Valvular heart disease in the dog

Adrian Boswood, MA, VetMB, DVC, Dipl. ECVIM (Cardiology), MRCVS

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Dr. Boswood graduated from The University of Cambridge in 1989. In 1990, following a period in general practice, he joined the Royal Veterinary College as an intern and remained at the Royal Veterinary College ever since where he is now a Senior Lecturer. Adrian Boswood's main clinical interest is in medical cardiology and his research interests are in cardiac biomarkers and valvular heart disease of dogs.

Acquired valvular heart disease in the dog is the most common cause of heart disease and heart failure in the canine population (1). Valvular heart disease in the dog is usually a chronic degenerative condition which is known by various terms including endocardiosis and myxomatous mitral valve disease. The disease most commonly affects the mitral valve and results in the development of mitral regurgitation. This mitral regurgitation leads to an increased volume of blood being pumped by the left ventricle due to the proportion of each ventricular ejection that goes back into the left atrium. Chronically this results in increased left ventricular and left atrial size and, in some affected animals, results in the development of clinical signs of heart failure. It typically affects older small breed dogs although certain breeds of dog, particularly Cavalier King Charles Spaniels, appear to have a higher prevalence of disease and an earlier onset of both disease and clinical signs.

In patients that are regularly examined by veterinarians the characteristic left-sided systolic murmur of mitral insufficiency is usually the first clinical abnormality identified. The development of a murmur often precedes the development of clinical signs by many years. In the SVEP study (2) Cavalier King Charles Spaniels with a heart murmur and no cardiac enlargement had a median period of well over three years before developing signs of heart failure. In a recent paper Borgarelli, *et al.* (3) showed that in a more mixed population of asymptomatic dogs with mitral regurgitation fewer than 50% of the dogs died as a consequence of their disease during the period of follow-up. Thus in some cases mitral valve disease can be a relatively benign slowly progressive condition that does not progress sufficiently to lead to the development of clinical signs. In others the disease may progress to the point where clinical signs of heart failure result. The challenge for the clinician faced with patients with this disease is to establish a diagnosis of the disease, recognize at which stage of this progressive disease the patient in question currently resides and to appropriately and optimally treat those patients that require treatment.

A diagnosis of mitral regurgitation can be suspected in any dog with a left apical systolic murmur, particularly if it is a small breed dog. There are some large breed dogs that are affected by primary mitral valve disease but this is a rarer form of the disease. Large breed dogs with primary valvular disease may have a slightly different course of disease compared to small breed dogs (4).

HOW I TREAT...

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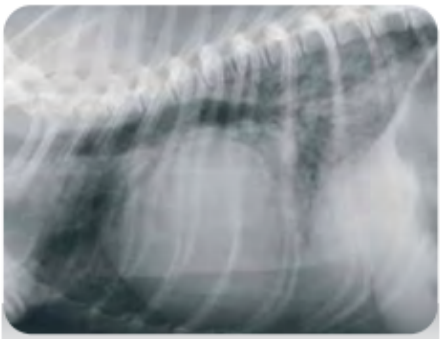

Figure 1.

A lateral thoracic radiograph from a dog with advanced mitral valve disease. There is marked cardiomegaly with craniocaudal widening of the cardiac silhouette and dorsal displacement of the trachea. The lung fields are diffusely opacified by the presence of an alveolar pattern indicating the presence of pulmonary edema, in this case secondary to left-sided congestive heart failure. This is a severe example of the radiographic changes that can be associated with advanced mitral valve disease.

Confirmation of the diagnosis of primary valvular disease requires two-dimensional and Doppler echocardiography but the clinical presentation is so typical, and the disease so common, that this is not a test that is necessary to perform in every case. Thoracic radiographs are particularly useful for determination of the stage of disease by demonstrating the presence or absence of cardiomegaly and the presence or absence of left-sided congestive heart failure ***(Figure 1)***.

Left apical systolic murmurs may also be caused by congenital heart disease and mitral regurgitation secondary to other causes including dilated cardiomyopathy and bacterial endocarditis. These conditions are however less commonly encountered and tend to occur in different types of dog.

