Efficacy of Enalapril for Prevention of Congestive Heart Failure in Dogs with Myxomatous Valve Disease and Asymptomatic Mitral Regurgitation

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We evaluated the long-term effect of early angiotensin-converting enzyme (ACE) inhibition (enalapril maleate) as monotherapy to postpone or prevent congestive heart failure (CHF) in asymptomatic dogs with mitral regurgitation (MR) attributable to myxomatous valvular disease (MVD) in a prospective, randomized, double-blinded, placebo-controlled multicenter trial involving 14 centers in Scandinavia. Two hundred twenty-nine Cavalier King Charles (CKC) Spaniels with MR attributable to MVD but no signs of CHF were randomly allocated to treatment with enalapril 0.25–0.5 mg daily (n = 116) or to placebo groups (n = 113). Each dog was evaluated by physical examination, electrocardiography, and thoracic radiography at entry and every 12 months (±30 days). The number of dogs developing heart failure was similar in the treatment and placebo groups (n = 50 [43%] and n = 48 [42%], respectively; P = .99). The estimated means, adjusted for censored observations, for the period from initiation of therapy to heart failure were 1,150 ± 50 days for dogs in the treatment group and 1,130 ± 50 days for dogs in the placebo group (P = .85).

When absence or presence of cardiomegaly at the entrance of the trial was considered, there were still no differences between the treatment and placebo groups (P = .98 and .51, respectively). Multivariate analysis showed that enalapril had no significant effect on the time from initiation of therapy to heart failure (P = .86). Long-term treatment with enalapril in asymptomatic dogs with MVD and MR did not delay the onset of heart failure regardless of whether or not cardiomegaly was present at initiation of the study.

Key words: Angiotensin-converting enzyme inhibitor; Canine; Myxomatous mitral valve disease; Preventive cardiac therapy.
Table 1. Modified NYHA system for heart failure in dogs with myxomatous valvular disease (MVD).

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asymptomatic dogs with murmur but no cardiac enlargement</td>
</tr>
<tr>
<td>II</td>
<td>Asymptomatic dogs with murmur and cardiac enlargement but no pulmonary edema</td>
</tr>
<tr>
<td>III</td>
<td>Slightly or moderately symptomatic dogs (dyspnea), increased heart rate and disappearance of sinus arrhythmia</td>
</tr>
<tr>
<td>IV</td>
<td>Severely symptomatic dogs with murmurs, cardiac enlargement, and interstitial pulmonary edema</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association.

diseases in dogs. Also, results concerning therapy of CHF should not be regarded as applicable to the asymptomatic phases of heart disease. Earlier studies concerning Cavalier King Charles (CKC) Spaniels have shown a high prevalence of mitral regurgitation (MR) caused by MVD even in middle-aged animals. With a high prevalence and an early onset of MVD, this breed is well suited to study the pharmaceutical effects of ACE inhibition on naturally occurring MR.

The objective of the present study was to test the long-term effect of ACE inhibition as monotherapy to postpone or prevent CHF in asymptomatic CKC Spaniels with MR caused by MVD. Results from this study have been presented earlier in abstracts at the American College of Veterinary Internal Medicine (ACVIM) forum in 1999 and 2000.

Materials and Methods

Animals

Two hundred thirty-seven client-owned CKC Spaniels were enrolled at 14 different centers in Scandinavia (8 in Sweden, 3 in Finland, 2 in Denmark, and 1 in Norway). Eight dogs were not reexamined after the 1st visit, leaving 229 dogs to continue in the study. Enrolled dogs comprised patients at each animal hospital, referral cases from colleagues, and dogs recruited at dog shows and through screening programs. Consent was obtained from all owners involved with the study.

Enrollment Criteria

Only CKC Spaniels afflicted with MR attributable to MVD in a modified New York Heart Association (NYHA) functional class I or II could be enrolled (see Table 1). Thus, all dogs included had a characteristic murmur. Some had enlargement of the left atrium and ventricle, but none had clinical or radiographic signs of cardiac failure.

