

Asymptomatic Canine Degenerative Valve Disease: Current and Future Therapies



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KEYWORDS

• Chronic • Mitral valve • Myxomatous • Preclinical • Stage B2 • Treatment

KEY POINTS

- Asymptomatic mature dogs with systolic heart murmurs characteristic of mitral regurgitation should undergo diagnostics to determine the presence or absence of heart enlargement and to document that the dog is normotensive.
- Treatment is not recommended in dogs with stage B1 degenerative valve disease (asymptomatic with normal heart size); this recommendation remains unchanged by new evidence.
- Treatment with pimobendan has been shown to extend symptom-free and overall survival of dogs with stage B2 degenerative valve disease (asymptomatic with heart enlargement).
- Scheduled follow-up and client communication regarding monitoring for the development of clinical signs associated with disease progression remains a cornerstone of management in all stages of degenerative valve disease.
- Left mainstem bronchial compression and pulmonary hypertension represent common sequelae of degenerative valve disease that can lead to the development of clinical signs requiring therapy before the onset of congestive heart failure.

INTRODUCTION

Degenerative valve disease (DVD) is the leading cause of heart disease and heart failure in the dog and has many recognized aliases, including myxomatous mitral valve disease, chronic degenerative valvular disease, endocardiosis of the atrioventricular

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valves, and mitral valve disease.^{1,2} Older small-breed dogs are predisposed, but large breeds also are at risk as they age.¹ Although dogs of any breed can develop DVD, some breeds, such as the Cavalier King Charles spaniel (CKCS) are known to suffer from a higher incidence overall and may be affected at younger ages, although their typical course of progression is not different from other small-breed dogs.^{3,4} Affected large-breed dogs may experience more rapid progression.⁵ The etiology of DVD remains unknown, but there is likely a genetic component in some breeds, such as the CKCS.^{2,3}

The underlying pathophysiology of DVD is characterized primarily by myxomatous degeneration of the mitral valve and associated chordae tendinae with concurrent involvement of the tricuspid valve in approximately 30% of cases.¹ The degenerating mitral \pm tricuspid valves become incompetent, leading to increasing volumes of regurgitation, commensurate volume overload, and associated atrial and ventricular chamber enlargement. Degeneration of the mitral valve is typically most severe, leading to progressive left atrial and left ventricular enlargement.

Degenerative valve disease is typically identified during the long asymptomatic or preclinical stage and progresses slowly over years; however, individual dogs may experience more rapid progression. Initial detection of DVD is typically related to the identification of a left apical systolic murmur characteristic of mitral regurgitation (MR) in a dog with no past or present clinical signs attributable to congestive heart failure (CHF). A staging scheme for DVD was introduced in the 2009 American College of Veterinary Internal Medicine (ACVIM) Consensus Statement⁶ and has been widely adopted (**Table 1**). An updated revision of the 2009 ACVIM Consensus statement

| Table 1 | |
|--|---|
| Degenerative valve disease staging scheme | |
| A | <ul style="list-style-type: none"> Dogs, who, based on signalment (age, breed/weight), have an increased risk of developing DVD. |
| B | <ul style="list-style-type: none"> Dogs with stage B have never suffered from any signs or symptoms attributable to CHF due to DVD. This is the asymptomatic or preclinical stage of DVD. All dogs with stage B DVD have a characteristic MR murmur without (B1) or with (B2) cardiac chamber enlargement. |
| C | <ul style="list-style-type: none"> Stage C stands for CHF. Dogs with past or current signs or symptoms of CHF in the presence of a characteristic MR murmur and obvious cardiac chamber enlargement. Dogs with stage C can be "stable" on CHF therapies or suffer from "active" signs or symptoms of CHF. |
| D | <ul style="list-style-type: none"> This is the end or refractory stage of CHF due to DVD. Dogs in this stage typically progress from stage C (ie, do not jump from stage B to D). Stage D dogs continue to suffer from persistent or intermittent clinical signs or symptoms that limit their quality of life despite appropriate therapies. |

Abbreviations: CHF, congestive heart failure; DVD, degenerative valve disease; MR, mitral regurgitation.

Adapted from the ACVIM Consensus Statement: Atkins C, Bonagura J, Ettinger S, et al. Guidelines for the diagnosis and treatment of canine chronic valvular heart disease. *J Vet Intern Med* 2009;23(6):1142–50.

concerning all stages of DVD is scheduled to be presented at the ACVIM Forum in June 2017 and published thereafter.

In this article, current and future therapies will be reviewed for stage B1 and B2 DVD, the asymptomatic or preclinical stage of DVD when dogs have no current or previous clinical signs or symptoms attributable to CHF. The main goal of initiating therapy in stage B DVD is to extend the asymptomatic period of the disease by delaying the onset of CHF. Historically, recommendations to accurately stage dogs with stage B1 and B2 DVD have suffered from low compliance among veterinarians and pet owners as a consequence of the lack of consensus regarding recommendations for treatment.^{7,8} In general, the sentiment often voiced is that the value of early diagnosis is somewhat mitigated when there is no proof of efficacy of early therapy before the onset of CHF. However, recent publication of the EPIC study (Effect of Pimobendan in Dogs with Preclinical Myxomatous Mitral Valve Disease and Cardiomegaly), and the results of other ongoing clinical studies are changing this paradigm.⁹ This article emphasizes the impact of new evidence on historical recommendations for asymptomatic DVD, and attempts to give the reader a glimpse into future therapy for stage B DVD.

STAGE B1

Current Recommendations

Asymptomatic dogs with left apical systolic murmurs characteristic of MR should undergo baseline diagnostics to establish the etiology of the murmur. If a diagnosis of stage B1 DVD is confirmed by echocardiography or presumed (in an older small-breed dog) based on the presence of a normal radiographic vertebral heart size (VHS), then no therapy is indicated. Recommendations for stage B1 DVD remain unchanged and are summarized in [Table 2](#).⁶ There is no historical or new evidence to support intervention with a specific therapy at this stage. Emphasis in this stage should include client communication concerning the value of scheduled follow-up evaluations to assess the presence and severity of any disease progression. In addition, comorbidities, such as systemic hypertension, that may impact the rate of DVD progression should be intermittently screened for during stage B1.

Future Therapies

Ideally, future therapies will be developed that focus on prevention or early termination of progressive valve degeneration in stage B1 dogs, rather than focusing exclusively on treatment options for dogs that have already progressed to more advanced stages of the disease. Frustratingly, despite the common nature of DVD in both humans and dogs, the pathophysiologic triggers that underlie the development of this disease remain largely unknown. One important structural transformation that has been associated with the development of DVD pathology involves the transformation of valvular interstitial cells, 1 of the 2 predominant cell types present in the mitral valve, from a typical quiescent cell to an activated myofibroblast phenotype.¹⁰ Triggers for this transformation have been associated with both the serotonin and transforming growth factor β 1 pathways.¹¹ Research into these lines of investigation suggest that clinical trials studying serotonin antagonists or serotonin receptor antagonists may be the next step forward in DVD research in dogs.¹² Active study in this arena is ongoing.