For the purposes of this article, I will discuss only the chronic management of patients with heart failure and not describe the acute management of patients with sudden onset of severe heart failure. The UK trade names and doses of all the drugs mentioned appear in ***Table 1***. I will divide patients into four stages and discuss the treatment options that are appropriate at each stage in the light of what I consider to be current best evidence.

These stages are as follows:

- Early disease: the patient without clinical signs and without significant cardiomegaly.
- Moderately progressed disease: A patient without overt clinical signs but with evidence of cardiomegaly implying the necessity to adapt to the increased volume of blood being encountered by both the left atrium and ventricle.
- Heart failure: A patient that has developed signs of congestive heart failure as a consequence of their mitral valve disease. Typically the first signs of heart failure will be left-sided failure and will include pulmonary congestion and edema.
- Refractory heart failure: A patient that has redeveloped clinical signs despite receiving therapy for heart failure.

Treatment of the patient with mitral regurgitation according to the stage of disease

Early disease

There is little evidence to suggest the benefit of any therapy in the early stages of mitral valve disease. Two published studies have evaluated the efficacy of treatment with angiotensin converting enzyme inhibitors (ACEI) in this population (2,5). These studies produced conflicting results. The study by Kvart, *et al.* was a double-blind placebo controlled prospective study performed only in Cavalier King Charles Spaniels (2). This study suggested that there was no benefit of administration of ACEI in dogs prior to the onset of clinical signs irrespective of whether there was any cardiomegaly. The more recent study by Pouchelon, *et al.* (5) is a retrospective study conducted in a small but more heterogeneous population of dogs (***Editor's note***: 141 dogs). The conclusion of the paper was that Benazepril administered in dogs with early disease may be of benefit in dogs of breeds other than Cavalier King Charles Spaniels. The fact that this was a retrospective, unblinded study with a low event rate (a low number of animals in the study reached the endpoints of cardiac death or onset of heart failure) and with different median follow-up periods for the treated and untreated groups mean that the conclusions should be interpreted with some caution. I would regard their conclusions as generating a useful hypothesis that should be tested in future in a placebo controlled, double-blind study and I am not yet convinced of the value of early therapy in this group.

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Table 1.
Proprietary names and doses of drugs

Generic drug name	Dose and frequency (These doses may differ from those given in the data sheet)
Enalapril	0.5 mg/kg s.i.d.-b.i.d.
Benazepril	0.25-0.5 mg/kg s.i.d.-b.i.d.
Pimobendan	0.2-0.6 mg/kg/day divided into two doses
Frusemide Furosemide	1-2 mg/kg b.i.d. initially increasing to a maximum of 4 mg/kg t.i.d.
Spironolactone	1-3 mg/kg b.i.d.
Digoxin	0.22 mg/m² b.i.d. check trough (8 hour post pill) serum digoxin levels after 5-7 days to ensure therapeutic and not excessive concentrations have been achieved
Amlodipine	0.05-0.1 mg/kg s.i.d.-b.i.d.
Hydralazine	0.5-3.0 mg/kg b.i.d.-t.i.d. (start with low dose and titrate to effect with blood pressure monitoring)
Sildenafil	0.5-3.0 mg/kg s.i.d.-t.i.d.
Theophylline	20 mg/kg s.i.d.
Etamiphylline Camsylate	10–33 mg/kg t.i.d. (according to data sheet)
Terbutaline	1.25-5 mg/dog b.i.d.-t.i.d.
Butorphanol	0.5 mg/kg b.i.d.-q.i.d.
Codeine	0.5-2 mg/kg b.i.d.

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No responsibility is accepted for adverse reactions to the drugs given at the dosages recommended and veterinarians are recommended to cross reference to other sources (e.g. BSAVA Small Animal Formulary) prior to administration.

Abbreviations used: s.i.d. once daily, b.i.d. twice daily, t.i.d. three times daily, q.i.d. four times daily, mg milligram, kg kilogram, m² meter squared.

