# Evidence-Based and Cost-Effective Management of CHF in Dogs

Dr. David Sisson, DVM, DACVIM-Cardiology, Oregon State University

## Treatment Objectives:

The primary objective of treatment is to resolve the underlying cause of heart failure. This is a real possibility in a very limited number of circumstances. Some resolvable causes of heart failure include 1) non-malignant pericardial effusion, 2) taurine-responsive and tachycardia-induced cardiomyopathy, 3) systemic hypertension, and 4) heartworm disease. For the most commonly encountered causes of heart failure in dogs (and cats), there is no cure but there are effective methods to palliate the debilitating effects of the heart disorder and to prolong life. Thus, the objectives of treatment are appropriately modified in dogs with degenerative valvular disease and idiopathic cardiomyopathy to provide an acceptable quality of life for as long as is possible. Rather than a cure, the goal is to slow down the progression of the disease and eliminate troublesome signs and symptoms.

Dogs with heart disease may die suddenly from an arrhythmia or more slowly as a result of intractable congestive or low output heart failure. A substantial percentage dies as a consequence of another disease process such as gastric dilatation, renal failure, or neoplasia. Many pets are euthanized at the request of their owners for these reasons or when the owner perceives that the animal's quality of life is unacceptable. Often times, owners become discouraged when their companion's basic behaviors are altered. A poor appetite, cachexia, perceived depression, urinary incontinence, and physical disability often prompt an owner to elect euthanasia even when death from heart failure is not imminent. Examination of the survival curves for dogs diagnosed with heart failure suggest that mortality is highest in the first few weeks following initial diagnosis. It follows that the best opportunity to improve overall outcome is early on, yet there has not been a single conscientiously performed prospective clinical trial directed at improving the outcome of treatment of acute heart failure in either dogs or cats. In fact most of the heart failure trials conducted in dogs eliminate those animals that die early on from the analysis of outcome and survival.

## Treatment of Acute Heart Failure:

In the setting of acute left-sided congestive heart failure, the main priority of the attending clinician is to resolve pulmonary congestion and improve the delivery of oxygen to the tissues. Pulmonary capillary wedge pressure (PCWP) initially increases when left ventricular systolic or diastolic function is altered and left ventricular end diastolic pressure is elevated. Systemic neuroendocrine responses, elicited in response to declining cardiac output and in response to hypoxemia, are prioritized to maintain systemic arterial pressure with little regard for filling pressures. As a consequence, there is a further increase in filling pressure due to 1) generalized

vasoconstriction and the resulting redistribution of the circulating blood volume and 2) retention of sodium and water evoked both by renal auto-regulatory responses and the activation and release of a plethora of neurohormones, including aldosterone and arginine vasopressin. The development of arterial hypoxemia heralds the onset of a downward spiral in cardiac function that further exacerbates these so called “compensatory responses”. The majority of dogs presenting with congestive heart failure are normothermic and normotensive but a substantial percentage (10 to 15%) suffer severe heart failure and are hypothermic or hypotensive, reflecting a profound deficit in cardiac output and tissue perfusion. In one of the few retrospective studies of dogs with congestive heart failure (Brady et al), non-surviving dogs were more likely to be hypothermic, hyponatremic and mildly hyperglycemic.

Dogs with respiratory distress due to severe pulmonary edema require oxygen supplementation and medical interventions designed to rapidly lower PCWP. In this circumstance, furosemide can be administered either as a continuous intravenous infusion (0.5-2.0 mg/kg/hr for the 4 to 8 hours) or via repeated IV bolus injections (2-4 mg/kg q 1-2 hrs) with the total daily dose not to exceed 10-12 mg/kg. In addition, oxygen can be delivered via an oxygen cage (concentration $\geq$ 40% $0_2$) or an intranasal cannula (flow rate = 50-100 ml/kg/min) and the response to treatment can be monitored by evaluating the respiration rate, arterial blood gases, or pulse oximetry. Supplemental oxygen may be discontinued in most cases when the respiratory rate is less than 30 breaths/min and when the $Pa0_2$ exceeds 65 mmHg and $O_2$sat rises above 90%. Failure to observe an adequate clinical response should prompt additional therapeutic measures to reduce preload.

