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Effect of Pimobendan or Benazepril Hydrochloride on Survival Times in Dogs with Congestive Heart Failure Caused by Naturally Occurring Myxomatous Mitral Valve Disease: The QUEST Study

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Background: Myxomatous mitral valve disease (MMVD) continues to be an important cause of morbidity and mortality in geriatric dogs despite conventional therapy.

Hypothesis: Pimobendan in addition to conventional therapy will extend time to sudden cardiac death, euthanasia for cardiac reasons, or treatment failure when compared with conventional therapy plus benazepril in dogs with congestive heart failure (CHF) attributable to MMVD.

Animals: Two hundred and sixty client-owned dogs in CHF caused by MMVD were recruited from 28 centers in Europe, Canada, and Australia.

Methods: A prospective single-blinded study with dogs randomized to PO receive pimobendan (0.4–0.6 mg/kg/d) or benazepril hydrochloride (0.25–1.0 mg/kg/d). The primary endpoint was a composite of cardiac death, euthanized for heart failure, or treatment failure.

Results: Eight dogs were excluded from analysis. One hundred and twenty-four dogs were randomized to pimobendan and 128 to benazepril. One hundred and ninety dogs reached the primary endpoint; the median time was 188 days (267 days for pimobendan, 140 days for benazepril hazard ratio = 0.688, 95% confidence limits [CL] = 0.516–0.916, $P = .0099$). The benefit of pimobendan persisted after adjusting for all baseline variables. A longer time to reach the endpoint was also associated with being a Cavalier King Charles Spaniel, requiring a lower furosemide dose, and having a higher creatinine concentration. Increases in several indicators of cardiac enlargement (left atrial to aortic root ratio, vertebral heart scale, and percentage increase in left ventricular internal diameter in systole) were associated with a shorter time to endpoint, as was a worse tolerance for exercise.

Conclusions and Clinical Importance: Pimobendan plus conventional therapy prolongs time to sudden death, euthanasia for cardiac reasons, or treatment failure in dogs with CHF caused by MMVD compared with benazepril plus conventional therapy.

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

Mitral regurgitation secondary to myxomatous degeneration of the mitral valve apparatus is the most common cause of heart failure in dogs.[1] Myxomatous mitral valve disease (MMVD) is typically a progressive disease characterized by a prolonged period during which affected animals demonstrate no outward clinical signs. In 1 study of Cavalier King Charles Spaniels (CKCS), the median period of time from diagnosis of disease to the onset of signs of congestive heart failure (CHF) was more than 3 years.[2] The median time to the development of heart failure was similarly greater than 2 years in dogs with MMVD not in heart failure, but with

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evidence of cardiac remodeling.[3] Thus, MMVD is a relatively benign condition in some dogs.[4] Those dogs with a more slowly progressive course of their disease can succumb to another disease before demonstrating any signs of ill health attributable to their valvular heart disease. However, animals that develop signs of CHF secondary to valvular heart disease have signs that are usually progressive, with the majority of animals dying within a year of the development of clinical signs.[5,6]

Treatment of dogs with CHF secondary to MMVD typically consists of diuretics and additional agents. When compared with placebo, the use of angiotensin converting enzyme inhibitors (ACEI) is associated with a significant prolongation of the time to death or withdrawal from the study in dogs with CHF caused by MMVD.[5,6]

More recently, the use of pimobendan in conjunction with or in place of an ACE inhibitor has been associated with an improvement in both clinical signs and quality of life,[7] and some measures of outcome.[8] The VetSCOPE study[8] suggested that outcome was better for dogs receiving pimobendan than for those not receiving pimobendan.

Because of the continuing controversy surrounding the optimal treatment for dogs with heart failure secondary to MMVD, we aimed to conduct a prospective, randomized, blinded study to compare the outcome of 2 groups of dogs with heart failure secondary to MMVD: 1 group would receive pimobendan and the other would receive benazepril hydrochloride. The study was designed to test the hypothesis that the group receiving pimobendan would have an improved outcome compared with the group receiving benazepril.

The aim of the trial was to assess the effect of pimobendan therapy on time to sudden cardiac death or time to euthanasia because of progressive heart disease or treatment failure in comparison with a positive control (benazepril hydrochloride) in dogs diagnosed as suffering from CHF attributable to MMVD.

Materials and Methods

Dogs

Client-owned dogs were recruited at 28 centers in Europe, Canada, and Australia (1 in Australia, 2 in Canada, 1 in Denmark, 1 in Finland, 1 in France, 5 in Germany, 3 in Italy, 1 in Norway, 4 in Sweden, 2 in Switzerland, and 7 in the United Kingdom) between October 2003 and February 2006. The dogs consisted of both first-opinion and second-opinion (referred) cases. The study was terminated on 31 October 2006.

Enrolment Criteria

Inclusion Criteria. Dogs were eligible for inclusion in the study provided that the owner had given informed consent.

To be eligible for inclusion at the time of the 1st examination, the dog must have been older than 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 and/or left ventricular enlargement, ie, left atrial to aortic root (LA/Ao) ratio >1.5[9] and LV values above normal reference range,[10] and demonstrated current or prior radiographic evidence of pulmonary edema and cardiomegaly (vertebral heart scale [VHS] > 10.5).[11] 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 significant cardiac disease (congenital or acquired) other than mitral regurgitation secondary to MMVD, or had another clinically significant systemic disease, or had evidence of other significant organ dysfunction such as liver disease, renal disease (azotemia considered by individual investigators to be prerenal in origin was not considered a reason for exclusion), or gastrointestinal disease that could interfere with drug absorption. Dogs with tricuspid insufficiency attributable to myxomatous valve disease were included if there was concurrent MMVD where the latter was judged to be the major contributor to the presenting signs.

Study Design

With the exception of the maintenance of a complete correspondence record, the study was conducted according to Good Clinical Practice. The contract between the sponsor and investigators stipulated that the latter have full access to all results and the right to independently publish, regardless of trial outcome.