My approach to this population of dogs is not to intervene pharmacologically but to advise and educate the client. If the animal is overweight then weight control is important. Continuing to regularly exercise the patient is in my opinion probably of benefit. There is no convincing evidence to suggest a benefit of sodium restriction at this stage of the disease. Clients should be advised about the signs that might indicate the development of heart failure and the necessity for treatment; such as exercise intolerance, increased respiratory rate and effort, cough, lethargy and unexplained weight loss. Regular re-examination of these patients may help pick up early signs of clinical deterioration and will also reassure the client that one is not simply ignoring the presence of a clinically significant disease. Client reassurance is important at the early stage of the disease because over-stressing the likelihood of development of problems in the near future may cause unnecessary worry. Many dogs remain at the early stage of mitral valve disease for many years and some will succumb to non-cardiac disease before they have ever had the opportunity to demonstrate signs of heart failure.

Moderately progressed disease

Two studies have evaluated the effects of ACEI in dogs with cardiomegaly prior to the onset of signs of heart failure these are the SVEP study (2) and the VETPROOF study (6). Both of these studies evaluated the effect of treatment prior to the onset of clinical signs in dogs with mitral valve disease. Some of the dogs in the SVEP study had cardiomegaly and left atrial enlargement was one of the inclusion criteria for the VETPROOF study – therefore all the dogs in this study had some degree of cardiac enlargement. Again these studies appear to generate conflicting conclusions. The SVEP study showed no benefit of ACEI therapy with respect to delaying the onset of heart failure in Cavalier King Charles Spaniels. The VETPROOF

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study did not show a significant effect of Enalapril on the primary endpoint of the study which was time to onset of congestive heart failure. Looking at a secondary combined endpoint of all cause mortality and onset of heart failure they appeared to show a significant difference after excluding those dogs that succumbed in the first 60 days of the study. This was not a pre-planned analysis but generates a fascinating hypothesis that there may be a non-cardiac beneficial effect on survival. The combination of results from these two studies is not enough to currently convince me of the benefit of therapy even in dogs with cardiomegaly at the time of diagnosis.

It is worth pointing out that only ACEI have been evaluated as potentially beneficial treatment prior to the onset of clinical signs in large well conducted studies. There are of course other candidates for early treatment that have not been evaluated as rigorously and all that one can say with respect to other therapy is "we don't know". It may be in the future that some therapy is proved to be beneficial at this stage in the disease but at the moment if we are to practice "evidence-based medicine" there is insufficient evidence of a convincing benefit of therapy for me to advocate its use.

A recent, as yet unpublished study, has claimed a benefit of Spironolactone prior to the onset of signs of heart failure however the absence of full disclosure of the results of this study through publication precludes further evaluation of this claim and it has not as yet changed my practice of not treating these patients.

Again my management of patients and their owners at this stage of the disease consists of education and monitoring. It is important that signs of heart failure are recognized as and when they occur so that treatment can be introduced when it is known to be effective. Clients can be instructed in how to take a respiratory rate at home and should also be advised to look out for subtle signs of intolerance of exercise. Having said this it is still the case that many dogs with mitral regurgitation and cardiomegaly live for years before developing signs of heart failure so over-stressing the likelihood of development of signs may lead to anxiety on the part of clients and plenty of "false alarms".

Onset of heart failure

The onset of congestive heart failure is best documented with thoracic radiographs. When a patient has developed signs of congestive heart failure secondary to mitral valve regurgitation there is convincing evidence of benefit of therapy both in terms of improvement of quality of life and, with some treatments, prolongation of life. Several controlled studies have been conducted from which valid conclusions on which to base our therapy can be drawn. There are multiple studies that have demonstrated the benefits of ACEI in the treatment of dogs with mitral valve disease. The LIVE study (7) and the BENCH study (8) were two of the earlier studies published. These showed that compared to placebo ACEI prolonged survival of dogs in heart failure when added to standard therapy of diuretics plus in some cases digoxin and other drugs. These studies both enrolled populations of dogs including those with mitral regurgitation. A sub-analysis of the LIVE study (7) showed benefit specifically in the group with mitral regurgitation. Thus ACEI are better than placebo in the treatment of dogs in heart failure secondary to mitral valve disease.

