PRACTICAL PHARMACOLOGY

Standard Medical Therapies for Preclinical Heart Disease and Congestive Heart Failure in Dogs

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Although innovative therapies for common acquired heart diseases in dogs are emerging, medical treatment with diuretics, pimobendan, renin-angiotensin-aldosterone system (RAAS) inhibitors, and aldosterone antagonists remains the mainstay for most dogs with congestive heart failure (CHF).

This first of 2 articles reviews drugs commonly used for the management of preclinical and clinical degenerative mitral valve disease (DMVD) and dilated cardiomyopathy (DCM) in dogs (**TABLE 1**). It includes insight regarding when to perform dose escalation, key clinical data available, monitoring plans, and side effects associated with these common therapies. **TABLE 2** summarizes the staging of heart disease and CHF according to the American College of Veterinary Internal Medicine consensus guidelines.

PIMOBENDAN
(Vetmedin, Vetmedin-CA1)

Approval status: Pimobendan is approved for management of CHF in dogs with DCM or DMVD and marketed as Vetmedin for this indication. It is also marketed as Vetmedin-CA1 for the indication of delaying CHF onset in dogs with preclinical DMVD (stage B2), for which it has been conditionally approved by the U.S. Food and Drug Administration (FDA) based on a study that showed clinical benefit in this population but was not designed to meet all FDA requirements for approval.[3] A pivotal study is currently in progress (EPOCHAL, dogheartstudy.com) that is designed to fulfill FDA requirements for approval of pimobendan for preclinical DMVD.

Abstract

Degenerative mitral valve disease and dilated cardiomyopathy are the most common types of acquired heart disease in dogs. Although innovative therapies such as surgical repair of the mitral valve and gene therapy are emerging, medical treatment remains the mainstay for most dogs in the preclinical phase as well as dogs with congestive heart failure. This article reviews drugs commonly used for the management of these common diseases: pimobendan, diuretics, renin-angiotensin-aldosterone system inhibitors, and aldosterone antagonists.

Take-Home Points

- According to the 2019 American College of Veterinary Internal Medicine consensus guidelines on the diagnosis and treatment of degenerative mitral valve disease in dogs (DMVD), the compilation of separate studies supports the use of diuretics, pimobendan, angiotensin-converting enzyme inhibitors (ACEIs), and spironolactone to treat dogs with congestive heart failure (CHF), although no single study has evaluated outcomes with all 4 medications.
- Furosemide is used to alleviate signs of CHF in dogs regardless of the cause. It is contraindicated in dogs with pericardial effusion causing right-sided CHF.
- The typical starting dosage for furosemide is 1 to 2 mg/kg PO q12h. Recurrent CHF episodes are typically addressed by increasing the dose or frequency, but adjunctive therapies or transition to torsemide should be considered if doses greater than 6 to 8 mg/kg/d are needed.
- Pimobendan is indicated for patients with preclinical (stage B2) or clinical (stage C/D) DMVD and dilated cardiomyopathy.
- Comprehensive renin-angiotensin-aldosterone system blockade with ACEIs and spironolactone is recommended for dogs with CHF. Concurrent administration of an ACEI and spironolactone also helps prevent or manage hypokalemia in patients treated with loop diuretics.

Manufacturer: Boehringer Ingelheim Animal Health (bi-animalhealth.com)

Mechanism of action: Pimobendan is an inodilator, meaning it has both positive inotropic and vasodilatory effects. Increased sensitization of the cardiomyocyte to calcium leads to increased contractility (inotropy), and inhibition of phosphodiesterase 3 and 5 enzymes leads to smooth muscle relaxation.[4] Both increased contractility and afterload reduction increase stroke volume and cardiac output.[4]

Cardiac indications: Pimobendan is indicated for preclinical (stage B2) and clinical (stage C and D) DMVD and DCM patients.[3,5-7]

Administration: The starting dosage is 0.25 to 0.3 mg/kg PO q12h, with higher doses and dose frequency in patients with refractory CHF. In the authors' experience, most dogs tolerate dosage increases, and the added inodilation could minimize the amount of diuretic needed to control signs of fluid retention. Pimobendan can be suspended with water immediately before administration. Some formulations have variable bioavailability and stability; therefore, consultation with a veterinary pharmacist is recommended if compounding is desired.

