

## **Chronic Valvular Disease: Current Therapeutic Approach and Future Directions**

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This session will focus on the two most common acquired canine heart diseases, dilated cardiomyopathy and chronic degenerative atrio ventricular valve disease.

### **Dilated Cardiomyopathy (DCM)**

**Definition:** Dilation of all 4 chambers with systolic dysfunction of one or both ventricles.

#### **Prevalence and background**

- ⇒ Relatively low compared to CVD
  - 0.35 to 0.5 % of diagnosis reported at a number of veterinary teaching hospitals (referral populations)
  - You can expect approximately 1/year/veterinarian in a primary care practice.
- ⇒ Rare in mixed breeds
- ⇒ >90% of affected dogs are purebreds
- ⇒ Dobermans have a reported prevalence > all other breeds combined
- ⇒ Other reported breed: Boxer, Great Dane, Labrador Retriever, American Cocker Spaniel, Golden Retriever, Irish Wolf Hound, Saint Bernard, Springer Spaniel, Newfoundland, English Sheepdog, Afghan, Scottish Deerhound, English Cocker Spaniel
- ⇒ Males>>females
- ⇒ Prevalence increases with increasing age
  - > 5 years old in most breeds
- ⇒ In the Boxer and Doberman it is probably inherited as an autosomal dominant trait with reduced penetrance
- ⇒ Arrhythmias are common

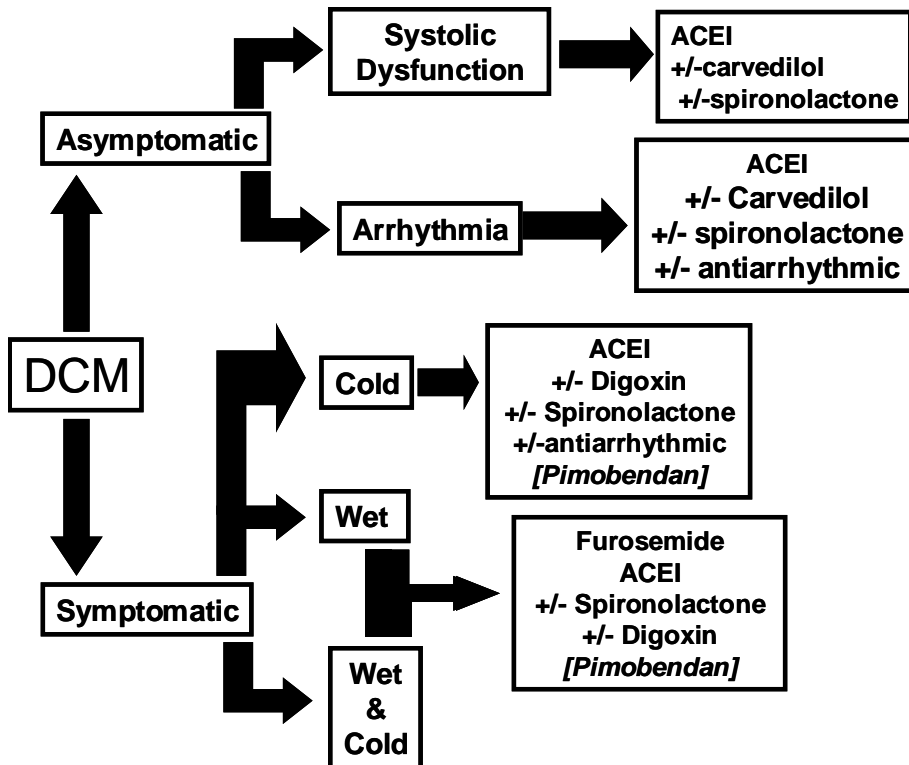
**Etiology:** For the most part unknown but there may be some exceptions to this statement.

**Natural history:** Occult or asymptomatic stage of some duration (1-2 years) followed by a period characterized by clinical signs of forward (exercise intolerance, weakness, syncope) and or backward heart failure (cardiogenic pulmonary edema and or ascites).

#### **Prognosis**

- ⇒ Symptomatic DCM
  - 4-6 months with therapy (may be worse for Dobermans)
- ⇒ Occult/asymptomatic DCM
  - Unknown but probably about 1-2 year to CHF from the time eccentric hypertrophy is recognized

## Therapeutic recommendations for DCM:



## Chronic degenerative atrio ventricular valve disease (CVD)

The most common cause of heart disease and CHF is CVD: A.K.A. acquired mitral/tricuspid regurgitation (MR), acquired mitral/tricuspid insufficiency (MI), endocardiosis, chronic myxomatous valve degeneration (MVD).

**Definition:** Myxomatous degeneration (marked increase in extracellular matrix without significant increase in mature collagen or fibrin) of the AV valves causes a leak and commiserate hemodynamic sequellae including atrial and ventricular dilation. It primarily affects the mitral and tricuspid leaflets and chordae tendineae. Mitral >Tricuspid. 60% cases mitral alone, tricuspid alone 10%, 30% both AV valves affected, rarely affects semilunar valves.