STAGE B2

Current Recommendations

Stage B2 is defined as dogs with DVD that have evidence of heart enlargement but have never suffered from signs or symptoms attributable to CHF. Dogs are typically

| Treatment Recommended | Diagnostic Criteria for Treatment ^a | Medication(s) | Other Recommendations |
|---|--|--|---|
| <ul style="list-style-type: none"> Asymptomatic older small-breed dog Systolic heart murmur characteristic of DVD Normal systemic blood pressure | No | None at this time | VHS <10.5: recheck q 12 mo All others: recheck q 6–12 mo, HRR q 1 wk |
| | Yes ^{b,c} | <ul style="list-style-type: none"> Echo LA:Ao (2D) ≥ 1.6 and LVIDDN $\geq 1.7 \pm VHS \geq 10.5^d$ No echo available <ul style="list-style-type: none"> Systolic MR murmur $\geq 3/6$ and <ul style="list-style-type: none"> VHS ≥ 11.5 Progressive \uparrow in heart size (\uparrow VHS by ≥ 0.5 in 6 mo [even if VHS <11.5]) | Initiate pimobendan ^d What about ACEIs <ul style="list-style-type: none"> Continue ACEI if dog already receiving one Initiate ACEI if there is evidence of progressive \uparrow in heart size (\uparrow VHS by ≥ 0.5 in 6 mo) despite pimobendan treatment Consider addition of ACEI if pimobendan treatment is declined |

This summary table reflects the opinions of the authors and is based on the results of the Evaluation of Pimobendan In dogs with Cardiomegaly paper and the Cardiac Education Group recommendations,²⁷ as well as the 2009 American College of Veterinary Internal Medicine Consensus statement.⁶

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; echo, echocardiogram with emphasis on 2-dimensional (2D) left atrial size and left ventricular internal dimension in diastole; HRR, owner counted home resting respiration rate; LA:Ao, left atrial to aortic ratio as measured from a 2D short-axis image (see Fig. 2); LVIDDN, normalized left ventricular internal diameter in diastole (see Fig. 3); q, every; VHS, radiographic vertebral heart size (see Fig. 1).

^a An echocardiogram is the gold standard for confirmation and staging of dogs with degenerative valve disease.

^b Evaluation of a biochemistry panel before the initiation of any chronic oral cardiac medication is recommended, and in the case of an ACEI one should be rechecked 10 to 14 days after initiation and/or following any increase in dosage.

^c Baseline thoracic radiographs should be recommended in dogs with a risk of developing congestive heart failure, particularly those at highest risk; for example, those with severe heart enlargement.

^d Highest priority recommendation.

identified in this stage based on the presence of a moderately loud (grade ≥ 3) systolic heart murmur characteristic of MR and heart enlargement, specifically left atrial enlargement, with or without left ventricular dilation.¹³ Definitive diagnosis of DVD and assessment of heart enlargement can be confirmed by echocardiography or

presumed (in an older small-breed dog with an MR murmur) based on the presence of an increased radiographic VHS.^{14,15} Because stage B2 includes all dogs with DVD and any magnitude of heart enlargement that have never suffered from CHF, it is a heterogeneous population. Dogs in this stage may be days away from developing CHF, or may never develop CHF in their lifetime. This is reflected in the long median time to onset of CHF, approximately 27 months, that has been reported in stage B2 DVD.^{7,8} However, it is important to recognize that all stage B2 dogs have a risk of going into CHF. Many studies have provided important information on the natural progression of stage B2 DVD and reported factors that can be used to identify which stage B2 dogs have higher versus lower risks of developing CHF.^{16–20} Known risk factors for development of CHF and a poor outcome in dogs with stage B2 DVD include larger heart size as measured by echocardiography or VHS, rapid progression of heart enlargement based on repeat evaluations, and high levels of cardiac biomarkers, such as N-terminal pro B-type natriuretic peptide. However, despite the wide body of knowledge concerning DVD, there has historically been no consensus with respect to therapeutic recommendations for stage B2 DVD.⁶ This is a consequence of the lack of published data confirming that initiation of any treatment in stage B2 DVD can significantly delay the onset of CHF.^{7,8} However, treatment with an angiotensin-converting enzyme (ACE) inhibitor has been historically advocated by some cardiologists for the treatment of some stage B2 dogs and is based predominantly on the results of the VETPROOF (Veterinary Enalapril Trial to Prove Reduction in Onset Of heart Failure) study in combination with their well-known safety profile.^{6–8,21}

Before publication of the EPIC study,⁹ the potential benefit of pimobendan (Vetmedin; Boehringer Ingelheim, Ingelheim am Rhein, Germany) therapy in delaying or preventing the onset of clinical signs in dogs with stage B2 DVD had not been evaluated and information regarding its hemodynamic effects in dogs with stage B1 and B2 DVD was sparse. Two small studies ($n = 12$,²² $n = 14$)²³ evaluated the hemodynamic effects of pimobendan in dogs with stage B DVD. One found no evidence of benefit in dogs with stage B2 DVD over 6 months of follow-up²³ and the other²² reported adverse cardiac functional and morphologic effects in dogs with stage B1 DVD when compared with an ACE inhibitor. However, recent publication of the EPIC study⁹ has provided new data with which to make evidence-based recommendations for stage B2 DVD. EPIC stands for *Evaluation of Pimobendan In dogs with preclinical myxomatous mitral valve disease and Cardiomegaly*. The EPIC study was a prospective double-blind, randomized, multicenter, placebo-controlled clinical trial designed to evaluate the effectiveness of pimobendan to delay the onset of left-sided CHF (pulmonary edema) or cardiac-related death (if it occurred before CHF) in dogs with heart enlargement secondary to asymptomatic DVD. Although this study was sponsored by Boehringer Ingelheim, the study protocol, data analysis, and preparation of the article were carried out by independent cardiologists with input from an independent statistician and a representative of the sponsor, and data management was carried out by an independent data management company. Experts in cardiology at 36 sites in 11 countries enrolled 360 dogs that were randomized to receive pimobendan or placebo (180 per treatment group), making this the largest randomized controlled clinical trial in veterinary cardiology to date (Box 1).

