Clinical Efficacy of Pimobendan Versus Benazepril for the Treatment of Acquired Atrioventricular Valvular Disease in Dogs

Seventy-six dogs with clinical acquired atrioventricular valvular disease were evaluated to determine the efficacy of pimobendan (n=41) versus benazepril hydrochloride (n=35) in a randomized, positive-controlled, multicenter study. The study was divided into 56-day and long-term evaluation periods. In a subgroup of dogs with concurrent furosemide treatment (pimobendan [n=31], benazepril [n=25]), the Heart Insufficiency Score improved in favor of pimobendan (*P*=0.0011), equating to a superior overall efficacy rating (*P*<0.0001) at day 56. Long-term median survival (i.e., death or treatment failure) for dogs receiving pimobendan was 415 days versus 128 days for dogs not on pimobendan (*P*=0.0022). **J Am Anim Hosp Assoc 2006;42:249-261.**

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Introduction

Atrioventricular (myxomatous) valvular disease is the most common acquired canine cardiac disease, with mitral valvular insufficiency predominating.[1-3] Atrioventricular valvular disease is slowly progressive, resulting in a prolonged asymptomatic or preclinical phase (International Small Animal Cardiac Health Council [ISACHC] Class Ia and Ib); however, once valvular disease progresses to overt clinical signs of heart failure (ISACHC ≥ II), therapeutic intervention is indicated. Therapeutic goals for treating heart failure from atrioventricular valvular disease are to mitigate the consequences of volume overload (preload and afterload reduction), to reduce cardiac workload, and to retard volume overload-mediated cardiac remodeling that, while beneficial in the short term, has negative implications for long-term cardiac function.[4] For treated dogs, long-term prognosis is predicated on response to treatment, the occurrence of cardiac complications (e.g., cardiac arrhythmias, cardiac tamponade secondary to atrial rupture, fulminant pulmonary edema from chordae tendineae rupture), and the occurrence of other illnesses (e.g., concurrent respiratory disease, renal failure, hyperadrenocorticism, etc.).

Data to date have defined a role for the use of diuretics (e.g., furosemide), hydralazine, and angiotensin-converting enzyme (ACE) inhibitors in symptomatic, but not asymptomatic (i.e., occult or preclinical) canine atrioventricular valvular disease.[5-10] Use of such agents results in improvements in both quality and quantity of life through reductions in preload, afterload, and cardiac workload; however, recent data derived from experimental canine heart failure models of atrioventricular valvular insufficiency have failed to identify improvements in cardiac remodeling with ACE-inhibitor use and have raised concern that ACE-inhibitors may limit long-term survival because of their negative impact on myocardial protein metabolism and myocardial function.[11,12] Additionally, new data have countered the long-held belief that myocardial systolic function remains adequate until advanced or late-stage

atrioventricular valvular disease, based on the findings of reduced pulmonary transit times that indicate reduced systolic/myocardial function even in early disease states.[13] As a result, various other pharmaceuticals are being investigated in an effort to improve both the quality of life and long-term prognosis of dogs with heart failure from atrioventricular valvular disease.

Pimobendan is a novel new cardiac pharmaceutical, termed an "inodilator" because it possesses both positive inotropic and balanced peripheral vasodilatation properties.[14] Unlike historical positive inotropes (e.g., digoxin, milrinone) that function by increasing intracellular calcium concentrations, resulting in increased cardiac energy and oxygen requirements, pimobendan acts as a positive inotrope principally by enhancing the affinity of myocardial troponin C to existing intracellular calcium.[15,16] The result is improved contractility without additional increased myocardial oxygen or energy requirements.[17] Peripherally, pimobendan is a phosphodiesterase III (PDE III) inhibitor, resulting in balanced peripheral vasodilatation through increased efflux of intracellular calcium from vascular smooth muscle.[14,18-20] Additional properties include reversal of desensitization of baroreceptors, improved cardiac relaxation (lusitropy), reduced platelet aggregation, and an anti-inflammatory effect mediated through favorable cytokine modulation.[21-24]

Based on pimobendan's pharmacodynamic profile, it appears to be ideally suited to the treatment of heart failure associated with atrioventricular valvular disease. Studies in Doberman pinschers with dilated cardiomyopathy (DCM) and in humans with heart failure have demonstrated improvement in quality and quantity of life when pimobendan was added to traditional (i.e., diuretic, ACE-inhibitor, and digoxin) therapy.[25-27] Preliminary data from dogs with overt, clinical heart failure from atrioventricular valvular disease support an early therapeutic role and an advantage of pimobendan over (or in addition to) ACE-inhibitor therapy.[28-31]

The primary goal of this study was to evaluate the efficacy of pimobendan, in comparison to benazepril hydrochloride, in improving the quality and quantity of life in dogs suffering from overt, clinical heart failure from atrioventricular valvular disease. In addition to evaluating efficacy, data were collected to evaluate product safety and any impact on radiographic and echocardiographic indices.