### **Prevalence and background:**

- ⇒ Accounts for 75% of cardiac disease in dogs.
- ⇒ Prevalence is age and breed related.
  - Older dogs and smaller breed have the highest incidence.
  - Can exist in large breed dogs.
  - Males slightly more affected than females.
  - Uncommon in dogs < 5 years of age
    - Exception is Cavalier (see pile #3-A)

⇒ Arrhythmias are uncommon

### **Etiology:**

⇒ Specific etiology is unknown

- ⇒ Endocardiosis is a degenerative process not associated with inflammation or infection (ie. not secondary to oral cavity disease)
- ⇒ Probably inherited as a collagen deformity

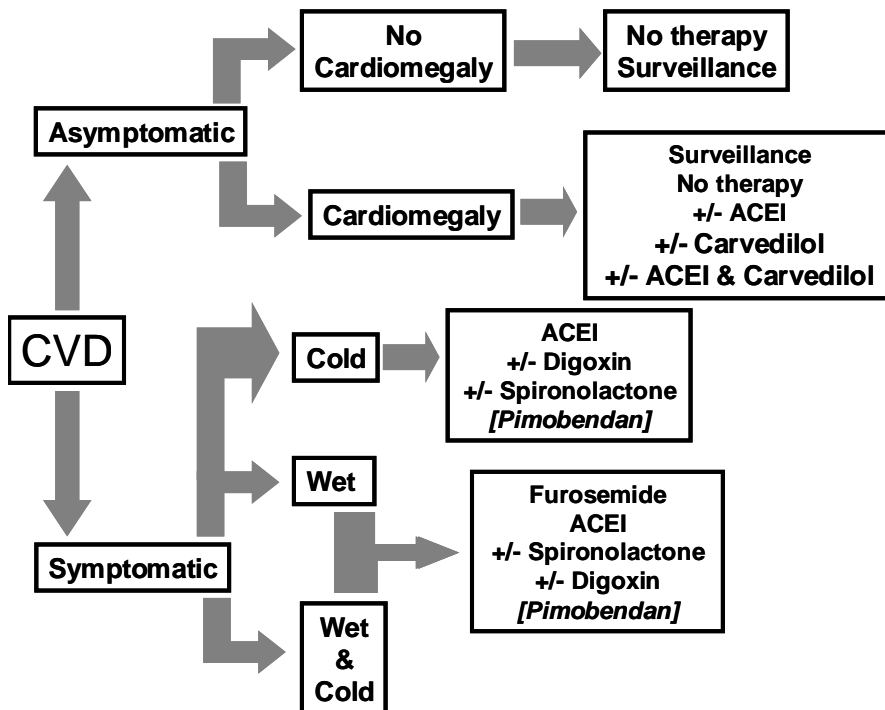
**Natural history:** Occult or asymptomatic stage of some duration (many years) followed by a period characterized by clinical signs of forward (exercise intolerance, weakness, syncope) and or backward heart failure (cardiogenic pulmonary edema and or ascites). Although it usually progresses slowly acute exacerbations such as chordal rupture may occur. The average age of development of CHF secondary to CVD is 12 years.

Note: It is common for the practicing veterinarian to be presented with a geriatric small breed dog with a cough and a systolic heart murmur. The murmur indicates that the patient has cardiac disease but does not necessarily prove that the patient's signs (cough) are caused by heart disease or heart failure. Differentiating primary pulmonary disease (Chronic Bronchitis or small airway disease) from primary cardiac disease can be a significant clinical challenge and it must be kept in mind that many patients have both types of disease concurrently.

