Pimobendan and Its Use in Treating Canine Congestive Heart Failure

Danielle Bowles, BVSc, FANZCVS
Veterinary Specialist Services
Brisbane, Queensland
Australia

Darren Fry, MA, VetMB, MRCVS, FANZCVS
Brisbane Veterinary Specialist Centre
Brisbane, Queensland
Australia

Abstract: Pimobendan, a calcium sensitizer and phosphodiesterase III inhibitor, has positive inotropic and vasodilatory properties. Its use in patients with naturally occurring congestive heart failure (CHF) has been studied in a number of blinded, randomized, multicenter clinical trials. It has been shown to improve quality of life, reduce heart insufficiency scores, and increase median survival times for patients with CHF due to dilated cardiomyopathy and myxomatous valvular disease. Although most studies have reported positive findings, some potential adverse effects have also been described. Studies are under way to further evaluate the effects of this novel positive inotrope and vasodilator in canine cardiac disease.

Heart disease is common in veterinary patients. A potential consequence of severe heart disease in canine patients is the development of congestive heart failure (CHF). Traditionally, the main therapeutics used in CHF treatment have included diuretics, angiotensin-converting enzyme inhibitors (ACEIs), and the positive inotrope digoxin. However, over the past 20 years, interest in the use of positive inotropic agents other than digoxin in the treatment of CHF in human and veterinary patients has increased. Positive inotropes are pharmacologic agents that improve the contractility of cardiac muscle. A novel positive inotropic agent, pimobendan, has been developed for use in canine CHF. This article briefly reviews cardiac muscle physiology; describes the human and veterinary experiences with and knowledge regarding pimobendan; and describes the pharmacology and clinical recommendations regarding pimobendan use in canine CHF.

Myocyte Structure, Physiology, and Contraction
Cardiac muscle is composed of cardiomyocytes and a connective tissue matrix. The contractile unit of the cardiomyocyte (the sarcomere) is primarily composed of thin filaments (actin) and thick filaments (myosin). These filaments overlap, and proteins (troponin I [inhibitory], troponin C [calcium binding], troponin T [tropomyosin binding], and tropomyosin2) regulate myosin and actin interaction based on cytosolic calcium levels, allowing contraction and relaxation to occur. In diastole, the extracellular calcium level is higher than cytosolic levels and calcium is sequestered in the sarcoplasmic reticulum.2,4 In this resting state, tropomyosin prevents actin-myosin interaction and contraction. In systole, cytosolic calcium levels increase, and calcium binds to troponin C to allow contraction. Systole ends and diastole begins again as cytosolic calcium levels decrease.2 These processes are regulated by intracellular messaging systems.5 Common messengers in this system include the nucleotides cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP).2,5 Phosphodiesterases (PDEs) are enzymes that are responsible for the degradation of these nucleotides. Inhibition of PDE prevents the degradation of cAMP and cGMP, thereby increasing their concentration. This affects cardiomyocyte and vascular smooth muscle contraction and relaxation.

