

# EPIC change to the management of mitral valve disease

An EPIC change to the management of canine mitral valve disease is discussed by Jenny Wilshaw BVet-Med MRCVS, PhD Student, Royal Veterinary College, London, UK



Stage	Definition	
<b>A (At risk)</b>	Individuals in this stage have no identifiable structural valve lesions but, based on signalment, are at risk of developing MVD	
<b>B (Asymptomatic)</b>	This is the asymptomatic (preclinical) stage of MVD. Stage B is used to identify patients that have valvular disease but do not have congestive heart failure (CHF). The stage is subcategorised numerically	<p><b>Stage B1:</b> No evidence of cardiomegaly</p> <p><b>Stage B2:</b> Echocardiographic and/or radiographic evidence of left-sided cardiac enlargement</p>
<b>C</b>	Patients have experienced clinical signs of CHF and require continuous medical therapy with a potent diuretic	
<b>D</b>	Patients have clinical signs of CHF that are refractory to standard therapies	

**Table 1: The American College of Veterinary Internal Medicine staging scheme for degenerative mitral valve disease. Adapted from: 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: 1 142- 1150.**

## ASYMPTOMATIC MVD AND THE EPIC STUDY

The EPIC study was a large, prospective, blinded, randomised placebo-controlled trial that evaluated the benefit of chronic oral administration of pimobendan to dogs with stage B2 disease (see Table 1).<sup>1,2</sup> The results of EPIC showed a significant benefit to treating these dogs with pimobendan (Vetmedin), as the risk of developing CHF or cardiac-related death was reduced by 36% for dogs in the treatment group. When control and treatment populations were compared, the dogs receiving pimobendan experienced a 60% prolongation of the preclinical period, taking on average 15 additional months to reach the study's primary endpoint. Considering the life expectancy of dogs commonly affected by MVD, this represents a significant additional period of symptom free survival for our patients.

## APPLYING THE RESULTS OF EPIC TO CLINICAL PRACTICE

In order to accurately identify those patients with left-sided cardiac enlargement, the inclusion criteria of the EPIC study stated that all participating dogs were required to demonstrate cardiomegaly by meeting or exceeding three measurements of cardiac size at the point of enrolment. These were a left atrial to aortic root ratio  $\geq 1.6$  (LA:Ao), a normalised left ventricular internal diameter in diastole  $\geq 1.7$  (LVIDDN) and a vertebral heart score  $> 10.5$  (VHS).<sup>3-5</sup> As the effect of treatment was only assessed in dogs that met these criteria, the generalisability of the study's findings to dogs with values that do not meet these criteria or dogs that have undergone an incomplete assessment is a common source of confusion.

Following the publication of the EPIC (Evaluation of Pimobendan In dogs with Cardiomegaly caused by preclinical mitral valve disease) study, the goalposts for initiating treatment in patients with mitral valve disease (MVD) have shifted.<sup>1</sup> Instead of waiting for the onset of congestive heart failure (CHF), we now know that disease management in the asymptomatic (preclinical) stages of the disease is of benefit to our patients. Given that the majority of cases of asymptomatic MVD are detected incidentally in first-opinion practice, one of the discussion points that has arisen post-EPIC is how to correctly identify those patients that would benefit from treatment in a primary care setting.

### IS INTERVENTION IN STAGE B1 INDICATED?

Previous clinical trials have similarly evaluated the effects of pimobendan in the later stages of MVD (stage C) and in dogs with dilated cardiomyopathy.<sup>6-8</sup> The findings of these studies, alongside those of EPIC, indicate that the administration of pimobendan is associated with a significant decrease in cardiac size in dogs with cardiomegaly.<sup>9</sup> This has led to speculation that the beneficial effect of pimobendan in progressive MVD is, in part, due to a reduction in heart size and a secondary decline in mitral regurgitant volume. Interestingly, this hypothesis brings into question whether it is appropriate to treat dogs that do not stand to benefit from a reduction in heart size. Given that, at present, there is no research to suggest otherwise, the treatment of dogs without evidence of cardiomegaly, ie. stage B1 disease is therefore, not advisable.

In addition to this, it is also important to recognise that, without appropriate investigation, it is not possible to conclude that the administration of pimobendan in the absence of cardiomegaly is benign. In a small population of laboratory Beagles with stage B1 disease, the chronic administration of pimobendan was apparently associated with detrimental effects to cardiac morphology and function.<sup>10</sup>

### SELECTING DIAGNOSTIC TESTS TO STAGE DISEASE

When considering the applications of EPIC in a clinical setting, the requirement to meet all three determinants of cardiomegaly has been questioned. If applied literally, this would mean that both echocardiography and radiography would need to be performed in asymptomatic dogs prior to providing treatment advice. Practically speaking, this is not attainable in all patients and may preclude access to pimobendan.