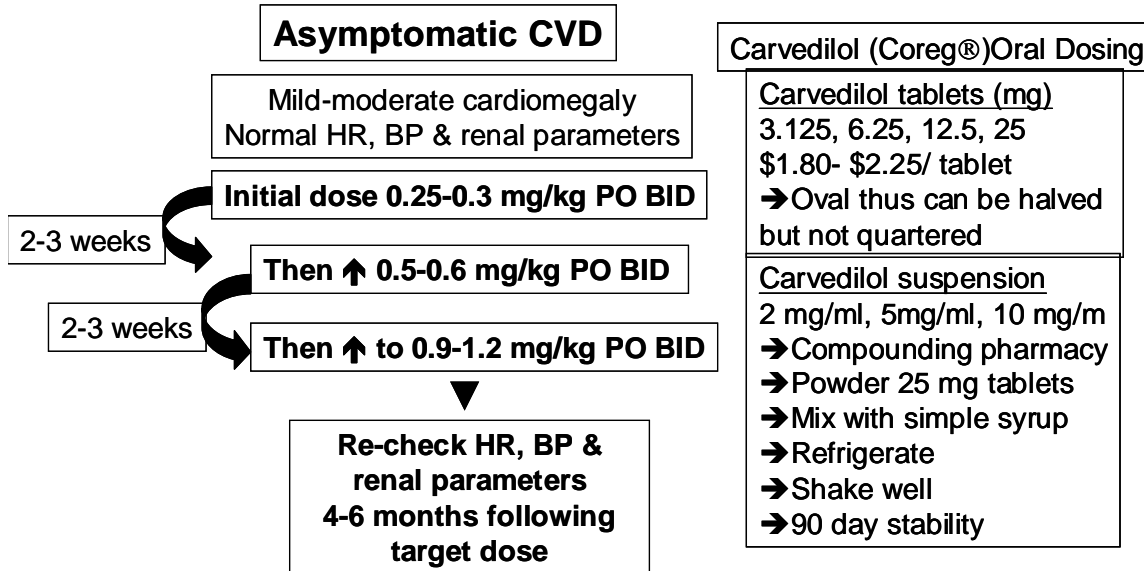
**Prognosis**

- ⇒ Symptomatic CVD
  - 6-12 months with therapy
- ⇒ Occult/asymptomatic CVD
  - The long term prognosis in the early stages is unknown but usually many years

**Therapeutic Recommendations for CVD:**

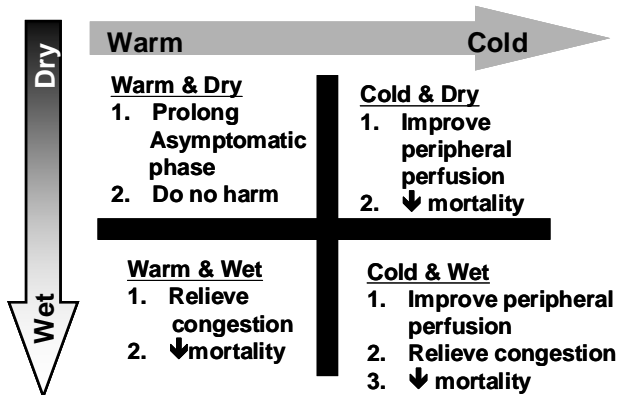


## Carvedilol Clinical Up titration Scheme



## Current and Future Recommendations for Heart Failure Therapy in CVD & DCM

### Therapeutic Rationale for DCM & CVD



### Uncomplicated Heart Failure-Current

Medication	Class	Dosage
Furosemide	▲ Diuretic	2-4mg/kg PO twice per day
+/- Spironolactone	▲ K <sup>+</sup> sparing diuretic ▲ anti-fibrotic	0.25-1 mg/kg PO twice per day
Enalapril or Benazepril	▲ ACEI	0.5 mg/kg PO twice per day
+/- Digoxin	▲ Weak positive inotrope ▲ Neuroendocrine-modulator	0.2 mg/m <sup>2</sup> PO twice per day

## Uncomplicated Heart Failure-Future

Medication	Class	Dosage
Furosemide	▲ Diuretic	2-4mg/kg PO twice per day
Spironolactone	▲K <sup>+</sup> sparing diuretic ▲ anti-fibrotic	0.25-1 mg/kg PO twice per day
Enalapril or Benazepril	▲ ACEI	0.5 mg/kg PO twice per day
Pimobendan	▲Positive inotrope ▲ Afterload reducer	0.25-0.3 mg/kg PO twice per day

## Heart Failure with Ventricular Arrhythmias-Current

Medication	Class	Dosage
Furosemide	▲ Diuretic	2-4 mg/kg PO twice per day
+/-Spironolactone	▲K <sup>+</sup> sparing diuretic ▲ anti-fibrotic	0.25-1 mg/kg PO twice per day
Enalapril or Benazepril	▲ ACEI	0.5 mg/kg PO twice per day
+/-Digoxin	▲Weak positive inotrope ▲ Neuroendocrine-modulator	0.2 mg/m <sup>2</sup> PO twice per day
*Sotalol	▲ Antiarrhythmic	0.5-2 mg/kg PO twice per day (may need to start low and increase)

\*Sotalol can be substituted with procainamide, amiodarone or mexiletine based on clinician preference or therapeutic drug failure

## Heart Failure with Ventricular Arrhythmias-Future

Medication	Class	Dosage
Furosemide	▲ Diuretic	2-4 mg/kg PO twice per day
Spironolactone	▲K <sup>+</sup> sparing diuretic ▲ anti-fibrotic	0.25-1 mg/kg PO twice per day
Enalapril or Benazepril	▲ ACEI	0.5 mg/kg PO twice per day
Pimobendan	▲ Positive inotrope ▲ Afterload reducer	0.25-0.3 mg/kg PO twice per day
*Sotalol	▲ Antiarrhythmic	0.5-2 mg/kg PO twice per day (may need to start low and increase)

\*Sotalol can be substituted with procainamide, amiodarone or mexiletine based on clinician preference or therapeutic drug failure