Mechanism of Action of Pimobendan
Pimobendan (4,5-dihydro-6-[2-(4-methoxyphenyl)-1H-benzimidazole-5-yl]-5-methyl-3(2H)-pyridazinone) is a benzimidazole-pyridazine derivative. It is a calcium sensitizer and a phosphodiesterase III (PDEIII) inhibitor. It has been termed an inodilator because of its dual action of positive inotropy and vasodilation.4 The positive inotropic effects of pimobendan are thought to be due to its calcium-sensitizing effects, which cause increased calcium-troponin C interaction and thus increased actin-myosin cross-binding to produce a greater force of contraction. The vasodilatory
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Duration</th>
<th>Underlying Disease Studied</th>
<th>Pimobendan Dose</th>
<th>Concurrent Medications (dose)</th>
<th>Treatment Groups</th>
<th>Number of Dogs Per Treatment Group</th>
<th>Breed(s)</th>
<th>Survival Data</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Justus et al19</td>
<td>Open label to establish effective doses</td>
<td>Not reported</td>
<td>Cardiac insufficiency (included MVD and DCM)</td>
<td>Increasing from 0.2–0.6 mg/kg/d</td>
<td>Furosemide (not reported)</td>
<td>PIMO (one group involving all patients)</td>
<td>n = 45</td>
<td>Not reported</td>
<td>88.9% of patients receiving 0.4–0.6 mg/kg/d had improvement of NYHA heart score</td>
<td>None reported</td>
</tr>
<tr>
<td>Kleeman et al 198010</td>
<td>Prospective, placebo-controlled, multicenter</td>
<td>4 wk; optional treatment for 4 mo</td>
<td>CHF (cause not reported)</td>
<td>0.5 mg/kg/d, divided twice daily</td>
<td>Furosemide (not reported)</td>
<td>PIMO (0.5 mg/kg/d); digoxin (0.010–0.015 mg/kg/d)</td>
<td>PIMO, n = 60; digoxin, n = 49</td>
<td>Not reported</td>
<td>86.7% PIMO patients had improvement of NYHA heart score</td>
<td>6.4% PIMO patients; included vomiting</td>
</tr>
<tr>
<td>Luis Fuentes et al 199815; 20022</td>
<td>Prospective, double-blind, placebo-controlled</td>
<td>Long-term survival analysis</td>
<td>CHF due to DCM</td>
<td>Not reported</td>
<td>Digoxin, enalapril, furosemide (not reported)</td>
<td>Treat and untreat DP: treated and untreated ACS</td>
<td>DP, n = 10 ACS; PIMO, n = 10 Placebo, n = 10</td>
<td>Not reported</td>
<td>None seen</td>
<td>Dogs treated with ramipril were 4× more likely to have an adverse CHF outcome than dogs treated with PIMO (P = 0.0046)</td>
</tr>
<tr>
<td>PITCH study Lombard 200011; 200312</td>
<td>Prospective, double-blind, placebo-controlled</td>
<td>28 d</td>
<td>CHF due to DCM (n = 81) or MVD (n = 24)</td>
<td>Not reported</td>
<td>Diuretics (dose and drug not reported)</td>
<td>PIMO: PIMO and BNZ; BNZ</td>
<td>PIMO, n = 32; PIMO + BNZ, n = 25; BNZ, n = 24</td>
<td>Not reported</td>
<td>PIMO: MST 217 d; PIMO + BNZ: MST 217 d; BNZ: MST 42 d</td>
<td>None reported</td>
</tr>
<tr>
<td>Smith et al 200513</td>
<td>Prospective, randomized, single-blind, parallel group</td>
<td>6 mo</td>
<td>CHF due to MVD</td>
<td>0.3 mg/kg PO bid</td>
<td>Furosemide ± digoxin (not reported)</td>
<td>Ramipril dose 0.125 mg/kg PO once daily</td>
<td>PIMO; ramipril</td>
<td>PIMO; PIMO, n = 22; ramipril, n = 21</td>
<td>58% CKCS</td>
<td>64% PIMO patients; 50% ramipril patients (P = 0.066)</td>
</tr>
<tr>
<td>VetSCOPE trial Lombard et al 200614</td>
<td>Prospective, randomized, double-blind, positive controlled</td>
<td>56 d; optional non-blinded, long-term, treatment period</td>
<td>CHF due to MVD</td>
<td>0.2–0.3 mg/ kg PO bid</td>
<td>Furosemide, antiarrhythmic (not specified); treatments for concurrent diseases (not specified)</td>
<td>BNZ 0.25–0.5 mg/kg PO once daily</td>
<td>PIMO + placebo; BNZ + placebo</td>
<td>PIMO, n = 41; BNZ, n = 35</td>
<td>17 different breeds, not specified</td>
<td>PIMO: improvement in ISACHC heart insufficiency score in 85% (P = 0.0001); MST 430 d; BNZ/ MST 228 d (P = 0.002)</td>
</tr>
<tr>
<td>O’Grady et al 200816</td>
<td>Prospective, randomized, double-blind, placebo controlled</td>
<td>Long-term survival analysis</td>
<td>CHF due to DCM</td>
<td>0.25 mg/kg PO bid</td>
<td>BNZ (0.5 mg/ kg PO bid); furosemide as necessary (not reported)</td>
<td>PIMO; placebo</td>
<td>PIMO, n = 8; placebo, n = 8</td>
<td>DP</td>
<td>Median time to treatment failure: PIMO, 130.5 d; placebo, 14 d (P = 0.003)</td>
<td>None reported</td>
</tr>
<tr>
<td>QUEST trial Haggstrom et al 200817</td>
<td>Prospective, randomized, blinded</td>
<td>Long-term survival analysis</td>
<td>CHF due to MVD</td>
<td>Dose not specified</td>
<td>Standard treatments (drugs not specified)</td>
<td>PIMO; BNZ</td>
<td>N = 260 (group numbers not specified)</td>
<td>Small and medium breeds (not specified)</td>
<td>Longer survival PIMO group (absolute data not specified)</td>
<td>PIMO side effects similar to BNZ</td>
</tr>
</tbody>
</table>