Randomization and Allocation

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

Block randomization[12] was used with a 1 : 1 allocation ratio to maintain similar sample sizes in both treatment groups. The study numbers were grouped into blocks of 20, and each study number within a block was randomly assigned to a treatment group (benazepril or pimobendan) by computer software.[a] Once a treatment had been assigned to 10 cases within a 20-case block, the remaining cases within that block were assigned to the alternative treatment group, to maintain the 1 : 1 allocation. Each investigator was assigned 10 consecutive study numbers. When an investigator subsequently recruited a new case, that case was assigned the next available study number that had been allocated to the investigator, along with the randomly preassigned treatment. This ensured that each investigator did not know how many cases assigned to each treatment were under their care. After initiation of recruitment, some case numbers were reallocated between investigators, but the maximum number of cases enrolled at any 1 center was 17. 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

The trial was designed as a single blinded study. In each center the blinding of the investigator was ensured by the use of a dispenser. The owner was supplied with treatment by the dispenser, who was made aware of the treatment allocation on a case-by-case basis. At inclusion and before each visit, the owner was instructed to discuss test treatments with the dispenser only. The investigator managed all other concomitant treatments by filling in a drug receipt form for the dispenser. Drugs were dispensed by the dispenser

in opaque boxes to prevent inadvertent disclosure of the treatment group to the investigator.

Test Treatments

Both treatments were administered according to the manufacturer's recommendations.

The pimobendan group received pimobendan[b] PO at a dose of 0.4–0.6 mg/kg/d. The calculated daily dose was divided in two 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[c] PO at a dose of 0.25–0.5 mg/kg once a day. In keeping with the manufacturer's recommendations, at the discretion of the investigator, the 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 dose was adjusted to a suitable number of 5 mg tablets.

Concomitant Treatments

Standard concomitant therapy 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 inhibitor was precluded as was the use of phenylalkylamine calcium channel antagonists, xanthines, or angiotensin II receptor antagonists. In the cases where dogs were already receiving an ACE-inhibitor or pimobendan therapy at inclusion, these drugs were discontinued immediately before allocation to either of the 2 test treatments. Doses of concomitant treatments could be modified, if needed, throughout the study.

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 a physical examination, electrocardiography (ECG), echocardiography, thoracic radiography, and routine hematology and blood biochemistry with a minimal database consisting of PCV and total protein, 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 occasion dogs were examined, the following occurred: a case history was obtained, a complete physical examination performed, a 3-minute ECG recorded, and blood was taken to measure creatinine, protein, sodium, and potassium concentrations. Echocardiography and thoracic radiographic examinations were scheduled every 6 months after inclusion. At the discretion of the investigator, additional testing and visits were permissible.

Clinical Evaluation

At inclusion, dog characteristics such as breed, age, sex, and neutering status were recorded. The time since onset of clinical signs and the duration, type, and efficacy of any pretreatment were recorded. At each examination the 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:

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 lethargic
	3	Moderately lethargic
	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 [2]	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.

appetite, demeanor, exercise tolerance, coughing, and nocturnal dyspnea.

Circulatory Variables

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. For the purposes of the multivariate analysis, dogs were simply classified as having either sinus rhythm or an arrhythmia.

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 2D view as previously described.[9] The left ventricular internal diameter in diastole (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.[13] 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 were calculated according to the following method: expected normal LVIDd = $1.53 \times (BW)^{0.294}$; expected normal LVIDs = $0.95 \times (BW)^{0.315}$.[10]

Thoracic Radiography

Thoracic radiography was used to confirm the presence of cardiomegaly and pulmonary edema, to exclude concurrent disease at inclusion into study, and to measure cardiac dimensions. Right lateral and dorso-ventral projections were used to evaluate the thorax. Cardiomegaly was assessed with the VHS method[11] and the presence of pulmonary edema 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).[2]

Endpoint

Dogs were considered to have reached the primary endpoint of the study 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. This composite primary endpoint was defined at the time of writing the protocol. Where the dog died spontaneously or was euthanized, the investigator specified whether they considered the cause of death to be cardiac or noncardiac. In cases where the cause of death was considered noncardiac, the reason for death or euthanasia was noted. Treatment failure was defined as one or more of the following: persistent dyspnea, progressive ascites, severe cardiac cachexia, or severe exercise intolerance (attributable to a cardiac cause), despite receiving or failing to tolerate a diuretic dosage of furosemide (12 mg/kg daily PO) and spironolactone (6 mg/kg daily PO) in addition to other concomitant medications and the test drug.

Outcome Measure

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

Data Management

All clinical and dispenser records were collected from the centers after the termination of the study, and data were tabulated and verified. The accuracy of this was confirmed by 2 investigators (J.H. and A.B.) randomly checking 10% of the original data. The error rate of data entry was found to be $<0.1\%$ on the basis of this sample. Blinding was maintained during data entry and data audit. Decisions on censoring and exclusions from the study were taken before unblinding of the investigators. Unblinding took place only once the database was locked and sent to an independent statistician.[d]

Statistical Analysis

Power calculations were based on data from previous studies available at that time: the BENCH study[5] and the PITCH study.[e] Assuming a similar overall event rate and median survival time in the reference population (benazepril group), it was estimated that a study population of 100–120 dogs would be required in each treatment group to provide a power of approximately 80% to demonstrate a 50% difference in median times to the primary endpoint between the treatment groups. To compensate for possible drop-outs, a sample size of 130 dogs was decided for each group.

Each of the variables obtained at enrollment was assessed for significant difference between treatment groups. All continuous baseline variables were compared by a Wilcoxon's signed-rank test to compare groups. For categorical data, a χ^2 or Fisher's exact test was used. No adjustment was made for multiple comparisons.

A log-rank test with right censoring was used to determine whether a significant difference existed between the 2 treatment groups, and the Kaplan-Meier method was used to estimate the median time to endpoint for each treatment group and plot time to event curves.

Univariate Cox proportional hazards analysis with right-censoring performed for each variable to determine whether any baseline variable was associated with time to endpoint and the hazard ratio (HR) and 95% confidence limits (CL) were calculated.

