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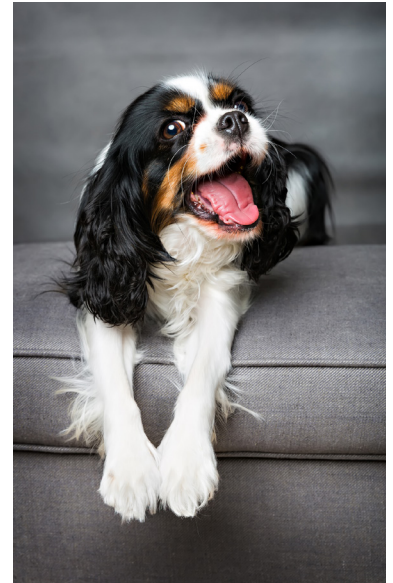
The EPIC Trial: Pimobendan in Preclinical Myxomatous Mitral Valve Disease

What is the EPIC trial?

The EPIC trial was a large randomized, multinational, multicenter study designed to investigate the effect of Vetmedin® (pimobendan) on the progression of myxomatous mitral valve disease in small breed dogs. The trial acronym (EPIC) stands for the “**E**valuation of **P**imobendan **I**n dogs with **C**ardiomegaly caused by preclinical myxomatous mitral valve disease.” The results of this trial were first published in the Journal of Veterinary Internal Medicine in September, 2016 ([link to manuscript](#)).¹

What was the purpose of the EPIC trial?

The purpose of the trial was to investigate whether or not pimobendan delayed the onset of congestive heart failure (CHF) or cardiac-related death/euthanasia in dogs with asymptomatic myxomatous mitral valve disease and cardiac enlargement, as compared to placebo. Additionally, the effect of pimobendan on all-cause mortality in this population was evaluated as a secondary endpoint.



What dogs were enrolled in the EPIC trial?

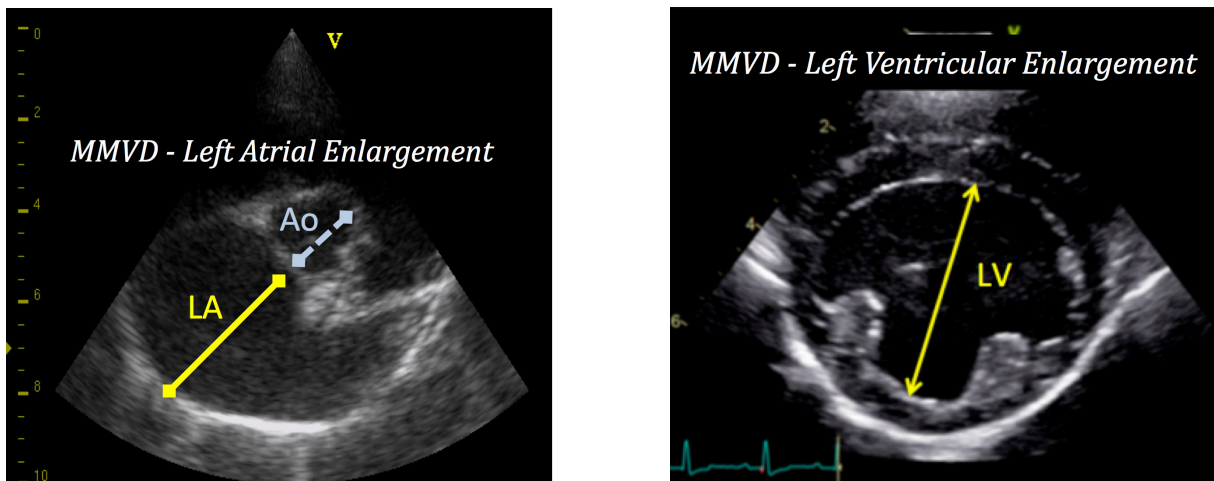
The EPIC trial enrolled 360 dogs with preclinical myxomatous mitral valve disease. To enter the study, cardiac enlargement was required based on the criteria above, meaning all dogs were ACVIM stage B2 with at least moderate cardiac enlargement ([link to ABCD handout](#)). Specifically, the inclusion criteria for the trial were:

- dogs over 6 years of age,
- with a body weight between 4 and 15kg,
- systolic heart murmur characteristic of mitral regurgitation (maximal intensity at the left cardiac apex) of moderate to high intensity (greater than or equal to grade 3 out of 6),
- cardiac enlargement, defined by:
 - vertebral heart size (VHS) had to equal or exceed 10.5²
 - left atrial-to-aortic root short-axis ratio (Figure 1) as measured by 2-dimensional echocardiography had to equal to or exceed 1.6, according to the Swedish method³
 - normalized left ventricular internal dimension in diastole (LVIDDN; Figure 1) had to equal or exceed 1.7⁴
 - The allometric formula for calculation of LVIDDN is:

$$\text{LVIDDN} = \frac{\text{measured LVIDD (cm)}}{\text{Weight (kg)}^{0.294}}$$
 - The approximate measured value of LVIDD that delivers a LVIDDN greater than or equal to 1.7 by body weight are shown in Table 1.

Dogs were excluded from the trial if they had other life-threatening disease, clinically significant arrhythmias, severe pulmonary hypertension, prior CHF, or had previously received cardiac medications. Dogs were enrolled in the study from October 2010 to June 2013 and then followed until the trial ended in March 2015.

FIGURE 1



The left atrium (LA) to aortic (Ao) ratio (LA size divided by Ao diameter) is measured at maximal LA size (end of ventricular systole) from a short-axis image. The Ao is measured along the junction of the non-coronary and left coronary valvar sinuses, while the LA is measured along this same line from inner edge to inner edge, without extending the line into a pulmonary vein. The left ventricular internal dimension is measured at end diastole, bisecting the chamber between the papillary muscles on either a 2D or M-mode image, and then normalized to body weight by the allometric equation shown above (see Table 1).

Were the 2 groups within the EPIC trial different from one another?

The 360 dogs were randomly divided into 2 groups of 180 each; one group received pimobendan at the labeled dose (target dose of 0.5 mg/kg/day divided into 2 doses) and the other received a placebo that was identical in appearance. Both the dog owners and the veterinarians caring for each dog were not told which medication the dogs were receiving. An analysis of the groups at the time of enrollment found no difference for all pertinent baseline characteristics.

What were the results of the EPIC trial?

The dogs were monitored and re-evaluated at 1 month and then every 4 months for the duration of the trial. If clinical signs developed at any point in the trial, the dogs underwent clinical evaluation to determine if congestive heart failure was present. The primary endpoint of CHF was verified by a separate endpoint committee who reviewed the radiographs without knowledge of the drug treatment. The trial underwent an interim analysis by an independent monitoring committee in January 2015, which found a significant benefit of pimobendan compared to placebo, and the trial was ended in March 2015. **The final analysis found that the median time to the primary endpoint (CHF or cardiac death) for dogs receiving pimobendan was 1228 days compared to 766 days for dogs in the placebo group (a statistically significant difference with a P value of 0.0038).**

A secondary endpoint of all-cause mortality was also in favor of pimobendan, with a median time from inclusion in the study to death of 1059 days for the pimobendan group compared to 902 days for the placebo group (a statistically significant difference with a P value of 0.012).

When the study results were analyzed, the variables that independently predicted which dogs would have the longest time to the primary endpoint were receipt of pimobendan (vs. placebo), a normal appetite (vs. a decreased appetite), smaller heart size (vs. a larger heart), and normal systolic heart function (% fractional shortening) compared to an increased % fractional shortening. If the echocardiographic variables were excluded, pimobendan (vs. placebo), slower heart rate on initial examination, normal systolic arterial blood pressure (vs. low normal blood pressure), and smaller radiographic heart size (VHS) predicted a longer time to the primary endpoint. Sporadic adverse events, primarily gastrointestinal in nature, were noted throughout the study period with equal prevalence between groups.

What other interesting findings arose from the EPIC trial?