Materials and Methods

Study Animals and Design

Seventy-six, privately owned dogs with spontaneous atrioventricular valvular disease that were presented to one of 11 different veterinary centers in Europe (Belgium [n=2], France [n=4], Germany [n=1], Italy [n=2], and Switzerland [n=2]) were enrolled in the Veterinary Study for the Confirmation of Pimobendan in Canine Endocardiosis (VetSCOPE) between November 23, 2001 and July 16, 2003. Enrollment was restricted to dogs that were diagnosed with ISACHC Class II (i.e., mild to moderate heart failure; clinical signs of heart failure that are evident at rest or with mild exercise, which adversely affect quality of life) or ISACHC Class III heart failure (i.e., advanced heart failure; IIIa, outpatient care possible; IIIb, hospitalization required) from acquired mitral and/or tricuspid valvular disease.[32] All dogs had symptomatic heart failure as indicated by signalment, history, general physical examination, plain radiography, and echocardiography. In addition to an ISACHC Class II or greater designation, enrolled dogs also had evidence of reduced cardiac function as demonstrated by one or more of the following abnormalities: pulmonary edema and increased vertebral heart size (>10.5) on thoracic radiography, and ventricular dilatation, left atrial dilatation, and normal to reduced fractional shortening (FS) on echocardiography.[33]

Exclusion criteria included concomitant congenital heart disease, hypertrophic or DCM, ISACHC Class I heart failure (i.e., asymptomatic; Ia, no signs of compensation; Ib, signs of compensation [e.g., cardiac enlargement]), renal disease (serum creatinine concentration >2.5 mg/dL [220 µmol/L]), severe endocrine diseases (e.g., diabetes mellitus or insipidus, hyperadrenocorticism), pregnancy, and body weight >40 kg. The last criterion was used because primary atrioventricular valvular disease is unlikely in dogs >40 kg, and the weight restriction allowed for a more homogeneous study population.

The study was conducted as a blinded, randomized, positive-controlled (i.e., benazepril hydrochloride), multicenter study. The study had a mandatory 56-day treatment period (as dictated by the French regulatory authorities) that was followed by an optional long-term treatment period and was conducted in accordance with guidelines for Good Clinical Practice.[a]

The 56-Day Treatment Period

In the 56-day treatment period, dogs were allocated at random to receive either pimobendan[b] (0.2 to 0.3 mg/kg per os [PO] *q* 12 hours) or benazepril hydrochloride[c] (0.25 to 0.5 mg/kg PO *q* 24 hours). In order to allow complete blinding of the study, all dogs received two treatments: either pimobendan with placebo (pimobendan group) or benazepril hydrochloride with placebo (benazepril hydrochloride group).

The dogs were examined on days 0 (prior to first treatment), 7, and 56. The primary variable investigated at each follow-up examination was the Heart Insufficiency Score derived from the ISACHC classification of the stage of atrioventricular valvular disease. The ISACHC classification was based on a combination of history, physical examination, and the results of diagnostic tests as listed below. Secondary variables recorded were exercise tolerance, demeanor, appetite, respiratory effort, cough frequency, and nocturnal dyspnea. Data from electrocardiography (ECG), thoracic radiography (i.e., presence of pulmonary edema, vertebral heart size), and M-mode echocardiography (i.e., FS, left atrial to aortic root ratio [La:Ao], end-systolic volume index [ESVI; left ventricular internal dimension at systole normalized to body surface area], and end-diastolic volume index [EDVI; left ventricular internal dimension at

diastole normalized to body surface area]) were collected on all dogs prior to initiation of the study. A serum biochemical profile and ECG were required as part of the initial evaluation in order to ensure that all inclusion/exclusion criteria were met, but it was left up to the discretion of the individual investigator as to whether these tests were repeated at subsequent examinations. Echocardiography was repeated at days 7 and 56, and thoracic radiography was repeated at day 56. At the end of the 56-day treatment period, an overall clinical efficacy assessment was made for each dog. Variable assessment in each dog was consistently done by the same investigator.

Grading of the primary variable Heart Insufficiency Score was based on assigning a score of 1 for ISACHC Class Ia; 2 for Class Ib; 3 for Class II; 4 for Class IIIa; and 5 for Class IIIb. Grading of secondary variables was done based on owner assessments using a numerical scale [Table 1]. Vertebral heart size scoring used a published methodology, with a reference range of 8.5 to 10.5.[33] Pulmonary edema was graded as 1 for no pulmonary edema; 2 for mild interstitial density; 3 for moderate interstitial density; 4 for the presence of an alveolar pattern; and 5 for severe consolidation. Electrocardiography was performed with the dogs in right lateral recumbency, and a standard six-lead ECG tracing was obtained for analysis.

At the 56-day examination, the subjective overall clinical efficacy was scored using the following scoring system: 1 = very good, clinical signs greatly improved with treatment; 2 = good, clinical signs improved with treatment; 3 = partial response, clinical signs slightly improved with treatment; 4 = insufficient response, clinical signs remained the same; and 5 = therapy failure, clinical signs worsened. For cases that did not complete the 56-day period because of a cardiac-specific reason, the overall clinical efficacy was calculated as a therapy failure for the final visit. Individual dog scores for each primary, secondary, and overall efficacy variable at each evaluation time were used to derive a group mean ± standard deviation (SD) for that variable/time point and were used to determine any statistically significant group differences.

At the end of the study, the survival status of each dog was evaluated. For dogs confirmed to be alive at the date of the final study visit, this date was taken as the survival date. For dogs not confirmed by the investigators to still be alive, the date of the last examination of the dog during the optional period was taken as the survival date. Cases still alive were censored by the statistician.

Concomitant Treatment

During the 56-day treatment period, furosemide was allowed, with the dosage left to the discretion of the investigator. An antiarrhythmic agent was also allowed in dogs with severe arrhythmias. Treatments for other concurrent diseases (e.g., respiratory tract infection) were allowed and entered as part of the study data. The use of other ACE-inhibitors, digoxin, or other positive inotropic drugs was not permitted.

Long-Term Optional Treatment Period

At the end of the 56-day treatment period, owners of surviving dogs were given the option of entering their dogs into a long-term treatment trial. For dogs that entered the optional long-term study period, the treatment code (i.e., blinding) was broken. Any needed treatments could be added; however, dogs in the benazepril hydrochloride group received pimobendan only if treatment failure made such a combination necessary.

