Medical management of myxomatous mitral valve disease: An evidence-based veterinary medicine approach

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Myxomatous mitral valve disease (MMVD) is the most common heart disease of dogs. The current management of MMVD in dogs is mostly pharmacological, and the recommendations for treatment are based on a number of veterinary studies. Notwithstanding the current consensus regarding the medical management of MMVD, there remains active debate as to which drugs are the most effective. In order to understand how recommendations are constructed in the pharmacological management of diseases, the veterinarian needs to understand the concept of evidence-based veterinary medicine, and how the findings of these studies can be applied in their own practices. This review summarises the current veterinary literature and explains how the consensus regarding the management of MMVD has been reached. This review highlights the limitations of veterinary studies in order to provide veterinary practitioners with a sense of the difficulty there is in establishing the benefit of one treatment over the other. Veterinarians should therefore apply treatment recommendations based on the best evidence, integrated with a pathomechanistic understanding of the disease process and clinical experience.

Introduction

The growing popularity of evidence-based medicine (EBM) has transformed the way clinical trials are performed and, indeed, their interpretation (Cockcroft & Holmes 2003; Geyman 2000; Hjørland 2011; Sackett, Straus & Richardson 2000). The notion of EBM is born out of the observation that clinical observations are prone to bias and that natural variations in clinical outcome of a disease course may be wrongfully attributed to a treatment intervention (Hjørland 2011). Medical practices, whilst firmly based on pure sciences, have retained an element of their artistic origins, with the result that hypothesis-driven research in clinical practice is a relatively new concept (Hjørland 2011). The opinion of experts and clinical experience are still heavily weighted in the clinical realm and a clinician is an individual who draws on many resources to ultimately tailor a clinical treatment for an individual patient. Whilst the role of the clinician's own experience and expertise cannot be undervalued, the observations of the physician, when contrasted with pathomechanistically rationalised treatments, are extremely prone to bias. Hence, with regard to 'strength of evidence', the opinion of experts is seen as the weakest grade of evidence (Hjørland 2011). The philosopher Karl Popper promoted the idea of conjecture and refutation, which states that a scientific experiment should seek to disprove a hypothesis, and that failure to do so would result in the adoption of an alternate hypothesis (Popper 1963). This thought process attempts to force researchers to conscientiously refute their own theories, and only to accept them if they are unable to do so. It becomes apparent, therefore, that clinical trials have to be designed to remove the human element of bias and thus prospective, randomised, blinded clinical trials are considered to yield the best grade of evidence (Hjørland 2011). As with any new paradigm, proselytes quickly accrue. This has certainly been the case with EBM, with a new generation of veterinarians and residents who have become EBM zealots to the point that they are hesitant to adopt any medical practice that cannot be backed up with a paper, thus discarding one of the greatest attributes of the clinician, namely experience and clinical intuition. Those subscribing to a purist EBM approach alone should be reminded of the maxim 'absence of evidence is not evidence of absence'.[1] Recommendations based on EBM, which is a sound practice, should be integrated with clinical experience and individual patient appraisal to achieve the best clinical treatment. Understanding the basis and context of EBM will help veterinarians understand why certain publications are given more weight than others in the development of recommendations, which is particularly true in the case of angiotensin-converting enzyme (ACE) inhibitors (ACEIs). Using the grading of evidence paradigm (Table 1), if grade 1 evidence is available it will generally override contrary evidence of a lower grade.

1.Attributed to cosmologist Martin Rees.

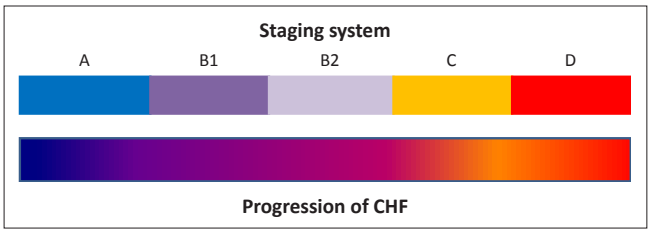
Randomised clinical trials (RCTs) that are blinded are considered the best grade of evidence. In the case of myxomatous mitral valve disease (MMVD), the benign nature of the disease in terms of progression and the natural variation in clinical presentation and outcome complicates the design of RCTs and increases the expense. Firstly, patients need to be classified according to a heart failure stage (Figure 1), which presents a challenge, as the onset of heart failure is gradual and multifactorial and by definition a continuous variable, which is categorised as an ordinal variable.

