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Efficacy of Benazepril Hydrochloride to Delay the Progression of Occult Dilated Cardiomyopathy in Doberman Pinschers

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Background: Angiotensin converting enzyme inhibitors (ACEIs) are recommended in people to treat asymptomatic (occult) dilated cardiomyopathy (DCM). Efficacy of therapy in occult DCM in dogs is unknown.

Hypothesis: ACEIs, specifically benazepril hydrochloride (BH), will delay the onset of overt DCM in Doberman Pinschers.

Animals: Ninety-one Doberman Pinschers were studied, 57 dogs received BH, and 34 dogs no ACEI.

Methods: Retrospective study of the medical records of all Doberman Pinschers with occult DCM that received BH or no ACEI between April 1989 and February 2003. Two criteria of left ventricular enlargement were used for enrollment: one independent of body weight (BW) (C1) and the other indexed to BW (C2). Cox proportional hazards analyses were used to identify variables associated with the onset of overt DCM.

Results: On univariate analysis the median time to onset of overt DCM was significantly longer for the benazepril group (for C1: 425 days for BH, 95% confidence interval [CI] 264–625 days; 339 days for no ACEI, CI 172–453 days, $P = .02$; for C2: 454 days for BH, CI 264–628 days; 356 days for no ACEI, CI 181–547 days, $P = .02$). The hazard ratio (HR) (benazepril/no ACEI) was 0.57, CI 0.35–0.94, $P = .03$ for C1; HR = 0.56, CI 0.34–0.93, $P = .02$ for C2. On multivariate analysis, BH significantly delayed onset of overt DCM (HR [benazepril/no ACEI] = 0.45, CI 0.26–0.78, $P < .01$, for C1; HR = 0.36, CI 0.21–0.63, $P < .01$, for C2).

Conclusions: BH in particular and ACEIs in general might delay the progression of occult DCM. Prospective studies are warranted to test this theory.

Key words: Angiotensin converting enzyme inhibitor; Asymptomatic left ventricular dysfunction; Canine; Preclinical heart failure; Retrospective study.

Dilated cardiomyopathy (DCM) continues to be an important cause of heart disease and morbidity and mortality in adult dogs of certain breeds, especially large breed dogs.[1–3] The Doberman Pinscher is the most commonly affected breed in North America.

The development of DCM appears to progress through 3 distinct phases in Doberman Pinschers: the 1st phase is characterized by a morphologically and electrically normal heart in an asymptomatic dog; the 2nd phase is characterized by evidence of a morphological (cardiac enlargement and reduced systolic dysfunction) or electrical (ventricular ectopy) derangement in an otherwise asymptomatic dog (occult or preclinical phase); and the 3rd phase is overt heart failure, characterized by clinical signs of forward or backward heart failure.[4]

Despite evidence supporting the benefits of angiotensin converting enzyme inhibitor (ACEI) therapy for people with left ventricular (LV) systolic dysfunction,[5] the effect of ACEIs to increase survival for dogs with congestive heart failure (CHF) because of DCM is unknown.[6,7]

The renin angiotensin aldosterone system (RAAS) is activated during occult DCM in people,[8] however, 3 studies in dogs failed to support these findings.[9–11] Studies in people with LV systolic dysfunction have demonstrated the benefit of ACEI therapy when initiated during the occult stage.[12] The American College of Cardiology and the American Heart Association guidelines recommend the use of ACEI therapy in people with asymptomatic LV dysfunction.[13]

Therefore, the goal of this retrospective study was to determine whether the initiation of ACEI therapy, specifically benazepril hydrochloride (BH), during the occult phase of DCM could delay the progression to overt DCM in a sample of Doberman Pinschers.

Abbreviations:

ACEI	angiotensin converting enzyme inhibitors
BH	benazepril hydrochloride
BW	body weight
CHF	congestive heart failure
CI	confidence interval
CMVD	chronic mitral valve disease
DCM	dilated cardiomyopathy
FS	fractional shortening
HR	hazard ratio
LV	left ventricular
LVFWd	left ventricular free wall dimension at end diastole
LVFWs	left ventricular free wall dimension at end systole
LVIDd	left ventricular internal dimension at end diastole
LVIDs	left ventricular internal dimension at end systole
RAAS	renin angiotensin aldosterone system
VPC	ventricular premature contraction
WSd	wall stress index at end diastole
WSs	wall stress index at end systole

Materials and Methods

Medical records from the Veterinary Teaching Hospital of the University of Guelph were reviewed from April 1989 to February

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2003 to identify Doberman Pinschers with occult DCM that were treated with either BH[a] or received no ACEI therapy.