The primary endpoint was a composite of the time to onset of left-sided CHF (pulmonary edema) or cardiac-related death (sudden or euthanasia) in the event that it happened before left-sided CHF. Additional secondary endpoint and safety analysis, including all-cause mortality, were also planned and executed. The study was stopped before the planned stopping point based on the favorable results of a preplanned interim analysis. The final analysis was performed after 80% of the planned study

Box 1**Pimobendan dose used in the Evaluation of Pimobendan In dogs with preclinical myxomatous mitral valve disease and Cardiomegaly (EPIC) study**

- The reported pimobendan dose received by dogs in the EPIC study is 0.49 mg/kg/d divided into 2 doses with an interquartile range of 0.44 to 0.53 mg/kg/d.
- The dose of pimobendan used in the study, 0.4 to 0.6 mg/kg/d divided into 2 doses given approximately 12 hours apart, is not different from the registered dose for the treatment of CHF secondary to DVD and dilated cardiomyopathy.

duration was complete. Many study design details, such as detailed inclusion and exclusion criteria, and specific endpoint definitions contributed to the high quality of the results. The final analysis of the composite primary endpoint demonstrated a significant ($P = .0038$) and clinically relevant extension of symptom-free survival, with most of the benefit attributable to delaying the onset of left-sided CHF, and the magnitude and significance of the benefit attributable to pimobendan remained in subsequent analyses that evaluated the effect of 32 baseline variables, such as heart size, on the study outcome. On average, dogs receiving pimobendan met the primary endpoint in 1228 days (40.9 months) versus 766 days (25.5 months) in the placebo group, which translates into an average of 462 additional days (15.4 months). This represents a 60% extension in symptom-free survival. The results also can be expressed as the risk (hazard ratio) that a dog in the study would experience the primary endpoint. All dogs receiving pimobendan in the study experienced a 36% reduction in risk in comparison with the placebo group. It is important to note that all dogs in the study had a risk of experiencing the primary endpoint, although we know that the absolute risk is different for individual dogs, whatever an individual dog's risk was, it was reduced by 36%. This is a good way in which to express the results of the study to an owner when discussing the recommendation to initiate lifelong pimobendan, expressing benefit as median or average number of months of extension of symptom-free survival does not help us predict what an individual dog will do, but understanding that your dog has a risk and initiating a medication can reduce that risk by a third is tangible. The results of the safety analyses supported the safety of pimobendan treatment in the study population, as number, type, and severity of adverse events were not different ($P = .82$) between the placebo and pimobendan group, although despite the fact that dogs in the pimobendan group remained in the study longer on average and overall their survival was prolonged ($P = .012$). The median time to death from any cause was 1052 days (35 months) in the pimobendan group versus 902 days (30 months) in the placebo group. It is important to understand the apparent reduction in magnitude of benefit on mortality compared with the primary endpoint should be considered only as part of the safety assessment, because the portion of the study after the primary endpoint was reached (eg, once a dog was in CHF) was not controlled and all dogs received pimobendan as part of their therapy.

In dogs with DVD, clinical signs related to pulmonary edema may not represent the first clinical signs a dog experiences that are attributable to DVD. Some dogs with stage B2 DVD develop clinical signs associated with poor perfusion, pulmonary hypertension (PH), ascites or cough related to left mainstem bronchial compression (LMSBC) before the onset of left-sided CHF. The EPIC study included a prespecified secondary endpoint that attempted to address this aspect of preclinical DVD. This analysis showed that in asymptomatic dogs with cardiomegaly secondary to DVD, treatment with pimobendan extended the time to the "first event." The "first event"

endpoint was a composite of many outcomes that a dog in the study could experience and, with the exception of death, resulted in treatment with a variety of medications listed as precluded in the study protocol. In general, these medications included those used to treat heart disease and heart failure, as well as those used to treat cough. The EPIC study did not regulate what specific medication(s) were administered by the attending cardiologist to manage the “first event,” but rather captured if, when, and why this occurred. Dogs that were still alive at the end of the study and had not developed pulmonary edema were censored in this analysis. Treatment for a cardiac indication, as classified by the attending cardiologist, included pulmonary edema (the primary endpoint), right-sided heart failure (ascites), cough, PH, weakness, collapse, syncope, new arrhythmia, and anorexia/weight loss. In comparison with the primary endpoint analysis, this secondary endpoint was more inclusive and thus relevant to dogs and dog owners, as the need to start any medication for a cardiac indication, even if the indication is not pulmonary edema, represents morbidity for the dog, and requires a visit to the veterinarian. The time to “first event” analysis was highly significant ($P < .0001$), demonstrating a clear statistical and clinically relevant difference between the 2 groups, with a median of 640 days (21.3 months) in the pimobendan group versus 406 days (13.5 months) in the placebo group that translates into an average of 234 additional days (7.8 months) of symptom-free survival. The results can also be expressed as the risk (hazard ratio) that a dog in the study would experience a “first event.” The 95% confidence interval for risk reduction in the time to “first event” analysis was 33.5% to 42.5% in favor of pimobendan. This suggests that the administration of pimobendan in asymptomatic dogs with cardiomegaly secondary to DVD may not only delay the onset of pulmonary edema, it may also delay the onset of a myriad of other signs or symptoms attributable to DVD if they occur before pulmonary edema.

The failure of previous studies to demonstrate a significant effect on time to onset of left-sided CHF in dogs with cardiomegaly treated with ACE inhibitors^{6,7} in combination with the positive results of the EPIC study allows new evidence-based recommendations for treatment in this population of dogs. It is important to note the EPIC study by design did not evaluate pimobendan treatment in dogs with DVD and no evidence of cardiomegaly (stage B1), and thus no conclusions regarding the safety or efficacy of treatment in this group can be drawn from the EPIC study.

CLINICAL APPLICATION OF THE EVALUATION OF PIMOBENDAN IN DOGS WITH CARDIOMEGALY STUDY RESULTS

The strict inclusion criteria in the EPIC study raise some questions as to what diagnostic tests and variables are required to select dogs with DVD that should have life-long pimobendan recommended (see [Table 2](#)). Stage B2 DVD dogs that fulfill the EPIC heart size inclusion criteria can be considered a specific subset of stage B2, which the authors have labeled stage B2^E: the superscript E stands for EPIC ([Box 2](#)).

The EPIC inclusion criteria required both radiographic and echocardiographic evidence of cardiomegaly. The requirement for an echocardiogram may in some cases exclude the recommendation for initiation of pimobendan. However, given the potential low accuracy of depending solely on a radiographic VHS greater than 10.5, which represents the 95% confidence interval of the reference range of normal, and that there are known breed-related differences in normal VHS reference ranges with much higher normal VHS ranges reported in some breeds, including the CKCS,^{14,15,26} it is prudent to use a higher VHS size if recommendations for treatment are based solely on history, physical examination, and thoracic radiographs. Selection of a VHS for this indication is warranted based on the results of previous studies that have demonstrated that dogs

Box 2**Summary of EPIC inclusion criteria (definition of stage B2^F)**

- Asymptomatic small-breed dog ≥ 6 years of age weighing between 4.1 and 15 kg
- No concurrent or prior treatment with cardiac medications such as an angiotensin-converting enzyme (ACE) inhibitor
- No evidence of a serious systemic disease expected to limit the dog's survival or require treatment with a cardiovascular medication during the study (eg, dogs requiring amlodipine for treatment of systemic hypertension were not eligible for inclusion)
- Heart murmur characteristic of mitral regurgitation (MR) ($\geq 3/6$)
- Radiographic cardiomegaly (vertebral heart size [VHS] >10.5) (see [Fig. 1](#))
- Echocardiographic criteria:
 - Evidence of DVD (MR and valvular changes)
 - Left atrial enlargement—2-dimensional left atrial-aortic ratio ($^{2D}LA:Ao$) $\geq 1.6^{24}$ (see [Fig. 2](#))
 - Normalized left ventricular internal dimension (LVIDDN) ≥ 1.7 (see [Fig. 3](#))
 - Calculation of LVIDDN²⁵

$$LVIDDN = \frac{LVIDD^a \text{ (cm)}}{\text{Weight (kg)}^{0.294}}$$
 - Example calculation of LVIDDN
 LVIDD = 4.4 cm, dog's body weight = 8.0 kg.