A secondary endpoint was the time to a composite endpoint of left-sided CHF, euthanasia or death for noncardiac reasons, initiation of non-CHF medications (e.g. cough suppressant), or non-confirmed CHF. This analysis was meant to better understand the real-world effect of the drug beyond and including the primary endpoint. **This secondary endpoint was also different between groups in favor of pimobendan at 640 days compared to 406 days in the placebo group at a P value of <0.001.**

Why was the trial stopped prematurely?

At first glance, it seems odd that the trial was ended before the expected timeframe. However, the decision to do so was made before the trial started if the independent interim analysis committee found certain conditions had been met. The rationale for this approach is well established in human medicine; namely, if there is a substantial safety concern that is different between groups, it is better to know sooner and address it. Similarly, if there is a clear outcome advantage for one group compared to the other, it is important to allow all dogs to receive this benefit as soon as it is clearly determined to be real. The final analysis confirmed the conclusion from the interim analysis.



TABLE 1

Dog Weight (kg)	LVIDD Measurement Equal to LVIDDN of 1.7		Dog Weight (kg)	LVIDD Measurement Equal to LVIDDN of 1.7
1	17.0		13	36.1
1.5	19.2		14	36.9
2	20.8		15	37.7
3	23.5		16	38.4
4	25.6		17	39.1
5	27.3		18	39.8
6	28.8		19	40.4
7	30.1		20	41.0
8	31.3		21	41.6
9	32.4		22	42.4
10	33.5		23	42.7
11	34.4		24	43.3
12	35.3		25	43.8

Ventricular enlargement was defined as a normalized left ventricular internal dimension in diastole (LVIDDN) greater than 1.7. For dogs of various size, the actual LVIDD measurement that equals this cut-off value is shown.

What is the significance of these results to the treatment of mitral valve disease?

For the first time in canine medicine, this trial has found a statistically-significant beneficial effect from the administration of a medication in dogs with asymptomatic myxomatous mitral valve disease and substantial cardiac enlargement. **For dogs that meet all the inclusion criteria of the EPIC trial, the data suggest that dogs that receive pimobendan will, on average, remain asymptomatic for ~15 months longer and live for ~5 months longer when compared to dogs that do not.** Analyses of the data tell us the drug appears safe to administer in this population compared to placebo. Overall, the dogs receiving pimobendan were less likely to require initiation of additional cardiopulmonary medications in the preclinical period compared to those taking the placebo.

How should I apply these findings to my clinical practice?

This is the most difficult question to answer about this trial and a matter that remains debated by veterinary cardiologists. We know that myxomatous mitral valve disease is the most common heart disease of dogs and many dogs with the disease will not progress to CHF. Because of this, **the CEG does not recommend administration of pimobendan to every dog with a heart murmur.**

It is the opinion of the CEG that dogs with asymptomatic mitral valve disease be examined closely to identify those dogs that may benefit from pimobendan. From this trial, we know that the dogs with substantial cardiac enlargement will benefit from pimobendan. Thus, **documentation of cardiac enlargement is critical to decide whether treatment is appropriate for a given patient (see algorithm).**

The strictest interpretation of the trial would suggest that all small breed dogs with a left apical systolic murmur of grade 3/6 or louder should have radiographs taken and an echocardiogram performed to determine if substantial cardiac enlargement is present and pimobendan therapy warranted. The practical impacts of this approach are challenging, since not all dogs with a murmur of this type will meet the EPIC inclusion criteria for cardiac enlargement, nor will all dog owners be willing to have these diagnostic tests performed or be able to afford lifetime pimobendan therapy.



How does the CEG advise practitioners to apply these results?

- Documentation of substantial cardiac enlargement (Figure 1 & algorithm) is critical to determine whether or not to start pimobendan in dogs with preclinical myxomatous mitral valve disease.
- If substantial cardiac enlargement is not documented by echocardiography and the VHS is <10.5 , reevaluation is advised in 12 months.
- If the VHS is between 10.5 and 11.5 and an echocardiogram is not performed or does not exceed enlargement criteria, reevaluation is advised in 6 months.
- If an echocardiogram is not available and only thoracic radiographs are performed, the CEG recommends starting pimobendan in dogs with heart murmurs of grade 3/6 or louder only when the VHS exceeds 11.5 vertebral bodies or an incremental increase of greater than 0.5 vertebral bodies per 6 months is accurately documented.
- See algorithm for a schematic representation of this approach.

