# Results of the veterinary enalapril trial to prove reduction in onset of heart failure in dogs chronically treated with enalapril alone for compensated, naturally occurring mitral valve insufficiency

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**Objective**—To determine the efficacy of long-term enalapril administration in delaying the onset of congestive heart failure (CHF).

**Design**—Placebo-controlled, double-blind, multicenter, randomized trial.

**Animals**—124 dogs with compensated mitral valve regurgitation (MR).

**Procedures**—Dogs randomly assigned to receive enalapril or placebo were monitored for the primary endpoint of onset of CHF for ≤ 58 months. Secondary endpoints included time from study entry to the combined endpoint of CHF–all-cause death; number of dogs free of CHF at 500, 1,000, and 1,500 days; and mean number of CHF-free days.

**Results**—Kaplan-Meier estimates of the effect of enalapril on the primary endpoint did not reveal a significant treatment benefit. Chronic enalapril administration did have a significant benefit on the combined endpoint of CHF–all-cause death (benefit was 317 days [10.6 months]). Dogs receiving enalapril remained free of CHF for a significantly longer time than those receiving placebo and were significantly more likely to be free of CHF at day 500 and at study end.

**Conclusions and Clinical Relevance**—Chronic enalapril treatment of dogs with naturally occurring, moderate to severe MR significantly delayed onset of CHF, compared with placebo, on the basis of number of CHF-free days, number of dogs free of CHF at days 500 and study end, and increased time to a combined secondary endpoint of CHF–all-cause death. Improvement in the primary endpoint, CHF-free survival, was not significant. Results suggest that enalapril modestly delays the onset of CHF in dogs with moderate to severe MR. (*J Am Vet Med Assoc* 2007;231:1061–1069)

Angiotensin-converting enzyme inhibitors have been useful in the management of hypertension and heart failure in humans[1–5] and CHF in dogs.[6–10] The role of ACE inhibitors administered prior to onset of heart failure is less clear. The Study Of Left Ventricular Dysfunction prevention trial[11] revealed that ACE inhibition decreased the incidence of CHF and hospitalization caused by CHF in humans with heart disease of various etiologies. Results of unpublished retrospective

**Abbreviations**

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|---|---|
| CHF | Congestive heart failure |
| ACE | Angiotensin-converting enzyme |
| VETPROOF | Veterinary enalapril trial to prove reduction in onset of heart failure |
| SVEP | Scandinavian Veterinary Enalapril Prevention |
| RAAS | Renin-angiotensin-aldosterone system |

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studies[a,b] in treatment-benefited Doberman Pinschers with occult dilated cardiomyopathy are supported by results of studies in humans. Mitral valve regurgitation, secondary to myxomatous valve degeneration (endocardiosis), is the most common heart disease in dogs.[12] This disease provides a wide temporal window of opportunity for therapeutic intervention because the associated murmur typically indicates the presence of disease years before the onset of heart failure.[12] Studies[6-10,13-27,c] in humans and dogs with natural and experimental mitral valve regurgitation have revealed beneficial effects of treatment with ACE inhibitors. The beneficial effect reported in most studies has not, however, been universal.[28-32] In addition, in a large, prospective, placebo-controlled, double-blind multicenter clinical trial performed in Scandinavia,[33] treatment with enalapril failed to yield a significant benefit in delaying onset of CHF in Cavalier King Charles Spaniels with compensated mitral valve regurgitation. The placebo-controlled, double-blind study, VETPROOF, reported here was similarly designed to prospectively evaluate the benefit of enalapril treatment in delaying the onset of CHF in dogs with moderate to severe compensated mitral valve regurgitation.

## Materials and Methods

**Selection of dogs**—Dogs were client owned, had not received treatment for heart failure or heart disease, and had initially been examined at or referred to 1 of 8 participating specialty centers. Dogs were eligible for inclusion if they were older than 5 years of age, normotensive, and weighed ≤ 20 kg (approx 45 lb). Participant dogs also had moderate to severe mitral valve regurgitation with at least a grade 3/6 heart murmur. Additional entry criteria included echocardiographic evidence of mitral valve endocardiosis and insufficiency, moderate to severe left atrial enlargement (left atrial-to-aortic diameter ratio ≥ 1.6 on an M-mode or 2-dimensional short axis view), and radiographic evidence of cardiomegaly with thoracic radiographs free of evidence of pulmonary edema. On the basis of results of previous studies[21,34] of the time course for cardiac remodeling, chronic treatment was defined as ≥ 60 days' treatment with enalapril. Dogs with dilated cardiomyopathy, systemic hypertension, radiographic evidence of pulmonary edema, or concurrent disease processes that, in the opinion of the admitting investigator, would result in death within 1 year were excluded. Owners of participant dogs provided informed consent.

**Study design**—The study design was modeled after the Study Of Left Ventricular Dysfunction prevention study[11] as a multicenter, randomized, double-blind, placebo-controlled trial in which the time to onset of heart failure in dogs receiving enalapril at an approximate dosage of 0.5 mg/kg (0.23 mg/lb) once daily was compared with that in dogs receiving placebo treatment. The trial was designed to determine whether chronic treatment with enalapril, begun prior to the onset of signs of CHF in dogs with New York Heart Association class-I or -II heart disease, would delay the onset of pulmonary edema. Board-certified cardiologists and internists at 8 university-based veterinary teaching hospitals and private veterinary referral practices enrolled dogs in the study.