Exclusion Criteria

Dogs could not have received any other treatment for heart failure within 2 months before entering the trial. Dogs with signs of other systemic disease and dogs outside the weight range of 5–15 kg could not be enrolled in the study. Finally, dogs could not have clinical or radiological signs of CHF (functional class III or IV; see Table 1).

Randomization and Allocation

At each clinic, the dogs were randomly assigned, in blocks of 8, to treatment or placebo groups.

Treatment

Dogs in the weight range of 5 but less than 10 kg (at entrance to trial) received 2.5 mg enalapril or placebo, and dogs in the range 10–15 kg received 5 mg enalapril or placebo. The tablets were administered PO once a day, and all dog owners were supplied with a daily log to record their drug administration. No other cardiac treatment was allowed while the dogs remained in the study.

Blinding

The study was conducted double blinded, ie, neither the clinician examining the dog nor the dog owner/handler was aware of whether the dog received enalapril or placebo tablets.

Evaluation Schedule

At entry and every 12 months (±30 days) until July 1, 1999, case history, clinical examination, thoracic radiography, and ECG examination were recorded for each dog. Two hundred thirteen dogs were enrolled during 1995, 23 during 1996, and 1 during 1997. All dogs remaining for examination during 1999 were examined before July 1, 1999, even if the interval from the last examination was shorter than 12 months. In addition to these scheduled visits, the dogs were examined as described above if they developed signs of CHF. When an individual dog entered CHF (modified NYHA III; see Table 1), the date was recorded, and the animal was considered to have reached end point and not examined further. If a dog was withdrawn for any other reason, time and cause were recorded. Date and cause of death were recorded for each dog that died during the study.

Clinical Evaluation

A special evaluation form was used at all examination centers to allow the evaluation of dogs in a uniform manner. Thoracic radiographs in left lateral and ventrodorsal projections were made for all dogs. All radiographs were evaluated for signs of cardiomegaly and interstitial or alveolar pulmonary edema. The radiographic examinations were reviewed at annual evaluation meetings to ensure uniform film readings. At the completion of the trial, all radiographs were evaluated by a certified veterinary radiologist (KH), blinded to drug assignment and dog identity. If not confirmed on radiographs by signs of cardiomegaly, including left atrial enlargement and presence of interstitial or alveolar pulmonary edema, the proposed clinical diagnosis and date for CHF were rejected.

End Point

The end point was defined as the time when heart failure (class III; Table 1) was diagnosed. The diagnosis of heart failure was accepted only when the data from the case history and physical examination were accompanied by cardiomegaly, including left atrial enlargement and interstitial or alveolar pulmonary edema on thoracic radiographs. Information of special interest from dog owners was dyspnea, cough, nocturnal restlessness, and exercise intolerance. End point was also considered to be reached if the diagnosis of heart failure, ie, pulmonary edema and pulmonary congestion, was confirmed by postmortem examination in case of spontaneous death.

Outcome Measure

The outcome measure was the time from initiation of therapy with enalapril or placebo to withdrawal due to heart failure confirmed by clinical signs and thoracic radiographs or postmortem examination.

Statistical Analysis

The statistical analyses were performed with the JMP version 3.2 software package. Differences between treatment groups in case of
Of the 229 dogs, 98 dogs (43%) developed heart failure in the treatment and placebo group (n = 50 [43%] and n = 48 [42%], respectively; P = .99). Likewise, the numbers of dogs withdrawn (n = 33 [28%] and n = 34 [30%]) or completing the study without CHF (n = 33 [28%] and n = 31 [27%]) were similar in the 2 groups (P = .89 and .88, respectively). Thus, 57% of the dogs in the treatment group and 56% of the dogs in the placebo group were censored. The mean number of days of censored observations was not significantly different between treatment and placebo groups (983 ± 450 and 898 ± 534 days, respectively; P = .32). Furthermore, there were no differences in the censoring pattern between the 2 groups with regard to time to censoring, initial age, gender, or stage of disease (initial cardiomegaly, heart murmur grade, or both). The mean time intervals from initiation of therapy to CHF were similar in dogs belonging to the treatment group and in dogs in the placebo group (743 ± 421 and 816 ± 406 days, respectively; P = .39). The estimated means adjusted for censored observations for the period from initiation of therapy to heart failure were 1,150 ± 50 days for dogs in the treatment group and 1,130 ± 50 days for dogs in the placebo group (P = .85, Fig 1a). The numbers of dogs remaining in the treatment and placebo groups were similar at 800 (63 and 63), 1,200 (36 and 40), and 1,400 (21 and 23) days (all P > .05). Dosage did not have any effect on the estimated means adjusted for censored observation for the period from initiation of therapy to heart failure, as dogs receiving a dosage between 0.38 and 0.5 mg/kg/d had a mean period comparable to those receiving a dosage between 0.25 and 0.38 mg/kg/d (1,110 ± 60 and 1,170 ± 80 days, respectively; Fig 1b). Furthermore, therapy had no effect on the time until CHF developed, when the material was divided in dogs with or without cardiomegaly at the entrance of the trial (P = .51 and .98, respectively; Fig 2a,b).