ACS = American cocker spaniel, BNZ = benazepril, CHF = congestive heart failure, CKCS = Cavalier King Charles spaniel, DCM = dilated cardiomyopathy, DP = Doberman pinscher, ISACHC = International Small Animal Cardiac Health Council, MST = median survival time, MVD = myxomatous valvular disease, NYHA = New York Heart Association, PIMO = pimobendan, PME = postmortem examination.
effects of pimobendan are thought to be mediated through PDEIII inhibition. A PDEIII-mediated increase in cAMP results in vascular smooth muscle relaxation (vasodilation).

**Veterinary Use of Pimobendan**

Many of the early experimental studies for human pimobendan use involved animal models of human cardiac disease. The positive results in these studies led to further evaluation of pimobendan in dogs with dilated cardiomyopathy (DCM) or myxomatous valvular disease (MVD; **TABLE 1**).

**Studies of Myxomatous Valvular Disease and Dilated Cardiomyopathy**

Three studies evaluated the use of pimobendan in dogs with CHF secondary to MVD or DCM. The first was an open-label study⁹ to establish an effective dose; the second¹⁰ compared pimobendan with digoxin over a 4-week period. Most patients receiving pimobendan (88.9%⁹ and 86.7%¹⁰) showed an improvement in the New York Heart Association (NYHA; **TABLE 2**) heart scores. A 0.4- to 0.6-mg/kg/d dose was established to be safe and effective.

The PITCH study¹¹,¹² also showed an improvement in median survival in dogs with CHF secondary to MVD or DCM when treated with pimobendan (survival: 217 days) with or without benazepril compared with benazepril alone (survival: 42 days). There was no significant difference between patients receiving pimobendan without benazepril and those receiving both drugs. The major limitation of all three studies was that dogs with CHF due to different etiologies (DCM and MVD) were grouped together, so it was not clear whether the improvement in NYHA scores and median survival time was solely due to results in dogs with DCM or also reflected results in dogs with MVD.

**Studies of Myxomatous Valvular Disease**

In 2005, Smith et al ¹³ published the first paper investigating pimobendan use only in dogs with CHF due to MVD. Two more papers were published in 2006 (VetSCOPE¹⁴) and 2008 (QUEST trial¹⁵) investigating pimobendan use in canine MVD patients. All three papers evaluated pimobendan in comparison with an ACEI (ramipril¹³ or benazepril¹⁴,¹⁶), and results were conflicting. Although the Smith paper showed no survival benefit for either treatment group, both the 56-day trial period and the optional long-term survival study published by the VetSCOPE group, as well as the QUEST trial, showed improved scores using the International Small Animal Cardiac Health Council (ISACHC; **TABLE 3**)¹⁴ or NYHA¹⁶ classification and improved median survival times in patients treated with pimobendan.