More recently Pimobendan has been shown to be efficacious. Mitral valve disease studies have demonstrated improvements in quality of life and time to events such as hospitalization are improved with Pimobendan (9). The VetSCOPE study suggested that the beneficial effects of Pimobendan may exceed those of ACEI (10) although substantial debate remained after the conclusion of this study. The recently reported QUEST study (11), a positive controlled, single-blind, prospective study comparing Benazepril to Pimobendan concluded that the benefits of Pimobendan exceeded those of Benazepril (and by inference probably other ACEI) with a 91% prolongation of the time to reach a composite end-point of death, euthanasia for cardiac reasons or treatment failure ***(Figure 2)***. This study suggests that if either an ACEI or Pimobendan is to be used in isolation, in conjunction with diuresis and other treatments, then Pimobendan is the preferred agent. What it does not enable us to conclude is whether not the combination of an ACEI and Pimobendan will be better still. There is also recent, as yet unpublished, evidence of a benefit of Spironolactone in dogs with mitral regurgitation and signs of heart failure.

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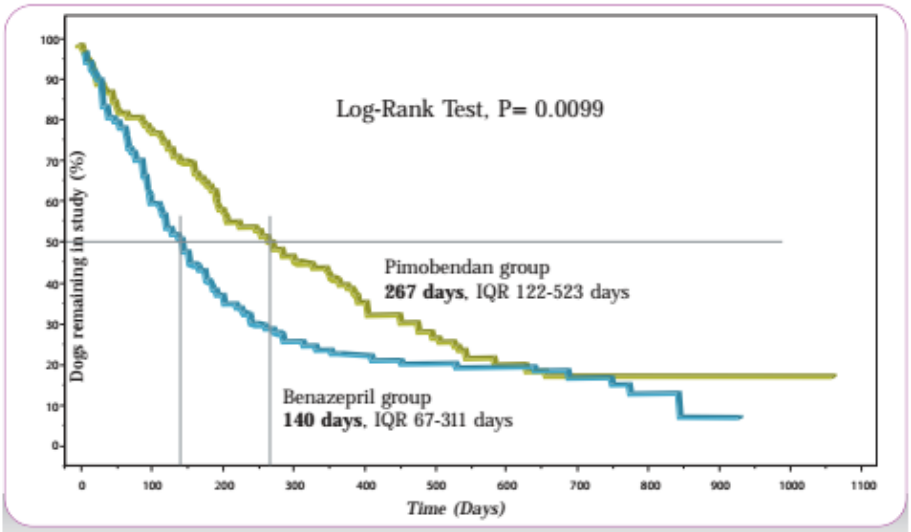


Figure 2.

Kaplan Meier survival analysis from the QUEST study. The median time to reaching the primary endpoint was 267 days in the Pimobendan group compared to 140 days in the Benazepril group suggesting a 91% prolongation of time to cardiac death, euthanasia for cardiac reasons or treatment failure in the group receiving Pimobendan.

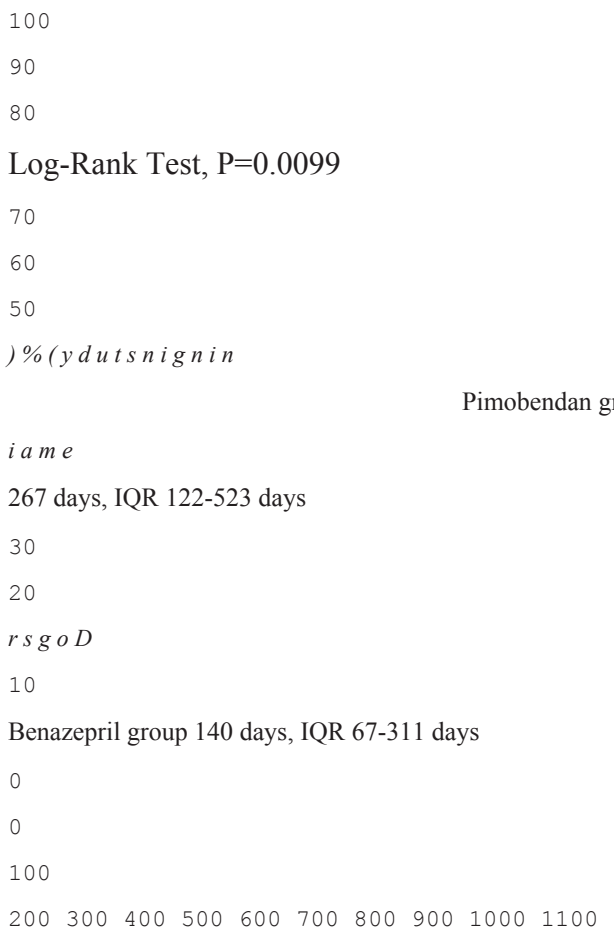
The way I treat patients at this stage depends to some extent on client preference and the feasibility of administering multiple medications in these patients. The optimum treatment could consist of up to four medications. What is not in doubt is the necessity for the administration of Frusemide to patients with congestive heart failure. Therefore the two, three and four drug regimes would be:

- Frusemide plus Pimobendan
- Frusemide plus Pimobendan plus ACEI; or
- Frusemide plus Pimobendan plus ACEI plus Spironolactone.

Where minimum therapy is dictated for either financial reasons or risks of poor compliance then the two drug regime will suffice. Optimal therapy may involve administration of either the three or four drug regime although evidence of additional benefit of these therapies when added to the two drug regime is currently lacking. However, the opinion is widely held among cardiologists that there are additional benefits.

Refractory heart failure

Once a patient is receiving optimal therapy following the onset of signs of heart failure there is often a period of several months when the patient is fairly stable and compensates for their heart failure (provided they continue to receive their treatment). Unfortunately, for most dogs there reaches a point where their clinical signs return despite receiving treatment and modification of treatment is necessary. Modification should consist of optimization of doses of drugs already being received plus the addition of further treatment. In this late stage of disease there is a lack of evidence of efficacy of any particular therapy and a plethora of individual opinion. If a patient is only receiving two or three of the drugs outlined in the different regimes above I would add the others to ensure that all four of Frusemide, Pimobendan, an ACEI and Spironolactone are being received by the patient. In addition to this combination there is the option to add further diuretics, further vasodilators and/or Digoxin to the treatment; the latter particularly where patients have atrial fibrillation.



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I undertake the following modifications to treatment:

- Increase the Frusemide dose and frequency up to a maximum of 4 mg/kg three times daily.
- Maximize the Spironolactone dose up to 2-3 mg/kg twice daily.
- Double the frequency of the ACEI administration (going from once daily to twice daily).

After this one can consider addition of further diuretics, particularly thiazide diuretics as these act elsewhere within the nephron (sequential nephron blockade) and further vasodilators including Amlodipine and Hydralazine. If patients develop signs of right-sided congestive heart failure these may be secondary to the development of pulmonary hypertension. Some authors have advocated the use of Sildenafil in these circumstances (12).

There are many risks associated with the administration of multiple drugs to patients with advanced valvular heart disease; the most frequently seen complications include compromised renal function and electrolyte disturbances (13). I would recommend checking a biochemistry profile in patients with mitral regurgitation prior to introduction of treatment and 7-10 days after any significant modification to therapy. In the later stages of disease it is almost inevitable that some degree of azotemia will develop. Provided this is modest then therapy can be continued but in some circumstances the creation of concurrent renal dysfunction can be a limiting factor in the ability to administer further therapy.

Ultimately the majority of patients that develop signs of heart failure secondary to mitral regurgitation will succumb to their disease (75% of dogs in the QUEST study reached the primary endpoint (11)), despite further attempts at therapy. In many cases it is necessary to consider euthanasia and the decision to undertake this should be informed by the quality of life enjoyed by the patient on treatment and client preferences.

Additional problems

There are two problems relating to the above classification. One is the artificial sense of certainty it creates about dogs fitting into one of the categories rather than hovering on the boundaries. The second problem relates to the clinical sign of intractable coughing that occurs in many dogs with valvular heart disease.