Certain changes were made in the original study design. The original study director was replaced prior to the onset of data collection but remained as a contributing investigator. The original study design permitted a maximum weight of 13.5 kg (30 lb), but the weight allowance was increased after the study commenced to allow inclusion of dogs weighing up to approximately 20 kg (45 lb). This change was made to enhance enrollment and allow inclusion of Cocker Spaniels with mitral valve regurgitation. At the study director's (CEA) request, the study was modified prior to onset of data collection to include a run-in period and measurement of plasma aldosterone concentrations; the latter was later abandoned because of budget considerations. Finally, 1 center that had enrolled no dogs was replaced during the first year of the study.

**Treatment and monitoring**—All dogs underwent complete physical examination. Echocardiographic and thoracic radiographic examinations, blood pressure measurement, and laboratory evaluations (CBC, urinalysis, and serum biochemical analysis) were also required at the time of enrollment. Dogs were randomly assigned to be treated with enalapril (0.5 mg/kg, PO, q 24 h) or a placebo at the same dosage (same milligram size and number of tablets for placebo- or enalapril-treated dogs). The group to which each dog was assigned was known by only 1 investigator (JRC), who played no role in clinical decision-making.

Owner compliance was determined by a combination of owner interrogation, examination of owner's required daily pill administration logs, and pill counts. Dogs were removed from the study if the attending clinician believed that owner compliance was inadequate. Serum urea nitrogen and creatinine concentrations were measured at the time of enrollment in the study; approximately 0.5, 3, 6, 9, 12, 15, and 18 months after enrollment; and approximately every 4 months thereafter, for as long as the dog remained in the study.[35] In addition, if signs compatible with heart failure (eg, cough or dyspnea) were detected during a routine follow-up examination or were reported by the owner, the dog was reevaluated and thoracic radiographs were obtained.

When CHF (manifested by radiographically evident pulmonary edema) was detected, the group assignment code was revealed and the dog exited the trial. At that time, the dog was treated as deemed necessary by the attending clinician. As an enrollment incentive, enalapril was offered gratis for life for all dogs that completed the study or that were free of CHF at the study termination.

**Monitoring and data management**—Study progress was monitored and decisions regarding protocol changes, site changes, run-in period, termination date, and data analysis were made by an oversight committee (CEA and BWK). The sponsor was not involved in data acquisition, handling, interpretation, or presentation. The study database was retained by the investigators.

**Statistical analysis**—Statistical analyses were performed by statisticians not employed by or responsible to the sponsor. Baseline characteristics were described

as mean ± SD or median (25th and 75th percentile) for continuous variables and as frequencies for categoric variables. To evaluate potential differences between treatment groups, the $\chi^2$ or Fisher exact tests were used for categoric analyses. The nonpaired Student *t* test and Wilcoxon rank sum tests were used to assess continuous variables. Kaplan-Meier survival curves, with endpoints defined as onset of CHF or the combined endpoint of all-cause death or onset of CHF (secondary endpoint), were constructed and analyzed for significance by use of the log-rank test. The oversight group had originally planned to use 1-tailed analysis of primary and secondary endpoints per the design of the Study Of Left Ventricular Dysfunction prevention study.[11] One-tailed analysis is appropriate because data published at the time of study design indicated that only beneficial results were associated with administration of ACE inhibitors in humans and other animals with CHF secondary to all causes, including mitral valve regurgitation, making the likelihood of a negative effect remote.[1-3,5-7,11] However, because of controversy surrounding use of ACE inhibitors prior to the onset of CHF, results of all Kaplan-Meier curves and their derivatives are presented with both 1- and 2-tailed analyses. In all other analyses, only the more conservative 2-tailed analysis was used. In all instances, a *P* value of 0.05 was considered significant. In addition to comparison of the Kaplan-Meier curves of the primary endpoint, secondary endpoints were evaluated. Number of CHF-free days (mean number of days dogs remained in the study alive and free of CHF [ie, number of days from study entry to detection of CHF, death, or drop-out from study]) and number of CHF-free dogs at days 500, 1,000, and 1,500 were analyzed using the $\chi^2$ test, while the combined endpoint of all-cause death and heart failure was evaluated using the Kaplan-Meier curve analysis. Statistical analyses were performed with commercial statistical packages.[d,e]

The prestudy power calculation was made without an accurate understanding of the magnitude of the variation in time to heart failure. It was estimated that dogs would remain in the study for a mean of 18 ± 9 months. Accepting the risk of a type I error at 5% and a type II error at 25% with the magnitude of identifiable benefit of 25%, the study had an estimated power of 65%.[36] The estimated number of dogs needed for 80% confidence in detecting a 25% benefit was 198. After the study was performed, post hoc analysis, performed with the knowledge of the time and variability observed in reaching the primary endpoint, indicated that the number of dogs needed for 80% certainty of detecting a 25% difference was 200 or that the study was powered to have a 61% chance of detecting a 25% benefit.[f]