## Heart Failure with Atrial Fibrillation-Current

Medication	Class	Dosage
Furosemide	▲ Diuretic	2-4 mg/kg PO twice per day
+/-Spironolactone	▲K <sup>+</sup> sparing diuretic ▲ anti-fibrotic	0.25-1 mg/kg PO twice per day
Enalapril or Benazepril	▲ ACEI	0.5 mg/kg PO twice per day
+/-Digoxin	▲Weak positive inotrope ▲ Neuroendocrine-modulator	0.2 mg/m <sup>2</sup> PO twice per day
*Amiodarone	▲ Antiarrhythmic	<u>Initial:</u> 15-20 mg/kg PO twice daily x 3-5 days <u>Then:</u> 5-15 mg/kg PO once daily

\*Amiodarone could be substituted with diltiazem or a beta blocker based on clinician preference or therapeutic drug failure

## Heart Failure with Atrial Fibrillation-Future

Medication	Class	Dosage
Furosemide	▲ Diuretic	2-4 mg/kg PO twice per day
Spironolactone	▲K <sup>+</sup> sparing diuretic ▲ anti-fibrotic	0.25-1 mg/kg PO twice per day
Enalapril or Benazepril	▲ ACEI	0.5 mg/kg PO twice per day
Pimobendan	▲ Positive inotrope ▲ Afterload reducer	0.25-0.3 mg/kg PO twice per day
*Amiodarone	▲ Antiarrhythmic	<u>Initial:</u> 15-20 mg/kg PO twice daily x 3-5 days <u>Then:</u> 5-15 mg/kg PO once daily

\* Synchronized DC cardioversion could be attempted or amiodarone could be substituted with diltiazem or a beta blocker based on clinician preference or therapeutic drug failure

## Advanced/Refractory Heart Failure -Current

Medication	Class	Dosage
∞ Furosemide	▲ Diuretic	2-5 mg/kg PO three times per day (↓ dose by 50% when start hydrochl)
∞ Spironolactone	▲K <sup>+</sup> sparing diuretic ▲ anti-fibrotic	1-2 mg/kg PO twice per day
∞ Hydrochlorothiazide	▲ Diuretic	2-4 mg/kg PO twice per day (start K <sup>+</sup> suppl when starting this drug)
Enalapril or Benazepril	▲ ACEI	0.5 mg/kg PO twice per day
+/-Digoxin	▲Weak positive inotrope ▲ Neuroendocrine-modulator	0.2 mg/m <sup>2</sup> PO twice per day
Hydralazine	▲ Afterload reducer	<u>Initial:</u> 0.25 mg/kg PO twice daily <u>Then:</u> up titration to maximum tolerated dose (1-3 mg/kg PO BID)

\*Hydralazine can be substituted with amlodipine based on clinician preference  
∞ Diuretics +/- intermittant abdomino- & pleurocentesis as required to keep patient free of signs of congestion

## Advanced/Refractory Heart Failure -Future

Medication	Class	Dosage
⌘ Furosemide	▲ Diuretic	2-5 mg/kg PO three times per day (↓ dose by 50% when start hydrochl)
⌘ Spironolactone	▲ K <sup>+</sup> sparing diuretic ▲ anti-fibrotic	1-2 mg/kg PO twice per day
⌘ Hydrochlorothiazide	▲ Diuretic	2-4 mg/kg PO twice per day (start K <sup>+</sup> suppl when starting this drug)
Enalapril or Benazepril	▲ ACEI	0.5 mg/kg PO twice per day
Pimobendan	▲ Positive inotrope ▲ Afterload reducer	0.25-0.3 mg/kg PO twice to three times per day

⌘ Diuretics +/- intermittent abdomino- & pleurocentesis as required to keep patient free of signs of congestion

Note: If patient has end stage pulmonary artery hypertension as a co morbidity sildenafil may be a useful addition

**References available from author.**

## **PIMOBENDAN IN HEART FAILURE THERAPY – A SILVER BULLET?**

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### **INTRODUCTION**

Many dogs with congestive heart failure (CHF) secondary to chronic degenerate atrioventricular valve disease (CVD) and dilated cardiomyopathy (DCM) enjoy good quality of life while receiving conventional therapy including furosemide and an angiotensin converting enzyme inhibitor (ACEI), with or without digoxin.<sup>1</sup> However, these dogs still have a poor long term prognosis.<sup>2,3</sup> Death in this patient population may be sudden, probably arrhythmic, but more often death results from client elected euthanasia due to progressive deterioration of quality of life. The most common reason for impaired quality of life is either failure to keep the patient free of signs of congestion with appropriate diuresis (+/- abdominocentesis as needed) alone or in combination with the development of severe signs of forward heart failure, including marked exercise intolerance, lethargy, collapse/syncope, or progressive renal insufficiency. Additionally, in dogs with CVD, clinical signs of forward heart failure may be exacerbated by the development of pulmonary artery hypertension (PAH). Clinically, our patients often meet these endpoints because the required level of diuresis is either inadequate or no longer tolerated by the patient. To reduce mortality in this patient population a medication will need to significantly reduce the morbidity associated with common clinical signs of progressive CHF.

