Cardiology Cogitations

with Stephen Ettinger

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Dr. Ettinger was the medical director of the California Hospital Veterinary Specialty Group in Los Angeles from 1980 until 2009. In 1970, Dr. Ettinger co-authored with Dr. P.F. Suter, the first veterinary small animal specialty textbook, Canine Cardiology (1971) and he has been the author and editor of the Textbook of Veterinary Internal Medicine, a two-volume treatise on veterinary medicine, available in five languages.

Dr. Ettinger has presented talks throughout the world and has published over 160 professional articles in the veterinary literature. His areas of specialization are small animal veterinary internal medicine, small animal cardiology, hospital management and professional veterinary development. He is a Diplomate of the American College of Veterinary Internal Medicine (Cardiology and Internal Medicine) and an Emeritus Fellow of the American College of Cardiology (FACC) and the American Heart Association (FAHA). Most recently, Dr. Ettinger was awarded the ACVIM Lifetime Specialty Achievement Award.

Stage your MMVD patients

Beyond the murmur intensity (grade I-VI/VI), these dogs should be staged based on objective, diagnostic parameters. A visual summary of the ACVIM guidelines staging is noted in Figure 1.

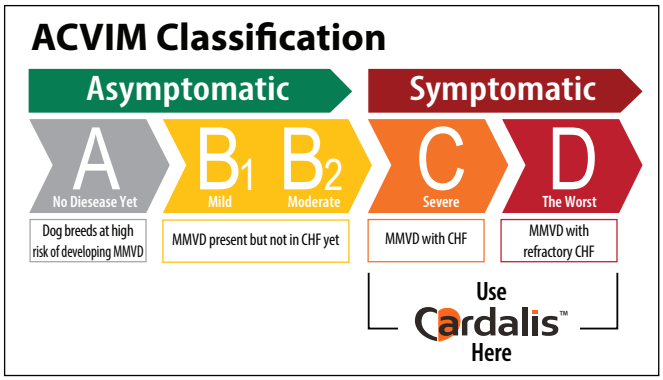

Figure 1. ACVIM classification of MMVD in dogs.

A. Stage A dogs are those at risk including all smaller dogs. Stage A dogs do not currently have a mitral valve abnormality. An example of a stage A patient would be the classic MMVD poster-child, the Cavalier King Charles Spaniel. There are however many other at-risk breeds that should be identified and evaluated.

B. Stage B dogs do have a mitral valve abnormality. They usually have a systolic heart murmur and may have some degree of cardiac enlargement. Stage B1 dogs have a murmur but no significant evidence of left atrial enlargement or cardiomegaly. B2 denotes dogs with a left atrium to aorta ratio (LA:Ao) of ≥1.6 and a left ventricular end diastolic diameter normalized for body weight (LVIDDn) ≥1.7. Because many veterinarians do not have access to echocardiography, the ACVIM does acknowledge that the vertebral heart score (VHS) > 11.5 with a systolic heart murmur ≥III/VI (or one of the newly recognized mensuration systems that have been published) can substitute for quantitative echocardiography to identify stage B2. Such measurement techniques provide similar, if not specific, evidence of changing cardiac (left atrial) enlargement patterns. While there are multiple techniques demonstrated to show close proximity to echocardiographic derived measurements, where possible the echocardiogram remains the standard of choice for identifying these morphologic changes in the heart affected by MMVD.

C. Stage C denotes dogs with current or past clinical signs of congestive heart failure secondary to MMVD.

D. Stage D dogs are end stage congestive heart failure patients. These dogs have either acute or past clinical signs of congestive heart failure and are refractory to the standard treatment. Usually, Stage D dogs require more than 8 mg/kg/day of furosemide or the equivalent dosage of torsemide (also known as torasemide or DEMADEX®, a registered trademark of Meda AB).

Quadruple therapy

The ACVIM endorsement of a quadruple therapy approach for CHF was a significant update to the consensus statement that was previously published a decade prior, in 2009. The addition of spironolactone is recommended not for its weak potassium sparing diuretic effects (as was originally thought to benefit the patient) but rather for its MRA effects. This rounds out the new

policy regarding suggested therapy in symptomatic MMVD dogs. The consensus panel agreed that a robust, broad-spectrum approach to suppression of the renin-angiotensin-aldosterone system (RAAS), including aldosterone inhibition, should be standard of care for CHF patients.

Why is control of the renin-angiotensin-aldosterone system (RAAS) important?

One consequence of MMVD is activation of the RAAS. The RAAS is a primal, lifesaving mechanism meant to detect and adjust for changes in body homeostasis. For instance, in situations where blood loss or dehydration occur, the kidneys detect decreased perfusion and release the enzyme renin. This begins the RAAS cascade which causes vasoconstriction and retention of sodium and water. These functions work to expand blood volume and maintain organ perfusion. When the bleeding is stopped or dehydration is corrected, the cascade is deactivated. Short-term activation is a good thing... a great thing, particularly if the animal is experiencing blood loss or dehydration. This is not the case for the dog with MMVD. Long-term, chronic, unchecked activation of the RAAS occurs with MMVD due to decreased cardiac output. Negative consequences occur due to excess production of angiotensin II and aldosterone. When this system is activated chronically, retention of sodium and water, chronic vasoconstriction, and cardiac remodeling or fibrosis result (see Figure 2).