Dogs with fulminant congestive heart failure and those that do not resolve with furosemide administration within a few hours can often be effectively treated by administration of nitroprusside (1.0 – 2.0 μg/kg/min), which is capable of dramatically reducing filling pressures in minutes via vasodilation and redistribution of the circulating blood volume. This effect has been documented in numerous studies dogs with experimentally induced heart failure. This remedy is not widely used by general practitioners due to the effort and expense of delivering the drug (CRI) and the requirement for intensive monitoring. The main limitations to nitroprusside treatment is pre-existing or developing hypotension, often complicated by reduced renal perfusion. In this situation, treatment with a positive inotropic agent such as dobutamine (2.0 -15 μg/kg/min) can help to mitigate any fall in arterial blood pressure. Such therapy is moderately expensive due to the requirements for constant rate infusion and the necessity of careful monitoring of vital signs.

Angiotensin converting enzyme inhibitors exert on modest acute effect on pulmonary capillary wedge pressures in dogs with naturally congestive heart failure (CONSENSUS TRIAL) limiting its utility for managing acute congestive heart failure in dogs. In contrast, the effects of pimobendan on left atrial pressure appear to be more substantial, at least in dogs with experimental mitral regurgitation induced by chordal rupture. In the United States pimobendan is available only as an oral formulation but it is rapidly absorbed after oral administration and begins to exert a hemodynamic effect in about 1 hour. There are anecdotal reports of its use in

dogs with acute heart failure but no clinical studies have been published. In Europe, an injectable formulation of pimobendan became available for clinical use in dogs as of February, 2013. At the time this manuscript was written, no published reports of its efficacy in acute heart failure are available. There is a possibility of severe hypotension if pimobendan and nitroprusside are used together and this combination should be avoided until appropriate investigations have been performed.

## Comparison of Positive Inotropic Drugs in Acute Heart Failure:

Calcium Mobilizers. Agents that act by increasing intracellular calcium concentrations, sometimes referred to as calcium mobilizers have been associated with poor outcomes and an increased risk of sudden death when chronically administered. Catecholamines, such as dopamine and dobutamine, exert their positive inotropic effect by stimulation of $ß_1$ receptors on the myocardial cell, increasing cyclic AMP levels via adenylate cyclase stimulation. The use of these agents for the routine treatment of acute heart failure has waned due to concerns surrounding their safety and overall efficacy, but they are still commonly relied on to improve cardiac output, maintain arterial blood pressure and improve renal perfusion in hypotensive patients with severe congestive heart failure.

Selective phosphodiesterase III (PDE III) inhibitors, such as amrinone and milrinone, are also considered calcium mobilizers as they increase cyclic AMP by inhibiting its degradation. Subsequent activation of cAMP-dependent protein kinase phosphorylates many target proteins resulting in increased $Ca^{2+}$ transport through membrane channels, increased storage of $Ca^{2+}$ in the sarcomplasmic reticulum, and a net increase in intracellular $Ca^{2+}$. Amrinone and milrinone are often referred to as inodilators and their administration can result in hypotension as a consequence of phosphodiesterase inhibition in vascular smooth muscle. The theoretical advantages anticipated from the use of these agents have not been realized in clinical practice and these agents do not enjoy widespread usage.

Digoxin is a weak positive inotrope that has unique anti-arrhythmic properties that make it particularly useful for the management of atrial fibrillation and sustained or paroxysmal supraventricular tachycardia. Adverse side effects can be largely avoided by appropriate dosing (0.002-0.003 mg/kg BID) and appropriate monitoring.

Calcium sensitizers. Agents such as levosimendan and pimobendan, represent a new class of inotropic drugs offering hemodynamic improvement without the liability of increasing cyclic AMP and intracellular $Ca^{2+}$ concentrations. Levosimendan increases myofilament calcium sensitivity by binding to cardiac troponin C and stabilizing the calcium-induced conformational change of troponin C. Actin-myosin cross-bridge kinetics are changed by this mechanism without increasing the cycling rate of the cross-bridges or myocardial ATP consumption. Levosimendan also induces vasodilation through the opening of ATP-sensitive potassium channels. In contrast, pimobendan increases myocardial contractility by two different mechanisms. It increases the $Ca^{2+}$ affinity of troponin C, the calcium-binding protein that plays a regulatory role in cardiac

muscle contraction and also inhibits phosphodiesterase III (PDE III), thereby elevating intracellular cAMP concentrations in the heart and vascular smooth muscle (inodilator effects). Pimobendan is a promising alternative for the management of dogs with acute heart failure, but this treatment application has not yet been critically evaluated.