For estimating long-term survival, death and treatment failure were considered the end points. For the benazepril hydrochloride group, treatment failure was defined as progressive clinical signs (as defined by the secondary variables) refractory to treatment that necessitated the addition of pimobendan or removal from the study. For the pimobendan group, treatment failure was defined as progressive clinical signs (as defined by the secondary variables) refractory to all treatment. Comparisons were made between pimobendan-treated and nonpimobendan-treated groups on a background of traditional therapies (i.e., ± furosemide and ± benazepril) as deemed necessary by the attending clinician. Dogs removed from the study because of treatment failure were evaluated statistically as nonsurvivors, and the day of removal was used to calculate survival time.

During the two phases of the study, adverse drug reactions were recorded, and the death of any dog was followed by a complete postmortem examination.

Statistical Analysis

The entire dataset derived from the 76 dogs enrolled in the study was evaluated for the primary variable of the Heart Insufficiency Score, the secondary variable of overall efficacy, and the survival times during both the 56-day and optional long-term portions of the study. To eliminate the confounding influence of the furosemide therapy, statistical analysis was performed separately on the dataset derived from the subpopulation of 56 dogs that were also treated with furosemide. This subpopulation was evaluated for the primary variable of the Heart Insufficiency Score; the secondary variables of demeanor, exercise tolerance, respiratory effort, appetite, cough, nocturnal dyspnea, and overall efficacy; as well as for survival during both the 56-day and optional long-term portions of the study.

The pimobendan group was said to be noninferior if the lower bound of the one-sided 95% confidence interval for the Mann-Whitney statistic was higher than the threshold value corresponding to the lower limit of the equivalence range of 0.3. Corresponding threshold values were calculated using the normal distribution. In cases of proven noninferiority, the pimobendan group was tested for superiority to the benazepril group by the Wilcoxon's Mann-Whitney test. With respect to the secondary variables, the groups were compared using the two-sided *t*-test for normally distributed data, and in other cases, the two-sided Wilcoxon's Mann-Whitney test or Fisher's exact test was used.

For all parameters, original data as well as changes from baseline (day 0) were evaluated. Repeated measures

Table 1

Scoring Protocol for Secondary Variables During the 56-Day Study Period

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 effort
	3	Labored
	4	Respiratory distress
Coughing	1	None
	2	Occasional
	3	Frequent
	4	Persistent
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

analysis of variables with more than one treatment time was substituted by the worst case (maximum score) for scored variables and by the last measured value for other variables. Repeated measures analysis was confined to the subpopulation of 56 dogs on concurrent furosemide therapy. All tests on differences between groups with respect to the secondary variables were designed as two-sided tests. A P value of <0.05 was considered statistically significant. Survival curves were estimated according to Kaplan-Meier. Cases were censored if animals were still alive at the day 56 visit or if death or withdrawal did not occur from heart failure. The logrank test was performed for the comparison of the two treatment groups. The statistical analysis was performed using statistical software programs.[d,e]

Results

Study Animals

Overall, 76 dogs (pimobendan treatment group [n=41], benazepril hydrochloride treatment group [n=35]) representing 31 different breeds were enrolled in the study. All dogs had clinical signs of heart failure secondary to atrioventricular valvular disease. Mean (± SD) duration of signs was 4.05±8.37 months for the pimobendan group and 2.77±4.62 months for the benazepril group. No clinically relevant differences were noted between the groups prior to the initiation of therapy. In the initial serum biochemical profiles, a mild but statistically significant (P=0.0175) difference in serum chloride was found between the pimobendan (114.0±7.19 mmol/L; reference range 102.0 to 118.0 mmol/L) and benazepril hydrochloride (108.7±8.91 mmol/L) groups; however, all values were in the normal reference range and not considered to be clinically significant. Follow-up evaluations did not always occur on day 7 or 56, but ranged from day 6 to 8 and day 51 to 62, respectively.

Electrocardiography

Arrhythmias were demonstrated on the pretreatment ECGs in 11/41 (27%) dogs in the pimobendan group and in 10/35 (29%) dogs in the benazepril hydrochloride group. Sinus tachycardia (pimobendan [n=3], benazepril [n=5]) and atrial premature complexes (pimobendan [n=5], benazepril [n=5]) predominated, and ventricular premature complexes (VPCs) were found in three dogs in the pimobendan group and in one dog in the benazepril group. One dog in the benazepril group had both VPCs and atrial premature complexes. Only one of the arrhythmias required treatment beginning at day 0 (i.e., atrial fibrillation was treated with diltiazem in a dog from the benazepril group). This dog was subsequently classified as a treatment failure during the 56-day portion of the study. Follow-up ECGs were not performed on any other dogs.

The 56-Day Study Period

The primary variable, the Heart Insufficiency Score based on ISACHC heart failure classification, improved in 31/37 (84%) dogs treated with pimobendan compared with 15/27 (56%) dogs treated with benazepril (P=0.023; Fisher's exact test). At the day 56 evaluation, ISACHC classification Ib (score = 2; i.e., no clinical signs) was recorded for 28/37 (76%) dogs on pimobendan versus 13/27 (48%) dogs treated with benazepril. Differences between the groups were statistically significant in favor of pimobendan on both day 7 (P=0.0280) and day 56 (P=0.0201). At day 56, overall efficacy was rated as very good or good in 33/39 (85%) dogs on pimobendan versus 14/34 (41%) dogs treated with benazepril (P<0.0001).