### **BACKGROUND**

Pimobendan is a benzimidazole pyridazinone derivative and is classified as an inodilator (positive inotrope and arteriovenous dilator). In failing hearts it exerts its positive inotropic effects primarily through sensitization of the cardiac contractile apparatus to intracellular calcium. As a phosphodiesterase (PDE) III inhibitor it could potentially increase intracellular calcium concentration and increase myocardial oxygen consumption. However, the cardiac PDE effects are reportedly minimal at pharmacologic doses in dogs with heart disease highlighting its advantage relative to other inotropes including other PDE inhibitors such as milrinone.<sup>4,5</sup> Calcium sensitization of the contractile apparatus by pimobendan is achieved by enhancement of the interaction between calcium and the troponin C complex resulting in a positive inotropic effect that does not increase myocardial oxygen consumption.<sup>6</sup> Overall, pimobendan's calcium sensitization property

enhances systolic function by improving the efficiency of contraction, limiting the potential negative repercussions such as pro-arrhythmia, a side effect of other positive inotropes whose sole mechanism inevitably involves increasing myocardial intracellular calcium. Calcium sensitizers such as pimobendan may represent a class of positive inotropes that can “safely” augment contractility.

Phosphodiesterase III and V can be found in vascular smooth muscle. Inhibitors of PDE III and V such as pimobendan lead to vasodilation resulting in preload and afterload reduction; cornerstones of therapy in CHF. In addition, PDE V concentrations may be relatively higher in the vascular smooth muscle of pulmonary arteries and thus non-selective PDE inhibition may help ameliorate elevations in pulmonary artery pressure that tend to parallel long standing elevations in left atrial pressure.

The significance of alterations in pro-inflammatory cytokines such as tumor necrosis factor alpha and interleukin 1-beta and 6 in the progression of heart failure has been documented in many forms of heart disease. Alterations in these cytokines are associated with increases in morbidity and mortality and pimobendan has demonstrated beneficial modulation of a variety of cytokines in various models of heart failure further contributing to its desirable properties.<sup>7,8</sup>

#### **THERAPEUTIC RATIONALE**

Tolerable reductions in preload and afterload through venous and arterial dilation respectively, is desirable in dogs with CHF secondary to both CVD and DCM and has long been a cornerstone of therapy. In contrast however, although the utility of “safe” augmentation of contractility is obvious in DCM, a disease characterized by global systolic dysfunction, the same cannot be said for CVD.

Canine patients with CVD develop compensatory left ventricular remodeling in the form of eccentric hypertrophy (dilation). Systolic function is often thought to be preserved until relatively late in the course of CVD. This is based on normal or exuberant echocardiographic surrogates for ejection fraction such as fractional shortening. Interrogation by more sophisticated techniques, has demonstrated reductions in left ventricular (LV) systolic function in both an experimental canine model of mitral regurgitation (MR) and in chronic human primary MR, a condition very similar to CVD in the dog.<sup>7,9,10</sup> Impaired systolic function in cases of CHF secondary to CVD may contribute significantly to clinical signs of lethargy and exercise intolerance secondary to important reductions in forward cardiac output. Although diuretics can relieve signs of congestion, they do little to alleviate and may exacerbate signs of forward failure. Traditionally, these patients have been managed with judicious afterload reduction using

agents such as ACEI and or more potent arteriolar dilators (i.e. hydralazine, amlodipine) in an attempt to reduce the differential in pressure between the periphery and the left atrium thereby reducing regurgitation fraction and augmenting forward cardiac output. However, patients with advanced CVD often do not tolerate afterload reduction well. Frequently, clinical signs of forward heart failure do not resolve and may be exacerbated by afterload reduction, further impairing quality of life. Additionally, many patients with advanced CVD and DCM have severe cardiomegaly leading to mitral annular dilation contributing to secondary functional MR. For CVD the obvious therapy involves surgical mitral valve repair and mitral annuloplasty in a timely manner, however this option is not routinely available in veterinary medicine. Furthermore, many patients with advanced disease or patients with important comorbidities such as renal insufficiency make poor open-heart surgery candidates even if clients wish to pursue this option. If a potent positive inotrope could enhance mitral annular and left ventricular (LV) papillary tone, optimizing LV and mitral apparatus geometry, functional MR might be reduced with augmentation of forward cardiac output making any concurrent reductions in afterload better tolerated. This combined mechanism of action could be considered a pharmacologic annuloplasty. Reductions in regurgitant fraction may also result in beneficial reverse remodeling (reduction in size) of the LV and left atrium. Finally, this constellation of hemodynamic effects may indirectly modulate neurohormonal systems responsible for the progression of heart failure.<sup>11</sup>