What about the co-administration of an Angiotensin Converting Enzyme Inhibitor (ACE-inhibitor) or an aldosterone antagonist?

The EPIC trial did not evaluate concurrent use of an ACE-inhibitor (e.g. enalapril or benazepril) or aldosterone antagonist (i.e. spironolactone) in the setting of preclinical myxomatous mitral valve disease. Interpretation of prior veterinary trials (SVEP⁵ and VETPROOF⁶) investigating enalapril in preclinical mitral valve disease dogs failed to achieve a statistically-significant benefit compared to placebo. However, in VETPROOF some secondary endpoints were in favor of enalapril and on average there was a modest delay in the onset of CHF by about four months.⁶ This delay is clearly inferior to that achieved in the EPIC trial using pimobendan, but we do not know if using both drugs would provide any incremental benefit. In short, cardiologists have not reached a consensus on when to initiate ACE inhibition or aldosterone antagonism at this stage of MMVD. The consensus of the CEG is to add an ACE-inhibitor to pimobendan when severe cardiac enlargement has occurred or if a large incremental change in heart size over time (e.g., greater than 0.5 vertebral bodies per 6 months) is documented despite pimobendan therapy. We also recognize that the cost of medication in a country can influence this decision. Overall, the CEG recommends that you discuss this issue with cardiologists within your referral area and continue to follow the literature for clinical trial evidence.

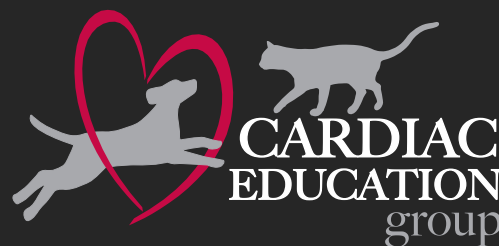
What about dogs in stage B2 that have been chronically receiving ACE-inhibitors or aldosterone antagonists?

The CEG recommends reevaluation of these dogs with imaging to investigate the degree of cardiac enlargement, as discussed above and in the algorithm. If the criteria discussed in this document are then met, administration of pimobendan is recommended with continuation of the previously-prescribed medication.