Figure 1 provides a diagrammatic representation of how a heart failure staging system seeks to categorise patients according to the severity of heart failure. The blocks with the associated letters represent the current stages according to the American College of Veterinary Internal Medicine (ACVIM) consensus statement (Atkins *et al.* 2009). A staging system represents an ordinal variable which assigns a diverse group of patients to a finite, predetermined, limited number of categories. The actual progression of congestive heart failure (CHF) is conceptually shown by the colour bar, which represents the progression as a continuous variable. On the basis of this diagram it can be appreciated that even within each category there is considerable variation between the individuals.

Secondly, because MMVD progresses slowly and the numbers of patients who deteriorate is not very high (Borgarelli *et al.* 2012), RCTs need to be conducted over a long period and with many patients per group. Notwithstanding these limitations, several RCTs published in the last 18 years have formed the basis of MMVD treatment recommendations. There are eight RCTs that have investigated the use of ACEIs in MMVD and two that have assessed the efficacy of pimobendan in the treatment of MMVD. One RCT trial was conducted using spironolactone in the management of MMVD (see below).

TABLE 1: Grades of evidence in medical research trials.

Grade of evidence	Description of evidence grading
Grade 1 (strongest)	Evidence derived from one or more properly designed, prospective clinical trials in the target species
Grade 2	Evidence derived from properly designed trials in the target species in a laboratory setting where disease is induced (for example, experimental induction of hypothyroidism)
Grade 3	Results of controlled retrospective studies, or cohort/case series studies, without randomisation
Grade 4 (weakest)	Evidence obtained from studies in other species, opinion of experts, descriptive studies, case reports



Source: Authors' own creation
CHF, congestive heart failure.

FIGURE 1: Diagram indicating the relationship between a heart failure staging system and natural disease progression.

In addition to a blinded RCT, experimental and mechanistic studies have also contributed to the understanding of the action and efficacy of cardiovascular drugs. Several studies have investigated the effects of cardiovascular drugs on echocardiographic parameters. Conceptually, if a drug has a beneficial or deleterious effect, then an improvement or worsening would be expected in certain echocardiographic parameters. Of interest are the studies pertaining to ACEI and pimobendan, as this remains a controversial issue. The reader should understand that at the heart of the pimobendan/ACEI debate is the battle for supremacy in the treatment of MMVD between proponents of these two drugs. It may seem a spurious comparison to the astute reader given the divergent mechanisms of action of the two drugs, and it would seem wiser to include both drugs in various treatment regimens. Notwithstanding the apparent wisdom of this view, vehement debate still exists as to the touted benefits of pimobendan in MMVD. Of particular interest to the reader would be that there is currently no evidence demonstrating synergistic benefit or adverse effects of pimobendan combined with an ACEI. In an experimental study in 12 beagles with experimentally induced MMVD, pimobendan was shown to have adverse effects on selected echocardiographic parameters and was associated with more severe mitral valve lesions on postmortem examination compared with an ACEI (Chetboul *et al.* 2007). This study was performed in asymptomatic dogs and the authors concluded that pimobendan should be assessed in symptomatic MMVD. Critics of this study (Corcoran *et al.* 2008) pointed out that the assessment of cardiac function (based on echocardiography) was flawed in this study. Furthermore, they contended that the progressive nature of the lesions in MMVD is not well understood, nor are the associations with progression, and therefore such a bold statement could not have been made. The findings of Chetboul *et al.* (2007) contradict those of two additional mechanistic studies. Ouellet *et al.* (2009) studied the effect of pimobendan versus control on selected echocardiographic parameters and found no significant changes between the two groups. In a small short-term experimental study, Kanno *et al.* (2007) found that pimobendan was associated with an improvement in mitral regurgitation (MR) and reduction in left atrial size. All three of these studies are within an experimental setting in the target species and are therefore considered grade 2 evidence. In addition, the ability of echocardiography to assess myocardial function remains an area of debate (Bonagura & Schober 2009) and thus the results of experiments utilising echocardiography should be understood in that context.

