



Cardiovascular Therapeutics for Advanced Practitioners Mini Series

Session One: Treatment of
asymptomatic and symptomatic
cardiac disease

Jose Novo Matos DVM DipECVIM (Cardiology)
MRCVS
RCVS and European Specialist in
Small Animal Cardiology



In the last couple of years several important clinical trials have been published in small animal cardiology, some of them with ground-breaking results that have changed our therapeutic approach in acquired cardiac disease. This presentation will review the most recent studies and recommendations to treat the most frequent cardiac diseases in small animals.

Myxomatous Mitral Valve Disease (MMVD)

MMVD classification/staging system (Atkins et al 2009) ⁶		
Stage A	Dogs <u>at high risk</u> for developing MMVD	
Stage B (preclinical period)	Dogs with MMVD, but <u>without signs</u> of CHF	
	B1	No evidence of cardiac enlargement
	B2	Cardiac enlargement
Stage C	Dogs with MMVD and <u>signs of CHF</u>	
Stage D	Dogs with MMVD and <u>refractory signs</u> of CHF	

Stage B2: treatment

Pimobendan

Boswood A, 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 Nov;30(6):1765–79

The EPIC study was a large prospective, randomized, placebo-controlled, blinded multicentre trial that evaluated the efficacy of pimobendan in delaying the onset of signs of CHF, cardiac-related death or euthanasia in dogs with increased heart size secondary to preclinical MMVD. All dogs enrolled in the study had cardiac enlargement documented on echo (LA/Ao ≥ 1.6 , LVDDN ≥ 1.7) and thoracic radiographs (VHS > 10.5) and were asymptomatic. Pimobendan prolonged the preclinical period by approximately 15 months and it was safe and well tolerated.

Angiotensin-converting enzyme inhibitors (ACEi)

Kvart et al. Efficacy of Enalapril for Prevention of Congestive Heart Failure in Dogs with Myxomatous Valve Disease and Asymptomatic Mitral Regurgitation. J Vet Intern Med 2002;16:80–88

Atkins et al. Results of the veterinary enalapril trial to prove reduction in onset of heart failure in dogs chronically treated with enalapril alone for compensated, naturally occurring mitral valve insufficiency. J Am Vet Med Assoc 2007;231:1061–1069

2 prospective, double-blinded, placebo-controlled, multicenter trials evaluated the efficacy of enalapril in delaying the onset of left-sided congestive heart failure in MMVD dogs at stage B2. In both studies, enalapril failed to delay the onset of heart failure.

At the moment, pimodendan is the only therapy indicated for dogs with MMVD at stage B2.

Stage C: treatment

Pimobendan

Haggstrom 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;22:1124–1135

The QUEST study was a prospective, single- blinded, positive controlled study that compare pimodendan with benazepril (plus conventional heart failure therapy) for the treatment of dogs with stage C MMVD. Pimobendan prolonged significantly the time to sudden cardiac death, euthanasia or treatment failure in comparison with benazepril.

Spirolactone

Bernay et al. Efficacy of Spirolactone on Survival in Dogs with Naturally Occurring Mitral Regurgitation Caused by Myxomatous Mitral Valve Disease. J Vet Intern Med 2010;24:331–341

Double-blinded, placebo-controlled study that compare spironolactone with placebo (plus conventional heart failure therapy) for the treatment of stage C MMVD. Spirolactone added to conventional heart failure therapy decreased the risk of dogs suffering cardiac-related death, euthanasia or worsening.

This study had some design flaws and the evidence for spironolactone at stage C is not at the moment as strong as for pimobendan. So if one has to choose one drug to treat congestive heart failure secondary to MMVD this should be a combination of pimobendan and diuretics. Considering that ACEi and spironolactone have been shown as well to be clinically useful in stage C it is frequent to combine these drugs to pimobendan and diuretics. Although it is unknown at the present time if these combinations (pimobendan +/- spironolactone +/- ACEi) are superior to pimobendan alone in the treatment of stage C dogs.