## Results

One hundred thirty-nine dogs (66 males and 73 females with a mean age of 10.3 ± 2.3 years) met the initial entry criteria and were provisionally enrolled into the study (**Table 1**). Of those, 31 were of mixed breeding; 12 each were Poodles and Cocker Spaniels; 10 each were Cavalier King Charles Spaniels and Shih Tzus; 8 were Miniature Schnauzers; 7 each were Chihuahuas, Dachshunds, and Yorkshire Terriers; and 6 were Lhasa Apsos. Fifteen other breeds with 1 to 5 dogs each were also represented. Of the 139 dogs, 46 died of causes other than heart failure or dropped out. Dogs dropped out of the study because of failure of owner compliance (7 in the enalapril group and 8 in the placebo group), death of the owner (1 in the enalapril group), owner relocation (1 in the enalapril group and 1 in the placebo group), and other causes (2 in the enalapril group and 2 in the placebo group). Of the dogs that died from noncardiac causes, 10 were in the enalapril group and 13 were in the placebo group. The endpoint of CHF was reached by 73 of the 139 dogs (36 in the treatment group and 37 in the placebo group), of which 2 in the enalapril and 2 in the placebo group died at the time of initial diagnosis of CHF.

Of the 139 dogs initially enrolled, 15 (11 in the enalapril group and 4 in the placebo group; $P > 0.05$)

Table 1—Mean values for physical examination and cardiac variables for 139 dogs originally enrolled in a study to evaluate long-term treatment with enalapril in dogs with compensated, naturally occurring mitral valve regurgitation and in 124 of those dogs that were used in chronic treatment analysis. The former group included dogs that reached the endpoint (heart failure) or dropped out < 60 days after entering the study and were not included in analysis of chronic treatment. Notice that initial randomization closely matched dogs in all characteristics except for radiographic evidence of severe left atrial size grade, for which there were twice as many in the enalapril group as in the control group. Entry characteristics were virtually identical for signalment and estimates of disease severity for the treatment and placebo groups in the 124 dogs used for analysis, and there were no significant differences between groups.

| | | | Males | | | | | Dogs with severe radiographic grade of left atrial dilatation | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | n | Weight (kg) | No. | % | Heart rate (beats/min) | Age (y) | Murmur grade | No. | % | LA:Ao | $LVID_d$/BW (cm/kg) | Enalapril dose (mg/kg) |
| Original (n = 139) | | | | | | | | | | | | |
| Enalapril | 70 | 7.8 (3.5) | 35 | 50 | 129 (20.1) | 10.0 (2.2) | 3.9 (0.57) | 6* | 9.0 | 1.9 (0.26) | 0. 48 (0.16) | 0.46 (0.10) |
| Placebo | 69 | 8.9 (4.5) | 31 | 45 | 130 (24.5) | 10.7 (2.3) | 3.9 (0.73) | 3* | 4.5 | 1.8 (0.27) | 0.47 (0.22) | 0 |
| Chronic treatment (n = 124) | | | | | | | | | | | | |
| Enalapril | 59 | 7.8 (3.6) | 31 | 53 | 129.1 (20.5) | 9.8 (2.25) | 3.9 (0.58) | 3 | 5.1 | 1.8 (0.26) | 0.50 (0.16) | 0.46 (0.10) |
| Placebo | 65 | 8.9 (4.5) | 29 | 45 | 131.1 (24) | 10.6 (2.3) | 4.0 (0.72) | 2 | 3.0 | 1.8 (0.27) | 0.47 (0.22) | 0 |

Values in parentheses are SD. *Radiographic evaluation performed on only 67 and 69 dogs for the enalapril and placebo dogs, respectively. LA:Ao = Ratio of left atrial to aortic dimension. $LVID_d$/BW = Left ventricular internal dimension in diastole, divided by body weight.

left the study within 60 days of enrollment (ie, during the run-in period) and were not included in chronic treatment data analysis (**Figure 1**). Dogs exiting the study in the first 60 days included those that died (3 in the enalapril group and 2 in the placebo group), dropped out (1 in the enalapril group and 2 in the placebo group), or had a diagnosis of heart failure (7 in the enalapril group). Inspection of the raw data for the 139 dogs revealed an early drop-off in enalapril-treated dogs, negating any significant difference in CHF-free survival times between groups (median CHF-free survival time difference of 73 days [851 vs 778 days; 9% benefit]) for enalapril-treated versus placebo-treated dogs, respectively. It is noteworthy that significantly ($P < 0.05$) more dogs in the enalapril-treated group (13 vs 6) remained free of CHF for the duration of the study. Of those 19 dogs, mean time in the study was 1,346 ± 301 days for the treatment group and 1,292 ± 239 days for the placebo group.