Any type of categorization of disease artificially divides a continuous spectrum of patients into a series of apparently distinct categories. There is often a problem with dogs lying on the boundaries between categories. There is an artificial level of certainty associated with a patient either having or not having signs of heart failure. In some patients it is difficult to judge, for instance in patients with moderate to marked intolerance of exercise, or patients with evidence of a mild interstitial lung pattern radiographically: are these patients in heart failure or not? It may be that in the future the use of biomarkers may help us to distinguish dogs that are more or less likely to be showing signs of heart failure and NTproBNP appears promising in this respect (14,15). See also first paper in this issue by M. Oyama and C. Reynolds. Sometimes however it is necessary to consider, where clinical signs and radiography or echocardiography suggest the disease is advanced, the introduction of empirical therapy to see if signs will improve. This strategy can sometimes be fraught with uncertainty because concurrent disease could be responsible for the signs that might either improve in response to the same therapy or simply resolve with time. Thus an apparent response to therapy is a tenuous reason to condemn a dog to lifelong therapy. It is very unlikely that a dog with a relatively quiet heart murmur that does not have evidence of cardiac enlargement will be showing any clinical signs as a consequence of their disease.

Coughing is one very specific clinical sign in dogs with mitral valve disease that may be a consequence of the disease but not necessarily a sign of heart failure. It is widely believed that the cough in dogs with mitral valve disease, which frequently precedes signs of heart failure, is due to the physical size of the enlarged left atrium leading to compression of the left mainstem bronchus. In this circumstance treatment aimed at controlling signs of congestive heart failure may not lead to a resolution of the signs of coughing because they do not necessarily reduce the size of the left atrium. Various strategies have been suggested in these patients in an effort to improve signs. These can all be tried in these patients but,

I undertake the following modifications to treat- ment:

• Increase the Frusemide dose and frequency up to a maximum of 4 mg/kg three times daily.

•Maximize the Spironolactone dose up to 2-3 mg/kg twice daily.

• Double the frequency of the ACEI administration (going from once daily to twice daily).

After this one can consider addition of further diuretics, particularly thiazide diuretics as these act elsewhere within the nephron (sequential nephron blockade) and further vasodilators including Amlodipine and Hydralazine. If patients develop signs of right-sided congestive heart failure these may be secondary to the development of pulmonary hypertension. Some authors have advocated the use of Sildenafil in these circumstances (12).

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despite the use of many or all of these, the cough frequently proves unresponsive to treatment. Strategies for treatment include:

- Bronchodilation: Theophylline, Etamiphylline and Terbutaline could be considered.
- Management changes: Weight loss, avoidance of smoky dusty environments, use of a harness rather than a collar to prevent further irritation to the airways.
- Introduction of low doses of vasodilators or diuretics: the rationale behind this approach is to try to physically reduce left atrial size.
- Cough suppressants: Butorphanol or Codeine can be used intermittently to suppress the cough when it is particularly problematic.
- Anti-inflammatory medication: some authors advocate the use of intermittent low dose corticosteroids or steroids by inhaler in these circumstances.

Future directions

One recent exciting development that may have significant ramifications for the identification and management of heart disease in dogs with mitral valve disease (and other cardiac diseases) is the development of assays for cardiac biomarkers (See article on page 2). The measurement of NTproBNP seems particularly promising. Several recent studies have outlined the value of this marker in the identification of patients with heart disease and heart failure (14,15). In human patients assessment of biomarkers can assist in both the identification of patients with more advanced disease and decisions with regard to their therapy. There are also prognostic implications of elevated levels of NTproBNP in human patients; preliminary data from dogs would also suggest that there is a strong predictive association between NTproBNP concentration and outcome.

It is conceivable that in future we may be able to initiate therapy with more confidence in patients with mitral valve disease that have elevated concentrations of NTproBNP. The potential for specifically targeting a reduction of natriuretic peptide concentrations in humans is already being explored (16,17) and this is an avenue worthy of further evaluation in dogs.