**Studies of Dilated Cardiomyopathy**

Two studies have evaluated the use of pimobendan in dogs with CHF due to DCM, and these studies have obtained the most profound results. Luis Fuentes and colleagues¹⁷ compared Doberman

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**Table 1. Studies of Veterinary Use of Pimobendan (cont.)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Duration</th>
<th>Underlying Disease Studied</th>
<th>Pimobendan Dose</th>
<th>Concurrent Medications (dose)</th>
<th>Treatment Groups</th>
<th>Number of Dogs Per Treatment Group</th>
<th>Breed(s)</th>
<th>Survival Data</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanno et al 2007¹⁹</td>
<td>Prospective, non-placebo study on experimentally induced MVD</td>
<td>4 wk</td>
<td>Experimentally induced asymptomatic MVD</td>
<td>0.25 mg/kg PO bid</td>
<td>None</td>
<td>PIMO</td>
<td>N = 4</td>
<td>Beagle</td>
<td>Decreased mitral regurgitation and increased cardiac contractility</td>
<td>None reported</td>
</tr>
<tr>
<td>Chetboul et al 2007²⁰</td>
<td>Prospective, blinded, randomized study</td>
<td>512 d</td>
<td>Mild asymptomatic MVD</td>
<td>0.25 mg/kg PO bid</td>
<td>BNZ 0.25 mg/kg once daily</td>
<td>PIMO; BNZ</td>
<td>PIMO, n = 6; BNZ; n = 6</td>
<td>Beagle</td>
<td>Not assessed</td>
<td>Increased heart murmur grade and severity of valve lesions on PME in PIMO dogs</td>
</tr>
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**Table 2. New York Heart Association (NYHA) Heart Insufficiency Score**

<table>
<thead>
<tr>
<th>Score</th>
<th>Clinical Signs</th>
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<tbody>
<tr>
<td>Class I (mild)</td>
<td>No limitation in physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>Class II (mild)</td>
<td>Slight limitation in physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>Class III (moderate)</td>
<td>Marked limitation in physical activity. Comfortable at rest, but less than ordinary physical activity causes fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>Class IV (severe)</td>
<td>Cannot perform any physical activity without discomfort. Clinical signs seen at rest. If physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>
pinschers and American cocker spaniels with DCM, while O’Grady et al. evaluated Doberman pinschers with DCM. In both studies, statistically significant improvements in the median survival time were seen in Doberman pinschers that were treated with pimobendan (329 and 130 days for the Luis Fuentes and O’Grady studies, respectively) compared with placebo (50 and 14 days for the Luis Fuentes and O’Grady studies, respectively).

One limitation of the Luis Fuentes study was that the placebo group contained a higher percentage of patients with atrial fibrillation than the pimobendan group (three of five dogs and one of five dogs, respectively). Atrial fibrillation has been reported as a negative prognostic factor in Doberman pinschers with DCM, although the affected Doberman in the Luis Fuentes study that received pimobendan survived 37 weeks compared with the 1 to 13 weeks previously reported. This limitation was not seen in the O’Grady paper because atrial fibrillation was an exclusion criterion.

No survival advantage was noted in the cocker spaniel group; however, only four of the 10 patients in this group reached the study end point, and of these, only one patient died of cardiac disease. Due to the small sample size and short evaluation period, further evaluation in cocker spaniels was recommended.

Studies of Asymptomatic Myxomatous Valvular Disease

Three studies have been published evaluating the effects of pimobendan on asymptomatic MVD in dogs. None of these studies assessed survival data, and conflicting findings were seen between the studies. The first study examined the effects of pimobendan in patients with experimentally induced asymptomatic MVD and showed a significant decrease in mitral regurgitation in patients receiving 0.25 mg/kg of pimobendan twice daily. The second evaluated spontaneous asymptomatic MVD in a colony of beagles. All patients were euthanized at the completion of the 512-day study period. Heart murmur grade, mitral valve thickness, and nodular changes were all increased in patients receiving pimobendan at standard doses (0.25 mg/kg PO bid). This finding prompted a recommendation that an echocardiographic analysis be performed before, and regularly throughout, pimobendan treatment in MVD patients.

The third paper evaluated patients with ISACHC IB asymptomatic MVD. At 30 days, patients receiving pimobendan (0.2 to 0.3 mg/kg bid) had an improvement in systolic function, as measured by increased injection fraction and left ventricular internal diameter in systole, compared with control patients, but this change was not sustained over the 6-month study period. These patients did not develop hypotension during the study period.