Enrollment Criteria

Enrollment was restricted to Doberman Pinschers diagnosed with occult DCM based on echocardiographic evidence of LV enlargement and absence of clinical signs of heart disease. Two criteria were used to define LV enlargement, one independent of body size (Criteria 1) and one indexed to body size (Criteria 2). For the former, occult DCM was present if LV internal dimension at end diastole (LVIDd) was $\geq$49 mm or LV internal dimension at end systole (LVIDs) was $\geq$42 mm as assessed by m-mode echocardiography. The second criterion for occult DCM was present if LVIDd was $\geq 0.1749 \times$ body weight (BW) (kg) + 40.3 mm or LVIDs was $\geq 0.1402 \times$ BW (kg) + 35.0 mm (O'Grady MR. Unpublished observations from 51 normal Doberman Pinschers that assessed the relation between left ventricular dimension and body weight). For dogs with multiple echocardiographic examinations during the occult phase of DCM, only 1 examination that met the enrollment criteria was used.

Exclusion Criteria

Dogs with concomitant congenital heart disease, evidence of mitral valvular disease (based on echocardiography), treated with another ACEI other than BH or other arterial vasodilator therapy were excluded.

Study Design

The following data were obtained on the date of enrollment from the medical records: age, BW, presence of a gallop or heart murmur on physical examination, frequency of ventricular premature contractions (VPCs) on a 3-minute electrocardiogram (categorized as absent, $<$1/min, $>$1/min), and m-mode echocardiographic measurements of LVIDd, LVIDs, LV-free wall dimension at end diastole (LVFWd) and systole (LVFWs), and E point to septal separation. The echocardiographic measures were obtained from the right parasternal long-axis view of the LV inflow and outflow tracts with the unsedated dog positioned in right lateral recumbency. Each echocardiographic variable was obtained in triplicate and the average was used in the analysis. In addition, the following echocardiographic variables were calculated: fractional shortening [((LVIDd-LVIDs)/LVIDd)$\times$100], wall stress index at end diastole (WSd) [LVIDd/LVFWd], wall stress index at end systole (WSs) [LVIDs/LVFWs], LV internal dimensions indexed to BW [LVIDd/BW] and [LVIDs/BW], and the % increase in LV internal dimensions over the expected normal dimensions. The latter variables were calculated as [((observed LVID $-$ predicted normal LVID)/predicted LVID) $\times$ 100]. The predicted normal LVIDd was calculated as $0.1749 \times$ BW + 32.0 mm and the predicted normal LVIDs was calculated as $0.1402 \times$ BW + 26.7 mm (O'Grady MR. Unpublished observations from 51 normal Doberman Pinschers that assessed the relation between left ventricular dimension and body weight).

Two enrollment dates were used: one for the date the echocardiographic measurements fulfilled Criteria 1 and the other for the date the echocardiographic measurements met Criteria 2. The date the BH therapy was initiated was recorded. The end point date was the date of onset of overt DCM defined as onset of CHF or sudden death if sudden death occurred before the onset of CHF or syncope if syncope occurred before the onset of CHF.

Dogs were censored if they were euthanized before the onset of clinical signs of CHF, lost to follow-up, or if still alive on July 21, 2006. For dogs lost to follow-up, the end point date was taken as the last date of contact with the owners and the dog was free of clinical signs of DCM.

Time to outcome was determined as the time from the enrollment date to the end point date independent of the date that BH treatment was initiated.

Concomitant Treatment

β-blocker therapy, anti-arrhythmic therapy, and thyroid supplementation were permitted.

Statistical Analysis

Each of the variables obtained at enrollment was assessed for significant difference between treatment groups. To determine whether the data were normally distributed, the residuals were fitted to a normal distribution, and the goodness of fit was tested with a Shapiro Wilk test. If the P value was >0.1 we concluded that the data were normal. For data that were not normally distributed a log transformation was performed and a Shapiro Wilk test was repeated. For normal data the variances were tested for equality with a Levine test. For data that were normal a t-test for equal or unequal variances was used. For nonnormal data the nonparametric Mann-Whitney Wilcoxon test was used.

A log-rank test with right censoring and the Kaplan-Meier method were used to determine whether the median time to overt DCM was different between treatment groups.