Of the 41 dogs in the pimobendan group, four were removed from the study during the 56-day period. Two dogs were removed because of noncompliance by the owner; one was removed because of cardiac-related euthanasia; and one was removed from sudden death assessed as cardiac related. In the benazepril group, eight dogs were removed from the study during the 56-day period. Three dogs died suddenly (assessed as cardiac related); two were euthanized (one for a cardiac reason and one because of seizures); and three were assessed as treatment failures from deterioration of cardiac signs. Therefore, two dogs in the pimobendan group and seven in the benazepril group were defined as dead or euthanized from cardiac disease. Survival analysis according to Kaplan-Meier calculations revealed a significant difference in favor of pimobendan (P=0.0386).

Four dogs experienced adverse events related to drug administration—not from cardiac disease—during the 56-day study period. Three adverse events occurred in pimobendan-treated animals, and one occurred in the benazepril group. Diarrhea (n=1), soft stool (n=1), and vomiting (n=1) occurred in dogs from the pimobendan group, and colitis (n=1) occurred in a benazepril-treated dog. Of the three pimobendan-treated dogs reported with gastrointestinal signs, one dog also experienced tachypnea, weakness, and excitation; another dog developed restlessness. No necropsies were performed during the 56-day study period.

Optional Long-Term Study Period

All dogs alive at the end of the 56-day study period were entered into the optional long-term study, which included 37 dogs from the pimobendan group and 27 dogs from the benazepril group. At the time of study conclusion, 25 dogs remained from the pimobendan group and 13 remained from the benazepril group. Necropsies were performed in two dogs that were euthanized. One dog on benazepril therapy had a hepatic carcinoma. One dog on pimobendan had pulmonary edema and pneumonia associated with congestive heart failure. Median survival time for dogs treated with pimobendan was 430 days versus 228 days for dogs that received no pimobendan, with Kaplan-Meier analysis revealing significant differences in favor of pimobendan (P=0.0020).

Concomitant Therapy

Thirty-one pimobendan-treated dogs and 25 benazepril-treated dogs were on furosemide treatment at the time of enrollment in the study. All dogs not on furosemide at day 0 completed the 56-day study period without requiring the addition of furosemide. Additional therapeutics used to address the progression of heart failure during the long-term portion of this study included aminophylline (n=3); dextromethorphan-containing cough syrup (n=2) or terbutaline (n=3) for intractable coughing; hydralazine (n=1) or amlodipine (n=1) for additional afterload reduction; spironolactone (n=6) for additional diuretic support; digoxin (n=2) for acute pulmonary edema or atrial fibrillation; and carvedilol (n=1) for lack of improvement of cardiac signs.

Concurrent Furosemide Therapy

The subpopulation of dogs on concurrent furosemide therapy included 56 dogs (31 in the pimobendan group and 25 in the benazepril group) [Table 2]. All dogs had overt signs of heart failure secondary to atrioventricular valvular disease.

Table 2

Initial Clinical Data on 56 Dogs Treated Concurrently With Furosemide

Variable	Pimobendan	Benazepril	Total
Total no. dogs	31	25	56
Number of breeds*	17	17	31
Mean age (y ± SD†)	10.8±1.99	11.68±3.01	11.2±2.51
Mean body weight (kg ± SD)	9.95±6.26	12.14±8.36	10.93±7.28
Sex			
Male	18	13	31
Castrated male	4	3	7
Female	5	3	8
Spayed female	4	6	10
Duration of cardiac signs prior to study (mos ± SD)	2.83±4.70	2.86±5.36	2.84±4.95
Diagnosis of valvular insufficiency (no. and percent of dogs)			
Mitral	19 (61%)	12 (48%)	31 (55%)
Tricuspid	0 (0%)	0 (0%)	0 (0%)
Mitral and tricuspid	12 (39%)	13 (52%)	25 (45%)
Class of heart failure‡			
ISACHC II	23 (74%)	16 (64%)	39 (70%)
ISACHC IIIa	7 (23%)	8 (32%)	15 (27%)
ISACHC IIIb	1 (3%)	1 (4%)	2 (4%)
Vertebral heart size (mean ± SD)	12.1±1.2	12.0±1.1	12.1±1.2
Mean furosemide dosage (mean ± SD mg/kg per d)	2.92±1.24	3.32±1.14	3.10±1.20

* Different types of mixed-breed dogs were counted as one breed.
† SD=standard deviation
‡ ISACHC=International Small Animal Cardiac Health Council Score; see text for class definitions

Mean durations of signs prior to study enrollment were 2.83±4.7 months for the pimobendan group and 2.86±5.36 months for the benazepril group. No statistically significant differences were found between the groups prior to the initiation of therapy for any parameter (i.e., age, sex, weight, duration of clinical signs, or Heart Insufficiency Score) other than serum chloride (pimobendan group, mean 113.4±6.93 mmol/L; benazepril group, mean 107.0±9.60 mmol/L; *P*=0.0084). These findings were similar to those of the entire 56-day group and were considered clinically irrelevant.

The overall dose of furosemide decreased from day 0 (mean 2.92±1.24 mg/kg per day; n=31) to day 56 (mean 2.70±0.95 mg/kg per day; n=27) in the pimobendan group, with a mean change from baseline of -0.32±0.85 mg/kg per day. The overall dose of furosemide increased from day 0 (mean 3.32±1.14 mg/kg per day; n=25) to day 56 (mean 3.82±1.49 mg/kg per day; n=17) in the benazepril group, with a mean change from baseline of +0.50±1.40 mg/kg per day. While there were no statistical differences between the mean values of day 0 and day 56 (both intra- or intergroup),

the difference in the furosemide dose change from baseline between the pimobendan and benazepril groups was statistically significant (P=0.0498).