Pimobendan Versus Angiotensin-Converting Enzyme Inhibitor Therapy

A recent study evaluated the effects of pimobendan and furosemide on the renin-angiotensin-alderosterone system (RAAS) in healthy dogs. Pimobendan did not activate the RAAS, and it did not prevent activation of this system associated with furosemide treatment. This finding suggests that patients receiving furosemide in conjunction with pimobendan should also be concurrently treated with an ACEI to facilitate angiotensin-converting enzyme inhibition.

Table 3. International Small Animal Cardiac Health Council (ISACHC) Classification

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Subclassification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Asymptomatic: Heart disease is detectable, but patient does not show clinical signs of heart failure.</td>
<td>IA: Heart disease is present, but patient shows no evidence of compensation (volume or pressure overload ventricular hypertrophy).</td>
</tr>
<tr>
<td>Class II</td>
<td>Mild to moderate: Clinical signs of heart failure present at rest or with minimal exercise. Quality of life is affected. Clinical signs include mild dyspnea, exercise intolerance, tachypnea, and ascites. Home treatment indicated.</td>
<td>IIIB: Hospitalization is necessary.</td>
</tr>
<tr>
<td>Class III</td>
<td>Advanced: Clinical signs of severe heart disease are obvious even at rest, with marked dyspnea, exercise intolerance, and hypoperfusion at rest. The most severe cases present with cardiogenic shock. Death or severe debilitation likely without treatment.</td>
<td>IIIIA: Home care is possible.</td>
</tr>
</tbody>
</table>

Summary

Treatment with pimobendan in Doberman pinschers with CHF due to DCM has resulted in a marked survival advantage. Further studies are needed to determine if pimobendan treatment is beneficial in American cocker spaniels and other breeds with CHF due to DCM. Although not as dramatic as the DCM results, a survival advantage has also been demonstrated in patients with CHF due to MVD. Long-term survival study data are needed before a recommendation to use pimobendan in asymptomatic MVD or DCM patients can be made. While most studies have reported no significant adverse effects, findings from one study suggest that the use of pimobendan in asymptomatic MVD dogs may exacerbate the disease, and further studies are necessary to evaluate this.

Currently, pimobendan is approved in the United States for the management of canine CHF due to atrioventricular valvular insufficiency or DCM, with concurrent therapy for CHF as appropriate. The recommended label dose is 0.1 to 0.3 mg/kg PO bid, given on an empty stomach at least 1 hour before food.

The Human Experience With Pimobendan

An early trial of the use of a pure PDEIII inhibitor, milrinone, found that patients with CHF had improved morbidity but a dramatic increase in mortality from all causes, including cardiovascular disease, compared with patients receiving a placebo. The
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Key Points

- Pimobendan sensitizes cardiomyocytes to calcium rather than causing absolute increases in myocardium calcium concentration in systole, thereby reducing the risk of calcium-mediated proarrhythmic effects.
- The labeled pimobendan dose is 0.1 to 0.3 mg/kg PO bid.
- Pimobendan is an inodilator: it is a calcium sensitizer and phosphodiesterase inhibitor.
- Pimobendan is approved for use in dogs with CHF secondary to DCM and MVD. It has been shown to improve quality of life, heart insufficiency scores, and overall mortality rates in canine patients with naturally occurring CHF.
- Pimobendan has been shown to induce valvular lesions in patients with asymptomatic MVD, raising the question as to its use in asymptomatic MVD patients.
- Further studies are under way to fully evaluate pimobendan use in dogs with naturally occurring heart disease secondary to MVD and DCM.

Findings from this study led to great reservations about the use of PDEIII inhibitors in people with CHF.

Two subsequent studies16,17 used pimobendan as a positive inotropic agent, with conflicting results. The first study13 failed to show improved quality of life or a survival benefit in patients receiving pimobendan. There was a trend toward higher mortality in patients receiving pimobendan; however, it failed to reach statistical significance. The second study18 showed a positive effect on quality of life, and an increase in mortality was not seen. Nevertheless, the results from these studies raised enough suspicion in the human cardiology field to result in pimobendan being removed from human trials. Currently, pimobendan is only licensed for use in people with CHF in Japan.