## **SAFETY & EFFICACY**

The efficacy of pimobendan in the treatment of CHF due to DCM and CVD has been evaluated more thoroughly than any other cardioactive medication to date, including ACEI. Available prospective data overwhelmingly supports its ability to significantly reduce morbidity in dogs with CHF secondary to CVD and DCM.<sup>7-11</sup> O'Grady et al. demonstrated a doubling of overall survival in Doberman pinschers with CHF secondary to DCM from 63 +/-14 days with furosemide, ACEI, and placebo to 128 +/- 29 days with furosemide, ACEI and 0.25 mg/kg pimobendan twice daily (p=0.04).<sup>12</sup> Additional studies suggest a survival benefit with the combination of pimobendan and furosemide with or without digoxin when compared to an ACEI and furosemide with or without digoxin in dogs with CHF due to DCM or CVD.<sup>13, 14</sup> Other studies offer conflicting evidence with respect to the superiority of a combination of pimobendan and furosemide versus an ACEI and furosemide for the treatment of CHF secondary to CVD.<sup>15, 16</sup> Preliminary analysis of an ongoing study by O'Grady et al. demonstrated no survival advantage with pimobendan and

furosemide over an ACEI and furosemide in dogs with CHF secondary to CVD.<sup>15</sup> Conversely, Smith et al. demonstrated a significant reduction of overall adverse outcomes including death due to heart failure (euthanized or died due to CHF) and treatment failure (discontinued study due to CHF) from 48% in the furosemide and Ramapril group to 18% in the furosemide and pimobendan group during six months of treatment of CHF due to CVD.<sup>16</sup> Both Smith and O'Grady failed to demonstrate significant adverse consequences suggesting that the combination of pimobendan and furosemide is likely to be at least as good as the combination of furosemide and an ACEI for the treatment of CHF secondary to CVD. To date pimobendan appears to be safe and well tolerated in dogs with CHF due to CVD. It has not however been prospectively evaluated on a background of conventional therapy including an ACEI and furosemide with and with out additional medications such as digoxin and spironolactone. Our cardiology group at Texas A&M has been using pimobendan (0.25-0.3 mg/kg twice daily) in addition to conventional therapy for the treatment of CHF due to both DCM and CVD for more than 4 years, managing over 250 patients. Survival and hemodynamic effects were reviewed in a subset of dogs with advanced CHF due to CVD. In addition to pimobendan these patients were receiving furosemide (100%, at least 3mg/kg BID), ACEI (100%), spironolactone (>75%), beta-blockers (20%), digoxin (11%) and hydrochlorothiazide (3%). The hemodynamic effects were evaluated prior to initiation of pimobendan and approximately 45 days later. There were no significant changes in indirect systemic blood pressure, body weight, PCV, total solids, creatinine or electrolytes ( $p=0.05$ ). BUN was increased (pre-pimobendan 29 vs post-pimobendan 33,  $p=0.05$ ). Heart rate and respiratory rate were reduced and there was no change in the combined frequency of arrhythmias (ventricular premature beats, ventricular tachycardia, supraventricular premature beats, supraventricular tachycardia and atrial fibrillation) as determined by surface ECG. The dose of furosemide in mg/kg/day showed a trend toward reduction,  $p=0.059$ . A variety of echocardiographic parameters suggested improvement in systolic function; reductions in LV internal dimension in systole, and LV end systolic area and an increase in percent LV area shortening. Finally, reductions in regurgitation fraction were suggested by a reduction in radiographic vertebral heart score, echocardiographic systolic left atrial diameter and the mmode derived ratio of left atrial to aortic size. Taken together these findings suggest that the addition of pimobendan to conventional CHF therapy in dogs with CVD had no negative side effects and

hemodynamic variables tended to improve suggestive of enhanced systolic function and reduced filling pressures. In addition, although these beneficial effects were observed on average 45 days after initiating pimobendan, more recent experience and pilot data suggest that these effects may be apparent as soon as 24 hours following initiation of pimobendan. This highlights its potential utility in acute decompensated CHF. The median survival of these patients was 17 months ranging from 2-50 months. The median was estimated from a Kaplan Meier curve where all cause mortality was the outcome variable and dogs were censored if still alive at the time of analysis (30%).

Our clinical experience is in agreement with available prospective data supporting the efficacy of adjunctive pimobendan therapy to improve both the quality and quantity of life in dogs with CHF due to both CVD and DCM. Our experience is that pimobendan is clinically easy to use, requires no additional monitoring and enjoys excellent client compliance. Pimobendan works very rapidly making it particularly useful in initial, often acute stabilization of heart failure (peak hemodynamic effects following oral administration on an empty stomach is approximately one hour and lasts 8-12 hours).<sup>17</sup> Clinical experience has led us to believe that the rapid onset of hemodynamic effects, ease of use (few if any side effects) and cost effectiveness of limiting hospitalization due to heart failure (i.e. initial response to therapy) has a great impact on the willingness of clients to elect chronic management of heart failure as well as overall client satisfaction with CHF therapy. Although there is currently no definitive evidence to support a survival benefit with pimobendan therapy in dogs with CHF due to CVD, ongoing studies (O'Grady and QUEST) are expected to answer this question.