The remaining 124 dogs (60 males and 64 females) were enrolled in the study and evaluated for the primary (ie, time to CHF) and secondary endpoints. Analysis of data from those 124 dogs (59 dogs in the enalapril group and 65 in the placebo group) revealed that there were no significant differences between the 2 groups in mean age, weight, percentage of males, murmur grade, left atrial-to-aortic ratio, left ventricular size (cm/kg), or percentage with radiographic evidence of severe left atrial enlargement (Table 1). Enalapril-treated dogs received a mean dosage of 0.46 ± 0.10 mg/kg (0.21 ± 0.05 mg/lb) orally, once daily (range, 0.23 to 0.66 mg/kg

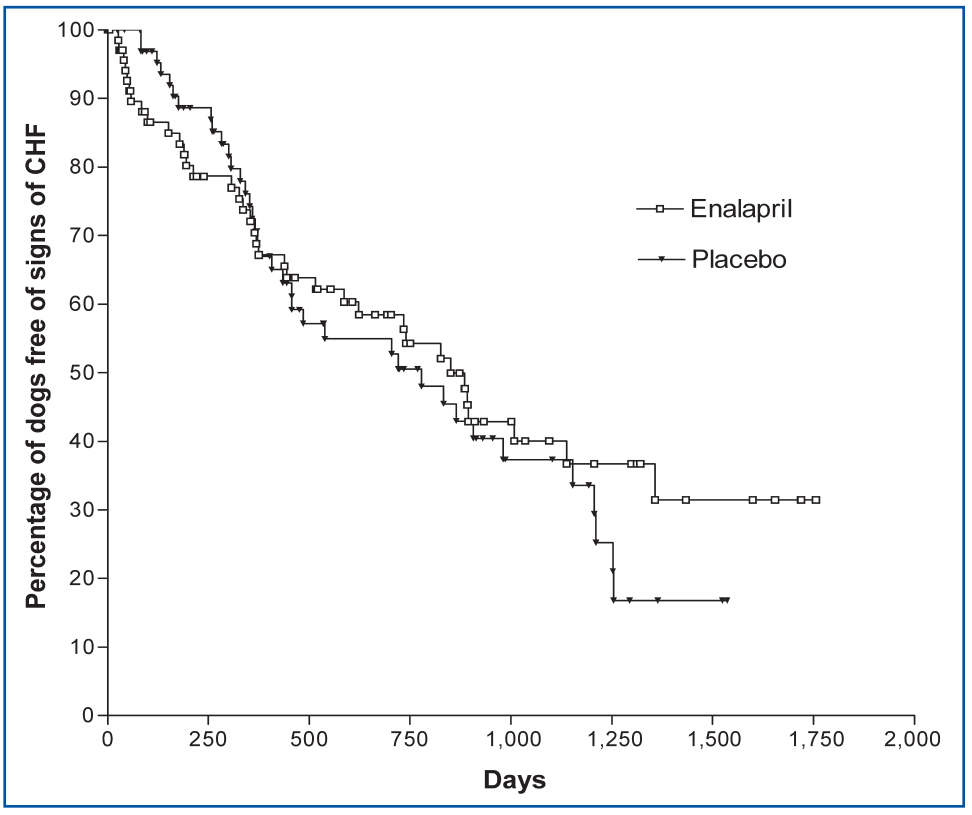


Figure 1—Graph depicting CHF-free survival times, expressed as Kaplan-Meier curves, for 139 dogs initially enrolled in a study to evaluate long-term treatment with enalapril in dogs with compensated, naturally occurring mitral valve regurgitation. Median CHF-free survival times for treatment and placebo groups were 851 and 778 days, respectively ($P > 0.05$).