Key clinical data: The EPIC trial showed that pimobendan delays the onset of CHF by approximately 15 months in dogs with preclinical DMVD compared to placebo.[3] The QUEST study showed that pimobendan was superior to benazepril in dogs with

TABLE 1 Standard Drugs for Management of Degenerative Mitral Valve Disease and Dilated Cardiomyopathy in Dogs

NAME(S)	DRUG CLASS	STARTING DOSE	INDICATION	ADVERSE EFFECTS
Pimobendan	Inodilator	▪ 0.25–0.3 mg/kg PO q12h	▪ Stage B2, C, or D DMVD and DCM	Gastrointestinal signs
Furosemide	Diuretic	▪ 1–2 mg/kg PO q12h or 2 mg/kg IV (acute CHF)	▪ Stage C DMVD and DCM	Azotemia, dehydration, electrolyte disturbances
Enalapril, benazepril	Angiotensin-converting enzyme inhibitor	▪ 0.25-0.5 mg/kg PO q12–24h (enalapril) ▪ 0.25–0.5 mg/kg PO q12–24h (benazepril)	▪ Stage C or D DMVD ± Stage B2 DMVD ▪ Stage B2, C, or D DCM	Azotemia, gastrointestinal signs, electrolyte disturbances
Spironolactone	Mineralocorticoid receptor antagonist	▪ 2 mg/kg PO q24h	▪ Stage C or D DMVD and DCM	Gastrointestinal signs, electrolyte disturbances

CHF = congestive heart failure; DCM = dilated cardiomyopathy; DMVD = degenerative mitral valve disease

TABLE 2 ACVIM Classification and Staging for Degenerative Mitral Valve Disease and Heart Failure[1,a]

STAGE	CHARACTERISTICS
A	Higher risk for developing the disease, but no current identifiable structural disorder
B1	Evidence of disease, but no or only mild radiographic or echocardiographic evidence of cardiac remodeling and no clinical signs of heart disease
B2	Evidence of disease (e.g., murmur, changes to the valve consistent with the disease) and significant left atrial and ventricular enlargement, but no clinical signs of heart disease
C	Current or past clinical signs of congestive heart failure caused by the disease
D	End-stage disease, in which congestive heart failure is refractory to standard treatment

ACVIM = American College of Veterinary Internal Medicine
[a]A similar staging system can be used for dilated cardiomyopathy.[2]

CHF secondary to DMVD.[5] The PROTECT study showed that pimobendan delays the onset of CHF and/or sudden cardiac death by approximately 9 months in Doberman pinschers with preclinical DCM.[7] An earlier study demonstrated a survival benefit of pimobendan in Doberman pinschers with DCM and CHF.[6]

Monitoring/side effects: No biochemical monitoring is necessary in patients treated solely with pimobendan. Vomiting, diarrhea, anorexia, and lethargy occur rarely.

FUROSEMIDE

Approval status: Furosemide is approved for the treatment of CHF in dogs.

Manufacturer: Various

Mechanism of action: Furosemide is a loop diuretic that binds to the sodium-potassium-chloride cotransporter in the kidney at the thick ascending limb of the loop of Henle. This inhibits electrolyte resorption, subsequently causing loss of sodium, potassium, chloride, and water in the urine. Magnesium and calcium are also lost into the renal tubule. The loss of sodium and water in the urine (diuresis) results in decongestion due to removal of excess fluid from the intracellular and intravascular spaces, driven by Starling's forces. Furosemide also causes pulmonary vasodilation and increased renal blood flow through prostaglandin synthesis, which is most evident when administered intravenously.

Cardiac indications: Furosemide is used to relieve fluid accumulation associated with CHF, regardless of underlying etiology. Furosemide is contraindicated when pericardial effusion is the cause of right-sided CHF because it reduces preload. Furosemide is not indicated in preclinical disease.

Administration: Pharmacokinetic differences related to administration route are important considerations for dosing frequency. Diuresis occurs for 1 hour after intravenous, 2 to 3 hours after intramuscular, 4 hours after subcutaneous, and 6 hours after oral administration.