Multivariate Cox proportional hazard analyses were performed in a backward stepwise manner. The analyses started with treatment group and all the other 33 baseline variables from the univariate analysis included in the model. The variable with the highest P-value was eliminated at each step, with reanalysis between steps, until the final model was obtained. Two separate multivariable analyses were performed: one in which the final model was reached when all remaining variables had a P-value $< .1$ and one in which the final model was reached when all the remaining variables had a P-value $< .05$. All variables were assessed only as main effects; no interaction terms were considered in modeling.

For all analyses except the multivariate Cox proportional hazard analysis (as outlined above), a P-value $< .05$ was considered significant. All analyses were two-tailed. Median values and interquartile ranges (IQR) are reported. Statistical analyses were performed with a commercially available software program.[f]

Results

Baseline Data

Two hundred and sixty dogs were recruited. Eight dogs were excluded from further analysis after the termination of the trial; 4 dogs because of violation of inclusion criteria (1 dog had a body weight < 5 kg, 1 dog had 3rd degree AV block, 2 dogs had never demonstrated signs of CHF), 2 dogs had treatment gaps extending more than 10% of the overall treatment time

for that particular dog, 1 dog received out of date test drug, and 1 dog failed to adhere to the schedule for reexaminations by more than 90 days. Of the remaining 252 dogs (116 males, 38 females, 37 neutered males, and 61 neutered females), the most commonly recruited breeds were CKCS (n = 82), Dachshunds (n = 44), Poodles (n = 9), Yorkshire Terriers (n = 9) and Jack Russell Terriers (n = 7). Twenty-six other breeds with 1–5 dogs each were also represented, and there were 50 mixed breed dogs. The median age at inclusion was 10.0 years (IQR 9.0–12.0 years) (range 5.5–17 years). The median body weight was 9.2 kg (IQR 7.4–11.4 kg) (range 5.0–20.0 kg). The dogs had demonstrated clinical signs for a median of 30 days (IQR 15–150 days) before inclusion, and 221 (88%) had received heart failure therapy before inclusion for a median of 60 days (IQR 8–240 days) (Table 2). One hundred and twenty-four dogs were allocated to the pimobendan group and 128 to the benazepril group. The dogs in the pimobendan group were treated with pimobendan at a median dose of 0.47 mg/kg/d (IQR 0.43–0.50) and the dogs in the benazepril group with benazepril at a median dose of 0.38 mg/kg/d (IQR 0.29–0.46). At baseline, the LVIDs was larger in the benazepril group (24.3 versus 22.0 mm, $P = .02$) (Table 2). The distribution of all other baseline variables was not significantly different between the 2 treatment groups.

Table 2. Summary of baseline characteristics in the 2 treatment groups (frequencies or medians [interquartile range]). Bold P-value numerals indicate statistical significance.

		Treatment Groups		
	Variable	Pimobendan	Benazepril	*P*-Value
Dog characteristics	Age (years)	10.0 (8.0–11.0)	10.0 (8.0–12.0)	.06
	Sex (M/F/MC/FC) (%)	59/14/24/27 (48/11/19/22%)	57/24/13/34 (44/19/10/27%)	.08
	Cavalier (yes/no) (%)	34/90 (27/73%)	48/80 (38/62%)	.09
Duration of clinical signs and pretrial treatment	Duration of clinical signs (days)	30.0 (15–120)	33.8 (15–150)	.60
	Pretrial treatment (yes/no) (%)	113/11 (91/9%)	108/20 (84/16%)	.13
	Duration of pretrial-treatment (days)	60 (7–165)	60 (7–334)	.22
	ACEI pretrial treatment (yes/no)[a]	70/54 (56/44%)	68/60 (53/47%)	.61
	Pimobendan pretrial treatment (yes/no) (%)[a]	6/118 (5/95%)	15/113 (12/88%)	.07
	Other pretrial treatment (yes/no) (%)	39/85 (31/69%)	31/97 (24/76%)	.21
Treatment at day 1 (in addition to pimobendan or benazepril)	Furosemide dose (mg/kg/day)	4.7 (3.4–6.7)	4.4 (3.0–6.4)	.43
	Digoxin (yes/no) (%)	16/108 (13/87%)	27/101 (21/79%)	.10
	Spironolactone (yes/no) (%)	21/103 (17/83%)	24/104 (19/81%)	.74
	Amlodipine (yes/no) (%)	0/124 (0/100%)	1/127 (1/99%)	1.00
Quality of life and respiratory variables (see Table 1 for levels)	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/ECG	Arrhythmia (yes/no) (%)	26/98 (21/79%)	18/110 (14/86%)	.15
	VHS score	12.5 (11.5–13.0)	12.5 (12.0–13.5)	.15
	PE (yes/no) (%)	111/13 (90/10%)	112/16 (88/12%)	.69
	Severity of PE (score 1–5)	2.5 (1.0–5.0)	3.0 (1.0–5.0)	.65
	LVIDs (mm)	22.0 (19.0–26.7)	24.3 (20.8–28.4)	**.02**
	LVIDs inc. (%)	19.7 (4.0–37.0)	24.5 (10.7–43.4)	.08
	LVIDd (mm)	41.5 (36.7–46.0)	42.9 (38.8–47.9)	.06
	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

[a]Eight dogs received a combination of ACEI and pimobendan.

M, male; F, female; MC, neutered male; FC, neutered female; ACEI, angiotensin-converting enzyme inhibitor; BPM, beats per minute; HF, heart failure, VHS, vertebral heart scale; PE, pulmonary edema; LVIDs, left ventricular internal diameter in systole; LVIDd, left ventricular internal diameter in diastole; LVIDs inc., percentage increase in LVIDs from expected values; 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.