Further mechanistic information regarding cardiovascular drugs has been obtained from invasive experimental studies. Devices implanted in the left atrium have been used to assess the effect of several drugs on left atrial pressure (Ishikawa *et al.* 2010; Suzuki, Fukushima, Ishikawa, Hamabe, Aytemiz, Huai-Che *et al.* 2011; Suzuki, Ishikawa, Hamabe, Aytemiz, Huai-Che, Fukushima *et al.* 2011; Suzuki *et al.* 2012). Drugs

with a beneficial effect in CHF would be expected to be associated with a reduction in left atrial pressure (LAP), which would be associated with a concomitant decrease in pulmonary vein hydrostatic pressure. In these experimental studies, increases in LAP were induced experimentally by transecting the *chordae tendinae*. Drugs were then administered whilst a telemetric device in the left atrium assessed the effect on LAP. Utilising this technology, furosemide (Suzuki, Ishikawa, Hamabe, Aytemiz, Huai-Che, Fukushima *et al.* 2011) and pimobendan (Suzuki, Fukushima, Ishikawa, Hamabe, Aytemiz, Huai-Che *et al.* 2011) were shown to exert a significant reduction in LAP in experimentally induced MMVD. In contrast, ACEIs were associated with a modest (Ishikawa *et al.* 2010) to no decrease in LAP (Suzuki *et al.* 2012).

Given the disparity in the results and inferences of experimental studies, veterinary practitioners are reliant on the outcome of clinical trials in natural disease settings to guide them in providing treatment recommendations to their clients.

Medical management of myxomatous mitral valve disease: An evidence-based approach

An ACE in the hole? The role of angiotensin-converting enzyme inhibitors in the management of myxomatous mitral valve disease

Angiotensin-converting enzyme inhibitors in the treatment of congestive heart failure

Angiotensin-converting enzyme inhibitors are the most intensively studied cardiac drugs in canine cardiology. The use of ACEI is rationalised based on the observation of the central role that the renin-angiotensin aldosterone-system (RAAS) plays in the pathogenesis of CHF (Benavente, Chue & Ferro 2010; Ma *et al.* 2010; Mochel *et al.* 2013). The RAAS system and its effects on blood pressure have been known since the 1940s, and the last 50 years have increased our understanding of the multiple deleterious effects of over-exuberant RAAS activation in CHF (for an excellent review see Ma *et al.* 2010). In addition to increasing the workload of the heart by increasing preload and afterload, angiotensin and aldosterone have been implicated in the development of fibrosis and hypertrophy of cardiac muscle (Bernay *et al.* 2010; Ma *et al.* 2010). Therefore, dysregulated RAAS activation further impairs the myocardium's ability to cope with the increased demands placed on the heart by volume retention, vasoconstriction and counterproductive remodelling of the myocardium. Given the elucidation of this elegant physiological system, ACEIs seem an extremely attractive option to attenuate the devastating effects of RAAS activation. Indeed, the development of ACEIs represents a triumph in the integration of physiological understanding of a disease process and the development of a drug to attenuate it.

There is often confusion amongst general practitioners regarding the use of ACEIs in MMVD. It would be naïve of the veterinary profession to ignore the input of marketing from drug companies that have developed these drugs on the prescribing practice within the profession. Therefore, practitioners are reliant on the evidence to support or refute the role of ACEIs in MMVD. There can be no doubt that the addition of an ACEI to diuretic therapy in CHF attributable to MMVD improves the quality of life and life expectancy of the patient. Both the IMPROVE (Sisson 1995) and the COVE (Woodfield 1995) studies demonstrated an improvement in the heart failure and pulmonary oedema scores compared with the placebo group. Both studies were double-blinded studies and neither the investigator nor the client knew which group the patient was in. The end point of both studies was under a month (21 and 28 days respectively) and therefore long-term tolerability was not demonstrable. Following these two landmark studies, three additional ACEI trials which investigated the effect of ACEI versus placebo on the survival of patients with CHF ensued. The LIVE study (Ettinger *et al.* 1998) demonstrated improved survival in the enalapril group (167 vs 87 days). This finding was supported by the BENCH study (BENCH Study Group 1999), which showed improved survival of patients being treated with benazepril versus placebo (436 vs 151 days). A notable difference between these two studies was that the BENCH study included patients from modified New York Heart Association (NYHA) stages 2 to 4, whilst the LIVE study included patients from NYHA stages 3 and 4. With the plethora of ACEIs on the market, which vary in price, it seems reasonable to assess possible differences in efficacy between currently available ACEIs. Veterinarians frequently ask the authors if there is a real difference between these drugs, given the cost sensitivity of some of their clients; so what does the evidence say?