**Effect of Cardiomegaly**

Dogs with initial cardiomegaly had a shorter estimated mean time to heart failure adjusted for censored observations (963 ± 50 and 1,290 ± 40 days, respectively; P < .001) with no difference between treatment and placebo groups (Fig 3).

**Effect of Heart Murmur Intensity**

Dogs with an initial heart murmur of moderate intensity had markedly shorter time to heart failure than did dogs with low-intensity murmurs, as indicated by a shorter estimated mean time to heart failure adjusted for censored observations (1,020 ± 50 and 1,330 ± 40 days; P < .001) (Fig 4) with no difference between treatment and placebo groups. Dogs with high-intensity heart murmurs had an even shorter period before heart failure (759 ± 179 days).

**Effect of Gender**

Males had a tendency toward a more rapid progression of the disease than females, as indicated by a shorter estimated mean time to heart failure adjusted for censored ob-
Enalapril and Heart Failure

Fig 1. Percentage of all dogs in the study versus time. (a) The difference in number of days in the study between placebo- and enalapril-treated dogs was not significant (log-rank test \(P = .85\)). (b) In the treatment group, there was no difference in number of days between dogs receiving enalapril in the dose range 0.25–0.38 mg/kg and those in the dose range 0.38–0.5 mg/kg.

Fig 2. Percentage of dogs in the study versus time. The difference in number of days in the study between placebo- and enalapril-treated dogs was not significant even when the analysis was performed separately in 2 subsets of dogs, i.e., (a) dogs with normal heart size (log-rank test \(P = .51\)) or (b) in dogs with radiographic evidence of cardiomegaly at entry into the study (log-rank test \(P = .98\)).

Potential Adverse Reactions and Causes of Withdrawal

In a total of 63 dogs, potential adverse reactions (not leading to withdrawal) were recorded (Table 3). The most common complaint was cough that disappeared after a variable period. Other common findings included eosinophilic granulomas in the pharynx and seizures. There was no statistically significant difference in the number of dogs with recorded possible adverse reactions in the placebo group (n = 30) compared with the treatment group (n = 26) (\(P = .11\)). The most common cause for withdrawal was lack of owner compliance (Table 4). Other common causes included neoplastic disease, diagnostic error, and cervical disc disease. There was no significant difference in the number of dogs withdrawn because of lack of owner compliance between the treatment and placebo groups (\(P = .43\)).

Multivariate Analysis

Multivariate analysis showed that age and cardiomegaly at entry had a significant effect on the time from initiation of therapy to heart failure (Table 5). Gender tended to in-
Fig 3. Percentage of all dogs in the study versus time. The difference in number of days in the study between dogs with radiographic evidence of cardiomegaly at entry of the study and dogs with normal cardiac size was significant (log-rank test $P < .001$).

Fig 4. Percentage of all dogs in the study versus time. The difference in number of days in the study between dogs with low, medium, and high heart murmur intensity at entry into the study was significant (log-rank test $P < .001$).

Fig 5. Percentage of all dogs in the study versus time. The difference in number of days in the study between female and male dogs was not significant, although the males tended to have a more rapid progression of the disease (log-rank test $P = .11$).

Table 3. Potential adverse reactions (not leading to withdrawal) in 229 dogs with myxomatous valvular disease (MVD).