Overall Outcome

Of the 252 included dogs, 190 (75%) dogs reached the primary endpoint: 68 (27%) died spontaneously of cardiac causes, 75 (30%) were euthanized for cardiac reasons, and 47 (19%) reached the treatment failure endpoint. The median time to reach the primary endpoint for all dogs in the study was 188 days (IQR 87–470 days). Sixty-two dogs (25%) were censored (Table 3): 5 (2%) dogs died spontaneously and 19 (7.5%) dogs were euthanized for noncardiac reasons, 25 (9.9%) dogs were alive at the termination of the trial, and 13 (5%) were removed from the study for various reasons (Table 3).

Effect of Therapy on Outcome

The proportion of dogs reaching the primary endpoint in the pimobendan group (88/124, 71%) was not different from the proportion reaching the endpoint in the benazepril group (102/128, 80%) ($P = .143$). The proportion of dogs dying for cardiac reasons was similar between the 2 groups (pimobendan 34/124, 27.4% versus benazepril 34/128, 26.5%; $P = .938$). There was no significant difference in the number of dogs in the 2 groups euthanized for cardiac reasons (pimobendan 34/124, 27.4% versus benazepril 41/128, 32.0%; $P = .491$), nor was there for dogs reaching the treatment failure endpoint (pimobendan 20/124, 16.0% versus benazepril 27/128, 21.0%; $P = .335$). The proportion of dogs censored in the pimobendan group (36/124, 29%) was not different from the proportion censored in the benazepril group (26/128, 20%) ($P = .143$). The reasons for the censoring in the 2 groups are listed in Table 3.

Table 3. Reasons for censoring of 62 dogs.

		Treatment Groups	
		Pimobendan	Benazepril
Spontaneous death (noncardiac)	Total	5	0
	Neoplasia	2	0
	Acute bronchopneumonia	1	0
	Neurologic disease	1	0
	Unknown	1	0
Euthanasia (noncardiac)	Total	11	8
	Neoplasia	4	1
	Renal failure	4	2
	Pyometra	0	2
	Arthrosis, vomiting, severe dental problems, owner's wish	0	1
	Behavioral problems	1	0
	Diabetes mellitus	0	1
	Hyperadrenocorticism	1	0
	Neurologic signs	1	0
	Trauma	0	1
Noncompliance	Total	6	7
	Owner noncompliance	4	5
	Removal by investigator[a]	2	2
Alive at the end of the study	Total	14	11
	Total	36	26

[a]The investigator determined that an illness, injury, complication, or adverse reaction to test article prohibited the animal from completing the study.

The median time to reach the primary endpoint was significantly greater in the pimobendan group (267 days, IQR 122–523 days) compared with the benazepril group (140 days, IQR 67–311 days) ($P = .0099$) (Fig 1).

Sub-Analyses of Primary Endpoint. The difference between groups remained significant if deaths related to a noncardiac cause were reclassified as cardiac related deaths ($P = .0260$), or if noncardiac deaths and euthanasia owing to a noncardiac cause were reclassified as cardiac related ($P = .0279$). The effect of treatment group on median time to reach each of the 3 individual outcomes for only those dogs that reached each outcome is summarized in Table 4. The median time that censored dogs had remained in the study at the time of censoring is shown in Table 5.

Potential Adverse Events Not Leading to Withdrawal. Both treatments appeared to be well tolerated, as indicated by a comparably low number of reported potential adverse side events not leading to withdrawal (Table 6).

Univariate Cox Proportional Hazard Analyses of the Effect of Treatment and Baseline Variables. The univariate analysis of treatment and of each of the 33 baseline variables assessed individually demonstrated that the pimobendan treated dogs had a significant risk reduction for reaching the composite endpoint when compared with the benazepril treated dogs (HR = 0.688; $P = .0105$; 95% CL = 0.516–0.916) (Fig 2). In this population, in addition to receiving pimobendan of the remaining 33 baseline variables, 12 variables were significantly associated with outcome when analyzed

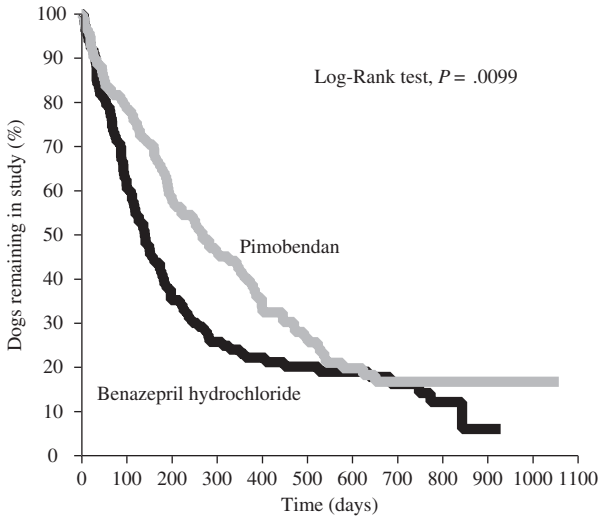

Fig 1. Kaplan-Meier plot of percentage of dogs in the study as a function of time in 124 dogs treated with pimobendan and in 128 dogs treated with benazepril. The pimobendan dogs had a significantly longer median time period in the study compared with the benazepril treated dogs (pimobendan 267 days, IQR 122–523 days versus benazepril 140 days, IQR 67–311 days; $P = .0099$). IQR, interquartile range.

Table 4. Comparison between treatment groups (censored dogs excluded) for the median time (interquartile range) to reach the endpoint for each of the individual endpoints, which were combined to create the composite primary endpoint of the study.

Endpoints	Median Time to Endpoint (days)		Log-Rank *P*-Value Fisher's Exact Test *P*-value
	Pimobendan	Benazepril	
All endpoints	189 (85–353) n = 88	111 (54–197) n = 102	.0251 .143
Cardiac death	122 (44–197) n = 34	87 (32–150) n = 34	.410 .938
Euthanasia for cardiac reasons	190 (68–387) n = 34	126 (69–197) n = 41	.128 .491
Time to treatment failure	268 (183–372) n = 20	118 (63–257) n = 27	.086 .335

The log-rank test was used to compare the survival times and Fisher's exact test to compare the percentage of dogs reaching each endpoint.

Table 6. Potential adverse events (not leading to withdrawal) in 252 dogs with MMVD.

