Of the 252 dogs included in the study, there was an intensification of heart failure treatment in 172 dogs (83 dogs in the pimobendan group and 89 in the benazepril group), whereas 80 dogs (41 dogs in the pimobendan group and 39 in the benazepril group) were censored in the statistical analyses. The proportions of censored dogs in the 2 treatment groups were not significantly different ($P = .69$), whereas the time in the study to censoring was significantly longer in the pimobendan group compared with the benazepril group (median, 123 days; IQR, 19.5–372 days versus median, 39 days; IQR, 26–92 days; $P = .038$). Dogs receiving pimobendan had a significantly longer time period (median, 98 days; IQR, 30–276 days) before experiencing any intensification in their treatment compared with those receiving benazepril (59 days; IQR, 11–121 days; Fig 1; $P = .0005$). This significant difference persisted ($P = .014$) if the desire to increase benazepril dosage was not considered as an intensification of heart failure treatment. Dogs receiving benazepril were 1.69 times more likely to undergo intensification of their treatment first (hazard ratio, 1.69; 95%, CI, 1.24–2.29; $P = .0008$) in the univariate analysis. This difference persisted after adjusting for all baseline variables in the multivariate Cox proportional hazard analysis.

Table 3. Median AUC adjusted for days in study and IQR for dogs treated with pimobendan and dogs treated with benazepril.

	Variable	Treatment	N	Median	IQR	*P* Value Wilcoxon
Quality of life and respiratory variables (see Table 1 for levels)	Appetite	Pimobendan	118	2.0	1.9–2.1	.12
		Benazepril	124	2.0	2.0–2.30	
	Cough	Pimobendan	118	2.3	1.6–2.9	.71
		Benazepril	124	2.3	1.9–2.8	
	Demeanor	Pimobendan	118	1.2	1.0–1.5	.86
		Benazepril	124	1.2	1.0–1.5	
	Exercise tolerance	Pimobendan	118	2.0	1.6–2.4	.73
		Benazepril	124	2.0	1.6–2.4	
	Nocturnal dyspnea	Pimobendan	118	1.4	1.0–2.0	.54
		Benazepril	124	1.4	1.0–2.0	
	Respiratory effort	Pimobendan	118	1.5	1.1–2.0	.47
		Benazepril	124	1.7	1.2–2.0	
Furosemide dose	Furosemide dose (mg/kg/day)	Pimobendan	117	4.8	3.4–6.6	.69
		Benazepril	121	5.1	3.7–6.8	
Physical examination	Rectal temperature (°C)	Pimobendan	118	38.6	38.3–38.8	.029
		Benazepril	124	38.5	38.2–38.7	
	Heart rate (bpm)	Pimobendan	118	137.6	128.1–151.8	.32
		Benazepril	124	140.9	128.6–156.8	
	Body weight (kg)	Pimobendan	118	9.0	7.1–11.3	.29
		Benazepril	124	9.4	7.6–11.6	
	HF score	Pimobendan	118	2.5	2.0–3.0	.44
		Benazepril	124	2.5	2.1–3.0	
Diagnostic imaging	VHS score	Pimobendan	69	12.4	11.5–13.0	.013
		Benazepril	49	12.9	11.9–13.8	
	Severity of PE (scores 1–5)	Pimobendan	69	2.0	1.5–2.5	.81
		Benazepril	49	2.0	1.5–2.5	
	LVIDs inc (%)	Pimobendan	67	15.2	−0.6–24.7	.0044
		Benazepril	49	24.3	14.6–39.0	
	LVIDd inc (%)	Pimobendan	67	36.3	28.4–50.9	.035
		Benazepril	49	46.5	33.0–61.1	
	FS (%)	Pimobendan	69	46.5	42.5–48.8	.11
		Benazepril	49	44.5	40.3–48.4	
	LA/AO	Pimobendan	69	2.2	1.9–2.6	.83
		Benazepril	49	2.3	2.0–2.6	
Laboratory variables	Na (%)	Pimobendan	117	148.7	146.2–150.7	.0027
		Benazepril	120	147.0	144.7–149.5	
	K (mmol/L)	Pimobendan	117	4.3	3.9–4.7	.92
		Benazepril	120	4.3	3.9–4.8	
	PCV (%)	Pimobendan	117	46.8	42.8–50.9	.030
		Benazepril	120	45.5	40.5–49.3	
	Creatinine (mg/dL)	Pimobendan	117	1.1	0.9–1.287	.58
		Benazepril	120	1.1	0.907–1.4	
	TPC (g/dL)	Pimobendan	117	6.7	6.4–7.2	.0003
		Benazepril	119	6.5	6.0–6.9	