REFERENCES

1. Buchanan JW. Prevalence of Cardiovascular Disorders. In: Fox PR, Sisson D, Moise NS, eds. *Textbook of Canine and Feline Cardiology*. Philadelphia: Saunders, W.B.; 1999: 457-470.
2. Kvart C, Haggstrom J, Pedersen HD, *et al*. Efficacy of enalapril for prevention of congestive heart failure in dogs with myxomatous valve disease and asymptomatic mitral regurgitation. *J Vet Intern Med* 2002; **16**: 80-88.
3. Borgarelli M, Savarino P, Crosara S, *et al*. Survival characteristics and prognostic variables of dogs with mitral regurgitation attributable to myxomatous valve disease. *J Vet Intern Med* 2008; **22**: 120-128.
4. Boegarelli M, Zini E, D'Agnolo G, et al. Comparison of primary mitral valve disease in German Shepherd dogs and in small breeds. *J Vet Cardiol* 2004; **6**: 27-34.
5. Pouchelon JL, Jamet N, Gouni V, *et al*. Effect of benazepril on survival and cardiac events in dogs with asymptomatic mitral valve disease: A retrospective study of 141 cases. *J Vet Intern Med* 2008; **22**: 905-914.
6. Atkins CE, Keene BW, Brown WA, *et al*. 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. *J Am Vet Med Assoc* 2007; **231**: 1061-1069.
7. Ettinger SJ, Benitz AM, Ericsson GF, *et al*. Effects of enalapril maleate on survival of dogs with naturally acquired heart failure. The Long-Term Investigation of Veterinary Enalapril (LIVE) Study Group. *J Am Vet Med Assoc* 1998; **213**: 1573-1577.
8. BENCH, Pouchelon JL, Martignoni L, *et al*. The effects of benazepril on survival times and clinical signs of dogs with congestive heart failure: Results of a multicenter, prospective, randomized, double-blinded, placebo-controlled, long-term clinical trial. *J Vet Cardiol* 1999; **1**: 7-18.
9. Smith PJ, French AT, Van Israel N, *et al*. Efficacy and safety of pimobendan in canine heart failure caused by myxomatous mitral valve disease. *J Small Anim Pract* 2005; **46**: 121-130.
10. Lombard CW, Jons O, Bussadori CM. Clinical efficacy of pimobendan versus benazepril for the treatment of acquired atrioventricular valvular disease in dogs. *J Am Anim Hosp Assoc* 2006; **42**: 249-261.
11. Häggström J, Boswood A, O'Grady M, *et al*. Effect of pimobendan versus benazepril hydrochloride on survival times in dogs with congestive heart failure due to naturally occurring myxomatous mitral valve disease: Results of the QUEST study. *J Vet Intern Med* 2008 Jul 11 (in press).
12. Bach JF, Rozanski EA, MacGregor J, *et al*. Retrospective evaluation of sildenafil citrate as a therapy for pulmonary hypertension in dogs. *J Vet Intern Med* 2006; **20**: 1132-1135.
13. Boswood A, Murphy A. The effect of heart disease, heart failure and diuresis on selected laboratory and electrocardiographic parameters in dogs. *J Vet Cardiol* 2006; **8**: 1-9.
14. Boswood A, Dukes-McEwan J, Louvieo J, *et al*. The diagnostic accuracy of different natriuretic peptides in the investigation of canine cardiac disease. *J Small Anim Pract* 2008; **49**: 26-32.
15. Oyama MA, Fox PR, Rush JE, *et al*. Clinical utility of serum N-terminal pro-B-type natriuretic peptide concentration for identifying cardiac disease in dogs and assessing disease severity. *J Am Vet Med Assoc* 2008; **232**: 1496-1503.
16. Troughton RW, Frampton CM, Yandle TG, *et al*. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *The Lancet* 2000; **355**: 1126-1130.
17. Lainchbury JG, Troughton RW, Frampton CM, *et al*. NTproBNP-guided drug treatment for chronic heart failure: design and methods in the "BATTLESCARRED" trial. *Eur J Heart Fail* 2006; **8**: 532-538.

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REFERENCES

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5. Pouchelon JL, Jamet N, Gouni V, et al. Effect of benazepril on survival

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6. Atkins CE, Keene BW, Brown WA, et al. Results of the veterinary enalapril

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7. Ettinger SJ, Benitz AM, Ericsson GF, et al. Effects of enalapril maleate

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8. BENCH, Pouchelon JL, Martignoni L, et al. The effects of benazepril on survival times and clinical signs of dogs with congestive heart failure: Results of a multicenter, prospective, randomized, double-blinded, placebo-controlled, long-term clinical trial. J Vet Cardiol 1999; 1: 7-18.

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11. Häggström J, Boswood A, O'Grady M, et al. Effect of pimobendan versus

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13. Boswood A, Murphy A. The effect of heart disease, heart failure and

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