- **Acute CHF:** Intravenous or intramuscular furosemide is commonly administered as a bolus of 2 mg/kg in dogs. This dose can be repeated at 1- to 2-hour intervals until the respiratory rate decreases, at which time the dose and/or frequency are reduced. Alternatively, furosemide can be administered as a constant-rate infusion starting at 0.6 mg/kg/h, which allows for downward dosage adjustments based on respiratory rates; the authors rarely use an infusion for longer than 6 to 8 hours. The infusion line should be covered to prevent light degradation. Regardless of method used, the cumulative intravenous furosemide dose for acute CHF should be tracked to avoid excessive doses. In the authors' practice, most patients require a cumulative intravenous furosemide dose <10 mg/kg to treat acute pulmonary edema.
- **Chronic CHF:** A typical starting dosage for orally administered furosemide in dogs is 1 to 2 mg/kg q12h. The dosage can be increased to address recurrent CHF by increasing the amount given or the frequency; however, if the total daily dose exceeds 6 to 8 mg/kg/d, transition to torsemide should be considered. Furosemide's variable bioavailability (10% to 90%) might account for poor diuretic responsiveness, especially in dogs with gastrointestinal disease or right-sided CHF. In humans, concurrent food administration reduces bioavailability by 30%, and nonsteroidal anti-inflammatory drugs decrease the efficacy of loop diuretics because they compete for secretion into the renal tubule.[8,9]

Key clinical data: Furosemide is generally accepted as lifesaving treatment in dogs with dyspnea from acute CHF, but no clinical trial data are available to

demonstrate a survival benefit. Multiple studies in healthy and diseased dogs provide pharmacokinetic and pharmacodynamic data to guide dosing.[10,11]

Monitoring: Body weight, hydration status, and select serum biochemical parameters (i.e., blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate) should be monitored in patients receiving furosemide 1 to 2 weeks after drug initiation or dosage change and at regular intervals thereafter.

Side effects: Diuresis and natriuresis cause polyuria with reactive polydipsia. If diuresis is excessive, it reduces intravascular volume and induces electrolyte loss with signs such as lethargy, weakness, loss of appetite, and vomiting. High furosemide doses can cause hypochloremic metabolic alkalosis in addition to azotemia. Furosemide stimulates the RAAS indirectly via volume depletion and directly by impairing salt sensing in the kidney. Chronic furosemide administration reduces its own efficacy (tolerance), likely due to RAAS activation and upregulation of sodium-retentive mechanisms distal to the loop of Henle. Loop diuretics should be used at the lowest effective dosages and with adjunctive therapies to minimize the risk of adverse effects.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS
(Enalapril, Benazepril, Ramipril, Captopril, Lisinopril)

Approval status: Enalapril is approved to treat CHF in dogs; however, the brand Enacard is no longer available. The combination of benazepril and spironolactone (Cardalis) is FDA approved for the treatment of CHF in dogs.

Manufacturer: Various. Cardalis is manufactured by Ceva Animal Health (cardalis.com).

Mechanism of action: Angiotensin-converting enzyme inhibitors (ACEIs) reduce the formation of angiotensin II (Ang II) by inhibiting angiotensin-converting enzyme, thereby lessening the vasoconstrictive, sodium-retentive, aldosterone-stimulating, and inflammatory actions of Ang II. ACEIs also reduce the metabolism of angiotensin 1–7 and bradykinin, both of which promote vasodilation and natriuresis.[12] They have minimal antihypertensive effects. While benazepril is eliminated through hepatic and renal mechanisms, enalapril is entirely renally excreted.

Cardiac indications: ACEIs are indicated for the treatment of stable CHF in dogs. They are not usually administered in the acute CHF setting. Because aldosterone is not adequately suppressed in 30% to 40% of dogs receiving ACEIs (aldosterone breakthrough), concurrent spironolactone is recommended. Strong evidence for benefit of ACEI therapy in preclinical DMVD is lacking, although some experts prescribe ACEIs in dogs with stage B2 DMVD.[1]

Administration: ACEIs are administered at 0.25 to 0.5 mg/kg PO q12h to q24h, with doses and frequency varying between agents. One study suggests that twice daily dosing optimizes cardioprotective benefits.[13] Reductions in enalapril dose or dose frequency should be considered for dogs with renal disease.