AUC, area under curve; IQR, interquartile range; bpm, beats per minute; HF, heart failure; VHS, vertebral heart scale; PE, pulmonary edema; LVIDs, left ventricular internal diameter in systole; LVIDs inc, percentage increase in LVIDs from expected values; LVIDd, left ventricular internal diameter in diastole; LVIDd inc, percentage increase in LVIDd from expected values; FS, fractional shortening; LA/Ao, left atrial to aortic root ratio; K, potassium; Na, sodium; PCV, packed cell volume; TPC, total protein concentration.

Discussion

The current report shows that in dogs receiving concurrent heart failure treatment, pimobendan when compared with benazepril treatment results in a similar QoL for the duration of the period of treatment, but increases the time period before it is necessary to intensify treatment, which, in turn, leads to a lower proportion of dogs receiving additional heart failure drugs. Furthermore, dogs receiving pimobendan had smaller heart size and higher body temperature, serum sodium concentration, TPC, and PCV by comparison to dogs receiving benazepril.

Quality of life is defined in people as a reflection of the way a person's mental and physical well-being is evident in their everyday life.[18] One of the main ways in which heart failure and its treatment affects QoL is through its impact on people's ability to perform their normal daily activities.[19] In some studies, QoL is

Table 4. Number and proportions of new arrhythmias by treatment groups over time in 252 dogs treated with pimobendan or benazepril.

Time (months)	Total Dogs Remaining in Study		Total Dogs with New Onset Arrhythmia, n (%)		*P* Value for Comparison	Dogs with New Onset SVPC, n (%)		Dogs with New Onset VPC, n (%)		Dogs with New Onset AF, n (%)	
	Pimobendan	Benazepril	Pimobendan	Benazepril		Pimobendan	Benazepril	Pimobendan	Benazepril	Pimobendan	Benazepril
1	108	111	7 (6.5)	14 (12.6)	.26	4 (3.7)	8 (7.2)	3 (2.8)	5 (4.5)	0 (0)	1 (0.9)
3	94	75	12 (12.8)	6 (8.0)	.45	7 (7.4)	3 (4.0)	3 (3.2)	2 (2.7)	2 (2.1)	1 (1.3)
6	70	50	9 (12.9)	13 (26.0)	.09	7 (10.0)	7 (14.0)	2 (2.9)	2 (4.0)	0 (0)	4 (8.0)
9	52	34	6 (11.5)	3 (8.8)	1.00	4 (7.7)	2 (5.9)	2 (3.8)	0 (0)	0 (0)	1 (2.9)
12	37	25	6 (16.2)	5 (20.0)	.74	3 (8.1)	4 (16.0)	3 (8.1)	1 (4.0)	0 (0)	0 (0)
15	25	19	4 (16.0)	2 (10.5)	.68	3 (12.0)	1 (5.3)	0 (0)	1 (5.3)	1 (4.0)	0 (0)
18	16	17	0 (0)	0 (0)	1.00	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

AF, atrial fibrillation; SVPC, supraventricular premature complex; VPC, ventricular premature complex.
The *P* value represents a comparison of the proportions of dogs in each treatment group with a new onset of an arrhythmia at each time point.