To assess the effect of each variable on the time to outcome, a univariate Cox proportional hazards test with right censoring was used and the hazard ratio (HR) and confidence intervals (CI) were determined. Next, more complex models were constructed by multivariable Cox proportional hazards models with right censoring to assess the difference between treatment groups on time to outcome when modeled with the 7 most significant variables identified from the univariate analysis. No more than 8 terms were ever simultaneously considered in the modeling. All nonsignificant terms were removed to simplify the model. Next all of the other variables (both significant and nonsignificant on univariate analysis) were individually added to the remaining model. With each iteration the added term was assessed to determine whether it remained significant within the model.

Comparisons of frequency of counts were performed using a 2-tailed Fisher's exact test.

The statistical analysis used a commercially available statistical software program.[b] Normal data are expressed as the mean $\pm$ the standard deviation. Nonnormal data are expressed as the median/lower quartile/upper quartile. Significance was set at a P value of $<$ .05 unless otherwise indicated. The P value was adjusted for multiple comparisons using the Bonferroni-Sidak method.[14]

Results

Ninety-one Dobermans met the enrollment criteria (BH = 57, no ACEI = 34). There were 40 (70.2%) males in the benazepril group and 18 (52.9%) in the no ACEI group. In 17 dogs the enrollment date differed for Criteria 1 and Criteria 2. In 16 dogs Criteria 2 was reached before Criteria 1 and in 1 dog Criteria 2 was met after Criteria 1. Of these 17 dogs the median difference in enrollment date between Criteria 2 and Criteria 1 was 0.4 years, mean 0.5 years, minimum 0.6 years, maximum 2.0 years. In the other 74 dogs both criteria were satisfied on the same echocardiographic examination.

Only BW was significantly different between treatment groups on the day of enrollment for both criteria (Tables 1a and b).

For the dogs that met Criteria 1, BH was started in 5 dogs after the day of enrollment (median, 154 days; range, 1–1099 days). For these dogs the median duration of therapy with BH was 341 days (range, 110–1138 days). It was initiated in 13 dogs before the day of enrollment (median, 183 days; range, 106–1003 days). In 39 dogs it was started on the day of enrollment. For the dogs that met Criteria 2, BH was started in 7 dogs after the day of enrollment (median, 175 days; range, 1–1267 days). For these dogs the median duration of therapy with BH was 341 days (range, 110–1138 days). It was started in 5 dogs before the day of enrollment (median, 365 days; range, 177–1003 days). In 45 dogs it was started on the day of enrollment.

Table 1a. Comparison of treatment groups at enrollment using Criteria 1.

Parameter	Benazepril	No ACEI	*P* Value	Adjusted *P* Value
Number	57	34		
Sex (M)	40 (70.2%)	18 (52.9%)	0.12[d]	0.96
Age (years)	7.1 ± 1.9	7.6 ± 2.3	0.28	1
Weight (kg)	39.8 ± 6.1	35.4 ± 5.6*	<0.01	0.03
LVIDd (mm)	50.6/48.9/52.8	48.9/48.3/50.6	0.01[a]	0.14
LVIDs (mm)	43.0/41.5/44.5	42.3/40.6/44.2	0.29[a]	1
FS (%)	15.2 ± 5.9	13.9 ± 5.5	0.32	1
LVFWd (mm)	8.5 ± 1.1	8.0 ± 1.1	0.04	0.61
LVFWs (mm)	10.9 ± 1.5	9.8 ± 1.6	<0.01	0.08
EPSS (mm)	8.6 ± 3.3[a]	7.5 ± 2.8	0.14	0.98
WSd	6.1 ± 0.9	6.3 ± 1.0	0.29[b]	1
WSs	4.1 ± 0.9	4.5 ± 0.9	0.05[b]	0.73
LVIDd/BW (mm/kg)	1.3 ± 0.2	1.4 ± 0.2*	0.03	0.54
LVIDs/BW (mm/kg)	1.1 ± 0.2	1.2 ± 0.2*	0.03[b]	0.48
% incr LVIDd	32.5 ± 10.3	30.2 ± 7.6*	0.33[b]	1
% incr LVIDs	33.9/27.8/38.6	33.3/26.9/40.8*	0.86[a]	1
Gallop	4(7.0%)	4(11.8%)	0.47[d]	1
Heart murmur	39(68.4%)	17(50%)	0.12[d]	0.96
β blockers**	16(28.1%)	1(2.94%)	<0.01[d]	0.05
Thyroid treatment**	16(28.1%)	5(14.7%)	0.20[d]	1
VPCs (0)	27(47.4%)	18(52.9%)	0.23[c]	1
VPCs (<1/min)	17(29.8%)	13(38.2%)		
VPCs (>1/min)	13(22.8%)	3(8.8%)		
SD***	12(27.3%)	11(39.3%)	0.31[d]	1
CHF***	32(72.7%)	17(60.7%)		
Censored***	12(21.0%)	6(17.6%)	0.79[d]	1

Data are presented as number (percentage), mean ± standard deviation for data that were normally distributed, median/lower quartile/upper quartile for data that were not normally distributed.