Anecdotal recommendations from the EPIC study's primary investigators indicate that while conducting both sets of imaging studies should be viewed as the gold-standard recommendation, meeting the echocardiographic criteria alone would still be considered a sufficient basis to initiate treatment.<sup>11,12</sup> When compared to radiography, echocardiography is considered the superior technique to stage preclinical MVD and provides a real-time assessment of cardiac morphology and function. Permitting the measurement of both left atrial and ventricular size relative to body size, echocardiography allows the practitioner to obtain a more accurate assessment of left-heart size, thus informing on disease stage, severity and prognosis.<sup>13,14</sup> If possible, echocardiography should be performed by an operator with a specialist interest in veterinary cardiology. As with most practical skills, performance is improved with experience, reducing the potential for inaccuracies in measurements, misdiagnoses and inappropriate treatment selections.<sup>15</sup> In addition to this, an echocardiographic study performed by a skilled ultrasonographer can provide a more complete assessment of general cardiac health, excluding alternative causes of left sided eccentric hypertrophy and

Grade	Description
1	Nearly imperceptible murmur. Only detected with careful auscultation.
2	Murmur quieter than normal heart sounds
3	Murmur volume equivalent to that of heart sounds
4	Murmur louder than heart sounds
5	Murmur louder than heart sounds with palpable precordial thrill
6	Murmur can be auscultated with stethoscope held away from thoracic wall. Again, accompanied by a precordial thrill.

**Table 2: The six-point Levine scale used to grade murmur intensity. Adapted from: Levine S, Systolic murmur: its clinical significance. JAMA 1933; 101: 436-438.**

identifying other cardiac comorbidities. If it is not possible to refer a patient for specialist-level evaluation, the right sided echocardiographic views required to measure LA:Ao and LVDDN can be obtained by general practitioners with the correct training, experience and equipment.

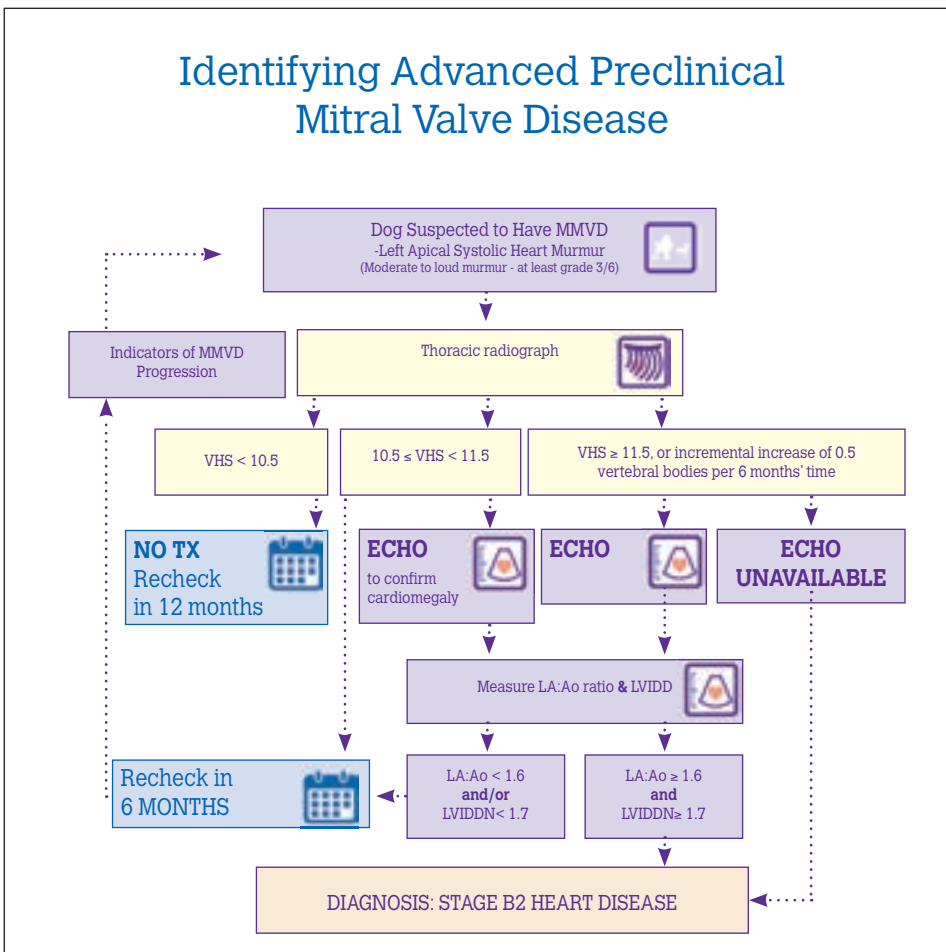
The radiographic assessment of heart size provides a potential alternative to cardiac ultrasound for practitioners that cannot confidently perform the latter technique. As previously discussed, in the EPIC study, the cut-off VHS value of 10.5 was used in combination with echocardiographic measurements to identify patients with cardiomegaly. If assessed in the absence of an echocardiogram, a larger value of VHS should be used to minimise the risk of false-positive diagnoses and to accommodate the well-documented breed-related variation in scores, particularly as many breeds, that are naturally predisposed to MVD, have mean scores that exceed 10.5.<sup>16-19</sup> The Cardiac Education Group (CEG) suggests instead using a VHS  $\geq 11.5$  to improve specificity when identifying stage B2 dogs.<sup>12</sup> Given the potential for false diagnoses when interpreting VHS, it is still advised to recommend echocardiography at this point prior to prescribing treatment with pimobendan. If this has been discussed with an owner and is still declined, CEG advises that the administration of pimobendan can be considered in dogs with a VHS  $\geq 11.5$  and murmur grade  $\geq 3/6$ .<sup>20</sup>