There is only one RCT in veterinary medicine that compares ACEIs in MMVD. The FIRST study showed no difference in the outcome in MMVD in patients treated with enalapril versus imidapril over a 12-month period (Amberger *et al.* 2004). In addition, Hamlin and Nakayama (1998) assessed the pharmacokinetics of five common ACEIs in healthy beagles and showed that there were no significant differences between these drugs, with the exception of captopril. Therefore, from an EBM point of view, there is no imperative to support the use of one of the commonly used ACEIs in veterinary medicine, namely enalapril and benazepril, over the other. Notwithstanding this observation, it bears mentioning that there is considerable debate amongst clinicians regarding this issue, as many clinicians report improved outcome with benazepril as compared with enalapril. Whilst in the hierarchy of evidence this is considered weak evidence, the input and experience of clinicians cannot be ignored. In addition, studies in humans have shown that compliance decreases when medication requires administration more than once a day (Eisen, Miller & Woodward 1990). Therefore, an ACEI such as benazepril that is dosed once a day may improve compliance and therefore outcome in some cases. It is the authors' opinion that a RCT comparison of benazepril and enalapril within the setting of CHF in MMVD as part of a polypharmacy treatment regimen is warranted, given the aggressive marketing of benazepril in the profession.

Angiotensin-converting enzyme inhibitors in delaying the onset of congestive heart failure

The benefits of ACEIs in the treatment of CHF in MMVD are unassailable and supported by a number of high-quality studies. The same cannot be said for the role of ACEIs in delaying the onset of CHF in MMVD. It seems reasonable to speculate whether pharmacological interventions during the long preclinical period of MMVD may be of benefit to the patients. In the authors' referral clinic, many patients have been referred having being placed on an ACEI based on the presence of a murmur or a cough in a small-breed dog. Many veterinarians in the area still advocate the use of ACEIs in preclinical MR as a result of MMVD, and are adamant that these drugs are beneficial to their patients. Currently there is no express recommendation based on the literature available. It seems intuitively logical that accretion of RAAS peptides in worsening MMVD will reach a crucial tipping point beyond which CHF will ensue. Therefore, it seems logical that attenuation of RAAS will delay the onset of CHF in MMVD. This is the rationale behind the use of ACEIs in preclinical MMVD. Two large RCTs assessing the effect of enalapril versus placebo in delaying the onset of CHF, namely the SVEP (Kvart *et al.* 2002) and VETPROOF (Atkins *et al.* 2007) trials, failed to show a clear benefit of enalapril in delaying the onset of CHF. This evidence contradicts the findings of two retrospective trials assessing the effect of benazepril in preclinical MMVD (Kitagawa *et al.* 1997; Pouchelon *et al.* 2008). The trial by Pouchelon *et al.* (2008) showed an impressive delay in onset of CHF in the treatment group. In the hierarchy of evidence, this study is a lower grade of evidence, given the fact that it was not randomised, prospective and blinded. It is therefore prone to bias and there are no clear indications as to why some subjects were treated and others were not. The divisions ensuing are seen in the lack of consensus over this issue in the ACVIM consensus statement regarding the medical management of MMVD.

Pimobendan: The perfect inotrope?

Prior to the availability of pimobendan, digoxin was typically used to provide inotropic support to the heart. Triple therapy consisted of an ACEI, furosemide and digoxin. In the authors' area digoxin is still widely used in many practices because of the low cost of the drug. Pimobendan is a drug with a novel classification and its mechanism of action is understood to work by increasing the sensitivity of the myocardial contraction apparatus to calcium (Boswood 2010; Boyle & Leech 2012). This purportedly improves the efficiency of contraction without increasing myocardial workload, because it does not increase the cytoplasmic calcium flux. A large part of cardiac adenosine triphosphate (ATP) is devoted to removing calcium from the cytoplasm via the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA) pump (Klabunde 2011) and dysregulation of this mechanism has been implicated in the diastolic failure of the heart and indeed part of the whole cascade of myocardial failure (Sisson 2010). The fact that pimobendan has a dual action – it also functions as a phosphodiesterase (PDE) inhibitor – has been touted as an additional benefit, as PDE inactivates cyclic adenosine monophosphate (cAMP), which is involved in the up-regulation of proteins responsible for arterial vasodilation (Boyle & Leech 2012). Because PDE functions by increasing cAMP, which in turn activates calcium channels leading to an influx of calcium in the myocardium, there has been debate as to whether the effect is a result of increased calcium in the myocardium or calcium sensitisation. This may seem a superfluous academic distinction, but it is potentially of great importance. The accretion of cellular calcium is associated with several key signalling cascades linked to apoptosis and necrosis. Intracellular calcium would be expected to increase ATP turnover (increasing energy demands and generating free radicals), reduce the efficiency of lusitropy (the ability of the heart to relax) and activate apoptotic pathways (Klabunde 2011). Recently a consensus statement was released regarding the proposed mechanism of action of levosimendan, a drug similar to pimobendan, with the conclusion that the drug functions mainly by increasing the sensitivity of cardiac troponin C to calcium by stabilising the saturation of the receptor by calcium (Papp *et al.* 2012; Yokoshiki *et al.* 1997). In addition, some *in vitro* studies have demonstrated up-regulation of rescue pathways by levosimendan in the case of cardiac muscle ischaemia, inferring a cardiomyocyte protective role for the drug (for a review see Antoniades *et al.* 2007). Furthermore, pimobendan has been shown to enhance lusitropy in human hearts through the phosphorylation of phospholamban (Bartel *et al.* 1996).