P value was determined by a *t*-test with equal variance unless indicated by "a", which was determined by the nonparametric Mann-Whitney-Wilcoxon test; or "b", which was determined using a log transformation to render the data normal; or "c", which was determined using an ANOVA; or "d", which was determined using a Fisher's exact test.

*Determined on 56 benazepril dogs or 33 no ACEI dogs.

**Were administered at some time during the study period.

***Are outcome variables not enrollment variables.

ACEI, angiotensin converting enzyme inhibitor; M, males; LVIDd and LVIDs, left ventricular internal dimension in diastole and systole, respectively; mm, millimeters; FS, fractional shortening; LVFWd and LVFWs, left ventricular free wall dimension in diastole and systole, respectively; EPSS, E point to septal separation; WSd and WSs, wall stress index in diastole and systole, respectively as described in "Materials and Methods"; BW, body weight; % incr, % increase measured as described in "Materials and Methods"; VPCs, ventricular premature contractions min, minutes; SD, sudden death; and CHF, congestive heart failure.

Table 1b. Comparison of treatment groups at enrollment using Criteria 2.

Parameter	Benazepril	No ACEI	*P* Value	Adjusted *P* Value
Number	57	34		
Sex (M)	40 (70.2%)	18 (52.9%)	0.12[d]	0.96
Age (years)	7.0 ±1.9	7.5 ±2.3	0.23	1
Weight (kg)	39.7 ±6.1	35.4 ±5.6*	<0.01	0.05
LVIDd (mm)	50.5/48.5/52.8	48.8/47.8/50.6	0.03[a]	0.51
LVIDs (mm)	42.8/40.7/44.4	42.2/40.4/44.3	0.44[a]	1
FS (%)	15.2 ±5.5	14.0 ±5.4	.3	1
LVFWd (mm)	8.6 ±1.1	8.0 ±1.1	0.02	0.40
LVFWs (mm)	10.8 ±1.5	9.9 ±1.6	0.01	0.24
EPSS (mm)	8.1 ±3.4	7.4 ±2.8	0.27	1
WSd	6.1 ±1.0	6.3 ±1.0	0.23[b]	1
WSs	4.1 ±0.9	4.5 ± 1.0	0.11[b]	0.94
LVIDd/BW	1.3 ±0.2	1.4 ±0.2*	0.03	0.56
LVIDs/BW	1.1 ±0.2	1.2 ±0.2*	0.03	0.50
% incr LVIDd	28.9/23.7/36.4	28.3/23.5/33.0*	0.50[a]	1
% incr LVIDs	32.7/25.0/38.5	33.4/26.1/40.8*	0.95[a]	1
Gallop	4 (7.0%)	4 (11.8%)	0.47[d]	1
Heart murmur	40 (70.2%)	16 (47.1%)	0.04[d]	0.68
β blockers**	16 (28.1%)	1 (2.94%)	<0.01[d]	0.05
Thyroid treatment**	16 (28.1%)	5 (14.7%)	0.20[d]	1
VPCs (0)	27 (47.4%)	18 (52.9%)	0.23[c]	1
VPCs (<1/min)	17 (29.8%)	13 (38.2%)		
VPCs (>1/min)	13 (22.8%)	3 (8.8%)		
SD***	12 (27.3%)	11 (39.3%)	0.31[d]	1
CHF***	32 (72.7%)	17 (60.7%)		
Censored***	12 (21.0%)	6 (17.6%)	1[d]	1

For abbreviations see Table 1a.

BH was administered for a median of 404 days (upper quartile, 775 days; lower quartile, 201 days; range, 1–2726 days). For dogs that received BH before the date of enrollment the duration of therapy for the purpose of this study was taken from the date of enrollment. The average dose was 0.52 mg/kg/d (median, 0.50; lower quartile, 0.47; upper quartile, 0.55; range, 0.35–1.07 mg/kg/d). It was administered once daily in all but 2 dogs in whom the dose was divided twice daily.

During the study period 17 dogs received β-blockers (8 carvedilol, 7 sotalol, and 2 both) (benazepril group, 16 dogs [28.1%]; no ACEI group, 1 dog [2.9%]; *P* adjusted = .05), and 21 received thyroid supplementation (benazepril group, 16 [28.1%] dogs; no ACEI group, 5 [14.7%]; *P* adjusted = 1.0). In 18 dogs thyroid supplementation was present on the day of enrollment; in 3 dogs supplementation began after the enrollment date.