Preclinical (asymptomatic) dilated cardiomyopathy (DCM)

Pimobendan

Summerfield 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

Randomized, blinded, placebo-controlled multicenter study that compared pimobendan with placebo in delaying the onset of heart failure or sudden death in Dobermans with preclinical DCM. Pimobendan prolonged by 9 months the time to heart failure or sudden cardiac death.

Benazepril

O' Grady et al. Efficacy of Benazepril Hydrochloride to Delay the Progression of Occult Dilated Cardiomyopathy in Doberman Pinschers. J Vet Intern Med 2009;23:977–983

Retrospective study that evaluated the effect of benazepril in delaying the onset of overt DCM (heart failure or sudden death) in Dobermans. Dogs receiving benazepril were 45% less likely to develop overt DCM.

Pimobendan is the therapy with the strongest evidence of clinical benefit in preclinical DCM, whilst ACEi (Benazepril) has a moderate evidence for a beneficial effect at this stage of DCM. It is unknown at the present time if pimobendan combined with benazepril is superior to pimobendan alone.

Preclinical (asymptomatic) hypertrophic cardiomyopathy (HCM)

ACEi and aldosterone antagonists

MacDonald et al. Effect of Spironolactone on Diastolic Function and Left Ventricular Mass in Maine Coon Cats with Familial Hypertrophic Cardiomyopathy. J Vet Intern Med 2008;22:335–341

MacDonald et al. The Effect of Ramipril on Left Ventricular Mass, Myocardial Fibrosis, Diastolic Function, and Plasma Neurohormones in Maine Coon Cats with Familial Hypertrophic Cardiomyopathy without Heart Failure. J Vet Intern Med 2006;20:1093–1105

2 placebo-controlled, blinded studies evaluated the effect of spironolactone and ramipril in asymptomatic HCM. There was no improvement on diastolic function or left ventricular wall thickness (mass) with either drug.

Schober et al. Effect of treatment with atenolol on 5-year survival in cats with preclinical (asymptomatic) hypertrophic cardiomyopathy. J Vet Cardiol 2013

Prospective, observational, open-label clinical study that investigated the effect of treatment with atenolol on 5-year survival in cats with preclinical HCM. The study failed to show an effect of atenolol on survival in HCM.

No therapy has been shown to improve cardiac function or prolong survival in cats with preclinical HCM.

Arterial thromboembolism in cats

Hogan et al. Secondary prevention of cardiogenic arterial thromboembolism in the cat: The double-blind, randomized, positive-controlled feline arterial thromboembolism; clopidogrel vs. aspirin trial (FAT CAT). Journal of Veterinary Cardiology (2015) 17, S306eS317

Multicenter, double-blind, randomized, positive-controlled study evaluated if clopidogrel administration was associated with a reduced likelihood of recurrent arterial thromboembolism in cats compared with aspirin. Clopidogrel significantly reduced the recurrence of ATE compared with aspirin in cats. No adverse effects (e.g. bleeding) were documented.

Clopidogrel is superior to aspirin for the prevention of recurrent ATE and may be used to primary prevention as well. It is unknown at the present time if clopidogrel combined with aspirin is superior to clopidogrel alone.

Recommended reading

1. Atkins C, Bonagura J, Ettinger S, Fox P, Gordon S, Haggstrom J, et al. Guidelines for the Diagnosis and Treatment of Canine Chronic Valvular Heart Disease. J Vet Intern Med. 2009 Nov;23(6):1142–50
2. Boswood A, Häggström J, Gordon SG, Wess G, Stepien RL, Oyama MA, 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 Nov;30(6):1765–79.
3. Häggström J, Boswood A, O’Grady M, Jöns O, Smith S, Swift S, 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 Am Coll Vet Intern Med. 2008 Oct;22(5):1124–35.
4. Summerfield NJ, Boswood A, O’Grady MR, Gordon SG, Dukes-McEwan J, Oyama MA, 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 Am Coll Vet Intern Med. 2012 Dec;26(6):1337–49.