$$LVIDDN = \frac{4.4}{8.0^{0.294}} = \frac{4.4}{1.84} = 2.39$$

^a LVIDD (cm) from M-mode or 2-dimensional image (see [Fig. 3](#)).

with asymptomatic DVD and a VHS of 11.5 to 12.5^{16,20} have a significant increase in risk of developing left-sided CHF in the near (6–12 months) future. In addition, the median VHS of dogs in the EPIC study was approximately 11.5 and an increase in heart size, as measured by VHS, 2 dimensional left atrial-aortic ratio ($^{2D}LA:Ao$) and normalized left ventricular internal diameter in diastole (LVIDDN), were found to be associated with a significant increase in risk of reaching the primary endpoint. An additional factor to consider is rate of progression of heart enlargement. Relatively large increases in heart size, even if the VHS is <11.5 , are known to be associated with an increased risk of CHF in dogs with DVD.²⁰ Therefore, another criterion to consider is an increase in VHS from one recheck to the next. The Cardiac Education Group (CEG) recommends that, in the absence of an echocardiogram, asymptomatic dogs with an MR murmur ($\geq 3/6$) and a VHS ≥ 11.5 or an increase in VHS of ≥ 0.5 or more in 6 months can be used to recommend pimobendan treatment.²⁷ Use of a VHS of ≥ 11.5 will improve the specificity (positive predictive value) of significant heart enlargement and guard against overtreatment of possible stage B1 dogs. However based on the reported inter-observer and intraobserver variability of VHS measurement, repeated measures of VHS to assess rate of disease progression should ideally be performed by the same observer.¹⁷ The CEG recommends that in dogs with a VHS between 10.6 and 11.4, an echocardiogram is needed to determine eligibility. The CEG is a group of board-certified veterinary cardiologists from both academia and private practice that offer independent recommendations for the evaluation and treatment of canine and feline heart disease²⁷ ([Box 3](#); see [Table 2](#)).

The CEG also addressed the use of concurrent ACE inhibitors in this population in light of the EPIC study results. Their recommendation is to continue ACE inhibitors in dogs already receiving them when the indication for pimobendan is met, but that initiation of an ACE inhibitor in stage B2^F DVD should be reserved until the onset of clinical signs or symptoms. Additionally, the addition of an ACE inhibitor also can be considered if or when reevaluation demonstrates an increase in VHS of ≥ 0.5 or more in

Box 3**Recommendations for pimobendan initiation in stage B2 DVD when an echocardiogram is not available**

- Asymptomatic small-breed dog
- Heart murmur characteristic of MR ($\geq 3/6$)
- VHS ≥ 11.5
- Progressive increase in VHS; \uparrow of ≥ 0.5 VHS units over 6 months

6 months in dogs with stage B2^E DVD already receiving pimobendan. Other medications can then be added as appropriate when clinical signs or disease progression develop. Ideal therapeutic plans for all dogs with stage B2 DVD include owner communication with emphasis on their role in monitoring for signs of disease progression, especially the value of home respiratory rates, and scheduled follow-up evaluations. The CEG recommends rechecks every 6 months in stage B2 dogs that did not meet both EPIC echocardiographic criteria and thus were not candidates for pimobendan treatment at that time.²⁷ In stage B2 dogs that are receiving pimobendan, the authors recommend rechecks every 6 to 8 months. Rechecks emphasize a thorough history, physical examination thoracic radiographs, and a systemic blood pressure. Routine blood work is typically recommended annually in these patients, barring any obvious indications to perform it more frequently. Publication of the second edition of the ACVIM Consensus Statement on DVD will undoubtedly further refine these recommendations (Box 4).

Future Therapies

Advancement in the treatment of stage B2 DVD dogs is likely to encompass both medical and surgical innovations. Potential targets for medical advancement include improvements in the treatment of existing disease as well as the development of treatments aimed at altering the course of valvular degeneration, as discussed in association with stage B1 dogs. Results of the DELAY study (DElay of Appearance of sYmptoms of canine degenerative mitral valve disease treated with spironolactone and benazepril), a double-blind, multicenter, placebo-controlled clinical trial evaluating the efficacy of spironolactone in combination with benazepril on delaying the time to development of clinical signs of CHF in stage B2 DVD dogs, are expected in 2018. This study addresses the question of whether multimodal neuroendocrine blockade is superior to ACE inhibition alone in stage B2 dogs. Significant aldosterone breakthrough has been documented in both experimental models and DVD dogs receiving ACE inhibitors alone.^{28,29} Excess aldosterone levels are associated with many adverse effects, including sodium retention, potassium loss, and the development of interstitial myocardial fibrosis. Additionally, urinary aldosterone excretion has been shown to increase in association with ventricular remodeling and is

Box 4**Current recommendation concerning the use of ACE inhibitors in stage B2 DVD**

- Initiation in stage B2 dogs already receiving pimobendan should be considered in if/when reevaluation demonstrates an increase in VHS of ≥ 0.5 or more in 6 months.
- ACE inhibitors can be continued in dogs already receiving them when they meet criteria to initiate pimobendan.

negatively associated with survival in dogs with DVD.³⁰ The addition of spironolactone, an aldosterone antagonist, has the potential to ameliorate some of the negative effects of excess aldosterone that develop in association with renin–angiotensin–aldosterone system activation in DVD dogs. Although the benefits of spironolactone are well proven in humans once CHF has developed,³¹ and data suggest the same may be true in advanced stages of DVD in dogs (Stage C and D),³² the results of the DELAY study are needed to clarify whether a benefit exists in stage B2 dogs.