Adverse Reactions

Numerous studies have shown that pimobendan is well tolerated in dogs with CHF.10,12-16,18 Adverse effects seen include a mild positive chronotropic effect and mild, dose-dependent gastrointestinal signs (vomiting, diarrhea, and soft stools).10,13,14 The potential hypotensive21 or proarrhythmic properties of pimobendan have not yet been documented in veterinary patients.

Conclusion

Pimobendan is a novel inodilator that has been shown to improve quality of life, heart insufficiency scores, and overall mortality rates in canine patients with naturally occurring CHF secondary to DCM and MVD when used in conjunction with conventional CHF treatment (e.g., furosemide, ACEI, antiarrhythmic medication). A treatment benefit for asymptomatic patients with DCM or MVD has not yet been established. Further studies are needed and are under way to assess the long-term effects of pimobendan in patients with naturally occurring CHF and with asymptomatic DCM or MVD.

References

9. Justus C, Kleemann R, Schmidt H. Clinical efficacy and tolerance of Vetmedin over the dose range of 0.2-0.6 mg/kg/day in dogs with congestive heart failure. Boehringer Ingelheim Vetmedica GmbH Internal Rep. no. UDC 6821 UDC 9201. Unpublished data.
1. Compared with extracellular levels, cardiomyocyte intracellular (cytosolic) calcium levels are ________ in diastole and ________ in systole.
   a. higher; lower
   b. lower; higher
   c. equal; unequal
   d. unequal; equal

2. Which statement is correct with regard to the effects of pimobendan?
   a. It is a pure PDE inhibitor.
   b. It has PDE inhibitory effects and calcium sensitizer effects.
   c. It increases intracellular calcium concentrations.
   d. Administration results in PDE inhibitor–mediated vasoconstriction.

3. Pimobendan’s two mechanisms of action are
   a. negative inotropy and vasoconstriction.
   b. negative inotropy and vasodilation.
   c. positive inotropy and vasoconstriction.
   d. positive inotropy and vasodilation.

4. Which statement is true with regard to the reported adverse effects of pimobendan?
   a. They are significant enough to contraindicate the use of pimobendan in veterinary patients.
   b. They include arrhythmias and sudden death.
   c. They include gastrointestinal effects, increased heart murmur grade, and increased severity of valve lesions.
   d. There are no adverse effects.

5. What is the recommended dose range for pimobendan in dogs?
   a. 0.1 to 0.3 mg/kg/d
   b. 0.1 to 0.3 mg/kg bid
   c. 0.3 to 0.6 mg/kg bid
   d. undetermined

6. The PITCH trial found that, in dogs with CHF due to DCM or MVD,
   a. patients receiving only benazepril had significant improvements in their heart failure scores.

7. Which statement regarding the studies of pimobendan in dogs with MVD is correct?
   a. Pimobendan was not compared with an ACEI.
   b. In the VetSCOPE and QUEST studies, most patients receiving pimobendan had an improvement in ISACHC scores.
   c. The Smith study showed a survival benefit for patients receiving pimobendan.
   d. The VetSCOPE and QUEST studies assessed asymptomatic MVD patients.

8. Which statement regarding the use of pimobendan in dogs with DCM is true?
   a. It has resulted in statistically significant improvements in survival time.
   b. It is unwarranted based on the current level of evidence.
   c. It results in markedly shortened survival times compared with placebo.
   d. It has not been evaluated in patients with atrial fibrillation.

9. What effect does pimobendan have on the RAAS?
   a. It activates the RAAS.
   b. It prevents activation of the RAAS when used with furosemide.
   c. It does not activate the RAAS.
   d. It has an adverse effect on the RAAS when used in conjunction with an ACEI.

10. Which statement is true with regard to pimobendan?
    a. It is recommended in addition to conventional heart failure treatment for use in canine CHF secondary to DCM and MVD.
    b. It has not been licensed for veterinary use in any country.
    c. It requires administration four times a day, limiting its clinical use.
    d. It should be used in all canine patients with an asymptomatic murmur.