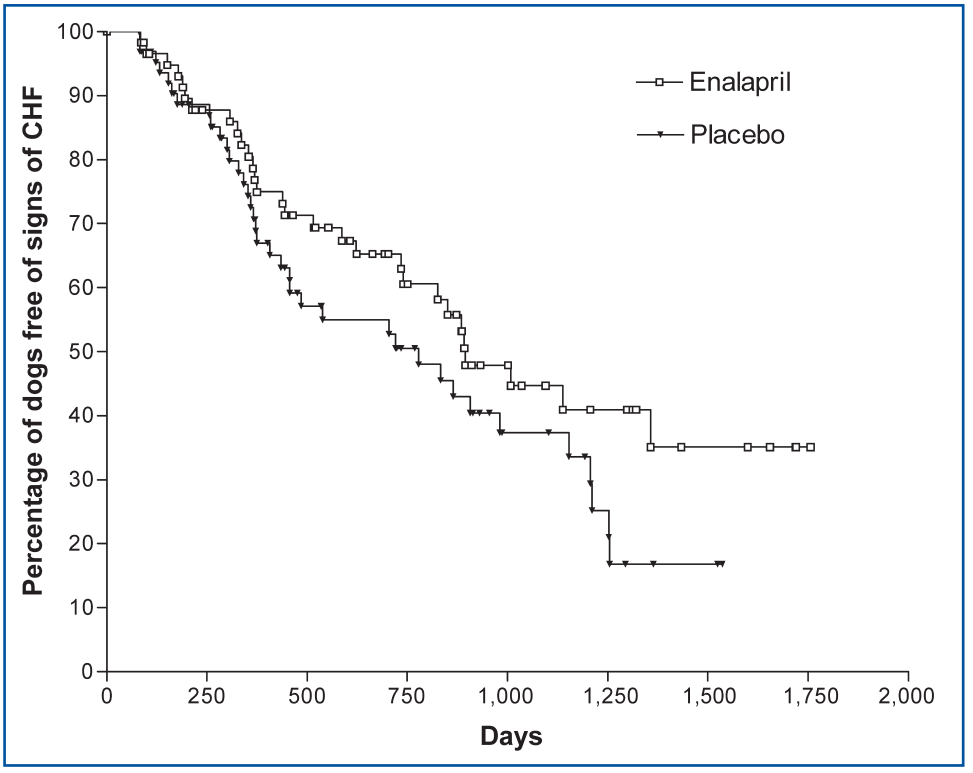


Figure 2—Graph depicting CHF-free survival times, expressed as Kaplan-Meier curves, for 124 of the original 139 dogs that met the requirements for inclusion in chronic treatment data analysis. Median CHF-free survival times in the treatment and placebo groups were 895 and 778 days, respectively ($P = 0.06$), yielding a 4-month (15%) CHF-free benefit. Notice that more than twice as many dogs in the treatment group remained free of signs of CHF at study termination. Also notice that significantly more dogs survived, free of signs of CHF, in the treatment group at 500 and 1,500 days.

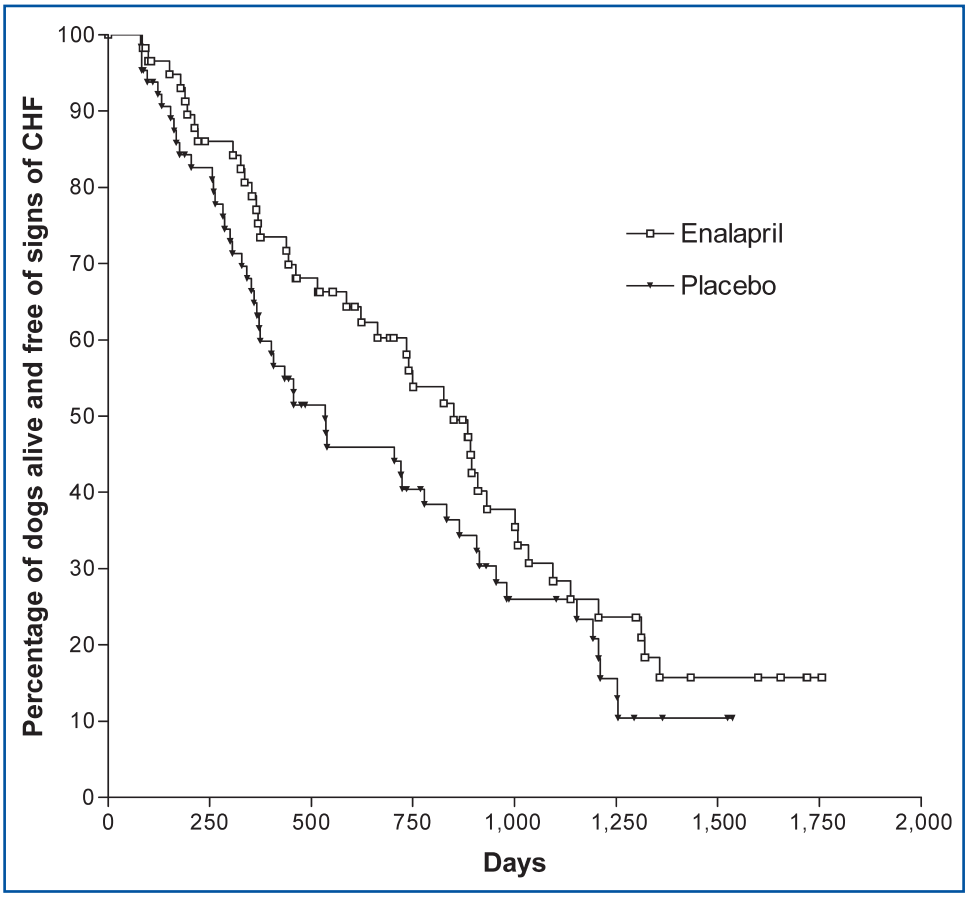


Figure 3—Graph depicting the combined endpoint of survival (all-cause death) and CHF-free survival, expressed as a Kaplan-Meier curve, for 124 dogs that met entry requirements. Median times to this combined endpoint in the treatment and placebo groups were 851 and 534 days (59% difference of 317 days [10.6 months] in heart failure and survival benefit), respectively ($P = 0.05$).