Future advancement in the surgical treatment of DVD in dogs may ultimately resemble current treatment recommendations in human medicine. In humans with severe MR and cardiac remodeling due to DVD, open surgical mitral valve repair is considered the standard of care,^{33,34} being preferred over mitral valve replacement.³⁵ Although less efficacious than open surgical repair, transcatheter mitral valve therapies are also widely used in human medicine. Transcatheter procedures are typically reserved for patients with unacceptably high anesthetic and surgical risks that are poor candidates for an open-heart procedure that requires cardiopulmonary bypass.^{33,34} Despite the widespread use of mitral valve surgery in people, comparable procedures for dogs remain largely out of reach for most patients at this time. Open surgical mitral valve repair has been successfully performed in dogs,^{36–38} although accessibility is limited and procedural costs are currently cost-prohibitive in most cases. At the leading center for mitral valve repair in dogs, perioperative and 3-month postoperative survival rates are reported to be more than 90%, with stage B2 dogs having better survival rates than stage C or D dogs.³⁹ This suggests that the optimal time for surgical intervention may be in stage B2 dogs once these treatment options become more widely available and reproducible. For open surgical mitral valve repair to become a more practical option, additional centers of excellence in cardiac surgery and cardiopulmonary bypass will need to be cultivated and optimal mitral valve repair techniques in the dog must be refined. In contrast, transcatheter mitral valve therapies, although still in the experimental stages in dogs at this time, have several potential advantages over open surgical approaches in this species. First, these options could circumvent the need for cardiopulmonary bypass in dogs altogether by using less-invasive alternatives. Second, accessibility is likely to be substantially improved due to the large number of centers with active interventional cardiology referral programs in which these techniques could be instituted in partnership with surgical support. At the time of writing, the MitralSeal device (Avalon Medical, Stillwater, MN), a bioprosthetic valve mounted within a self-expanding Nitinol stent, is undergoing a third-generation design modification, with a clinical trial in stage C dogs scheduled to begin in 2017.⁴⁰ This device is deployed through the left ventricular apex using a hybrid surgical-transcatheter approach. Other transcatheter or hybrid surgical-transcatheter procedures aimed at mitral valve repair, such as the MitraClip (Abbott Laboratories, Chicago, IL), an edge-to-edge valve leaflet repair system, or artificial chordae tendineae systems, such as the NeoChord (NeoChord Inc, Minneapolis, MN) or the Harpoon Medical device (Harpoon Medical, Inc, Baltimore, MD) may also be adaptable for dogs, although some design modification may be required to downsize for the veterinary population and active clinical trials are not yet under way.^{41,42}

SPECIAL CONSIDERATIONS IN STAGE B DEGENERATIVE VALVE DISEASE

Most clinical trials performed in dogs with asymptomatic DVD are designed to prove whether a given therapy can delay the onset of pulmonary edema (left-sided CHF),^{7–9} but symptoms of pulmonary edema may not represent the first clinical signs a dog experiences that are attributable to DVD. In addition, the ACVIM staging scheme focuses

on development of clinical signs attributable to CHF secondary to DVD (stage C), in particular those attributable to pulmonary edema, but also includes those attributable to right heart failure, such as ascites. However, some dogs with stage B2 DVD develop clinical signs associated with poor perfusion, PH, or cough related to LMSBC (see Fig. 4) before the onset of CHF and therefore remain classified as stage B2. The authors classify these dogs as stage B+: the “+” indicates the presence of clinical signs attributable to DVD that are not related to active CHF. Another way to include these dogs in the current staging scheme could be to broaden the definition of stage C to include dogs with any previous or current clinical signs attributable to DVD, rather than those attributed solely to CHF. Regardless of how these dogs are staged, they represent a subset of the DVD population with signs related to their heart disease but unrelated to CHF that can impair the quality of their life, and, by extension, their owners’ quality of life. Thus, despite a lack of evidence-based recommendations, this group of dogs often requires therapy. Many therapeutic recommendations for stage B+ are therefore based on experience and professional opinion and often stem from treatment of these conditions when they occur as comorbidities in dogs with stages C and D DVD. The EPIC study⁹ included a prespecified secondary endpoint that attempted to address this aspect of preclinical DVD. This analysis showed that the administration of pimobendan in asymptomatic dogs with cardiomegaly secondary to DVD may not only delay the onset of pulmonary edema, it may also significantly delay the onset of a myriad of other signs or symptoms attributable to DVD if they occur before pulmonary edema.

Pulmonary Hypertension in Stage B Degenerative Valve Disease

PH is a consequence of a variety of etiologies that are not mutually exclusive, one of which is DVD. Dogs with DVD commonly develop concurrent PH as a complication of their left-sided heart disease.^{43–45} Development of PH has prognostic significance, as dogs with DVD and an echocardiographically estimated systolic pulmonary artery pressure of greater than 55 mm Hg (moderate PH) have a poorer long-term outcome.⁴⁵ Clinical signs associated with PH can mimic those characteristic of pulmonary edema, poor perfusion, and LMSBC, and include exercise intolerance, syncope, cough, or dyspnea. In addition, dogs with PH can go on to develop signs of right-sided CHF (ascites) or remain entirely asymptomatic.⁴³ The therapeutic approach to treating PH in dogs with DVD requires an understanding of the underlying disease pathophysiology. In these dogs, PH is typically a result of chronic elevation in left atrial pressure and pulmonary venous hypertension. In some dogs, secondary reactive pulmonary arterial vasoconstriction and remodeling also can develop as a result of chronic hypoxic change.⁴³ In both scenarios, PH secondary to DVD is almost always associated with left atrial enlargement, making its presence solely related to DVD very unlikely in stage B1 dogs but possible to probable in stage B2, C, and D. PH due solely to DVD is, however, unlikely to be severe. Other etiologies of PH always should be considered, including heartworm disease, chronic pulmonary disease, or chronic pulmonary thromboembolic disease. If present, these comorbidities can contribute to the development of vascular remodeling and PH in dogs with DVD. Although PH associated with chronic elevations in left atrial pressure and pulmonary venous hypertension can be reversible with appropriate therapy, dogs with chronic pulmonary arterial remodeling likely have a more irreversible form of the disease.

Definitive diagnosis of PH in veterinary patients is typically dependent on Doppler echocardiography, which is specific, but not 100% sensitive.⁴⁴ That is, a definitive diagnosis is not always possible and often a presumptive diagnosis is made based on the presence of indirect markers of PH that are identified during a complete

echocardiogram and, in some cases, thoracic radiographs. In some symptomatic cases, the diagnosis is based on the exclusion of other etiologies to explain the clinical signs and/or the response to therapy for PH; for example, in a dog with stage B2 DVD with active respiratory distress and no evidence of radiographic pulmonary infiltrates in which pulmonary edema (left-sided CHF) can be ruled out.

Once PH is identified via Doppler echocardiography in a dog with DVD, optimization of treatment for their underlying left-sided heart disease should be the first course of action. Thoracic radiographs are recommended to screen for any evidence of active pulmonary edema and home monitoring of the resting respiratory rate should be emphasized (if not already on going) to gauge the likelihood of early CHF that was not radiographically obvious. If evidence of CHF is appreciated, standard therapy for stage C DVD should be instituted.⁶ In asymptomatic stage B1 or B2 dogs, identification of mild PH (estimated systolic pulmonary artery pressure >30 to <50 mm Hg) may warrant periodic monitoring alone as recommended for all stage B dogs. In stage B2 dogs with mild PH that have already met the EPIC criteria to receive⁹ pimobendan (Figs. 1–3), the addition of an ACE inhibitor also can be considered if the dog is not already receiving one, particularly if and when clinical signs associated with PH are suspected. For stage B2 dogs that are receiving both an ACE inhibitor and pimobendan, documentation of moderate (>50 to <75 mm Hg) to severe (>75 mm Hg) PH in association with clinical signs, such as an increase in respiratory rate (not attributable