The primary variable (i.e., Heart Insufficiency Score based on ISACHC heart failure classification) was improved in 23/27 (85%) pimobendan/furosemide-treated dogs compared with 7/17 (41%) benazepril/furosemide-treated dogs at the end of the 56-day treatment period (P=0.0064; Fisher's exact test). At day 56, an ISACHC classification Ib (score = 2; i.e., no clinical signs) was reported for 20/27 (74%) dogs in the pimobendan/furosemide group versus 5/17 (29%) dogs in the benazepril/furosemide group (P=0.0053; Fisher's exact test). Differences between the groups for Heart Insufficiency Score were statistically significant in favor of pimobendan on day 7 (P=0.0367) and day 56 (P=0.0011) [Table 3].

At the 56-day evaluation, overall efficacy was rated as very good or good in 25/29 (86%) dogs treated with pimobendan versus 6/24 (25%) dogs treated with benazepril. Overall efficacy was significantly higher (P<0.0001) for the pimobendan/furosemide group (mean score 1.93±1.10; median 2.0; range 1 to 5) than the benazepril/furosemide group (mean score 3.42±1.28; median 3.0; range 1 to 5) [Figure 1].

Results for secondary variables supported the clinical results of the ISACHC heart failure classification. Statistically significant differences occurred at day 56 between the two treatment groups for exercise tolerance, demeanor, and respiratory effort [Table 4]. No statistically significant differences were found between the two groups at day 7 and day 56 for appetite, coughing, and nocturnal dyspnea. The same dogs that were withdrawn from the total study group were also part of the subpopulation of dogs on concurrent therapy with furosemide. Survival analysis according to Kaplan-Meier calculations revealed significantly prolonged survival in the pimobendan-treated dogs (P=0.0246) [Figure 2].

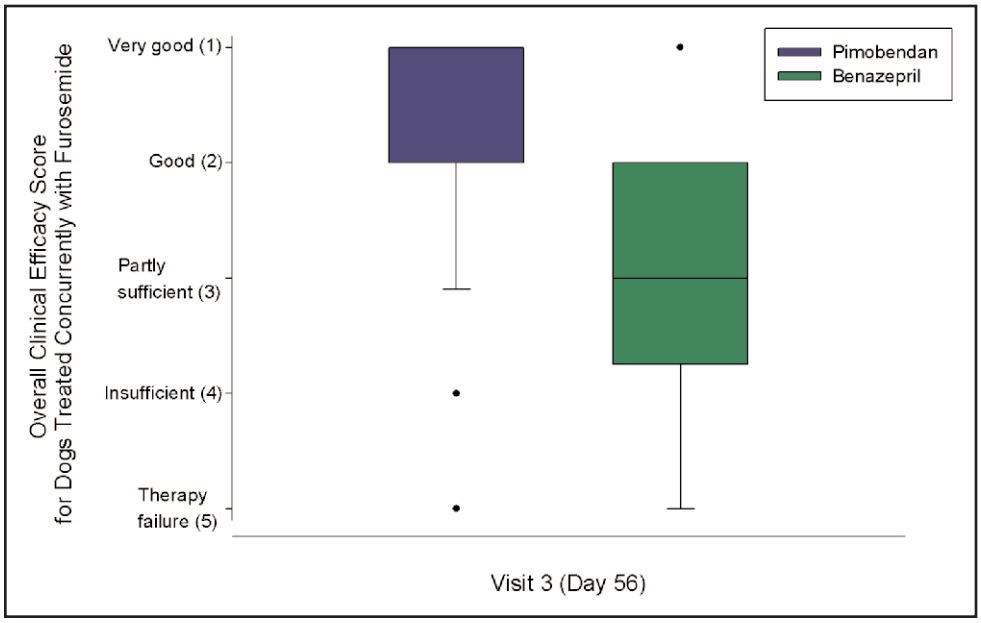

Figure 1—Box and whiskers plot illustrating the overall clinical efficacy assessment on day 56 in the subpopulation of 56 dogs on concurrent furosemide therapy. Box-plots include the median values, and the 10/90 percentiles are presented as whiskers. The points are single outliers. Efficacy was rated as very good or good in 86% of the pimobendan-treated cases versus 25% of the benazepril-treated cases (P<0.0001). On the Y-axis, the numbers in parentheses represent efficacy scores. These results indicate a statistical difference (P<0.0001) based on Wilcoxon's Mann-Whitney test.

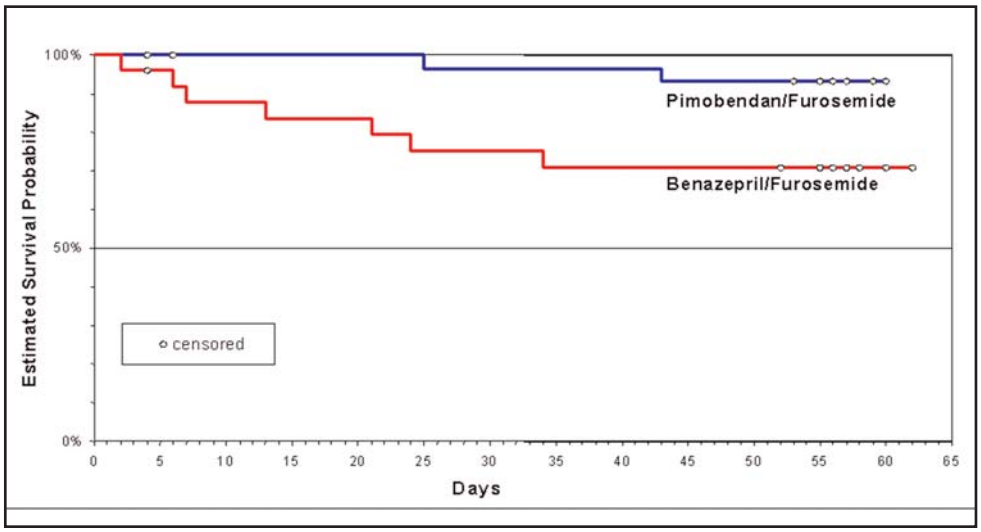

Figure 2—Kaplan-Meier estimate demonstrating the percentage of dogs from the subpopulation of 56 dogs on concurrent furosemide therapy that survived over time during the 56-day treatment period. The pimobendan treatment group had a significantly greater (P=0.0246) percentage of survival than the benazepril treatment group. Dogs were censored if they were still alive or if withdrawal from the study was not related to heart failure.