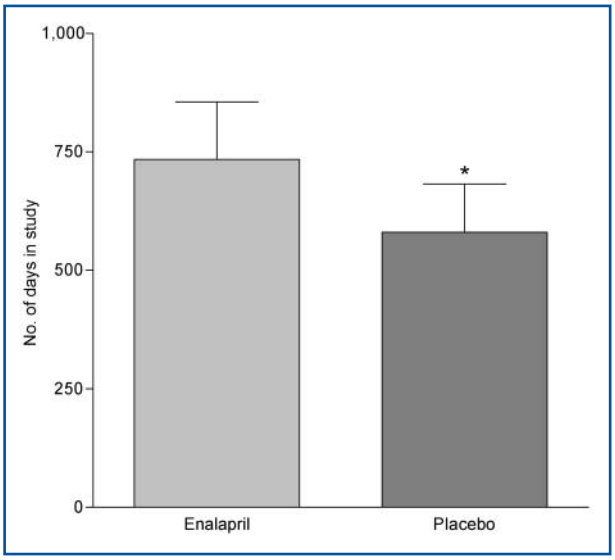


Figure 4—Plot depicting mean ± SD number of days in which dogs receiving enalapril and placebo remained free of signs of CHF. Notice that chronic treatment with enalapril yielded a significant benefit (734 vs 581 days [a difference of 5.1 months]; $P < 0.03$). *Difference in mean number of days was significant.

[0.11 to 0.3 mg/lb]; 22 [37%] received ≥ 0.5 mg/kg and 1 [1.7%] received < 0.25 mg/kg [0.11 mg/lb]).

The study was completed in October 2001, 5 years after its inception, with 53% (29/59 [49%] of dogs from the treatment group and 37/65 [57%] dogs from the placebo group) reaching the endpoint of CHF. These 124 dogs remained enrolled in the study for a mean duration of 654 ± 443 days (21.8 months [1.8 years]). More than twice as many dogs in the treatment group, compared with the placebo group (13 vs 6; [1-tailed $P = 0.02$; 2-tailed $P < 0.05$]), remained free of CHF at the time of study termination, indicating that a CHF-free survival benefit was conferred by chronic enalapril treatment (**Figure 2**). Two dogs in each group died on the same day that heart failure was diagnosed, and 7 dogs (3 in the treatment group and 4 in the placebo group) were found dead. Although analysis of Kaplan-Meier curves revealed the difference to be insignificant, dogs treated with enalapril had a higher median estimated time to onset of heart failure, compared with placebo-treated dogs (895 vs 778 days [15% difference of 117 days or 3.9 months {1-tailed $P = 0.06$; 2-tailed $P = 0.12$}]). Results favoring enalapril treatment were found with analysis of the combined endpoint of onset of CHF and all-cause death (851 vs 534 days [59% difference of 317 days or 10.6 months]; $P = 0.05$ with a 1-tailed test, and $P = 0.10$ with a 2-tailed test; **Figure 3**).

Evaluation of other secondary endpoints suggested that there was a benefit in dogs treated chronically with enalapril. Treated dogs remained free of CHF for significantly ($P < 0.03$ with a 1-tailed test, and $P = 0.05$ with a 2-tailed test; **Figure 4**) longer than those that received placebo (median [25th, 75th percentiles] 693 [354, 1,008] vs 444 [262, 911] days, for an 8.3-month or 56% difference; mean, 734 ± 466 days vs 581 ± 410 days, for a 5.1-month or 26% difference). Significantly more dogs remained free of CHF on day 500 (38/59 [64%] vs 29/65 [44.6%]; $P < 0.02$ with a 1-tailed test, and $P < 0.05$ with a 2-tailed test) and at the termination of the study (13/59 [22%] vs 6/65 [9.2%]; $P = 0.02$ with a 1-tailed test, and $P < 0.05$ with a 2-tailed test; Figure 2), compared with placebo-treated dogs.

## Discussion

Mitral valve regurgitation is one of the most important cardiovascular diseases in veterinary medicine because of its prevalence, the popularity of affected breeds, and its associated high morbidity and eventual mortality rates.[12] The disease is characterized by a

large window of treatment opportunity, often a period of years, between the time at which the disease can be easily recognized by a characteristic murmur and the onset of clinical signs. Although mitral valve regurgitation is primarily considered to be a surgical disease in humans, most veterinarians have only the option of medical management because of the high cost and risk associated with surgical valve replacement and repair.[37,38] Administration of ACE inhibitors improves the quality of life and longevity of dogs with CHF secondary to mitral valve regurgitation,[6-10] making them a logical initial choice for evaluation in the search for a medical strategy for delaying progression of disease to CHF and death. Treatment of dogs with spontaneous subclinical mitral valve regurgitation with enalapril with the goal of delaying onset of CHF has been evaluated in 2 clinical trials, the SVEP trial[33] and the VETPROOF. The VETPROOF, reported here and carried out by internal medicine– and cardiology-boarded specialists in the United States, was not completed until 2 years after results of the SVEP study were revealed. The authors believe the 2 trials should be discussed and considered together in light of their temporal relationship, common hypothesis and design similarities, and differing results. The VETPROOF, reported here, suggests that enalapril treatment provides a modest benefit in delaying onset of CHF, whereas the first and larger of these studies, the SVEP trial, does not.[33]