Other interesting and novel approaches to heart failure treatment do not rely on the use of positive inotropic agents. Instead they are directed at fluid retention, vasodilation, neuroendocrine and other regulatory peptides. Of particular interest are recent developments utilizing ultrafiltration, arginine vasopressin antagonists (such as conivaptan, tolvaptan, and lixivaptan), adenosine antagonists, renin inhibitors, and resynchronization therapy.

## Treatment of Chronic Heart Failure:

Furosemide, angiotensin converting enzyme (ACE) inhibitors, spironolactone and pimobendan are reported to improve survival of dogs with heart failure. The efficacy of furosemide for treatment of dogs in heart failure has never been critically evaluated in clinical trials. Its fundamental role in managing heart failure will likely be challenged by the other available loop diuretics, such as bumetanide or torsemide. Torsemide has some particular advantages including increased bioavailability, longer duration of action, reduced potassium excretion, and other anti-aldosterone related effects.

The efficacy of ACE inhibitors, in combination with furosemide and administered with or without digoxin, has long been established in dogs as shown by in two large, conscientiously performed clinical trials. Based on these studies, survival, exercise tolerance and quality of life are convincingly improved in dogs with DCM or CDVD when an ACE inhibitor is employed in the treatment regimen. The rationale for ACE inhibition, activation of the renin-angiotensin-aldosterone system (RAAS), has been verified by several independent studies of neurohormonal activation in clinically relevant populations. The most common undesirable effect of ACE inhibitors in dogs with heart failure is impaired renal function and appropriate monitoring is advisable. The efficacy of spironolactone, when added to background treatment with furosemide, an ACE inhibitor, +/- digoxin was recently evaluated in dogs with chronic mitral regurgitation in a trial conducted in Europe (Bernay F et al). This report concluded that spironolactone decreased the risk of cardiac death, euthanasia or severe worsening of heart failure. Hyperkalemia is a possible but uncommon adverse effect of spironolactone administration.

The efficacy of pimobendan in dogs with mitral regurgitation was first reported in two veterinary trials conducted in Europe (Smith PJ et al. and Lombard CW et al) and again, more recently, in the **QUEST** (**Qu**ality of life and **E**xtension of **S**urvival **T**ime) trial conducted in Europe, Canada, and Australia. Interestingly, there no difference in quality of life variable was found between pimobendan and benazepril-treated groups, but the time from inclusion to the first intensification of CHF treatment (increased furosemide dose) was longer in the pimobendan group. Importantly, the median survival time for dogs treated with pimobendan (267 days) in the

QUEST study was significantly longer than that for dogs treated with benazepril (140 days). Pimobendan also produces more dramatic hemodynamic effects than ACE inhibitors in dogs with mitral regurgitation. Clinical trials involving pimobendan in dogs with mitral regurgitation have emphasized in their design a head-to-head comparison with an ACE inhibitor (typically benazepril) and there is not a single published study evaluating the potential advantages (or disadvantages) of using pimobendan in combination with ACE inhibitors. This is unfortunate because pimobendan does not act to inhibit the operation of the renin-angiotensin-aldosterone system and most veterinary cardiologists advocate using pimobendan in combination with an ACE inhibitor without the benefit of a controlled clinical trial.

Early studies of the efficacy of pimobendan in dogs with CHF due to dilated cardiomyopathy were somewhat encouraging, but the trials were all very small and not well designed. Fuentes and coworkers reported improved survival in Doberman pinschers treated with pimobendan (N=5, 329 days) compared to placebo (N=5, 50 days) as did O'Grady and coworkers where survival was 130 days in pimobendan-treated dogs and 14 days in the placebo group, but fewer than 20 dogs were studied. The trial conducted to gain FDA approval for pimobendan in the United States was never published. However, this study indicated that pimobendan was not superior to enalapril and there was no identifiable treatment advantage in dogs with heart failure due to DCM in the data submitted to the FDA.