## **SUMMARY**

Pimobendan is a novel agent with properties that are highly desirable in the clinical management of CHF secondary to both DCM and CVD in dogs. Review of available data supports that pimobendan is safe, well tolerated and leads to enhanced quality of life in canine patients with CHF due to DCM or CVD when used in combination with furosemide or on a background of conventional therapy including furosemide and ACEI with or without digoxin. Pimobendan leads to a reduction in mortality from CHF due to DCM. Ongoing studies will better determine its effects if any on mortality from CHF due to CVD. Any medication, however that ameliorates the clinical signs of CHF can be expected to reduce mortality in patients who often meet their demise through owner elected euthanasia when treatment fails to maintain good quality of life.

Pimobendan has been licensed since 2000 for the treatment of CHF due to DCM and CVD in many countries around the world including Europe, Great Britain, Australia and more recently Canada and Mexico<sup>18</sup>. Pimobendan is produced and marketed by Boehringer Ingelheim under the trade name Vetmedin®. A licensing study is currently under review in the United States with an optimistic forecast for release early in 2007. Until such time that pimobendan is licensed in the United States it can be legally imported on a case by case basis with permission from the FDA.

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### Medications commonly used in the treatment of feline heart disease

Drug	Class	Dose (per cat)	Dose (mg/kg)
Enalapril* or Benazepril*	ACEI	PO: 1-2.5 mg q 12-24 hrs	PO: 0.2-0.7 mg/kg q 12-24 hrs
1.Diltiazem 2.Cardizem CD 3.Dilacor XR	Calcium channel blocker	1.PO: 7.5 mg q 8 hr  3.PO: 30-60 mg q 12-24 hrs	2.PO:10 mg/kg q 24 hr
Atenolol*	Beta blocker	PO:3.125-12.5 mg q 12-24 hrs	PO:1.1-2.5 mg/kg q 12-24 hrs
Atenolol-low dose*	Beta blocker	PO:1- 3.125 mg q 24 hrs Up titrate if well tolerated	
Furosemide*	Diuretic	PO:3.125-12.5 mg q 12-48 hrs	PO:1-2 mg/kg q 12-48 hrs IV/IM/SQ:0.5-2mg/kg PRN
Hydrochlorothiazide*	Diuretic	PO:6.25-12.5 mg q 12 hrs	PO:2-4 mg/kg q 12 hrs
Spironolactone*	Aldosterone antagonist	PO:6.25 mg q 12 hrs	PO:1-2 mg/kg q 12 hrs
Digoxin	Cardiac glycoside	PO:0.31 mg q24-48 hrs	
Aspirin	NSAID	PO:81mg q 3 days	PO:25mg/kg q 3 days
Sotalol*	Antiarrhythmic Beta blocker	PO: 10mg q 12 hrs	
Nitroglycerine paste	Vasodilator	Topical:1/8-1/4 inch q 6-8 hrs	
Low molecular weight heparin	Anti-thrombotic		SQ:100 IU/kg q 12-24 hrs
Butorphanol	Anxiolytic		IV/IM/SQ: 0.2 mg/kg PRN
Taurine	Amino acid	PO: 250-500 mg q 12 hours	
Clopidogrel	Thienopyridine	18.75-75mg PO q 24 hours	

\* available as a suspension from a formulation pharmacy

**DRUGS COMMONLY USED FOR THE THERAPY OF CANINE HEART FAILURE**

<b>DRUG</b>	<b>PREPARATION</b>	<b>DOSAGE</b>	<b>INDICATIONS (I) AND POTENTIAL TOXICITY (T)</b>
AMIODARONE	Cordarone or generic (cheaper): 200, 400 mg tablets	DOG- 10-20 mg/kg q 24 hours for 7-10 days then reduce to 3-15 mg/kg q 24 to 48 hours chronically	I: hemodynamically significant ventricular or supraventricular arrhythmias (SVT, atrial fib) T: anorexia and elevated liver enzymes, neutropenia etc. & potential proarrhythmic
AMLODIPINE Note: gradual up - titration required	Norvasc: 2.5, 5 mg tablets	DOG-0.01-1 mg/kg PO q 12-24 hours	I: hypertension T: hypotension
ATENOLOL Note: gradual up - titration required	Tenormin: 25, 50, 100 mg tablets	DOG - 6.25-12.5 mg q12h;	I: diastolic dysfunction & hemodynamically significant ventricular or supraventricular arrhythmias (SVT, atrial fib) T: negative inotrope & chronotrope beware decompensation
BENZAEPRIIL	Lotensin: 5, 10, 20, 40 mg tablets	DOG –0.3-0.5 mg/kg q 12-24 hours	I: CHF (CVD, DCM), systemic hypertension T: Beware azotemia and potetial for interaction with NSAIDS
CARVEDILOL Note: gradual up - titration required	Coreg: 3.125, 6.25, 12.5 25 mg tablets Note: can split in two but hard to split in 4. Can be formulated into suspension.	DOG –0.1-1mg/kg PO q 12 hours Note: 1 mg/kg is target dose and you will need to uptitrate to achieve this does safely	I: occult systolic dysfunction (CVD, DCM) T: negative inotrope & chronotrope beware decompensation
DIGOXIN	Lanoxin, Cardoxin, Digoxin USP: 0.125, .25, .5 mg tablets; 0.05 mg/ml and 0.15 mg/ml elixirs	DOG - 0.0055 to 0.011 mg/kg q12h; or 0.22 mg/meter sq body surface area q12h. Note: error on low dose side to limit toxicity	I: heart failure, supraventricular tachyarrhythmias, (SVT, atrial fib) T: GI (anorexia & vomiting), arrhythmias Note: toxicity potentiated by renal insufficiency
DILTIAZEM Note: gradual up - titration required	A- Non-sustained release: Cardizem: 30, 60, 90, 120 mg tablets B- Sustained release: Dilacor XR	A- DOG - 0.5 to 1.3 mg/kg orally q8h B-DOG – 2-4 mg/kg orally q 12 hours	I: hemodynamically significant supraventricular arrhythmias (SVT, atrial fib) T: negative inotrope & chronotrope beware decompensation
DOBUTAMINE	Dobutrex: 250 mg (20 ml) vial for injection	DOG - 2.5 to 20 micrograms/kg/min, constant rate IV infusion.	I: severe systolic dysfunction (CVD & DCM) T: tachyarrhythmias
ENALAPRIL	Enacard: 1, 2.5, 5, 10 mg tablets	DOG - 0.25-0.5 mg/kg orally once or twice daily	I: CHF (CVD, DCM), systemic hypertension T: Beware azotemia and potential for interaction with NSAIDS
FUROSEMIDE	Lasix: 12.5 [Vet] mg, 20, 40, 50 [Vet], 80 mg tablets; 1% syrup (10 mg/ml)	DOG - 2-6 mg/kg repeated q6-12h as needed (IV, IM, SQ, oral)	I: CHF T: hypotension, dehydration, hypokalemia, met. Alk