Examination of VETPROOF Kaplan-Meier survival curves revealed an insignificant delay in onset of CHF when enalapril was chronically administered to dogs with hemodynamically important mitral valve regurgitation and left atrial enlargement at a mean dosage of 0.46 mg/kg, administered once daily. Although the difference between groups was not significant, this finding suggested a mean delay of approximately 4 months in the median number of days until onset of CHF for dogs in the enalapril group, compared with dogs that received placebo. We believe that this finding in the primary trial endpoint is buttressed by a number of beneficial effects that enalapril treatment yielded on secondary trial endpoints, including mean and median CHF-free interval (ie, CHF-free days [days from study entry until CHF, death, or dropping out of study]), number of dogs remaining CHF free 500 days into the study, and number of dogs remaining CHF free at the end of the study; each of those factors was significantly different, compared with placebo-treated dogs. Additionally, the longer CHF-free survival time in the enalapril treatment group was strengthened when the results were analyzed with the combined endpoints of time to CHF or death, which revealed a significant 10.6 months' improvement in CHF-free survival time. The latter finding may indicate that ACE inhibition yields additional survival benefit, although combining the endpoints also allows more dogs to reach an endpoint and thereby complete the trial. These dogs are uncensored in the Kaplan-Meier curve analysis, increasing the power of the analysis and the probability of detecting a significant difference.

Although there was an overall mild CHF-free survival benefit associated with early ACE inhibition, a large subpopulation (22%) of the dogs received a substantially greater benefit. In the enalapril treatment group, significantly more dogs reached the study's end without developing CHF (mean number of days in the study, 1,346). This finding suggests that certain subpopulations of dogs derive greater benefit from early enalapril treatment than did the general population. This hypothesis is indirectly supported by studies in which variable sympathetic nervous system or RAAS activation prior to the onset of CHF,[39-42] the interrelationship between or cross-activation of these systems,[43] and suppression of sympathetic nervous system activity with ACE inhibition[43] were reported. Evidence of potential subpopulation benefits from ACE inhibition was also found in the CONSENSUS I trial at 10-year follow-up.[44] In that trial, a subset of humans originally treated with enalapril survived beyond the study termination date and had > 50% survival benefit, compared with the group that originally received placebo.

Results of the SVEP, a double-blinded, placebo-controlled trial in which a population of 229 dogs with mild to severe mitral valve regurgitation was evaluated, did not indicate that there was a clinically or statistically significant delay in onset of heart failure with enalapril treatment.[33] In addition to the possibility that a small benefit was missed in the SVEP trial that was discovered in the VETPROOF, there are other possible explanations for the somewhat discrepant results of the 2 trials. Differences in the populations and methods used in the 2 trials may have influenced the outcomes. For example, dogs in the SVEP trial were younger than dogs in the VETPROOF (mean ± SD age, 6.7 ± 2.0 years vs 10.3 ± 2.3 years) and had a significantly different sex distribution (male-to-female ratio, 135:94 vs 60:64), and only Cavalier King Charles Spaniels were used in the SVEP trial, whereas 24 breeds of dogs and dogs of mixed breeds were included in the VETPROOF. It is noteworthy that the natural history of mitral valve regurgitation and the RAAS in Cavalier King Charles Spaniels are different from those of other breeds,[45,46] suggesting that 1 explanation for the discrepant trial results might be pharmacogenomic differences between the dogs evaluated in each. Another relevant and potentially important difference between the studies was the lower mean dose of enalapril used in the SVEP trial (mean dosage, 0.37 mg/kg [0.17 mg/lb] per day, with half of the dogs receiving 0.25 to 0.38 mg/kg [0.17 mg/lb] per day [ie, 50% to 75% of the lowest recommended dosage]), compared with a mean dose of 0.46 mg/kg per day, the approximate low end of the manufacturer's recommendation, in the VETPROOF. It is also possible that a threshold dose of enalapril is required for clinical efficacy and that this dose was not reached in an adequate number of SVEP trial dogs but was reached in the VETPROOF. Inclusion of less severely affected dogs in the SVEP trial (< 50% of those dogs had cardiomegaly, no minimum echocardiographic left-atrial dimension was required for participation, and time to onset of CHF was nearly twice as long in dogs in the SVEP trial, compared with those in the VETPROOF) may also have played a role in the differing results. Lastly, fewer than half (43%) of the enrolled dogs reached the study endpoint in the SVEP trial.

It is generally accepted that treatment with ACE inhibitors is beneficial early in diseases that are asso-

ciated primarily with myocardial failure (eg, dilated cardiomyopathy and ischemic heart disease).[11,a,b] Recently, however, some authors have argued that ACE inhibitors are not a logical choice in the treatment of mitral valve regurgitation, particularly prior to the onset of CHF,[33] and that administration of ACE inhibitors may even be detrimental in dogs with this syndrome.[47] These viewpoints have been proposed on the basis of results of the SVEP trial[33] and experimental work involving an acute surgical model of mitral valve regurgitation that indicated that neither ramipril nor irbesartan prevented myocardial remodeling when administered for 4 months.[30,48] Primary mitral valve regurgitation is a surgically managed disease in humans and has received little interest with regard to medical management. In a recent editorial[49] it was suggested that most research in treatments for mitral valve regurgitation in humans involves studies of small numbers that are not blinded and that tend to yield negative results. However, scrutiny of the literature reveals that although the first 2 concerns are legitimate, the third is not. A review of 27 studies in dogs[6–10,22,26,30,33] and humans[13–19,23–25,27–29,31,c] with naturally occurring mitral valve regurgitation and dogs with experimental mitral valve regurgitation[20,21,32] reveals hemodynamic, clinical, or survival benefit in most (21/27 [78%]).[6–10,13–27] Furthermore, if ACE inhibition was truly harmful in dogs with naturally occurring mitral valve regurgitation, as has been suggested from the experimental model,[30,47,48] it seems logical that an overall negative effect of ACE inhibition would have been detected in dogs in the SVEP[33] and VETPROOF trials. Data from those 2 studies do not support that conclusion. The positive role of ACE inhibition in management of spontaneous mitral valve regurgitation in dogs is further supported by a number of well-designed and randomized trials that indicated clinical and survival benefits when ACE inhibitors were administered to dogs with CHF, most of which had mitral valve regurgitation.[6–10]