<table>
<thead>
<tr>
<th>Potential Adverse Reactions</th>
<th>Enalapril</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough (resolving)</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Eosinophilic granulomas, pharynx</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Epileptic seizures</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Dyspnea (intermittent)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Back pain</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fainting</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>VPC</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Restlessness</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Anal bursitis</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Polyuria/polydipsia</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Leg pain</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Reduced appetite</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>SVPC</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Weight loss</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Increased weight</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mammary tumor</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Pseudopregnancy</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Deafness</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Otitis externa</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Seminoma</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>37</td>
</tr>
</tbody>
</table>

VPC, ventricular premature complexes; SVPC, supraventricular premature complexes.

Discussion

The Scandinavian veterinary enalapril prevention trial is, so far, the largest and most comprehensive clinical trial completed studying the issue of whether ACE inhibition is effective to prevent CHF in symptomatic dogs with MVD. It must be remembered that the preventive effect was not studied in the IMPROVE, COVE, LIVE, and BENCH trials.3–5,7 Two other studies published on monotherapy with benazepril over shorter periods had enrollment criteria, designs, and low number of animals not allowing conclusions regarding efficacy to asymptomatic dogs.6,8 The present
Table 4. Causes for withdrawal in 67 of 229 dogs with myxomatous mitral valve disease.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Enalapril</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Owner compliance</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Neoplastic disease</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Diagnostic error</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Disc herniation</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Clinic compliance</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Owner died</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Other causes (1 case)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological crisis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otitis media</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paralysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritonitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urolithiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facial paralysis/vestibular syndrome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total 33 34

Table 5. Multivariate analysis (Cox Proportional Hazard Model) of time to heart failure by baseline, heart size, age, gender, and treatment in 229 Cavalier King Charles Spaniels with mitral regurgitation (MR) attributable to myxomatous valvular disease (MVD).

<table>
<thead>
<tr>
<th>Term</th>
<th>Est</th>
<th>SEM</th>
<th>P Value</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomegaly (Yes/No)</td>
<td>0.84</td>
<td>0.21</td>
<td>&lt;.001</td>
<td>2.31</td>
<td>1.53–3.52</td>
</tr>
<tr>
<td>Initial age (Years)</td>
<td>0.15</td>
<td>0.05</td>
<td>&lt;.01</td>
<td>1.16</td>
<td>1.04–1.29</td>
</tr>
<tr>
<td>Gender (Female/Male)</td>
<td>-0.20</td>
<td>0.11</td>
<td>.06</td>
<td>0.82</td>
<td>0.65–1.01</td>
</tr>
<tr>
<td>Therapy (Enalapril/Placebo)</td>
<td>-0.02</td>
<td>0.10</td>
<td>.86</td>
<td>0.98</td>
<td>0.80–1.20</td>
</tr>
</tbody>
</table>

n = 229, LogLikelihood 440.5, P < .001

Est, estimate; SEM, standard error of the mean; RR, risk ratio.
trations after ACE inhibition. An interesting finding was that, although left ventricular myocyte cell length was greater in the dogs with MR compared to the control dogs, it also tended (not dramatically) to be greater in dogs with MR that received ramipril than in dogs receiving placebo. Indeed, the finding in this study, ie, that enalapril did not prevent CHF regardless of whether the dogs had cardiomegaly or not at the time of initiation of therapy, speaks against the possibility that ACE inhibition prevents progression of dilatation. Accordingly, the practice of starting ACE inhibitor treatment in dogs with MVD as soon as cardiomegaly is evident, as is commonly recommended and used in clinical practice, is not supported by the present study. In this context, it is interesting that a 6-month study comparing enalapril with hydralazine in dogs with naturally occurring CHF (NYHA class III) caused by MVD showed that the enalapril group continued dilating their hearts, whereas the group on hydralazine did not. Possible explanations for this finding could be that hydralazine is a more potent vasodilator than enalapril and that the cardiotoxic effect of angiotensin II in the hydralazine group, in which the RAAS activity was markedly increased, helped prevent progression of cardiac dilatation.