According to the Freedom of Information Summary of the application for FDA approval of pimobendan, treatment effects were evaluated in 49 dogs with DCM (14 with atrial fibrillation, 23 Dobermans) treated with pimobendan in comparison to an active control group of 50 dogs treated with enalapril (10 dogs with atrial fibrillation, 20 Dobermans). Treatment success, defined by the combined use of a heart insufficiency score, pulmonary edema score and overall improvement score, at 29 days post-initiation of therapy was 60.6% in the pimobendan-treated group versus 74.2% in the enalapril-treated group. Sixty-four dogs continued in an effectiveness phase of the study until day 56; 33 of these dogs were treated with pimobendan (9 had atrial fibrillation, 18 Dobermans) and 31 were treated with enalapril (4 had atrial fibrillation, 12 were Dobermans). Treatment success at 56 days was 46.4% in the pimobendan-treated group versus 68.0% in the enalapril-treated group.

Overall, there were 18 deaths (36.7%) in the pimobendan-treated group (16 attributed to progression of CHF) and 11 deaths (22%) in the enalapril-treated group (10 attributed to progression of CHF) at day 60. Five dogs in the pimobendan-treated group died suddenly compared to 6 dogs in the enalapril-treated group. New episodes of atrial fibrillation occurred in 5 dogs in the pimobendan group compared to 2 dogs in the enalapril-treated group. New episodes of ventricular tachycardia occurred in 3 dogs in the pimobendan group compared to 1 dog in the enalapril-treated group. While none of the differences between the groups was judged to be statistically significant, the results do appear discordant with other published outcomes. Certainly, this data provides some encouragement to clients that are unable to afford the expense of pimobendan. Substantial questions remain regarding the role of pimobendan and the development of atrial fibrillation and worsening ventricular arrhythmia.

This author, as routine practice, advises therapy with furosemide (1.0 – 4.0 mg/kg BID), an ACE inhibitor (typically enalapril at 0.5 mg/kg BID), and pimobendan (0.3 mg/kg BID), +/- spironolactone (2.0 mg/kg/day) and digoxin (0.002 - 0.003 mg/kg for atrial fibrillation and supraventricular tachycardia). This approach is based on available published clinical trials. In dogs that do not tolerate an ACE inhibitor, spironolactone is advised to achieve some degree of RAAS inhibition. A complete blood count and biochemistry profile are advisable at the onset of treatment. Renal function and electrolytes are evaluated at a recheck appointment 7 to 10 days later and at the time of re-evaluation, which is encouraged at 3 month intervals.

## Comments on Beta-receptor blocking drugs in dogs with CHF:

Beta-receptor blocking drugs, including bisoprolol, metoprolol, and carvedilol, are proven to be efficacious in humans with DCM but are of unproven value in dogs. No substantial benefit has been identified in the few small trials employing these agents in dogs. Congestive signs must be resolved before treatment is initiated using a low starting dose with titration to the target dose over a one to two month period. Setbacks are common and human patients often must wait several months after reaching the target dose before experiencing a clinical response. Target doses of these agents have not been determined in dogs and many owners are reluctant to embark on such a demanding protocol and as yet unproved course of treatment. However, given their established benefit in human patients with DCM, beta blockers deserve consideration in a well designed clinical trial in dogs with DCM. Pimobendan may facilitate this approach by reducing the prevalence of worsening heart failure during up-titration.

## Treatment of Difficult and Refractory CHF:

The efficacy of diuretics in the latter stages of heart failure depends on adherence to a restricted sodium diet. In most dogs with heart failure, moderate restriction of sodium intake is adequate. Renal blood flow and glomerular filtration rate decline with progressive reductions of cardiac output and delivery of furosemide to its site of action decreases as heart failure worsens. This fundamental limitation of diuretic therapy is further complicated during chronic therapy by hypertrophy of the distal renal tubule. This adaptive change increases the rate of sodium reabsorption, diminishing the natriuretic effect of furosemide. Contraction of the extracellular fluid volume following bolus administration of furosemide further stimulates the renal tubules to retain sodium chloride until the next dose is administered. Increasing the frequency of administration of furosemide can often resolve diuretic resistance. Others have advocated using a loop diuretic with higher bioavailability when administered orally, such as bumetanide or torsemide. Other potential advantages of torsemide include its antialdosterone activity and longer half-life than furosemide. Torsemide is dosed at 1/10$^{th}$ the daily dose of furosemide divided in two daily doses.