A potentially important and unexpected finding in the original raw data (from the 139 dogs that met the initial entry criteria) from the VETPROOF is the early drop-off in the enalapril group (4 drop-outs and 7 with CHF). This finding did not reach significance, compared with the placebo group, but it raises the possibility that administration of enalapril to dogs with subclinical mitral valve regurgitation may have hastened the onset of heart failure. Although this hypothesis warrants consideration, particularly in light of data from experimental mitral valve regurgitation models,[47,48] the finding is more likely explained by chance in the randomization process. Although the treatment and control groups were closely matched for age, sex, weight, murmur grade, and selected echocardiographic variables (ratio of left atrial to aortic dimension and diastolic left ventricular internal dimension indexed to body weight), there were more severely affected dogs in the original treatment group. The treatment group contained twice as many dogs with radiographically determined severe left atrial enlargement as the control group. The strongest predictor of early onset of CHF in the present trial was radiographically evident severe left atrial enlargement (data not included). Nevertheless, further study of this potential adverse effect is warranted. At the very least, inspection of the raw data from 139 dogs indicates that ACE inhibition with enalapril does not prevent early decompensation in dogs with severe mitral valve regurgitation, arguing that most benefits attributable to ACE inhibition in mitral valve regurgitation are more likely caused by chronic blunting of cardiac remodeling than by acute vasodilatory effects.

Finally, it is noteworthy that results of both of these long-term clinical studies involving dogs that had not developed CHF revealed that enalapril given chronically to middle-aged or aged dogs with compensated heart disease was safe. The drug did not induce coughing,[33] as has been reported[50] in humans receiving ACE inhibitors, or renal dysfunction.[35]

Although results of the present study do not support a substantial benefit in delaying onset of CHF with early, chronic enalapril treatment in dogs with naturally occurring, moderate to severe mitral valve regurgitation, they do suggest that there is a benefit with treatment. This conclusion is supported by most experimental and clinical data derived from studies[6-10,13-27,c] in humans and dogs. It remains to be seen whether early ACE inhibition yields a survival benefit or acts synergistically with other drugs. Regarding the latter point, amlodipine treatment reduces mitral valve regurgitation in dogs,[g] and administration of felodipine adds to the proven benefits of enalapril treatment in humans with CHF.[51] Furthermore, experimental data suggest that amlodipine treatment may activate the RAAS through its vasodilatory effect on renal arterioles, and therefore, its use should be accompanied by ACE inhibition.[45,52] Treatment with β-adrenergic receptor blockers is beneficial in dogs with experimentally induced mitral valve regurgitation[32] and in conjunction with enalapril in humans with heart disease of various etiologies and severity.[53] Finally, treatment with the inodilator (drugs that have both positive inotropic and vasodilatory effects) pimobendan has benefits in dogs with CHF resulting from naturally occurring mitral valve regurgitation when accompanied with standard treatment that often includes ACE inhibition.[54] On the basis of the modest benefits seen in the VETPROOF, it is logical to postulate that 1 or more of these agents might be useful and possibly synergistic when administered in combination with ACE inhibitors in the management of subclinical mitral valve regurgitation in dogs, a hypothesis that will require further studies to test.

Although the present study was designed and performed as a double-blind, placebo-controlled, prospective study, certain weaknesses are evident. First, the number of dogs was small, rendering the study underpowered to detect all but the most dramatic of findings. This shortcoming was compounded by the fact that only 53% of the 124 dogs reached the endpoint of CHF. The dosage was aimed at 0.5 mg/kg per day, but fewer than 40% of the dogs actually received ≥ 0.5 mg/kg per day, which may have limited the drug's beneficial effects. Each of these weaknesses decreased the ability of the present study to reveal beneficial effects of enalapril treatment in dogs with compensated, moderate to severe mitral valve regurgitation. Finally, results of this study cannot be extrapolated to young dogs (< 5 years of age), dogs weighing > 20 kg, or dogs mildly affected

(murmurs < grade 3, dogs with radiographically normal hearts, and dogs with left atrial-to-aortic dimension ratio < 1.6). Data supported the hypothesis that enalapril administered chronically at approximately 0.5 mg/kg per day to dogs with compensated, moderate to severe mitral valve regurgitation yields a modest delay in the onset of CHF, with certain dogs possibly deriving greater benefit.

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