Table 3

Heart Insufficiency Score Based on ISACHC* Heart Disease Classification in the 56 Dogs on Concurrent Furosemide Therapy

Day	Treatment Group	No. Dogs	Heart Insufficiency Score*					Median	Mean Score ± SD†	*P* Value‡
			1 (Class Ia)	2 (Class Ib)	3 (Class II)	4 (Class IIIa)	5 (Class IIIb)			
0	Pimobendan	31	0 (0%)	0 (0%)	23 (74%)	7 (23%)	1 (3%)	3	3.29±0.5	0.5092
	Benazepril	25	0 (0%)	0 (0%)	16 (64%)	8 (32%)	1 (4%)	3	3.40±0.6	
7	Pimobendan	29	0 (0%)	16 (55%)	11 (38%)	1 (3%)	1 (3%)	2	2.71±0.9	0.0367
	Benazepril	22	0 (0%)	5 (23%)	16 (73%)	0 (0%)	1 (5%)	3	3.12±0.9	
56	Pimobendan	27	0 (0%)	20 (74%)	7 (26%)	0 (0%)	0 (0%)	2	2.61±1.0	0.0011
	Benazepril	17	0 (0%)	5 (29%)	10 (59%)	2 (12%)	0 (0%)	3	3.52±1.2	

* ISACHC=International Small Animal Cardiac Health Council Score[32]; no. dog (percentage)
† SD=standard deviation, means and standard deviations are based on repeated measures analysis
‡ *P* values represent differences between pimobendan and benazepril groups for each respective day, based on repeated measures analysis.

Table 4

Scores for Secondary Variables in the 56 Dogs on Concurrent Furosemide Therapy*

		Pimobendan Group (n=31)			Benazepril Group (n=25)			
Variable		**Mean**	**Median**	**Range**	**Mean**	**Median**	**Range**	***P* Value†**
Exercise tolerance	Day 0	2.45	3	1-4	2.68	3	1-4	0.4157
	Day 7	2.06	2	1-4	2.40	2	1-4	0.1657
	Day 56	1.87	2	1-4	2.60	2	1-4	0.0115‡
Demeanor	Day 0	1.71	1	1-4	2.16	2	1-4	0.0664
	Day 7	1.61	1	1-5	2.20	2	1-5	0.0858
	Day 56	1.61	1	1-5	2.64	2	1-5	0.0071‡
Appetite	Day 0	2.29	2	1-4	2.40	2	1-4	0.7156
	Day 7	2.19	2	1-4	2.48	2	1-4	0.3047
	Day 56	2.16	2	1-4	2.72	2	1-4	0.0544
Respiratory effort	Day 0	2.19	2	1-4	2.16	2	1-4	0.7993
	Day 7	1.61	1	1-4	2.00	2	1-4	0.1200
	Day 56	1.65	1	1-4	2.36	2	1-4	0.0168‡
Cough	Day 0	2.39	2	1-4	2.44	3	1-3	0.7039
	Day 7	1.94	2	1-4	2.32	2	1-4	0.0964
	Day 56	2.03	2	1-4	2.52	2	1-4	0.1389
Nocturnal dyspnea	Day 0	2.30	2	1-3	2.04	2	1-3	0.2738
	Day 7	1.65	1	1-3	1.76	1	1-3	0.6607
	Day 56	1.61	1	1-3	2.04	2	1-3	0.0773

* See Table 1 for definitions of scoring for each variable.
† *P* values represent differences between pimobendan and benazepril groups for each respective day, based on repeated measures analysis.
‡ Statistically significant

While no statistically significant differences between the two treatment groups were found regarding pulmonary edema, noticeable differences occurred in vertebral heart size. Compared to baseline values of vertebral heart size, a mean reduction in vertebral heart size was noted in the pimobendan/furosemide group (-0.13±0.64; range -1.9 to 0.8). In the benazepril/furosemide group, a slight increase in mean heart size was seen (0.36±0.58; range -0.5 to 1.5), which was similar to findings in dogs from the full study population. Differences in mean change from baseline for vertebral heart size between the two groups were statistically significant (*P*=0.0287). No statistical differences were identified between the treatment groups for mean FS, La:Ao, ESVI, and EDVI at day 0. Significant differences in favor of the pimobendan group were found for changes from baseline for FS at day 7 (*P*=0.0451), La:Ao at day 56 (*P*=0.0361), ESVI at day 7 (*P*=0.0022), and EDVI at day 7 (*P*=0.0023) and day 56 (*P*=0.0406) [Table 5].

Analysis of long-term survival data demonstrated a median survival time of 415 days for pimobendan-treated dogs versus 128 days for dogs that received no pimobendan, with Kaplan-Meier analysis revealing significant differences in favor of pimobendan (*P*=0.0022) [Figure 3; Table 6].