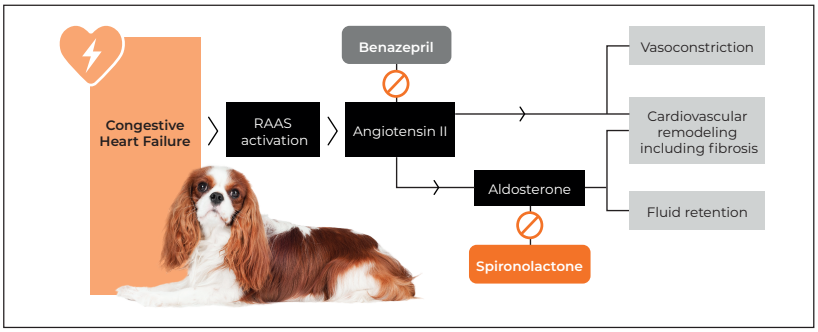

Figure 2: Activation of the RAAS in the mitral valve disease patient leads to deleterious effects. Even with the use of an ACEI, aldosterone can be present (both as a function of stimulation from sources other than angiotensin II and aldosterone breakthrough).

What about the ACEIs that we've always used? Isn't that enough to suppress RAAS?

It was long-believed that inhibition of angiotensin II production (with the use of ACEIs such as benazepril or enalapril) would benefit the patient both by reduction of overall angiotensin II concentration and by preventing the downstream production of aldosterone. While this is true in many cases, aldosterone breakthrough (ABT) occurs in approximately 30-40% of dogs on ACEIs[2]. Because there are non-ACE dependent pathways of aldosterone production and possibly some negative-feedback mechanisms at play, we now know that ACEIs alone are not enough. In fact, broad-spectrum inhibition of this deleterious system with a combination of spironolactone and benazepril (CARDALIS™) resulted in better outcomes for patients in a recently completed clinical trial[3]. As with so many diseases that we treat in veterinary medicine, a broad-spectrum approach is often the path to success.

Compliance is key.

If we know that quadruple therapy is best for the patient, then what's the problem? There are inevitable challenges posed by polypharmacy. With more drugs comes poor compliance which leads to less effective clinical outcomes and lowered client satisfaction.

In early 2021, Ceva Animal Health, LLC came to market with a solution to the issue of polypharmacy and compliance in the cardiac patient. CARDALIS™ is a combination of spironolactone and benazepril hydrochloride developed to provide comprehensive RAAS blockade. Available in a convenient, once-per-day, flavored, chewable tablet, CARDALIS™ was found to be safe and effective by the FDA and is approved for mild, moderate, and severe congestive heart failure (CHF) in dogs.

CARDALIS™ provides half of the ACVIM quad-therapy recommendation for CHF due to MMVD in dogs (see Figure 3).

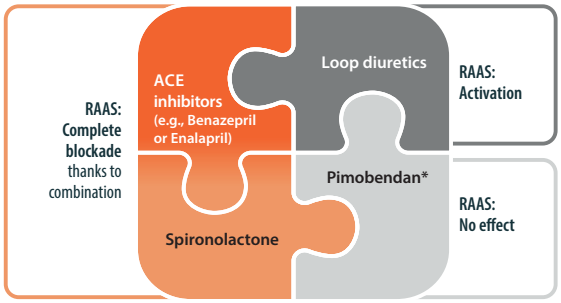

Figure 3: A quad-therapy approach to CHF management in dogs is recommended by the ACVIM.[1] Loop diuretics activate RAAS. Pimobendan has no effect on RAAS...it neither activates it nor blocks it[4]. ACEI and Spironolactone together provide comprehensive RAAS blockade.

A convenient, chewable option will provide the owner and mitral valve disease patient with a more pleasant, effective, and superior medication experience. Improved compliance results in a longer life, better quality of life, and increased client satisfaction. Now veterinarians have an alternative to human generics. CARDALIS™ is an FDA-approved, once-daily medication with proven safety and efficacy data specifically for dogs. It provides practitioners with peace-of-mind when prescribing for one of their most vulnerable (and difficult to medicate) patient populations[3].

The small, chewable tablets were found to be palatable and well accepted in 87.6% of patients in the pivotal efficacy trial for FDA approval for CARDALIS™[3]. The yeast-based, beef flavoring contains no beef protein and would not be expected to create a beef-allergy challenge for food allergic patients.

To support the product, Ceva is providing the practicing veterinarian with numerous virtual educational experiences at www.cevaconnect.com as well as ongoing live, continuing education events throughout 2021 and 2022. Additional tools, including client communication aids and the free CARDALIS™ resting respiratory rate app, offer the practitioner a variety of helpful resources (see figure 4).

CARDALIS RRR App

Figure 4: Resting Respiratory Rate App QR code

*In 2019, the ACVIM published new guidelines recommending a quadruple therapy approach for the treatment of CHF in dogs. The safety and efficacy of CARDALIS™ has not been investigated with pimobendan[3].

For full prescribing information click here.

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: 1127–1140. https://doi.org/10.1111/jvim.15488
2. Ames MK, Atkins CE, Eriksson A, Hess AM. Aldosterone breakthrough in dogs with naturally occurring myxomatous mitral valve disease. J Vet Cardiol. 2017 Jun;19(3):218-227. doi: 10.1016/j.jvc.2017.03.001. Epub 2017 May 31. PMID: 28576479.
3. 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; 1– 15. https://doi.org/10.1111/jvim.16155
4. Sayer, M., Atkins, C., Fujii, Y., et al. (2009), Acute effect of pimobendan and furosemide on the circulating renin-angiotensin-aldosterone system in healthy dogs. Journal of Veterinary Internal Medicine, 23: 1003-1006. https://doi:10.1111/j.1939-1676.2009.0367.x