The present study indicates that initial heart size as estimated by thoracic radiographs and initial intensity of the heart murmur affected the time to develop CHF. Dogs with cardiomegaly at presentation developed CHF in less time, which is a natural finding, as they were in a more advanced stage of MVD and had more severe MR when entering the trial. Murmur intensity at entrance to the trial also had a dramatic effect on the prognosis (Fig 4). Dogs with murmurs of moderate intensity had a shorter estimated mean time to CHF than did dogs with low-intensity murmurs, and dogs with initial high-intensity murmurs had the shortest mean time to overt heart failure. This finding is in agreement with earlier studies in which the murmur intensity showed a marked correlation to the severity of MVD. Thus, dogs with initial high-intensity murmurs had a more advanced stage of MVD and MR with a shorter expected time to reach CHF than dogs with low-intensity murmurs. Male dogs tended to have a more rapid progression of the disease than female dogs (Cox Proportional Hazard Model \[P = .061\]), suggesting an 18% increase of risk for developing CHF (Table 5). This finding is expected, as a more rapid course for MVD has been found for male dogs in earlier studies, but the cause for this difference between the genders is unknown at present.

In accordance with other studies involving ACE inhibitor therapy in dogs, this study also showed that adverse effects are few with this type of therapy, even with a 4.5-year follow-up period. The treatment group was not different from the placebo group with regard to potential adverse reactions. Thus, it is unlikely that any of the potential adverse effects listed in the enalapril group in Tables 3 and 4 are actually caused by enalapril therapy.

Compared to many large human multicenter trials, the number of included dogs in this study (229 dogs) may appear modest. A low number of included dogs may lead to a low power of the study. However, statistical power is determined not only by the number of observations but also by the interindividual variation. Many large human multicenter trials are designed to give results valid for a wide variety of patients regarding age, lifestyle, detrimental factors such as smoking, genotype, and type of underlying disease. This is achieved by having wide inclusion criteria and, to get sufficient statistical power, a large number of patients. Also, the other large veterinary multicenter trials have had less strict inclusion criteria than the present study, in which we studied 229 dogs of 1 breed affected by 1 cardiac disease, it may be argued that MR and MVD may be different in CKC Spaniels than in other breeds. However, to our knowledge, this has never been shown, and it is our experience that the lesions are macro- and microscopically identical to those found in other breeds. The only known difference appears to be that CKC Spaniels develop the disease at a younger age than other breeds.

Any trial aimed at studying the long-term effects of a drug in a naturally occurring disease in dogs is bound to have many censored observations. Data from censored patients are included in the statistical analysis only until the time they are removed from the study, even though the treatment may have been effective beyond that time. Statistically, large numbers of censored values decrease the number of subjects exposed (at risk) at later times, making the Kaplan-Meier estimates less reliable. At present, there is, to our knowledge, no recommendation of an acceptable level of censoring. The LIVE study had an overall rate of censored observations of 44% (52% in the enalapril group and 36% in the placebo group) over a maximal period of 17 months. The BENCH trial had an overall rate of censored observations of 53% (62% benazepril group and 53% placebo group) over a maximal study period of approximately 2 years. This study had a rate of censored values similar to the other 2 trials (57%), largely from having subjects withdrawn (29%) and lost to follow-up and from having the study end while many dogs had not yet developed heart failure (28%). In that context, it should be noted that the maximal study period in this trial was long, approximately 4.5 years, and that a similar number of dogs were censored in the placebo and treatment groups.