Discussion

Clinical correlates of pharmaceutical success in the management of heart failure secondary to atrioventricular valvular disease are improvements in the animal's quality and

Table 5

Echocardiographic Parameters in the 56 Dogs on Concurrent Furosemide Therapy

Variable	Day	Pimobendan Group (n=31)	Benazepril Group (n=25)	*P* Value*
Fractional shortening (%)				
Mean ± SD†	0	43.00±8.87	44.48±9.29	0.5458
Mean change vs. baseline ± SD	7	2.87±5.75	-0.12±4.98	0.0451‡
Mean change vs. baseline ± SD	56	1.81±5.37	-0.16±6.05	0.2033
Left atrial to aortic root ratio (La:Ao)				
Mean ± SD	0	2.269±0.581	2.174±0.409	0.7604
Mean change vs. baseline ± SD	7	-0.058±0.317	-0.011±0.259	0.1528
Mean change vs. baseline ± SD	56	-0.122±0.460	0.134±0.285	0.0361‡
End systolic volume index (mL/m^2)				
Mean ± SD	0	45.3±24.4	44.5±27.6	0.7920
Mean change vs. baseline ± SD	7	-8.4±14.4	4.6±18.7	0.0022‡
Mean change vs. baseline ± SD	56	-4.3±12.8	5.5±19.5	0.0503
End diastolic volume index (mL/m^2)				
Mean ± SD	0	171.3±57.7	169.5±71.0	0.6094
Mean change vs. baseline ± SD	7	-14.9±30.4	17.2±40.7	0.0023‡
Mean change vs. baseline ± SD	56	-6.1±34.9	18.3±35.4	0.0406‡

* *P* values represent differences between pimobendan and benazepril groups for each respective day, based on repeated measures analysis.
† SD=standard deviation
‡ Statistically significant

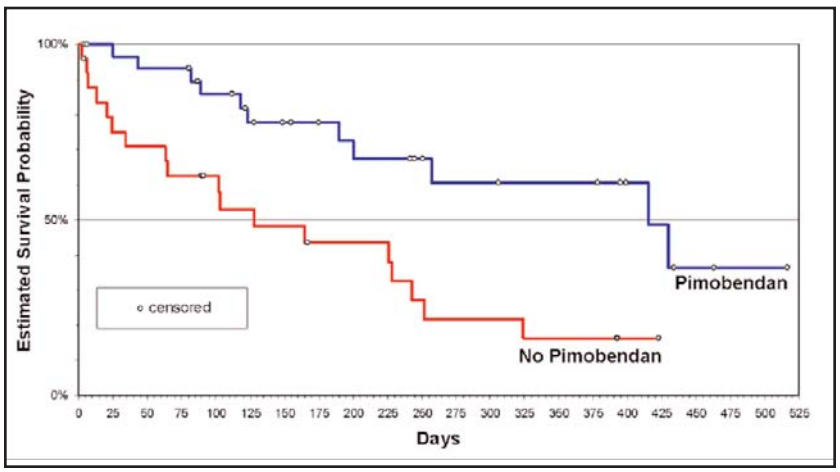

Figure 3—Kaplan-Meier estimate demonstrating the percentage of dogs from the subpopulation of 56 dogs on concurrent furosemide therapy surviving over time during the long-term treatment period. Dogs in the pimobendan treatment group had a significantly greater (*P*=0.0022) percentage of survival than dogs not receiving pimobendan, with median survival times being 415 and 128 days, respectively. Dogs were censored if they were still alive or if withdrawal from the study was not related to heart failure.

Table 6

Outcomes of the Long-Term Study Period for the 56 Dogs on Concurrent Furosemide Therapy

	Pimobendan Group No. Dogs (%)	Benazepril Group No. Dogs (%)
Total	27 (100%)	17 (100%)
Died from cardiac dysfunction	6 (22%)	4 (23.5%)
Euthanasia from cardiac dysfunction	3 (11%)	3 (18%)
Therapy failure	0 (0%)	4 (23.5%)
Alive	18 (67%)	6 (35%)

duration of life. The results of this study demonstrated that pimobendan, compared to benazepril hydrochloride therapy, provided statistically significant improvements in outcomes for dogs suffering from overt, clinical heart failure caused by atrioventricular valvular disease. For the primary variable of Heart Insufficiency Score, the secondary clinical study variables (i.e., exercise tolerance, demeanor, and respiratory effort), and for the day 56 overall efficacy evaluation, pimobendan demonstrated improvements from baseline that were statistically better than those of the benazepril group. At no time or for any variable measured, did the benazepril-treated group show an advantage over the pimobendan-treated group.

All three of these assessment modalities (ISACHC, secondary variables, and overall efficacy) are based on subjective improvements in clinical signs and directly relate to quality-of-life assessment; therefore, the findings of this study define that pimobendan provided a significant advantage over benazepril in improving quality of life in affected dogs. While subjective evaluations introduce inherent variability, the protocol employed in this study for evaluating clinical heart disease has been validated through other animal and human studies that evaluated the responses of various heart diseases to pharmaceutical intervention (e.g., ACE-inhibitors, pimobendan).[6,7,25,26,28,34] Although some prior studies have used the New York Heart Association heart disease classification scheme, both the ISACHC and New York heart classifications assess similar clinical parameters using similar clinical interpretations, with ISACHC taking into account the clinical nuances of heart disease in animals.[8,9,25,32]

Survival time, as defined (in this study) by either cardiac death or cardiac treatment failure, is a more objective assessment variable. In the study reported here, pimobendan-treated dogs had improved overall survival in both the 56-day and long-term study periods and higher median survival times during the long-term treatment period.