Key clinical data: Early clinical studies demonstrated reductions in mortality and morbidity in dogs with CHF treated with ACEIs.[14-16] More recently, a prospective study did not find additional benefit of ACEIs over pimobendan and diuretic therapy[17]; however, dogs in this study were not receiving spironolactone and were on low ACEI doses and high furosemide doses. The importance of comprehensive RAAS suppression in dogs with CHF was evidenced by the BESST trial, which showed superior outcomes for dogs treated with benazepril and spironolactone compared to benazepril alone.[18] The BESST was the basis for the FDA approval of Cardalis; however, this study did not include pimobendan.[18]

Monitoring: Select serum biochemical variables (i.e., blood urea nitrogen, creatinine, sodium, potassium, chloride) should be evaluated before treatment, 1 to 2 weeks after initiation of therapy, and periodically thereafter or as dictated clinically. ACEIs can cause hyperkalemia, although this occurs infrequently, especially with concurrent diuretic use. A small rise in serum creatinine (typically <0.3 mg/dL) is expected after ACEI initiation due to reduction of Ang II, resulting in efferent arteriolar vasodilation. Increases greater than 0.3 mg/dL warrant consideration of diuretic or ACEI dose adjustments. Although the antihypertensive effect of ACEIs is minimal, blood pressure monitoring should ideally be performed at each recheck.

Side effects: Adverse effects are uncommon but can include gastrointestinal upset, weakness, or lethargy. ACEIs are generally well tolerated; however, bloodwork and blood pressure monitoring are indicated to

monitor for azotemia, hyperkalemia, and hypotension. ACEI administration in patients that are highly dependent on Ang II for maintenance of renal function (e.g., dogs with hypotension, hyponatremia, volume depletion) risks functional azotemia, which is why these drugs are not used for treatment of acute CHF.

MINERALOCORTICOID RECEPTOR BLOCKERS (Spironolactone)

Approval status: Cardalis (combination tablet of spironolactone and benazepril) is FDA approved for the treatment of CHF in dogs. Other formulations of spironolactone are available and used, but Cardalis is the only one with FDA approval at this time.

Manufacturer: Ceva Animal Health (Cardalis)

Mechanism of action: Spironolactone blocks the aldosterone receptor in the distal renal tubule and collecting duct, which impairs sodium resorption and promotes potassium retention but does not cause appreciable diuresis. The clinical benefit of spironolactone is from antagonism of maladaptive aldosterone effects in the kidney, heart, and vasculature.[19,20] Spironolactone is an important addition to CHF therapy, as 30% to 40% of dogs show aldosterone breakthrough with ACEI therapy alone.[21]

Cardiac indications: Spironolactone is indicated for chronic management of CHF. Benefit in preclinical disease has not been proven.

Administration: The dose of spironolactone is 2 mg/kg PO q24h. Doses up to 4 mg/kg/d have been described.

Key clinical data: One study showed increased survival in dogs with DMVD with the addition of spironolactone to conventional medications (ACEI ± furosemide ± digoxin) compared to placebo.[19] The BESST showed an end-point benefit for dogs with CHF that received spironolactone and benazepril compared to benazepril alone.[18] The DELAY study was not able to show additive benefit of spironolactone and benazepril compared to benazepril alone in dogs with preclinical DMVD; however, some secondary end points were improved.[22]

Monitoring: Serum electrolytes should be evaluated 1 to 2 weeks after starting spironolactone and at periodic intervals thereafter to monitor for hyperkalemia.

Side effects: Hyperkalemia can occur with spironolactone administration; however, this is uncommon, especially when loop diuretics are concurrently administered. The authors refrain from prescribing spironolactone in patients with primary hypoadrenocorticism.

SUMMARY

Although CHF is a devastating diagnosis, many dogs respond well to standard medical therapy for some time. Common therapies for CHF treatment include diuretics, pimobendan, and RAAS inhibitors, which are prescribed to relieve congestion, improve contractility, and counteract maladaptive RAAS activation. TVP