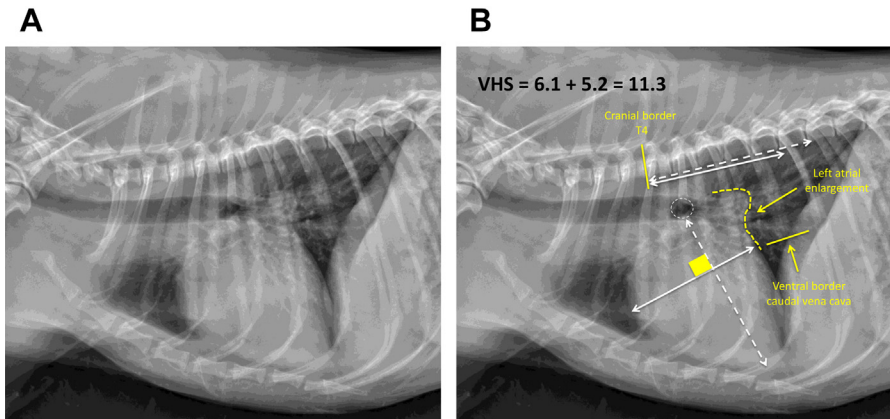


Fig. 1. Accurate measurement of VHS is an important aspect of staging DVD and helps to determine therapeutic recommendations. (A) Right lateral radiograph from a dog with asymptomatic DVD. (B) Step 1: Identify the long axis of the heart (*dashed line*) beginning at the bottom of the carina (*dashed circle*) and ending at the apex. Step 2: Identify the short axis of the heart (*solid line*) at the level of the ventral border of the caudal vena cava and perpendicular (90°) to the long axis. This is typically the widest portion of the heart but may not be in dogs with severe left atrial enlargement. Step 3: Identify the fourth thoracic vertebra (T4), and place 2 lines equal in length to the long and short axis lines at the beginning of T4 parallel to the vertebrae. Step 4: Determine the length of both lines to the nearest 0.1 thoracic vertebra and add them together, this is the VHS. Note: The vertebral disc space is considered to be part of the vertebra that precedes it and should be taken into account when estimating to the nearest 0.1 thoracic vertebra. The normal canine VHS reference range is 8.7 to 10.5. (Data from Buchanan JW, Bücheler J. Vertebral scale system to measure canine heart size in radiographs. *J Am Vet Med Assoc* 1995;206(2):194–9; and Hansson K, Haggstrom J, Kwart C, et al. Interobserver variability of vertebral heart size measurements in dogs with normal and enlarged hearts. *Vet Radiol Ultrasound* 2005;46:122–30.)

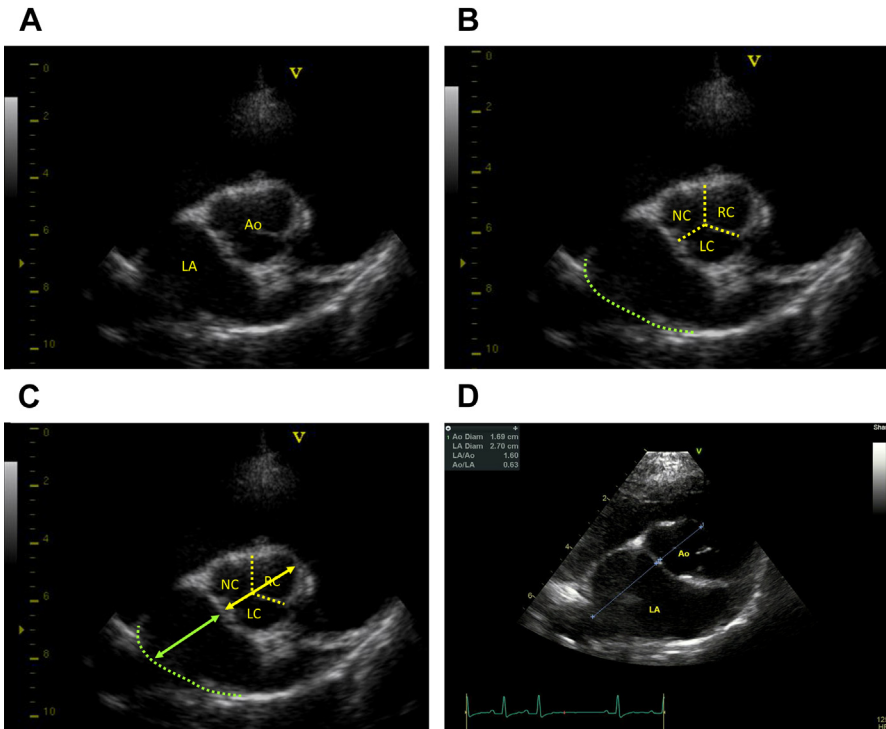


Fig. 2. There are a variety of methods to measure the left atrium (LA). The EPIC study evaluated the LA from a 2D image acquired from the right parasternal short-axis window at the level of the aortic valve, an image routinely acquired in basic echocardiographic examinations. The LA is measured at maximum size (the end of systole or soon after the T wave ends on simultaneous ECG), which is the first frame in which aortic valve closure can be seen. Incorrectly measuring the LA in diastole (close to the next QRS) can lead to underestimation of LA size. The aorta (Ao) is measured from inside to inside edge along the junction of the non-coronary (NC) and left-coronary (LC) cusps according to the published Swedish method.²⁴ The dashed yellow lines identify edges of the aortic valve cusps. All cusps are not typically visualized but can be assumed as long as one is seen clearly. The LA dimension is measured from inside edge to inside edge on the same line as the Ao, as if the line used to measure the aorta is extended through the LA. It is important when measuring the LA to be careful not to overestimate its size by measuring beyond the wall of the LA (*dashed green line*) into a pulmonary vein. The LA:Ao is derived from dividing the Ao dimension into the LA dimension. An LA:Ao ≥ 1.6 was used to select dogs for the EPIC trial. The normal reference range for LA:Ao when measured by the Swedish method is 0.9 to 1.3. (A–C) demonstrate the landmarks that are required to measure the LA:Ao by the Swedish method in a dog with normal left atrial size (LA:Ao = 1.2). (D) demonstrates measurements in a dog with DVD and left atrial enlargement (LA:Ao = 1.6). (A–C) An LA:Ao between 0.9 and 1.3 is within the normal range for the typical small-breed dog, regardless of breed. This method was never investigated scientifically in large breed dogs. V identifies the echocardiographic reference mark. (Data from Hansson K, Haggstrom J, Kvarn C, et al. Left atrial to aortic root indices using two-dimensional and M-mode echocardiography in cavalier King Charles spaniels with and without left atrial enlargement. *Vet Radiol Ultrasound* 2002;43:568–75.)

to pulmonary edema), exercise intolerance, or syncope, warrants treatment with a phosphodiesterase-5 (PDE-5) inhibitor, such as sildenafil, with or without the addition of L-arginine.⁴⁴ Documentation of moderate PH in a reportedly asymptomatic dog with stage B DVD is less clear-cut with regard to treatment recommendations. Dogs in this