Explanations for these improvements are rooted in recent findings that atrioventricular valvular disease is complicated by systolic failure much earlier than previously believed.[13] The current therapeutic regime of using an ACE-inhibitor and/or a diuretic can heighten the activation and negative impact of neurohormonal compensatory mechanisms (via volume reduction and/or hypotension), and ACE-inhibitors have been implicated in negatively impacting myocardial function (by altering myocardial protein metabolism) or having their pharmacological effect mitigated by alternate compensatory mechanism pathways.[4,11,12]

Because of its unique inodilator pharmacological profile of acting as both a calcium sensitizer (resulting in energy-neutral increases in myocardial contractility) and a peripheral balanced vasodilator, pimobendan effectively addresses the need for preload and afterload reduction and provides inotropic support for systolic dysfunction. The end results are not only improvements in early signs of reduced cardiac output (e.g., demeanor, exercise tolerance) and backward failure (e.g., congestion), but also mitigation in the decline of cardiac output and blood pressure that initiate and perpetuate compensatory mechanisms.[19,20] In the current study, this was demonstrated in animals via both clinical (i.e., improvements in quality of life as evaluated by improvements in ISACHC classification) and diagnostic (i.e., reduction in vertebral heart size, ESVI, EDVI, and La:Ao) assessment. While not a primary study parameter, the improvement seen in cardiac size in this study suggested pimobendan may potentially mitigate pathological cardiac remodeling, which warrants further investigation.

Of the cases enrolled in the study reported here, 10/41 pimobendan-treated dogs and 10/35 benazepril-treated dogs did not receive concurrent furosemide. While it may be argued that these dogs represented asymptomatic rather than clinical atrioventricular valvular disease, all dogs in the study were deemed to have overt, clinical heart failure based on the findings of the ISACHC heart

disease classification (i.e., ≥ Class II), which were supported by abnormal scores for all secondary variables and abnormal findings on thoracic radiography and echocardiography. The use of an ISACHC classification of ≥ Class II as a correlate of clinical heart failure has been validated previously in dogs.[34] The decision not to use furosemide in all dogs may have arisen from varying opinions among veterinary cardiologists as to the appropriateness of furosemide as a first-line therapy in mild heart failure, and this may represent a European versus North American difference in attitude. Regardless, when statistical evaluations of group differences were confined to those animals that did receive concurrent furosemide, results demonstrated a statistical advantage to pimobendan-treated dogs in primary variable and survival assessment, which mirrored the results of the entire study population.

Pimobendan treatment was found to be very safe in this study, with only three dogs having side effects associated with the drug. Initial concerns raised regarding the potential for pimobendan to be arrhythmogenic (as with other positive inotropes) have been unfounded, as reported in various other human and animal studies.[27,28,35]

The study reported here has potential limitations that should be taken into account when interpreting the results. Such limitations include the use of ISACHC as a criterion for enrollment, the study size, the lack of follow-up data for some variables, and the ability to extrapolate these findings to the effects of ACE-inhibitors as a whole. Validity of ISACHC as an enrollment/outcome variable is not without debate because of its subjective nature. However, the entry and exit ISACHC classifications for each study participant were validated with the use of objective data derived from radiography and echocardiography, and ISACHC assessment was consistently done by the same evaluator to avoid introducing interpreter variability.

Based on the current study design and the marked outcome differences between the two treatment groups (with respect to the primary variable of Heart Insufficiency Score and survival), the study numbers were sufficient to statistically support the conclusion that pimobendan was therapeutically superior to benazepril in the treatment of overt, clinical heart failure secondary to atrioventricular valvular disease. While increased study numbers may have allowed for more definitive conclusions about differences between treatment groups regarding the secondary study variables, the reality is that if differences are small, they may not be clinically relevant. Regardless, for none of the variables evaluated did the results in the benazepril group exceed the results in the pimobendan group.

Lack of follow-up laboratory and ECG assessments after inititation of therapy was also a study limitation; however, it was never the intent of the study to evaluate these variables, because prior studies have defined the biochemical safety of both pimobendan and ACE-inhibitors as well as a lack of arrhythmogenic properties for pimobendan.[9,28,35]

The study reported here specifically compared pimobendan to benazepril hydrochloride and used the label dose for both; therefore, it could be argued that its results cannot be extrapolated to other ACE-inhibitors. The authors are unaware of any prior studies that clearly define a therapeutic advantage (other than client compliance) for one ACE-inhibitor over another; hence, it is likely that the findings of this study are relevant to comparison with other ACE-inhibitors as well.

Conclusion

Dogs suffering from overt, clinical heart failure from atrioventricular valvular disease had improved quality of life and survival times when treated with pimobendan with or without furosemide, compared to those given benazepril hydrochloride with or without furosemide. Based on these results, pimobendan should be considered as a primary treatment modality when atrioventricular valvular disease progresses to overt, clinical heart failure. Whether or not the combination of pimobendan with or without furosemide and an ACE-inhibitor will confer additional improvements in outcome is unknown and requires further study.

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[a] Annex to Directive 92/18/EEC as specified in the Note for Guidance: "Good clinical practice for the conduct of clinical trials for veterinary medicinal products in the European Union," published by the European Commission in The Rules Governing Medicinal Products in the European Union. Vol. VII. Guidelines for the Testing of Veterinary Medicinal Products (September 1994).
[b] Vetmedin; Boehringer Ingelheim Pharma KG, Ingelheim, Germany
[c] Fortekor; Novartis Tiergesundheit GmbH, Eschborn, Germany
[d] SAS version 8.2; SAS Institute, Inc., Cary, NC 27513-2414
[e] TESTIMATE version 6; IDV, Gauting, Germany

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