Addition of a different class of diuretic blocks some of the adaptive responses that limit single-agent therapy, often resulting in a synergistic diuretic effect. Thus, resolution of refractory pulmonary edema may require the combined use of furosemide, spironolactone, and either

chlorothiazide or hydrochlorothiazide. Daily combined treatment with furosemide and a thiazide diuretic shares the same liabilities as high-dose furosemide therapy, namely dehydration and electrolyte depletion. Limiting treatment with the thiazide diuretic to every 2nd day usually resolves refractory pulmonary congestion without these adverse consequences. Body weight, sodium and water consumption, serum electrolytes, renal function and urine production should be monitored when employing aggressive diuretic strategies. Plasma aldosterone concentrations are often elevated in dogs already receiving therapeutic doses of an ACE inhibitor as part of the *triple drug* protocol.

Arterial vasodilators can be used to reduce the volume of mitral regurgitation and to increase cardiac output in normotensive dogs with refractory heart failure. Of the available alternatives, only hydralazine and amlodipine, and sildenafil have been used in dogs. I prefer amlodipine to hydralazine given its more gradual onset of action and better tolerability. Sildenafil is often useful for treating dogs with mitral regurgitation and pulmonary hypertension. Nitrogenous venodilators are often advocated to help resolve refractory pulmonary edema in dogs. I prefer oral administration of isosorbide dinitrate or isosorbide mononitrate to nitroglycerine paste or patches. Such therapy is usually well tolerated, but the efficacy of this class of drugs in dogs with refractory heart failure has not been determined. One study of 6 dogs with CHF indicated that isosorbide mononitrate failed to reduce thoracic blood volume, suggesting no significant change in systemic venous capacitance.

Substantial volumes of fluid accumulating in the chest, abdomen, or pericardial sac should be manually drained, and drug therapy should be adjusted to prevent their re-accumulation. Measurement of central venous pressure provides an objective measure of the success of treatment. Some patients with refractory heart failure require periodic centesis to remain comfortable. The procedure is easy to accomplish and is well tolerated by most dogs, many of which will survive months or years in this condition. The finding of hyponatremia in dogs with congestive heart failure usually portends a poor prognosis. The pathophysiology of this phenomenon is thought to primarily involve excess levels of arginine vasopressin. Treatment options in this circumstance are quite limited and have mainly included restricted water intact which, in my experience, is usually unsuccessful in dogs. Another treatment option is the use of hypertonic saline administered together with diuretics. There is some risk to this form of therapy including the development of CNS signs and the possibility of worsening pulmonary congestion.

## Initiation of Treatment in Dogs with Heart Disease:

*Dogs with MR with no signs of CHF*. Two large studies have evaluated ACE inhibitor treatment of dogs with MR prior to the onset of heart failure. Time to onset of congestive heart failure was not different between control dogs and the dogs treated with enalapril as monotherapy. Boehringer Ingelheim is sponsoring the EPIC (Evaluation of Pimobendan In dogs with Cardiomegaly caused by preclinical mitral valve disease) trial which is scheduled to present its conclusion in 2015. For this trial dogs were enrolled in Australia, Canada, France, Germany, Italy, Japan, the Netherlands, Spain, Sweden, United Kingdom and the United States. No

studies of other drugs have been performed in asymptomatic dogs with spontaneously occurring mitral regurgitation. In this context, the most appropriate course of action is to advise no treatment but with scheduled revaluations at 3 to 6 month intervals depending on disease severity. Common sense, however, should prevail when the onset of CHF is deemed likely to develop in the very near future (large heart with an accelerated rate of enlargement over the last 6 months). It is not necessary to delay treatment until affected dogs present at the local emergency clinic.

*Dogs with DCM with no signs of CHF*. Studies performed in humans with asymptomatic LV dysfunction favor the use of ACE inhibitors and beta blockers, notably enalapril and carvedilol. O'Grady et al published a retrospective study indicating that benazepril delayed the onset of heart failure in Doberman pinscher dogs with DCM. Most recently, the **P**imobendan **R**andomized **O**ccult DCM **T**rial to **E**valuate **C**linical symptoms & **T**ime to heart failure (PROTECT) trial investigators reported that pimobendan reduced the chance of sudden death or development of heart failure (combined endpoint) in Dobermanns with pre-clinical DCM. This study had some serious design flaws and its restrictive entry criteria make it very hard to extrapolate its conclusions to a real-world population. To date, treatment of asymptomatic dogs with arrhythmias has been mainly focused on the management of arrhythmias such atrial fibrillation (Great Danes and Irish Wolfhounds) or ventricular ectopy (Boxers and Doberman Pinschers). See presentation on management of arrhythmias.

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