Primary End Points

Seventy-three dogs reached a cardiac end point (benazepril group, 12 sudden death, 32 CHF, 1 syncope; no ACEI group, 11 sudden death, 17 CHF; *P* adjusted =

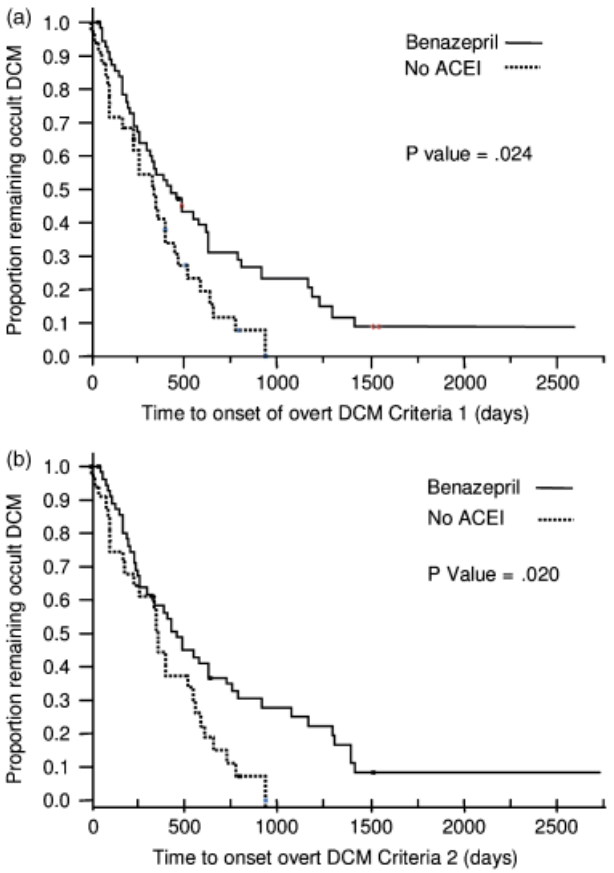

Fig 1. (**a**) Time to onset of overt DCM using Criteria 1, (**b**) time to onset of overt DCM using Criteria 2.

1.0); 18 were censored (benazepril group, 8 euthanized for noncardiac causes, 2 died of a noncardiac reason, 1 lost to follow-up, 1 alive; no ACEI group, 6 euthanized for noncardiac causes [*P* adjusted = 1.0]). The time to onset of overt DCM was significantly longer (25% for Criteria 1 and 28% for Criteria 2) in the dogs receiving BH (Criteria 1, $P = .02$; Criteria 2, $P = .02$) with estimated medians for Criteria 1 benazepril group, 425 days, 95% CI 264–625 days; no ACEI group, 339 days, 95% CI 172–453 days and Criteria 2 benazepril group, 454 days, 95% CI 264–628 days; no ACEI group, 356 days, 95% CI 181–547 days (Fig 1a and b).

The effect of ACEI therapy was also assessed on the likelihood of developing the outcome of CHF or sudden death. There was no effect of therapy on the likelihood of developing CHF or sudden death (*P* adjusted = 1.0).

Univariate Analysis

Treatment with BH was associated with significantly delayed onset of overt DCM. For dogs that met enrollment Criteria 1 the HR for the effect of benazepril treatment was 0.57; $P = .03$ (95% CI 0.35–0.94). For dogs that met enrollment Criteria 2 the HR for the effect of benazepril treatment was 0.56; $P = .02$ (95% CI 0.34–93). The following additional variables at enrollment were individually significantly associated with the time

Table 2a. Effect of variables on time to overt DCM: Results of the Cox proportional hazards univariate analysis using enrollment Criteria 1.