considered the most important outcome in symptomatic people with heart failure even surpassing quantity of life.[20] Comparatively little work has evaluated the assessment of QoL in veterinary cardiac patients or addressed the importance of preservation of QoL in the face of terminal disease. A recent study demonstrated that owners of dogs with heart disease place a high value on preservation of QoL and, in fact, most of these owners valued preservation of QoL over survival.[6]

The area under the curve approach used in this report is, in this setting, a novel method to deal with missing data and variable periods of follow-up. This technique has been used previously for the analysis of longitudinal data in veterinary studies.[21] The summary statistic (area under the curve) was used to compare QoL and other indices between treatment groups. This technique has the advantage that data from every visit of every dog for which longitudinal measurements are available can be included and yet it reduces the values of the variable over multiple observations to a single index. It does not require comparisons between groups at multiple time points (repeated measures analysis), a technique with statistical limitations.[17] Finally, it does not require the carrying forward of any data for dogs that have already reached the primary endpoint, a technique which may bias the outcome when there is an unequal rate of removal from the study.[22]

In studies in which determination of the effect of a drug on QoL is a primary aim, it is necessary to maintain background treatment at a constant level to identify differences between groups as a consequence of the drug being studied.[23] In long-term studies, it is not ethically acceptable to deny modification in background treatment to patients, particularly those that are doing poorly. It has been argued that intensification of treatment represents evidence of a patient's condition worsening.[24] Recognition of this fact has been employed in developing a composite index of a patient's overall experience in heart failure trials in humans referred to as the "Patient Journey."[24,25] This index was used in the COMET trial and patients in whom treatment was intensified were considered to score 1 rank worse than those in whom intensification was not required.[25]

We examined the necessity for intensification of concurrent treatment in patients in the QUEST study by looking at the time to intensification of treatment and the frequency of use of common concurrent medications. We presumed that the reason an investigator decided to increase the dosage of one or more of the baseline therapies or to add another agent was because he or she believed the dog would benefit from the change because of a deterioration in the condition of the dog or the owner being concerned that their pet was failing to achieve an adequate QoL on their current treatment regimen.

Thus, although the average values for QoL variables were found to be similar in the 2 treatment groups over the duration of the study, dogs in the benazepril group required intensification of treatment earlier to maintain their QoL. The intensification of heart failure

Table 5. Number and proportion of all dogs in the 2 treatment groups that underwent intensification of heart failure treatment and the number and proportion of those dogs that underwent a change, that experienced the 4 most common changes. Notice that dogs could experience an intensification of heart failure treatment consisting of more than one change.

	Pimobendan (%)	Benazepril (%)	*P* Value
Change in treatment	83/124 (67)	89/128 (70)	.69
Nature of 1st treatment change			
Increased furosemide dose	71/83 (86)	77/89 (87)	1.0
Added spironolactone	43/83 (52)	55/89 (62)	.21
Indicated desire to increase ACE-inhibitor dose[a]	20/83 (24)	31/89 (35)	.14
Added digoxin	16/83 (19)	23/89 (26)	.36

[a]A desire to increase the ACE-inhibitor dose, without any other changes to the medication, occurred in 4 dogs in the benazepril group and 2 dogs in the pimobendan group.

treatment could consist of more than 1 change in the medication. Among several possible changes in medication in this study, the investigators had the opportunity to indicate that an increase in benazepril dosage was desired, and this was considered an intensification of the treatment. Because dogs in the pimobendan group could not receive this intensification of treatment, this potentially could be a confounder in this study. However, only 6 dogs (4 in the benazepril and 2 in the pimobendan group) had an intended increase in benazepril dosage as the only intensification. All other dogs had a change (intensification) in more than 1 drug. Furthermore, the significant difference in time to intensification persisted after having ignored a desire to increase benazepril dosage as an intensification of heart failure treatment. The similarity of QoL in the 2 groups is therefore probably a consequence of investigators being at liberty to modify medication to maintain an acceptable QoL for their patients. As we have already shown, the administration of pimobendan was associated with a prolongation of survival[5] and this analysis suggests that dogs receiving pimobendan have a longer life of a similar quality. We also can conclude that this prolongation of survival was achieved without the need for more intensive treatment. In fact, it appears that dogs in the benazepril group required alteration of their treatment sooner and more frequent administration of other medications (eg, spironolactone, digoxin) to maintain the same QoL. We consider this finding clinically relevant because one of the goals of treating any condition (and especially CHF) in view of maintaining a good QoL is to do so with the fewest number of different drugs necessary. Polypharmacy has the potential to decrease owner compliance, increases the risk of accidental dosage errors and omission of drug administration by the owner, and increases the total cost of treatment.