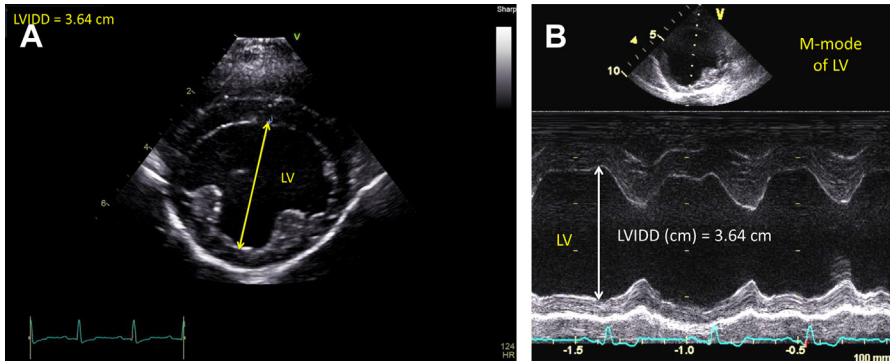


Fig. 3. There are a variety of methods to measure the left ventricle (LV) and thus many ways to assess for LV enlargement. The EPIC study evaluated the LV size from an M-mode image acquired from the right parasternal short-axis window at the level of the tips of the mitral valve (*white arrow*). This is a common image routinely acquired in basic echocardiographic examinations. A standard measurement from this image includes the internal dimension of the LV in diastole (LVIDD), which is the maximum size of the LV chamber. Alternatively, the LVIDD can be measured from a 2D (*yellow arrow*) image taken from the same image that would be used for an M-mode. For this method of measurement of LVIDD, a loop is saved and the largest chamber size is selected for measurement by scrolling slowly through the loop. The 2D method (A) may be easier and more accurate when the image is difficult to align properly for M-mode (B). The LVIDD (cm) can be used in an equation to normalize the value for the dog's weight (kg). This is the normalized LVIDD index (LVIDDN).²⁵ It is important that the LVIDD measurement is in centimeters (not millimeters as it is sometimes reported) and the weight is in kilograms when calculating the LVIDDN. In this example, the LVIDD is 3.64 cm in a dog that weighs 8 kg. The calculated LVIDDN is 1.98. The formula to calculate the LVIDDN = (LVIDD[cm]) / (Weight [kg]^{0.294}). The reference range for LVIDDN is 1.27 to 1.85. An LVIDD of ≥ 1.7 was used to select dogs for the EPIC study. The reason for selection of an LVIDDN that was not above the upper normal reference range is related to a previous study that demonstrated dogs with DVD and an LVIDDN ≥ 1.7 had a worse clinical outcome than dogs with an LVIDDN less than 1.7, although it was within the reported normal range.

category that are stage B2 and meet the EPIC criteria for pimobendan should receive this drug. The addition of other medications, such as an ACE inhibitor and a PDE-5 inhibitor, with or without L-arginine, also can be considered, especially if the severity of PH worsens or clinical signs attributable to PH develop over time. Careful monitoring for disease progression and the development of clinical signs is warranted, and emphasizes the need for follow-up evaluations in this population. Identification of severe PH in reportedly asymptomatic dogs with stage B DVD likely warrants therapy with a PDE-5 inhibitor, with or without L-arginine, regardless of a lack of reported clinical signs.

In all dogs with PH secondary solely to stage B DVD, severe PH is unlikely, particularly in stage B1. Additionally, noncardiac comorbidities causing PH of varying degrees can develop during any stage of DVD. This emphasizes the need to investigate for other possible concurrent etiologies of PH in many cases. Recommended diagnostics in these dogs include heartworm antigen test (if appropriate), complete blood count, biochemistry profile, and urinalysis to screen for other etiologies of PH, such as heartworm disease or prothrombotic conditions, including hyperadrenocorticism, protein-losing diseases, and neoplasia that could predispose to chronic pulmonary thromboembolic disease. Referral for advanced respiratory diagnostics,

such as fluoroscopy, bronchoscopy, or airway cytology and culture via bronchoalveolar lavage, also may be indicated if uncontrolled chronic respiratory disease is suspected. If identified, definitive treatment for these conditions should be instituted as appropriate. See [Table 3](#) for a summary of these recommendations.

Left Mainstem Bronchial Compression in Stage B2 Degenerative Valve Disease

Cough attributable solely to LMSBC is not associated with concurrent tachypnea or dyspnea, is often chronic and exacerbated by excitement, and therefore mimics many primary airway diseases. This condition alone is rarely life-threatening, but coughing that is severe enough to impair a dog's or owner's quality of life represents a common complaint in older small-breed dogs with stage B2, C, and D DVD and frequently requires treatment. Cough in these dogs is often multifactorial and generally not attributable to active pulmonary edema.⁴⁶ Some common etiologies for a severe cough in these dogs include collapsing trachea, bronchitis, PH, and LMSBC. The first clinical step in these cases always includes the elimination of active pulmonary edema as a contributing cause to the cough and respiratory signs. In stage B dogs this would represent first-onset CHF versus recurrence in stages C and D. Thoracic radiography will allow active pulmonary edema to be ruled out and allow the overall VHS, in particular the degree of left atrial enlargement, to be assessed ([Fig. 4](#)). In some cases, there will be obvious evidence of bronchial collapse dorsal to the enlarged left atrium; however, even if this is not clearly visualized, LMSBC should be considered a rule-out for cough in any small-breed dog with moderate to severe left atrial enlargement.⁴⁶ Fluoroscopy is often able to confirm the presence and severity of LMSBC but is not absolutely necessary. Treatment can be initiated based on a presumptive diagnosis when other etiologies are ruled out.

The interaction between cardiomegaly, in particular left atrial enlargement, and collapse of the left mainstem bronchus is not well defined. There is no single accepted hypothesis for cough in these dogs.⁴⁷ Breeds that are predisposed to DVD are also predisposed to the development of structural airway collapse and airway inflammation.⁴⁷ Regardless, the probable role of an underlying primary large airway disease in combination with left atrial enlargement and the relatively high chronic left atrial pressure in dogs with stage B2 DVD often leads to permanent or intermittent clinically relevant cough. LMSBC should not be considered a differential diagnosis in dogs with stage B1 DVD, as by definition these dogs have no heart enlargement, therefore other etiologies for cough should be investigated. The complex etiology for cough due to LMSBC is best approached conceptually as an airway disease that is exacerbated by an enlarged heart. Successful management, therefore, includes strategies that address both the heart disease and respiratory component and response to treatment through scheduled follow-up. Scheduled follow-up also should include surveillance for the development of CHF, in particular, owner-recorded home breathing rates. Cough secondary to LMSBC is often not curable, thus the goal for minimizing the cough to a clinically tolerable level should be clearly communicated to the owner. Nonspecific palliative treatment of dogs with stage B2 DVD and cough due to LMSBC includes cough suppressants, weight loss (if appropriate), and modification of any potential environmental contributing causes (smoking). Specific airway therapies include intermittent antibiotics (doxycycline), bronchodilators, and corticosteroids. Corticosteroids should be used with caution in these dogs, but can be used in short courses at anti-inflammatory doses. Inhaled corticosteroids may be better tolerated if required chronically. Cardiac-specific therapies are aimed at reducing heart size and left atrial pressure and include pimobendan, ACE inhibitors, and in some cases low-dose furosemide. The optimum therapy must be tailored to an individual dog, and even