Parameter	Hazard Ratio	Lo CI	Up CI	*P* Value
Benazepril/no ACEI	0.57	0.35	0.94	0.03
Age (years)	1.14	1.02	1.28	0.02
Sex M/F	1.00	0.62	1.64	1
BW (kg)	0.94	0.91	0.98	<0.01
LVIDd (mm)	1.11	1.04	1.18	<0.01
LVIDs (mm)	1.13	1.08	1.19	<0.01
FS (%)	0.93	0.89	0.98	<0.01
LVFWd (mm)	0.91	0.72	1.14	0.42
LVFWs (mm)	0.81	0.69	0.93	<0.01
EPSS (mm)	1.06	0.98	1.14	0.16
WSd	1.37	1.03	1.83	0.03
WSs	1.81	1.37	2.41	<0.01
LVIDd/BW	8.52	2.92	24.52	<0.01
LVIDs/BW	11.09	3.86	30.95	<0.01
% incr LVIDd	1.05	1.02	1.07	<0.01
% incr LVIDs	1.04	1.03	1.06	<0.01
Gallop Y/N	2.29	0.999	4.59	0.05
Heart murmur Y/N	2.31	1.39	3.95	<0.01
β blockers Y/N	0.95	0.52	1.63	0.85
Thyroid treatment Y/N	0.6	0.33	1.03	0.06
VPCs				0.03
<1/min ‖ 0/min	1.51	0.88	2.55	0.13
>1/min ‖ 0/min	2.35	1.21	4.34	0.01
>1/min ‖ <1/min	1.55	0.78	3	0.20
SD/CHF	1.4	0.83	2.29	0.20

For abbreviations see Table 1a. Lo CI, 5% lower confidence interval; Up CI, 95% upper confidence interval.

Table 2b. Effect of variables on time to overt DCM: Results of the Cox proportional hazards univariate analysis using enrollment Criteria 2.

Parameter	Hazard Ratio	Lo CI	Up CI	*P* Value
Benazepril/no ACEI	0.56	0.34	0.93	0.02
Age (years)	1.15	1.02	1.3	0.02
Sex M/F	1.12	0.7	1.83	0.65
BW (kg)	0.96	0.92	0.998	0.04
LVIDd (mm)	1.12	1.05	1.19	<0.01
LVIDs (mm)	1.14	1.08	1.19	<0.01
FS (%)	0.93	0.89	0.97	<0.01
LVFWd (mm)	0.85	0.68	1.06	0.15
LVFWs (mm)	0.81	0.7	0.94	0.01
EPSS (mm)	1.07	0.99	1.16	0.09
WSd	1.49	1.12	1.96	0.01
WSs	1.84	1.38	2.45	<0.01
LVIDd/BW	6.9	2.32	20.16	<0.01
LVIDs/BW	9.99	3.35	28.81	<0.01
% incr LVIDd	1.05	1.03	1.07	<0.01
% incr LVIDs	1.04	1.03	1.06	<0.01
Gallop Y/N	2.58	1.12	5.21	0.03
Heart murmur Y/N	2.55	1.53	4.37	<0.01
β blockers Y/N	0.9	0.49	1.56	0.73
Thyroid treatment Y/N	0.61	0.33	1.05	0.07
VPCs				0.03
<1/min ‖ 0/min	1.48	0.87	2.5	0.14
>1/min ‖ <1/min	1.6	0.8	3.11	0.17
>1/min ‖ 0/min	2.38	1.22	4.39	0.01
SD/CHF	1.39	0.83	2.28	0.21

For abbreviations see Table 1a.

to onset of overt DCM using both Criteria: age, BW, LVIDd, LVIDs, FS, LVFWs, WSd, WSs, LVIDd/BW, LVIDs/BW, % increase in LVIDd, % increase in LVIDs, presence of a heart murmur, and presence of VPCs (Tables 2a and b). Presence of a gallop was also significantly associated with the time to onset of overt DCM using Criteria 2.

A subanalysis was performed that consisted of excluding those dogs that began BH after the date of enrollment. For dogs that met enrollment Criteria 1 the HR for the effect of benazepril treatment was 0.59; $P = .04$ (95% CI 0.36–0.98). For dogs that met enrollment Criteria 2 the HR for the effect of benazepril treatment was 0.61; $P = .06$ (95% CI 0.37–1.02). Additionally, the effect of ACEI therapy was assessed on the time to the CHF and sudden death outcomes separately. There was no significant effect of benazepril therapy on the time to either outcome with either enrollment criteria (for CHF Criteria 1: HR = 0.72, $P = .30$; Criteria 2: HR = 0.71, $P = .29$) (for sudden death Criteria 1: HR = 0.64, $P = .31$; Criteria 2: HR = 0.59, $P = .24$).

Multivariate Analysis

BH treatment continued to be significantly associated with reduced time to onset of overt DCM after adjusting for all the other variables measured at enrollment using both criteria (Criteria 1, HR = 0.45, 95% CI = 0.26–0.78; Criteria 2, HR = 0.36, 95% CI = 0.21–0.63) (Table 3). In addition to treatment group the final model consisted of the following significant terms using Criteria 1: LVIDs, presence of a heart murmur, LVIDd/BW, % increase in LVIDd, and LVIDs/BW (Table 3). For Criteria 2 the final model consisted of the following significant terms in addition to treatment: presence of a heart murmur, % increase LVIDs, LVIDs/BW, % increase in LVIDd, LVIDd/BW, and LVIDd (Table 3).