Observed Adverse Events	Pimobendan	Benazepril
Gastrointestinal disorders (eg, vomiting, diarrhea, anorexia)	6	4
Abnormal behavior (eg, lethargy, confusion, uneasiness)	3	4
Tachycardia (supra or ventricular or both)	1	1
Seizure	3	—
Polyuria, polydipsia, incontinence	1	2
Dyspnea (intermittent)	1	2
Hepatic enzyme elevation	2	—
Syncope	1	1
Keratoconjunctivitis	—	1
Otitis externa	—	1
Purulent local dermatitis	—	1
Total	18	17

MMVD, myxomatous mitral valve disease.

independently. Improved outcome was associated with, having a lower heart rate ($P < .0001$), having a lower heart failure score ($P = .0027$), and being a CKCS ($P = .0264$). Worse outcome was associated with a greater VHS score ($P < .0001$), a greater LA/Ao ratio ($P < .0001$), a larger or greater increase in left ventricular internal diameter in systole (LVIDs, $P < .0001$, LVIDs inc., $P < .0001$) and left ventricular internal diameter in diastole (LVIDd, $P < .0001$, LVIDd inc., $P < .0001$), a higher pulmonary edema score ($P = .0011$), a greater increase in respiratory effort ($P = .0144$), and a worse tolerance for exercise ($P = .0118$).

Multivariate Cox Proportional Hazard Analyses of the Effect of Treatment and Baseline Variables. In the multivariate analyses, after controlling for the effect of 33 other variables measured at baseline, pimobendan therapy continued to confer a significant risk reduction for reaching the primary endpoint compared with benazepril therapy (HR = 0.630; $P = .0057$; 95% CL = 0.454–0.874). Seven other baseline variables had a significant effect on the risk for reaching the primary endpoint: those having a beneficial effect were being a CKCS ($P = .0006$) and having a higher creatinine concentration ($P = .0260$); those having a detrimental effect were having a higher VHS score ($P = .0063$), a greater LA/Ao ratio ($P = .0065$), having greater intolerance of exercise ($P = .0146$), a higher LVIDs inc. ($P = .0195$) and receiving a higher daily furosemide dose ($P = .0253$) (Fig 3).

Discussion

This study offers the most compelling evidence to date demonstrating the beneficial effect of pimobendan when compared with benazepril for extending survival in dogs with CHF caused by MMVD when used in conjunction with other standard therapy. The median time to reach a composite endpoint for the dogs treated with pimobendan was almost twice as great as for dogs treated with benazepril (267 versus 140 days respectively). This repre-

Table 5. Comparison between treatment groups (dogs reaching the endpoint excluded) for the median time (interquartile range) to censoring for each censored group.

Reason for Censoring	Median Time to Censoring (days)		Log-Rank *P*-Value Fisher's Exact Test *P*-Value
	Pimobendan	Benazepril	
All censored	352 (172–733) n = 36	513 (159–708) n = 26	.509 .143
Death noncardiac	257 (215–583) n = 5	NA, n = 0	NA .0277
Euthanasia for noncardiac reasons	298 (142–487) n = 11	680 (354–821) n = 8	.261 .481
Owner noncompliance	91 (2–175) n = 6	28 (14–159) n = 7	.607 1.00
Still alive	742 (554–1015) n = 14	645 (421–729) n = 11	.055 .531

The log-rank test was used to compare the survival times and Fisher's exact test to compare the percentage of dogs reaching each endpoint.
NA; not applicable.