### ADDITIONAL FACTORS THAT CAN BE USED TO INCREASE CLINICAL SUSPICION OF STAGE B2 DISEASE

Given that the course of MVD is typically long and slowly progressive, a common problem that may now be faced when managing preclinical MVD, is how to determine the points at which diagnostic evaluation will be most valuable. While it is the gold standard, it is unrealistic to anticipate that every patient will be able to undergo specialist imaging studies every six to 12 months over the course of several

years. In these patients, considering a patient's pre-test probability of being diagnosed with stage B2 disease may assist with resource allocation. In-house assessments can be used to increase the clinical suspicion that a patient may have advanced preclinical disease and cardiac enlargement. A simplistic recommendation would be to interpret the intensity of the characteristic murmur associated with MVD. Previous research has shown that the intensity of this murmur is positively associated with echocardiographic measurements of left atrial and ventricular size, as well as with the volume of the mitral regurgitant jet itself.<sup>21-23</sup> Studies have shown that quieter murmurs (grade 3/6) are typically auscultated in dogs with mild, stage B1 disease, whilst moderate to loud murmurs, excluding those with a thrill, can be appreciated in both preclinical stages. Although not directly assessed, it appears that murmur grade possesses negative predictive value, meaning that patients with soft murmurs (<grade 3/6 [see Table 2]) are unlikely to be in stage B2. Asymptomatic dogs with a murmur that is grade 3/6 or louder could be considered at higher risk and may stand to benefit from further investigations.

While the diagnostic accuracy of the VHS has been previously discussed, the VHS may be more appropriately interpreted as an approximation of cardiac size and used to detect patients that are at risk of being in stage B2. Though the value of 10.5 does not indicate the presence of cardiomegaly to a sufficiently accurate degree to dictate the onset of treatment, measurements that are greater than 10.5 (or the relevant breed-specific range) may still be considered abnormal and represent underlying pathology in some individuals. In these patients, VHS could therefore be used as a screening tool to guide the recommendation that echocardiography may be of further diagnostic value. In addition to its short-term use, a study by Lord et al (2011) observed that VHS increased as the severity of preclinical disease advanced, indicating a longitudinal benefit to obtaining repeated measurements of radiographic heart size.<sup>24</sup> Increases in VHS may represent disease progression and could be used to advise that echocardiographic staging is now indicated. The CEG recommend that treatment with pimobendan could be considered when the VHS has increased by 0.5 vertebral bodies over a six-month period.



**SUMMARY**

In conclusion, patients with preclinical MVD stand to experience the greatest benefit to the longevity and quality of their life if appropriate treatment is recommended following accurate staging of their disease. The gold-standard approach to work up a patient with asymptomatic mitral valve disease is to conduct echocardiographic and radiographic studies. In patients where this is not attainable, alternative approaches to staging disease are available, though practitioners should endeavour to make considered and informed evaluations of their findings in order to minimise the risk of false diagnoses.

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**Figure 1:** A diagnostic algorithm which can be used to identify dogs in stage B2. Picture: Boehringer Ingelheim Animal Health, 2017 [epictrial.com/epic-study-results-preclinical-mmvd].

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