A multivariate analysis was also performed on the subgroup that excluded those dogs that began BH after the date of enrollment. With each iteration of the development of the final multivariate model the effect of BH treatment continued to be significantly associated with delayed onset of overt DCM for both Criteria 1 and 2 (Criteria 1: HR = 0.48, $P = .01$ [95% CI 0.28–0.82]; Criteria 2: HR = 0.44, $P = < .01$ [95% CI 0.25–0.77]).

Table 3a. Effect of variables on time to overt DCM: Results of the Cox proportional hazards multivariate analysis using enrollment Criteria 1.

Parameter	Hazard Ratio	Lo CI	Up CI	*P* Value
Benazepril/no ACEI	0.45	0.26	0.78	<0.01
LVIDs	2.06	1.14	3.66	0.02
Murmur	1.88	1.09	3.30	0.02
LVIDd/BW×100	1.50	1.12	1.98	0.03
% incr LVIDd	0.43	0.24	0.83	0.04
LVIDs/BW×100	0.69	0.52	0.92	0.04

Lo CI, 5% lower confidence interval; Up CI, 95% upper confidence interval; ACEI, angiotensin converting enzyme inhibitor; LVIDs and LVIDd, left ventricular internal dimension in systole and diastole, respectively; BW, body weight; % incr, % increase measured as described in "Materials and Methods".

Table 3b. Effect of variables on time to overt DCM: Results of the Cox proportional hazards multivariate analysis using enrollment Criteria 2.

Parameter	Hazard Ratio	Lo CI	Up Cl	*P* Value
Benazepril/no ACEI	0.36	0.21	0.63	<0.01
Murmur	3.03	1.68	6.61	<0.01
% incr LVIDs	1.43	1.11	1.83	0.01
LVIDd/BW×100	1.50	1.12	1.98	0.01
LVIDs/BW×100	0.69	0.52	0.92	0.01
% incr LVIDd	0.43	0.24	0.83	0.01
LVIDd	3.09	1.04	8.14	0.04

For abbreviations see Table 3a.

Discussion

This retrospective study demonstrates that there is a significant association between administration of BH and the onset of overt DCM in Doberman Pinschers with asymptomatic DCM. The dogs that received BH had a 43 or 44% decrease in the likelihood of developing overt DCM, for Criteria 1 and Criteria 2, respectively. In addition, this beneficial effect of benazepril persisted after adjusting for all covariates measured. In fact the benefit of benazepril was increased when examined in the multivariate setting; the HR decreased from 0.57 to 0.45 for Criteria 1 and from 0.56 to 0.36 for Criteria 2.

The subanalysis failed to demonstrate a significant effect of treatment on the time to the CHF or sudden death outcomes. The hazard however was reduced for the benazepril group with respect to both outcomes. These findings suggest that the benefit of BH was because of a combined effect on each outcome rather than a favorable effect on just 1 outcome. By separating the 2 major outcomes we essentially divide the number of events thus substantially reducing the sample size for each analysis. It is likely the smaller sample sizes precluded finding a significant effect on time to these individual outcomes. Additionally, there was no difference in the likelihood of either treatment group developing the outcome of CHF or sudden death.

This study agrees with a report that assessed the benefit of ACEI therapy in people with asymptomatic LV dysfunction.[12] This finding is expected because people with reduced LV systolic function have an activated RAAS and should benefit from ACEI therapy.[8,15–17] Current evidence suggests that ACE inhibitors are not effective in all forms of cardiovascular disease, only in disorders associated with an activated RAAS.[16,17] Three previous studies in dogs failed to demonstrate an elevated RAAS in cases of occult DCM.[9–11] They may have failed because the sample sizes were quite small, they did not assess tissue RAAS activation, or it is not activated in the occult phase of DCM.

Two studies assessed the merits of ACEI therapy in dogs with CHF because of DCM.[6,7] In both studies ACEIs failed to increase survival. Because there is a plethora of evidence in favor of the benefits of ACEI therapy in people with DCM why then did these trials fail

to show benefit in favor of the ACEI therapy?[5] Both of these studies were limited because of very small sample sizes. [6,7] In the LIVE Trial, 21 dogs were randomized to the placebo and 22 to enalapril.[6] Dogs with an "expected" survival of <1 month were excluded in the LIVE Trial.[6] In the BENCH Trial 16 dogs, 10 randomized to benazepril and 6 to placebo (it is unspecified whether these dogs had DCM or chronic mitral valve disease [CMVD]), received no diuretics during the trial.[7] This study appears to have included preclinical patients complicating interpretation.