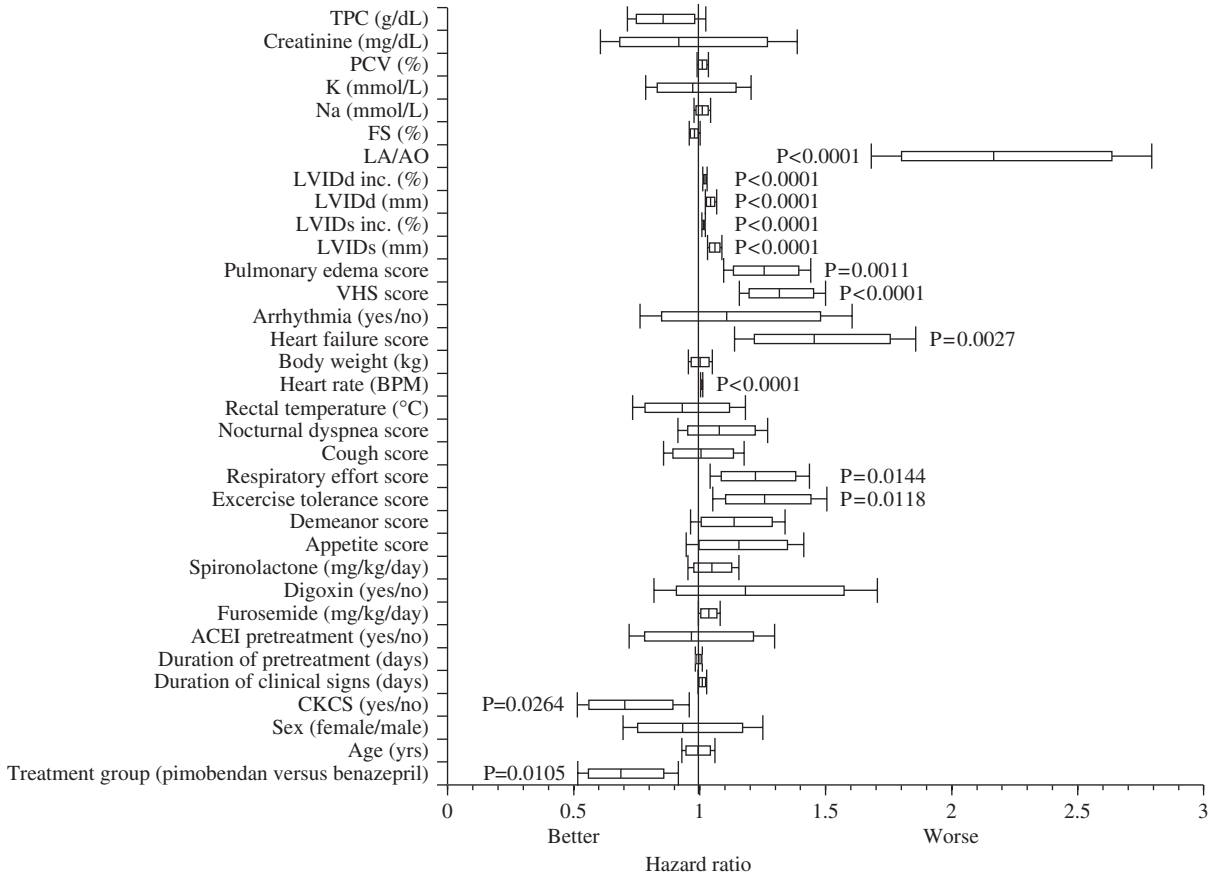

Fig 2. Hazard ratios (HR) and 95% confidence limits obtained from the univariate Cox proportional hazard analysis, including treatment allocation and 33 possible confounding baseline variables in 252 dogs. Variables associated with a reduction in HR were pimobendan treatment and the breed Cavalier King Charles Spaniels (CKCS). Variables associated with an increased HR included worse exercise tolerance score, worse respiratory effort score, increased heart rate, increased heart failure class, VHS score, increased pulmonary edema score, increased LVIDs measurement (LVIDs and LVIDs inc.), increased LVIDd measurement (LVIDd and LVIDd inc.), and increased LA/Ao ratio. Abbreviations, see Table 2 for key.

sented a 32% relative risk reduction of reaching the composite endpoint for the pimobendan group. This study also demonstrated that the benefit of pimobendan persisted after adjusting for all baseline variables. In addition to the use of pimobendan, other baseline variables associated with a reduced risk of reaching the composite endpoint were being a CKCS, receiving a lower dose of furosemide, and having a higher creatinine concentration. Additionally, a number of baseline variables were associated with an increased risk of reaching the composite endpoint; these were several indices of cardiac enlargement and poorer exercise tolerance.

Although the primary endpoint in our study was a composite of 3 possible outcomes, we would argue this is a genuine reflection of survival in this population, and therefore conclusions about the effect of therapy on survival can be drawn. Two of the 3 outcomes resulted in the death of the dog (spontaneous death and euthanasia for cardiac reasons). The 3rd component of our composite endpoint was treatment failure. Although this latter endpoint lacks the incontrovertible nature of death we had to include it for ethical reasons. Treatment failure, as outlined above, was a predefined endpoint in the study that necessitated the dog having clinical signs of heart failure refractory to maximal diuresis or failure to tolerate a maximal dose of diuretics while remaining on treatments stipulated in the protocol. The only reason an investigator would consider that a dog had reached this endpoint was that they felt the dog would not survive without receiving further treatment that was precluded within the protocol. This would suggest that at this point dogs had advanced and poorly controlled disease as well as clinical signs of heart failure and that although this is a surrogate for the dog dying, a dog would reach this end point only if it was close to death as a consequence of their progressive disease.

This study contains both the largest sample of dogs involved in a prospective veterinary cardiovascular study and the highest event rate in a study sample (75%). Previous investigations that assessed the merits of therapy for CHF caused by MMVD offered a limited analysis of the amount of benefit experienced by dogs in the treatment group. The LIVE Study failed to assess the risk reduction associated with the use of enalapril.[6] The BENCH study performed a limited multivariable analysis (few covariates assessed) and demonstrated risk

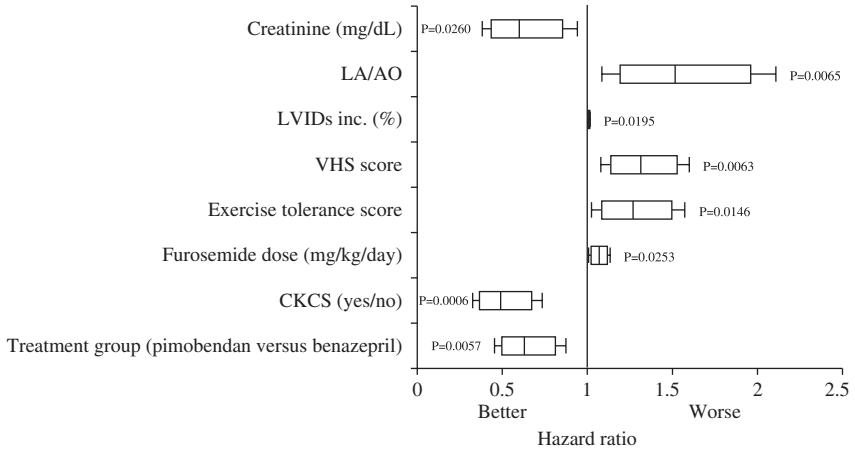

Fig 3. Hazard ratios (HR) and 95% confidence limits obtained from the final model of the backward multivariate Cox proportional hazard analysis, including treatment allocation and all 33 baseline variables from the univariate analysis in 252 dogs. Factors associated with a reduction in HR included pimobendan treatment, the breed Cavalier King Charles Spaniels, and increased serum creatinine concentrations. Variables associated with an increased HR included higher increased daily furosemide dose, worse exercise tolerance score, higher increased VHS score, LVIDs inc. and LA/Ao ratio. LA/Ao, left atrial to aortic root ratio; LVIDs, left ventricular internal diameter in systole; LVIDd, left ventricular internal diameter in diastole; inc., increase; VHS, vertebral heart scale.

reduction of 51%.[5] The more recent VetSCOPE study also failed to assess the risk reduction associated with the use of pimobendan.[8] The study by Smith et al. demonstrated that the likelihood (odds ratio) of dogs receiving pimobendan developing an adverse heart failure outcome was 25% of those receiving the ACEI ramipril.[7,14] This is different from the HR we obtained in our study, and one cannot be compared with the other. The current study offers the most extensive analysis of covariates. It demonstrated that the benefit of pimobendan persisted after adjusting for multiple signalment, historical, clinical, and therapeutic covariates.