Table 3
Recommendations for chronic treatment of pulmonary hypertension in dogs with stage B DVD

| Clinical Signs/Symptoms of PH | DVD Stage | Mild PH, 30–50 mm Hg | Moderate PH, 50–75 mm Hg | Severe PH, >75 mm Hg |
|--|-----------------|---|---|----------------------|
| Yes <ul style="list-style-type: none"> • Rule out active pulmonary edema with thoracic radiographs in dogs with DVD and active respiratory signs^a • Monitor for PH and DVD progression^a | B1 | <ul style="list-style-type: none"> • Unlikely to cause clinical signs but severity of PH can be underestimated by echo. • Investigate other causes of PH for the clinical signs.^a | <ul style="list-style-type: none"> • Investigate other etiologies for PH.^a • Treat underlying etiology of PH if possible.^a • Initiate treatment with PDE-5 inhibitor ± L-arginine.^a • Initiate treatment for right heart failure if ascites is documented. | |
| | B2 | <ul style="list-style-type: none"> • As per stage B1 above.^a • If underestimation of severity of PH is possible, consider trial therapy with a PDE-5 inhibitor ± L-arginine and evaluate clinical response to treatment. | <ul style="list-style-type: none"> • As per stage B1 above.^a • Consider initiating an ACE inhibitor. | |
| | B2 ^E | <ul style="list-style-type: none"> • Initiate pimobendan.^a | <ul style="list-style-type: none"> • Investigate other etiologies for PH. • Treat underlying etiology of PH if possible. • Initiate pimobendan.^a • Consider initiation of treatment with a PDE-5 inhibitor ± L-arginine, particularly if pimobendan alone fails to palliate clinical signs or if clinical signs are severe enough at the time of diagnosis of PH that they limit the ability to wait and determine if monotherapy with pimobendan is efficacious.^a • Consider initiating an ACE inhibitor. • Add other medications as needed to treat right heart failure if ascites is present. • Monitor clinical response to treatment.^a | |

| | | | | |
|---|-----------------|--|---|---|
| No <ul style="list-style-type: none"> • Monitor for PH and DVD progression^a | B1 | <ul style="list-style-type: none"> • Investigate other etiologies for PH. • Treat underlying etiology of PH if possible. | <ul style="list-style-type: none"> • Investigate other etiologies for PH.^a • Treat underlying etiology of PH if possible.^a • Consider the initiation of a PDE-5 inhibitor ± L-arginine.^a | |
| | B2 | <ul style="list-style-type: none"> • No specific recommendations. | <ul style="list-style-type: none"> • Investigate other etiologies for PH. • Treat underlying etiology of PH if possible. • Consider initiating an ACE inhibitor. • Monitor for PH and DVD progression.^a | <ul style="list-style-type: none"> • Investigate other etiologies for PH. • Treat underlying etiology of PH if possible. • Consider the initiation of a PDE-5 inhibitor ± L-arginine.^a |
| | B2 ^E | <ul style="list-style-type: none"> • Initiate pimobendan.^a | <ul style="list-style-type: none"> • Investigate other etiologies for PH. • Treat underlying etiology of PH if possible. • Consider initiating an ACE inhibitor. • Initiate treatment with pimobendan.^a • Monitor for PH and DVD progression.^a | <ul style="list-style-type: none"> • Investigate other etiologies for PH. • Treat underlying etiology of PH if possible. • Initiate treatment with pimobendan.^a • Consider the initiation of a PDE-5 inhibitor ± L-arginine.^a |

Abbreviations: ACE, angiotensin-converting enzyme; B2^E, stage B2 DVD that meets EPIC criteria for initiation of pimobendan; DVD, degenerative valve disease; echo, Doppler echocardiography; PDE, phosphodiesterase; PH, pulmonary hypertension.

^a Highest priority recommendation.

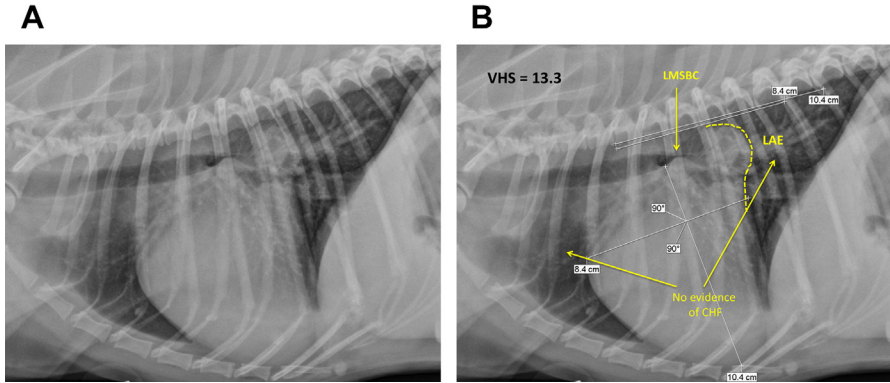


Fig. 4. (A, B) A right lateral radiograph from a dog with DVD that presented for evaluation of a chronic, harsh cough. The dog had never been in CHF and was thus classified as stage B2. The VHS is 13.3. The left atrium is severely enlarged and appears to compress the airway directly dorsal to it consistent with LMSBC. There is no evidence of pulmonary edema (yellow arrows). In some cases, direct visualization of LMSBC may not be possible, but it can be considered a possible rule-out or contributing cause for any dog with a cough and significant cardiomegaly, especially with moderate to severe left atrial enlargement (yellow dashed line). An echocardiogram should be recommended in this dog to confirm the diagnosis and directly assess left atrial and ventricular size. If an echocardiogram is not available, initial treatment recommendations for this dog should include pimobendan (based on $VHS \geq 11.5$). Other palliative treatments can be added as needed as outlined in the text. LAE, left atrial enlargement.

therapies that are clinically successful can fail intermittently and need to be revisited. In general, the authors attempt to never initiate more than 2 to 3 therapies on a given day and then make changes based on clinical response. In some cases, changes to therapy may include changes in dose, and in other dogs it may require discontinuation of one medication to initiate another one in the hope of a better clinical outcome. There is no recommended definitive therapy for this condition. Stenting for bronchial collapse is possible in select dogs without complicating concurrent bronchomalacia or chronic inflammatory airway disease and is considered palliative, not curative.⁴⁸ It has been associated with an increased risk of complications related to stent migration, infection, and clinical decompensation, and is not routinely performed. Perhaps in the future, newer devices will make this possible. Reduction of heart size via valve repair or replacement could be considered if the patient was a good candidate for this procedure. Surgical repair of DVD can result in significant reductions in heart size and might be palliative for severe cough related to LMSBC, assuming the dog was considered a good candidate for repair.

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