References

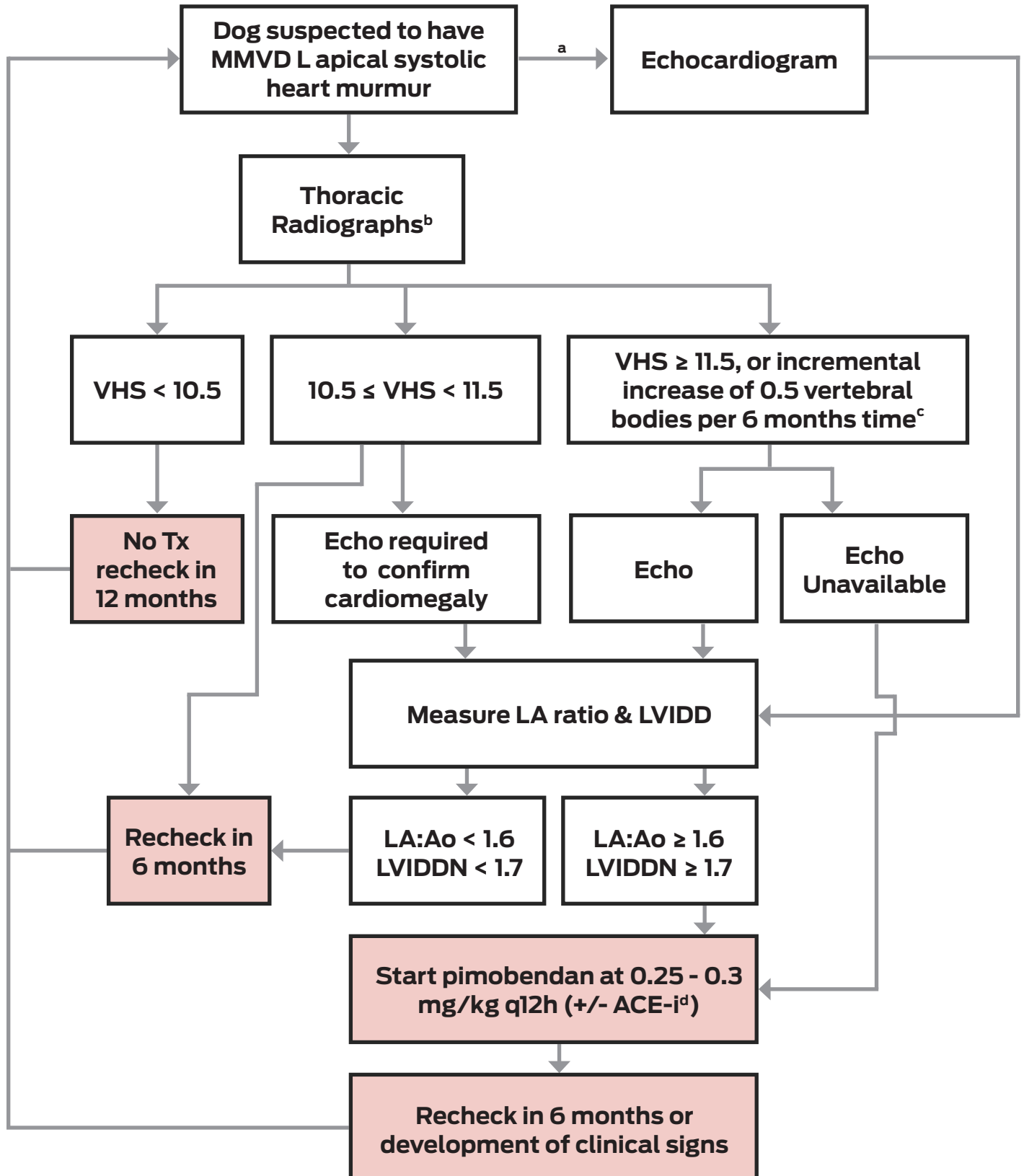
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ALGORITHM

CEG Recommendations for Therapy in Preclinical Myxomatous Mitral Valve Disease



Algorithm Footnotes

- a. Diagnostic imaging becomes especially meaningful in dogs when the murmur is no longer soft or focal. Imaging studies are always recommended for evaluation of a moderate to loud murmur of mitral regurgitation (grade 3/6 or louder). Echocardiography is also indicated if the cause of the heart murmur is in doubt, as with a younger dog who might have congenital heart disease or in a dog with a breed-risk for dilated cardiomyopathy.
- b. While both thoracic radiography and echocardiography can be used to identify cardiac enlargement, the echocardiogram is generally preferred if the cause of the systolic murmur is uncertain and to more precisely measure chamber sizes. If there is evidence of cardiomegaly/remodeling on the echocardiogram, then radiographs are also suggested to measure vertebral heart size (VHS), evaluate the cardiac chambers subjectively, and obtain a “baseline” for the appearance of pulmonary vasculature and parenchyma. In situations where the client declines echocardiography, the thoracic radiograph path can be followed in the primary care practice. ACVIM guidelines recommend **both** imaging methods for optimal evaluation of a dog with suspected MMVD.
- c. The EPIC trial did not investigate a cutoff for cardiac enlargement by VHS alone at which to start pimobendan therapy. This algorithm represents the consensus of the CEG to initiate therapy when echocardiography is not available, but is not based on evidence.
- d. Cardiologists have not reached a consensus on when to initiate angiotensin converting enzyme (ACE) inhibition or aldosterone antagonism at this stage of MMVD. The consensus of the CEG is to add an ACE-inhibitor to pimobendan when severe cardiac enlargement has occurred or if a large incremental change in heart size over time.

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