The relative benefit of treatment can be quantified by use of the median survival times or by using HRs. HRs derived from the Cox proportional hazard model do not provide time to event information. However, to quantify the treatment benefit in time, the ratio between the median times in the study is calculated, and in this study that ratio was 267 days (pimobendan)/140 days (benazepril) = 1.91, which indicates that the median time in the pimobendan group was prolonged by 91% of that in the benazepril group. The HR is equivalent to the odds that an individual in the group reaches the endpoint first. The odds of reaching the endpoint first can be calculated as follows (HR/[1 + HR]) = 0.688/(1 + 0.688) = 0.41.[15] This indicates that dogs in the pimobendan group had a 41% chance of reaching the endpoint first; conversely dogs in the benazepril group had a 59% chance of reaching the endpoint first. Similar odds were obtained using the HR from the multivariate Cox proportional hazard model (39%). We therefore believe that the differences demonstrated in this study are of genuine clinical importance as well as being statistically significantly different.

The duration of clinical signs of heart failure at the time of enrollment was shorter than the duration of therapy with heart failure medication. This occurred because of the use of ACEI before the onset of clinical signs of heart failure despite the lack of evidence of efficacy of this class of drug at this stage in the course of MMVD.[2,3] In addition, prior studies demonstrated very high censor rates, with at least 50% of the dogs censored in these studies.[2,3,5–8] In the present study, only 25% of the dogs were censored. Finally, the restriction of enrollment to dogs of body weight between 5 and 20 kg promoted a high degree of disease homogeneity within the study sample.

The categorization of the endpoint as ''death caused by noncardiac disease'' or ''euthanized for noncardiac disease'' can be subjective in cohorts of cases such as in this study. Presumably with both of these endpoints death occurs because of the combination of cardiac causes and noncardiac causes. Therefore, in an attempt to assess whether the categorization of dogs as censored or noncensored for the death endpoints could have contributed to the outcome in favor of pimobendan, the data were reanalyzed. When all death endpoints were reclassified as noncensored and censoring remained for all other endpoints as described in the Materials and Methods, time to endpoint continued to be significantly longer for the pimobendan dogs. Subgroup analysis was performed for the noncensored dogs that reached each of the individual endpoints that contributed to the primary combined endpoint (Table 4). For each of these subgroups, there was no significant difference in the median time to endpoint for the pimobendan dogs versus the benazepril dogs. The significant difference in outcome obtained in the final analysis is because of a significant effect observed when all 3 outcomes are combined to create the predefined composite primary endpoint rather than an overwhelming effect on any one of these endpoints with a neutral or detrimental effect on the others. This suggests that the effect of pimobendan is not restricted to only one of these outcomes. The study was not designed, and therefore was not adequately powered, to demonstrate significant differences between the

groups for these 3 individual endpoints. The only difference between groups in analyses of the median time to a censored endpoint and frequency of reaching a censored endpoint was the significantly greater number of dogs that died of a noncardiac cause in the pimobendan group (Table 5). The median time to endpoint for all censored dogs was not different between treatment groups ($P = .509$). More dogs in the pimobendan group were censored (not significant) in this study. This may be an effect of the greater period of time these dogs spent in the study. The median time to composite primary endpoint was 91% longer in the pimobendan dogs. If the risk of reaching a censored endpoint was constant in this population of aged dogs, then the longer dogs spent in the study, the more likely they would be to reach such an endpoint. Thus one would expect a proportionately greater number of pimobendan dogs to reach a censored outcome. Alternatively one could speculate that the explanation is that the increased number of noncardiac deaths in the pimobendan group could be related to an unmeasured noncardiac beneficial effect of benazepril, an unmeasured detrimental noncardiac effect of pimobendan, or both, although we consider this quite unlikely.

As indicated previously, this study assessed an extensive number of covariates in the multivariate Cox proportional hazards analysis. Previous studies were limited in their ability to employ these methods because of the low number of noncensored dogs (known as the event rate) in each treatment group. The strength of the multivariate analysis is the ability to adjust for the effect of baseline variables on the outcome, ie, Is one treatment superior to the other after one accounts for the effect of these variables? Thus, where differences exist between baseline variables in spite of randomization, as in the case of LVIDs, the multivariate Cox proportional hazards analysis enables one to determine whether there is an effect of treatment after accounting (adjusting) for the effect of this difference. The difference in LVIDs that existed at baseline did not alter the significant effect of pimobendan on the outcome. Furthermore, variables that are not different at baseline or in the univariate analysis can still have an effect on outcome, as demonstrated by the variable creatinine, when these variables are analyzed in the multivariate analysis. Therefore, where previous studies compared treatment groups by way of a univariate analysis (log-rank test), they relied on comparing baseline variables in an effort to determine that the 2 treatment groups were "not different" at the start of the trial. When no difference existed between these baseline variables, investigators would conclude that potential confounders could not have affected the outcome. This approach is flawed, and potential confounders can be screened from the study only by performing multivariate analyses. It is also for this reason that a statistical adjustment for the effect of the multiple comparisons undertaken with the baseline variables (Table 2) was not performed. Whether there was or was not a statistical difference in the baseline variables between treatment groups, using whatever statistical methodology, is not relevant when one is able to use a multivariate analysis to account for the effect of these variables as performed in the present study.