In addition to the QoL indices, we also compared clinical, radiographic, echocardiographic, and laboratory variables between the groups of dogs in our study using the area under the curve statistic. We found that 7 variables differed significantly between the pimobendan and benazepril groups over the duration of the study. One was rectal temperature, 3 were indicators of heart size (VHS, LVIDs inc, and LVIDd inc) and 3 were blood constituents (TPC, PCV, and serum sodium concentration). Rectal temperature previously has been shown in Doberman Pinschers with heart failure secondary to dilated cardiomyopathy to be an independent predictor of outcome.[26] In human heart failure patients, low body temperature at time of hospital admission[27] and decreasing body temperature over time[28] both are predictors of poor outcome. The median values of rectal temperature were within the normal reference range for dogs in both treatment groups with a difference of 0.1°C. Although this difference between treatment groups was statistically significant ($P = .030$), it is too small a change to be of clinical value in monitoring individual patients. It has been speculated that lower body temperature may be a result of lower cardiac output,[26] and the small difference between our treatment groups may have been because of improved perfusion in the pimobendan group.

Differences in heart size between groups of dogs treated with pimobendan and dogs receiving an ACE-I have been demonstrated previously.[9,29] Several mechanisms could be responsible for changes in heart size. The reduction in vascular resistance and enhancement of cardiac contractility achieved with an inodilator may allow the heart to contract down to a smaller end-systolic diameter and maintain an adequate stroke volume with a lower end-diastolic diameter. A larger ventricular diameter will be directly associated with an increase in systolic wall stress and worse secondary mitral regurgitation, and may therefore be associated with worse outcome.[30,31]

Three of the variables that differed significantly between groups were blood constituents: TPC, PCV, and serum sodium concentration. Over the period of time that dogs spent in the study, the median values for these variables differed by only a relatively small amount and neither group had a median value outside the reference range, but median values were consistently lower in the benazepril group (1.6 mmol/L lower sodium concentration, 1.2% lower PCV, and 0.2 g/dL lower TPC; $P = .0027$, $P = .0299$, and $P = .0003$, respectively). Although these differences between treatment groups were statistically significant, they are too small to be of clinical value in monitoring individual

Table 6. Total number of dogs in each treatment group remaining in the study, and number and proportion of dogs in each treatment group receiving spironolactone, digoxin, or both over time in 252 dogs.

	Dogs Remaining in Study		Dogs Receiving Spironolactone			Dogs Receiving Digoxin		
Time of Examination	Pimobendan	Benazepril	Pimobendan, n (%)	Benazepril, n (%)	*P* Value for Comparison	Pimobendan, n (%)	Benazepril, n (%)	*P* Value for Comparison
Day 1	124	128	21 (16.9)	26 (20.3)	.52	19 (15.3)	28 (21.9)	.20
Day 7	119	124	20 (16.8)	33 (26.6)	.087	17 (14.3)	32 (25.8)	.037
Day 28	108	115	21 (19.4)	39 (33.9)	.016	17 (15.7)	33 (28.7)	.025
3 months	95	81	26 (27.4)	37 (45.7)	.018	15 (15.8)	25 (30.9)	.020
6 months	72	48	21 (29.2)	28 (58.3)	.0023	13 (18.1)	17 (35.4)	.052
9 months	52	34	19 (36.5)	16 (47.1)	.37	11 (21.2)	8 (23.5)	.80
12 months	39	25	16 (41.0)	12 (48.0)	.61	12 (30.8)	8 (32.0)	1.0
15 months	27	19	12 (44.4)	10 (52.6)	.77	8 (29.6)	4 (21.1)	.72
18 months	19	17	9 (47.4)	10 (58.8)	.53	6 (31.6)	4 (23.5)	.72

The *P* values represent a comparison of the proportions of dogs in each treatment group receiving spironolactone, digoxin, or both at each time point.