The average dosage of enalapril in this study was 0.37 ± 0.08 mg/kg (range, 0.25–0.5 mg/kg), which is the recommended dosage of enalapril. There was no difference in outcome between dogs receiving a dosage in the upper range (0.38–0.5 mg/kg) and the lower range (0.25–0.38 mg/kg). In earlier studies investigating the effects of enalapril in naturally occurring heart disease, a dosage of “approximately 0.5 mg/kg” has been used. A certain range in dosage is unavoidable in any patient-based study, as there are only a few fixed tablet sizes to choose from. To reduce dosage variation and avoid over- or underdosage, the present trial involved dogs with a fixed weight range and 4 types of tablets: 2.5- and 5-mg enalapril tablets and macросcopically identical placebo tablets. Earlier studies have shown that a dosage of approximately 0.5 mg/kg leads to a maximum reduction of serum ACE activity of 75–85%, which in turn has effects on hemodynamics. Indeed, it is difficult to obtain 100% inhibition of ACE with the currently available ACE inhibitors, a finding that has been attributed to the presence of enzymatic systems other than ACE that can convert angiotensin I to angiotensin II.
available, it is not clear how it should be defined clinically in dogs. In the Scandinavian veterinary enalapril prevention trial, we used a special modification of the NYHA classification adapted to canine CHF (Table 1). Ramipril is considered to have a greater tissue penetration than the other 2 drugs. However, as ACE inhibitors such as benazepril and ramipril would have different effects in trials similar to that described in this paper, Ramipril is considered to have a greater tissue penetration than the other 2 drugs. However, as ACE appears to be scant in canine atrioventricular valves and angiotensin II receptors and ramipril has been shown to have no effect on preventing volume-overload cardiac hypertrophy, it appears less likely that a higher tissue penetration would yield any major advantages in cases of MVD.

In conclusion, long-term treatment with ACE inhibition in asymptomatic dogs with MVD does not delay the onset of CHF regardless of whether cardiomegaly is present at initiation of therapy or not. Basic mechanisms responsible for the valvular degeneration should be further studied to create a scientific basis for development of future efficient preventive therapy for MVD. MVD is a slowly progressing disease, and dogs may remain asymptomatic without any therapy for many years after the onset of heart murmurs. Research trials designed to evaluate “prophylactic” therapy for asymptomatic dogs with MVD must, accordingly, involve long-term treatment over several years rather than a few weeks or months.

Acknowledgments

The investigators are grateful to Merck Research Laboratories (later Merital Ltd) for supporting the study, and we thank the Small Animal hospitals involved (Albano Stockholm, Bagarmossen Stockholm, Blå stjärnan Gothenburg, Helsingborg, Hau-Mau Helsinki, Mevet Helsinki, Middelfart, Sandviken, Strömsholm, and Örnsköldsvik) and the Schools of Veterinary Medicine in Copenhagen, Helsinki, Oslo, and Uppsala for their efforts and additional economical support enabling a successful completion of the study.

References

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dystrophic changes including marked endomysial fibrosis, myofiber necrosis, variability of fiber size, and perimysial
lipid accumulation. Immunohistochemistry showed that laminin α2 chain was absent or reduced, while dystrophin
and all the components of the dystrophin-associated glycoprotein complex were present and normal. One cat was examined in detail. Motor nerve conduction velocity (MNCV) was decreased, and ultrastructurally the peripheral nerves showed Schwann cell degeneration and demyelina-
tion. Brain imaging was not performed, but white matter changes were not apparent in the brain at necropsy. The
disease in these cats is similar to primary or secondary merosin (laminin α2)-deficient congenital muscular dystro-
phy (CMD) in humans and to dystrophia muscularis in mice.

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We report laminin α2 (merosin)-Deficient Muscular Dystrophy and Demyelinating Neuropathy in Two Cats.
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We report laminin α2 (merosin) deficiency associated with muscular dystrophy and demyelinating neuropathy in two
cats. The cats developed progressive muscle weakness, and
atrophy. Either hypotonia or contractures resulted in recumbency, necessitating euthanasia. Muscle biopsies showed
dystrophic changes including marked endomysial fibrosis, myofiber necrosis, variability of fiber size, and perimysial
lipid accumulation. Immunohistochemistry showed that laminin α2 chain was absent or reduced, while dystrophin
and all the components of the dystrophin-associated glycoprotein complex were present and normal. One cat was examined in detail. Motor nerve conduction velocity (MNCV) was decreased, and ultrastructurally the peripheral nerves showed Schwann cell degeneration and demyelina-
tion. Brain imaging was not performed, but white matter changes were not apparent in the brain at necropsy. The
disease in these cats is similar to primary or secondary merosin (laminin α2)-deficient congenital muscular dystro-
phy (CMD) in humans and to dystrophia muscularis in mice.