There are no reports of the use of ACEIs in dogs with occult DCM other than in abstract form.[c,d] Only 2 studies demonstrated a benefit with any form of therapy for dogs with any form of DCM, occult or overt.[19,20] In these, pimobendan reduced mortality relative to a placebo in Doberman Pinschers with CHF because of DCM.

Angiotensin-converting enzyme inhibitor therapy has failed to benefit dogs with occult CMVD.[20,21] Why would ACEI therapy be useful for occult DCM but not for occult CMVD? In part this may be because the RAAS is more likely to be activated in DCM than in CMVD.[9–11,20,21] Although LV enlargement is common with both disorders, the cause of enlargement is different. In DCM there is an increase in myocardial fibrosis because of an increase in collagen deposition in the extracellular matrix. The beneficial effect of ACEIs is mediated at least in part by a reversal of myocardial fibrosis.[22] However, CMVD causes LV volume overload by collagen dissolution. ACEIs and angiotensin II receptor blockers have failed to reverse collagen dissolution and may even enhance it, at least in experimental canine CMVD. Thus these agents have failed to reverse the remodeling associated with experimental occult CMVD despite reducing the LV angiotensin II levels, reducing afterload and reducing the regurgitant fraction. [22,23]

The 2 treatment groups had substantial differences at the time of enrollment. However, only BW was significantly different between treatment groups: greater in the benazepril group. Differences are expected because the dogs were not randomly assigned to treatment groups. However, multivariate analysis adjusts for the effect of differences in variables between treatment groups on the effect of treatment. In addition, variables that were not different between treatment groups may still influence the effect of treatment. With each iteration of the multivariate analysis, treatment continued to significantly delay the onset of overt DCM.

Limitations

Retrospective studies are limited by their lack of randomization and blinding. Randomization is important to equalize between the 2 treatment groups, the impact of variables that cannot be measured. For those variables that can be measured, a multivariable Cox proportional hazards analysis can be used to adjust for the effect of any differences in these variables at enrollment on the effect of treatment group.

To reduce the effect of a lack of blinding, one can employ objective entry and end point criteria. The entry and end point criteria used here were objective.

This study involves a relatively small sample size. It would have been preferable to study several hundred patients, permitting the inclusion of all the variables simultaneously into the multivariate Cox proportional hazards model, including interaction terms.

The dogs that received the ACEI did not all receive therapy on the date of enrollment. Five dogs studied with Criteria 1 and 7 dogs using Criteria 2 began BH after the day of enrollment. We performed a separate analysis to investigate the effect of excluding these dogs from the analyses. The hazard was significantly reduced in the multivariate analysis for dogs that received BH in Criteria 1 and Criteria 2. These findings suggest that the benefit of ACEI therapy was not a result of including the few dogs that began ACEI therapy after the study enrollment date.

Additionally, most of the no ACEI group was studied before the benazepril group. Only 5 of the 34 no ACEI dogs were examined after the first of the benazepril group.

The effect of ventricular ectopy as a covariate would have been better addressed with the use of 24-hour Holter data as opposed to a 3-minute electrocardiogram.

Doberman Pinschers were studied as opposed to a study sample consisting of many breeds with DCM. The advantage to studying just 1 breed is that it offers a greater degree of homogeneity to the course of the disease, which should permit observing a difference between treatment groups with a smaller sample size. However, it remains to be demonstrated that other breeds would respond as did this Doberman Pinscher sample.

Conclusions

ACEI therapy has been demonstrated to be important in the management of people with occult DCM. This study suggests a similar benefit in Doberman Pinschers with occult DCM. Prospective randomized, blinded clinical trials are recommended to validate these findings in both Doberman Pinchers as well as a mixed breed cohort of dogs with occult DCM.

Footnotes

[a] Fortekor; Novartis Animal Health, Mississauga, ON, Canada
[b] JMP version 7.0; SAS Institute Inc, Cary, NC
[c] O'Grady MR, Horne R, Gordon SG. Does angiotensin converting enzyme inhibitor therapy delay the onset of congestive heart failure or sudden death in Doberman Pinschers with occult dilated cardiomyopathy? J Vet Intern Med 1997;11:138 (abstract)
[d] O'Sullivan ML, O'Grady MR, Minors SL, Kean KMT, Horne R. Occult dilated cardiomyopathy in the Doberman Pinscher: A retrospective study of prognosis in 163 cases. J Vet Intern Med 2005;19:406 (abstract)

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