Fig 1. Kaplan–Meier plot of percentage dogs with no intensification of heart failure therapy as a function of time in 124 dogs treated with pimobendan and in 128 dogs treated with benazepril. Dogs receiving pimobendan had a significantly longer time period (median, 98 days; IQR, 30–276 days) before experiencing any intensification in their treatment compared to those receiving benazepril (median, 59 days; IQR, 11–121 days; $P = 0.0005$).

patients. These differences, however, are unlikely to be caused by hemoconcentration in the pimobendan group because the furosemide dosage and serum creatinine concentrations were similar in the treatment groups. Hyponatraemia,[32] hypoalbuminemia,[33] and anemia[34] all have been shown to be independent predictors of poor outcome in human heart failure patients, although this has not been demonstrated in veterinary patients.

There are multiple factors that can lead to alterations in PCV and TPC in heart failure, including hemodilution, malnutrition, and chronic inflammation.[33,34] In the absence of unmeasured osmoles (eg, glucose), the most likely reason for a decrease in serum sodium concentration is an excess of free water retention (or failure of free water clearance), which occurs either in the presence of sodium depletion or in isolation.[35] The combination of higher serum sodium concentration, plasma proteins, and PCV in dogs receiving pimobendan suggests that there may be decreased free water retention or improved free water excretion associated with the administration of this agent in comparison with the administration of benazepril. Increasing serum sodium concentrations have been shown to indicate a more favorable prognosis in hospitalized human heart failure patients.[36,37] To our knowledge, ours is the 1st veterinary study showing differences in PCV, TPC, and serum sodium concentrations arising from differences in the administration of standard heart failure therapies.

Our electrocardiographic findings suggest that the pimobendan and benazepril groups had a similar frequency of onset of new arrhythmias. This finding indicates that neither treatment was associated with an

increased likelihood of development of arrhythmia in dogs with advanced MMVD.

Limitations

As with the original report,[5] the principal limitation is the single-blinded nature of the study. Owners were aware of the medication used on their pets, whereas the investigators were not. The risk with a single-blinded design is that the unblinded party (the owner) may influence the outcome based on some preconceived or acquired sense that one treatment may be superior to the other. QoL variables are inherently subjective and so it is possible that this design may affect these variables more than objective variables.

The area under the curve statistic uses 1 value for the variable measured over multiple time points. However, the time points were not equally distributed in time. Thus, variations in values in the first 30 days could have more influence on the summary statistic than later observations.

The method of acquiring the QoL data used in this study has not been analyzed with respect to validity, reliability, and responsiveness as a metric tool. The use of the FETCH questionnaire[38] may have enabled the detection of more subtle differences between treatment groups. However, this particular instrument was not available at the time the QUEST study was designed and has yet to be fully evaluated in the setting of a large clinical trial.

Conclusions

Pimobendan plus conventional treatment compared with benazepril plus conventional treatment resulted in similar QoL during the study, but conferred an increased time before intensification of heart failure treatment was deemed necessary, leading to a lower proportion of dogs receiving additional treatments at certain time points. Pimobendan treatment also was associated with a smaller heart size, higher body temperature, and less tendency to retain free water, as indicated by certain laboratory variables. There was no difference in arrhythmia incidence between treatment groups.

Footnotes

[a] Vetmedin; Boehringer Ingelheim Vetmedica, Ingelheim, Germany
[b] Fortekor; Novartis Animal Health, Basel, Switzerland
[c] Dr Martin Vanselow; Biometrie & Statistik, Hannover, Germany
[d] SAS Version 8.2; SAS Institute Inc., Cary, NC

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