HYDRALAZINE Note: gradual up - titration required	Apresoline: 10, 25, 50 mg tablets	DOG - 1-3 mg/kg orally q12h (initial dose 0.5 mg/kg, titrate to effect or to at least 1 mg/kg q12h)	I: CHF, hypertension T: hypotension, GI
HYDROCHLOROTHIAZIDE (HCT) & SPIRONOLACTONE	Hydrodiuril, USP: 25, 50 mg tablets; Aldactazide: 25 mg HCT combined with 25 mg spironolactone	DOG - 2-4 mg/kg twice daily of either HCT or combined product. Note: these are monotherapy doses	I: CHF T: hypotension, dehydration, hypokalemia, azotemia Note: reduce furosemide dose by 50% when starting HCT
LISINAPRIL	Zestril, Prinavil	DOG - 0.5 mg/kg PO q24h	I: CHF (CVD, DCM), systemic hypertension T: Beware azotemia and potential for interaction with NSAIDS
MEXILITINE	Mexitil: 150, 200, 250 mg capsules	DOG- 4-8 mg/kg PO q 8 hours	I: hemodynamically significant ventricular arrhythmias T: anorexia and liver toxicity & potential proarrhythmic Note: may work best when combined with atenolol
PIMOBENDAN	Vetmedin: 1.25, 2.5, 5 mg capsules Note: not available in USA yet	DOG – 0.25-0.3 mg/kg PO q 12 hours	I: CHF (CVD, DCM), pulmonary artery hypertension T: potential proarrhythmic?, hypotension
PROCAINAMIDE (sustained release)	Pronestyl SR or generic procainamide SR 250, 500, 750, 1000 mg oral 100 mg/ml, 10 ml vial or 500 mg/ml, 2 ml vial	DOG- 10-20 mg/kg PO q 8hours 5-25 mg/kg slow IV (10 min) 25-50 ug/kg/min as CRI to effect	I: hemodynamically significant ventricular and supraventricular (IV only) arrhythmias T: Oral- anorexia, coat colour change, IV-hypotension & potential proarrhythmic
NITROGLYCERINE	Nitrol, Nitro-bid, Nitrostat: one inch = 15 mg NTG; Minitran transderm patches 2.5, 5, 10, 15 mg/24 hrs	DOG - 4-12 mg (up to 15 mg) topically q12h;	I: CHF T: hypotension
SILDENAFIL Note: gradual up - titration required	Viagra: 25, 50, 100 mg tablets	DOG- 0.25-2.5 mg/kg PO q 12 hrs	I: end stage pulmonary artery hypertension T: hypotension Note: slow up titration required
SOTALOL	Betapace: 80, 160, 240 mg tablets	DOG- 0.5-2 mg/kg PO q 12 hours	I: hemodynamically significant ventricular arrhythmias T: negative inotrope & chronotrope beware decompensation & potential proarrhythmic
SPIRONOLACTONE	Aldactone: 25, 50, 100 mg tablets	DOG-0.25-1 mg/kg PO q 12 hours antifibrotic effects 1-2 mg/kg PO q 12 hours for diuretic effect	I: reverse remodeling, K sparing diuresis, RAAS inhibition T: hyperkalemia especially when combined with an ACEI in the absence of furosemide