In addition to treatment with pimobendan, 7 other baseline variables were found to have a significant favorable effect on survival in the multivariate Cox proportional hazard model. These were being a CKCS, receiving a lower daily furosemide dose, and having better exercise tolerance, a lower VHS score, a lower LA/Ao ratio, a lower LVIDs inc., and a higher serum creatinine concentration. Some of these factors have already been shown to affect long-term prognosis, such as heart size (LA/Ao and VHS).[4] The percentage increase over expected LVID values (LVIDs inc.) could also reflect the disease severity, because increased LVIDs indicates a reduced systolic function as previously described.[16] This LV dysfunction is presumably secondary to the chronic volume overload, and it is known to develop with progressing heart failure in mitral valve disease.[16] Reduced systolic function has been shown to confer a worse prognosis in human patients with mitral regurgitation.[17] The required maintenance dose of furosemide might also reflect disease severity because the more severe the disease, the more furosemide is needed to alleviate the signs of pulmonary congestion and edema. Exercise tolerance is well known to be associated with severity of heart failure. In our dogs, lower serum creatinine concentrations were associated with a worse outcome, which was an unexpected finding. Heart failure is associated with the development of prerenal azotemia[18] and creatinine concentrations are known to become increased in particular after initiation of furosemide therapy as a consequence of contracted extracellular fluid compartment.[19,20] It might be expected that higher maintenance doses of furosemide would be necessary in dogs with more advanced disease, leading to an increased creatinine concentration being associated with a poorer prognosis. In human patients, the presence of concurrent renal insufficiency confers a worse prognosis in patients with heart failure.[21] However, in our analysis, the effect of furosemide and disease severity is already accounted for by other variables in the multivariate model. It is, however, possible that more aggressive use of treatment was not entirely accounted for in the multivariate model using dose of furosemide alone, and this may underlie the apparently improved outcome associated with a higher creatinine concentration. An alternative explanation for the detrimental effect of a lower creatinine concentration may be the existence of cardiac cachexia. Total plasma creatinine is intrinsically linked to striated muscle mass in dogs.[22] In the presence of an increased plasma volume (heart failure) and with a decreased muscle mass (cardiac cachexia), a decreased concentration of creatinine might be expected. Dogs with significant concurrent disease were excluded from this study, including those with pre-existing renal disease. Unfortunately, we did not obtain body condition scores from our dogs and therefore are unable to further establish any possible association between cardiac cachexia and creatinine concentration.

Finally, although it has been shown before that breed can influence the onset of mitral valve disease[23,24] and death/euthanasia owing to heart failure,[25] this is the first

time, to our knowledge, that breed has been shown to affect the outcome after the onset of heart failure. The favorable effect on outcome conferred by being a CKCS was an unexpected effect for which we do not have an adequate explanation. This observation seems to contradict previous anecdotal evidence suggesting a worse outcome for this breed. We cannot discount the effect of confounding factors unaccounted for by our model leading to this apparent effect, although it was observed in both the univariate and multivariate analyses. The study was not designed to evaluate the effect of breed on outcome, and we were not able to examine the effect of breeds other than CKCS on survival because of inadequate sample sizes.

Limitations

The most important limitation is that this was a single-blinded study. The owners were aware of the medication used on their pets, whereas the investigators were not. To maintain blinding of the investigator, an intermediate (the dispenser) was used to interface with the owner concerning all issues relative to the administration of the investigational drugs. The use of a single-blinded design runs the risk that the unblinded party (the owner) may have influenced the outcomes based on some preconceived or acquired sense that 1 agent was superior to the other.

It would have been preferable to conduct a study that enrolled thousands of cases, as we note in the human trials, to enable a comparison of the individual endpoints of death caused by progressive heart failure and euthanasia for refractory heart failure. However, in smaller studies such as the current study and previous veterinary clinical trials, there is a need to utilize combined endpoints to increase the event rate for comparisons. The combined endpoint that we used was defined before the inception of the study and was the basis of the power calculation we undertook.

Defining cause of death or euthanasia as cardiac or noncardiac in an aging population is problematic because of inevitable comorbidity. We attempted to address the impact of censoring for dogs with a death endpoint by assessing the impact of categorizing all death endpoints as noncensored. The relatively low frequency of censoring and the similar numbers of censored dogs for death outcomes between treatment groups may have reduced the impact of the problem of categorizing dogs as censored or noncensored.

Treatment failure was used as a surrogate for survival in 20 pimobendan and 27 benazepril dogs (Table 4). It remains to be validated that this is a good surrogate for survival, however; our reasons for believing this to be a valid and necessary inclusion are outlined above.

This study enrolled a higher percentage of CKCS and Dachshunds than previous large clinical trials. Whether the current distribution of breeds with MMVD confers a different outcome as compared with the distributions noted in previous studies is unknown. The enrolled population is representative of the dogs presented to veterinarians with heart failure secondary to MMVD in the countries in which the study was conducted, and therefore the conclusions drawn from this study should allow us to predict the expected effect in treating this population.

This study fails to address the potential benefit of the combined therapy of pimobendan and an ACEI such as benazepril on survival in dogs with CHF caused by MMVD. It also fails to examine the utility of pimobendan as compared with benazepril in dogs under 5 kg or more than 20 kg with CHF because of MMVD.

Finally, although a comparably large set of potential confounders was controlled for in the present study, it is possible that the results could have been systematically influenced by unmeasured variables. However, the strength of prospective randomized trials is that they minimize the influence of unmeasured variables.

Conclusions

This study provides compelling evidence that treatment of small to medium-sized dogs, between 5 and 20 kg body weight, suffering from CHF secondary to MMVD with pimobendan in combination with standard therapy lengthens time to death, euthanasia, or treatment failure compared with treatment with benazepril plus standard therapy. This benefit persists after adjusting for the effect of covariates.

Further studies are required to address the impact of combined pimobendan and ACEI therapy and to address the importance of pimobendan in large breed dogs with CHF secondary to MMVD.

Footnotes

[a] ClinPro software, Clinical Systems, Garden City, NY
[b] Vetmedin, Boehringer Ingelheim Vetmedicia GmbH, Ingelheim/Rhein, Germany
[c] Fortekor, Novartis Animal Health Inc., Basel, Switzerland
[d] Dr Martin Vanselow, Biometrie & Statistik, Hannover, Germany
[e] Lombard CW. Clinical experience with pimobendan. Proceedings of the Veterinary Cardiovascular Society, Birmingham, UK, 2001
[f] SAS Version 8.2; SAS Institute Inc, Cary, NC

Acknowledgments

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