References

1. Keene BW, Atkins CE, Bonagura JD, et al. ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs. *J Vet Intern Med*. 2019;33(3):1127-1140.
2. Wess G. Screening for dilated cardiomyopathy in dogs. *J Vet Cardiol*. 2022;40:51-68.
3. Boswood A, Häggström J, Gordon SG, et al. Effect of pimobendan in dogs with preclinical myxomatous mitral valve disease and cardiomegaly: the EPIC study—a randomized clinical trial. *J Vet Intern Med*. 2016;30(6):1765-1779.
4. van Meel JC, Diederen W. Hemodynamic profile of the cardiotonic agent pimobendan. *J Cardiovasc Pharmacol*. 1989;14 Suppl 2:S1-S6.
5. Häggström J, Boswood A, O'Grady M, et al. Effect of pimobendan or benazepril hydrochloride on survival times in dogs with congestive heart failure caused by naturally occurring myxomatous mitral valve disease: the QUEST study. *J Vet Intern Med*. 2008;22(5):1124-1135.
6. O'Grady MR, Minors SL, O'Sullivan ML, Horne R. Effect of pimobendan on case fatality rate in Doberman pinschers with congestive heart failure caused by dilated cardiomyopathy. *J Vet Intern Med*. 2008;22(4):897-904.
7. Summerfield NJ, Boswood A, O'Grady MR, et al. Efficacy of pimobendan in the prevention of congestive heart failure or sudden death in Doberman pinschers with preclinical dilated cardiomyopathy (the PROTECT study). *J Vet Intern Med*. 2012;26(6):1337-1349.
8. Reyes JL, Aldana I, Barbier O, Parrales AA, Melendez E. Indomethacin decreases furosemide-induced natriuresis and diuresis on the neonatal kidney. *Pediatr Nephrol*. 2006;21(11):1690-1697.
9. Bard RL, Bleske BE, Nicklas JM. Food: an unrecognized source of loop diuretic resistance. *Pharmacotherapy*. 2004;24(5):630-637.
10. Harada K, Ukai Y, Kanakubo K, et al. Comparison of the diuretic effect of furosemide by different methods of administration in healthy dogs. *J Vet Emerg Crit Care (San Antonio)*. 2015;25(3):364-371.
11. Adin DB, Taylor AW, Hill RC, Scott KC, Martin FG. Intermittent bolus injection versus continuous infusion of furosemide in normal adult greyhound dogs. *J Vet Intern Med*. 2003;17(5):632-636.
12. Ames MK, Atkins CE, Pitt B. The renin-angiotensin-aldosterone system and its suppression. *J Vet Intern Med*. 2019;33(2):363-382.
13. Ward JL, Chou YY, Yuan L, Dorman KS, Mochel JP. Retrospective evaluation of a dose-dependent effect of angiotensin-converting enzyme inhibitors on long-term outcome in dogs with cardiac disease. *J Vet Intern Med*. 2021;35(5):2102-2111.
14. The IMPROVE Study Group. Acute and short-term hemodynamic, echocardiographic, and clinical effects of enalapril maleate in dogs with naturally acquired heart failure: results of the Invasive Multicenter PROspective Veterinary Evaluation of Enalapril study. *J Vet Intern Med*. 1995;9(4):234-242.

15. The COVE Study Group. Controlled clinical evaluation of enalapril in dogs with heart failure: Results of the Cooperative Veterinary Enalapril Study Group. *J Vet Intern Med*. 1995:9(4):243-252.
16. Ettinger SJ, Benitz AM, Ericsson GF, et al. Effects of enalapril maleate on survival of dogs with naturally acquired heart failure. The Long-Term Investigation of Veterinary Enalapril (LIVE) Study Group. *JAVMA*. 1998;213(11):1573-1577.
17. Wess G, Kresken JG, Wendt R, et al. Efficacy of adding ramipril (VAsotop) to the combination of furosemide (Lasix) and pimobendan (VEtmedin) in dogs with mitral valve degeneration: The VALVE trial. *J Vet Intern Med*. 2020;34(6):2232-2241.
18. Coffman M, Guillot E, Blondel T, et al. Clinical efficacy of a benazepril and spironolactone combination in dogs with congestive heart failure due to myxomatous mitral valve disease: The BEnazepril Spironolactone STudy (BESST). *J Vet Intern Med*. 2021;35(4):1673-1687.
19. Bernay F, Bland JM, Häggström J, et al. Efficacy of spironolactone on survival in dogs with naturally occurring mitral regurgitation caused by myxomatous mitral valve disease. *J Vet Intern Med*. 2010;24(2):331-341.
20. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341(10):709-717.
21. Ames MK, Atkins CE, Eriksson A, Hess AM. Aldosterone breakthrough in dogs with naturally occurring myxomatous mitral valve disease. *J Vet Cardiol*. 2017;19(3):218-227.
22. Borgarelli M, Ferasin L, Lamb K, et al. DELay of Appearance of symptoms of canine degenerative mitral valve disease treated with spironolactone and benazepril: the DELAY study. *J Vet Cardiol*. 2020;27:34-53.

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