Notwithstanding the elucidation of this elegant mechanism, the performance of the drug in the clinic is ultimately the true test of efficacy. One RCT comparing the addition of pimobendan versus benazepril in the treatment of MMVD has been performed (Häggström *et al.* 2008). In this study a clear benefit of pimobendan was seen when compared with benazepril. Pimobendan has also been shown to improve the outcome of dilated cardiomyopathy (DCM) when compared with ACEI therapy and has recently been shown to delay the onset of clinical DCM in the Dobermann Pinscher (Summerfield *et al.* 2012). One criticism of this RCT has been that monotherapy drug comparisons (i.e. benazepril and furosemide vs pimobendan and furosemide) cannot be extrapolated easily to the clinic, because most practitioners tend to treat with a polytherapy approach. It must be understood, however, that the results from studies are not always duplicated even between two studies with virtually identical study design, and that addition of therapeutic interventions causes additional variation that cannot be accounted for. It is difficult to design blinded trials that assess clinical adjustments, or take the 'best medicine' approach. It is for this reason that trials have compared drugs with disparate mechanisms of action such as an ACEI and pimobendan. Having established the benefit of the addition of these drugs in a RCT, combinations can be assessed in future trials. Therefore, whilst pimobendan has been shown to improve the outcome compared with an ACEI, the ACVIM consensus statement recommends treatment of CHF in MMVD with both drugs (Atkins *et al.* 2009; Atkins & Häggström 2012). A trial is currently underway assessing the efficacy of pimobendan in delaying the onset of CHF

in MMVD, the results of which are anticipated in 2017 (A. Boswood [Royal Veterinary College], pers. comm., 2011).

Spironolactone

In addition to the physiological effects of the RAAS system on fluid retention and vascular tone, angiotensin and aldosterone have been implicated in remodelling of cardiac muscle, leading to fibrosis (Ma *et al.* 2010). Therefore, RAAS attenuation can be seen to have a dual action, reducing the workload of the heart and causing the remodelling of the heart muscle which compromises contractile function. The homeostatic regulation of the RAAS is unfortunately not as simple as it was once thought to be. Angiotensin I can be converted to angiotensin II (AT II) by alternate pathways, and thus there is a RAAS 'escape' mechanism, referred to as tissue or local RAAS (Benavente *et al.* 2010). Studies have shown that AT II levels are not consistently supressed with ACEI therapy and that urinary aldosterone (uALD) levels are not reduced (Atkins *et al.* 2012). One pharmacokinetic study investigated benazepril in healthy beagles with experimental RAAS activation and demonstrated a decrease in plasma aldosterone but not uALD. The authors postulated that uALD may rise as a result of renal production of aldosterone, which does not enter circulation and therefore may be clinically less significant (Mochel *et al.* 2013).

These findings have occasioned the use of AT II receptor blockers and aldosterone antagonists to circumvent the deleterious effects of RAAS escape in human medicine. The RALES study (Pitt *et al.* 1999) in humans investigating the effects of the addition of spironolactone demonstrated a reduction in cardiac events when spironolactone was added to conventional therapy. These findings prompted a veterinary multicentre RCT assessing the addition of spironolactone to conventional therapy in CHF (Bernay *et al.* 2010). The findings of the study were impressive and a significant reduction in cardiac events was seen in the spironolactone group. Nevertheless, the findings of the study have not been universally accepted (see Kittleson & Bonagura 2010). Concerns have been raised regarding the study design of the project, based on the fact that the criteria for confirming heart failure were not clearly defined. It has been pointed out that the low numbers of patients that succumbed to heart failure or experienced events raises the concern that many of the patients were still in preclinical MMVD (Kittleson & Bonagura 2010). Therefore, the low number of events may have statistically skewed the results. The fact that the study made use of diverse researchers, from cardiologists to first opinion practices, has also been seen as a weakness in the study design (Kittleson & Bonagura 2010). These are all compelling arguments and it cannot be denied that the conclusions of a study are as strong as its design. Recently, Lefebvre *et al.* (2013) demonstrated the safety of spironolactone in the treatment of MMVD with early CHF. These authors showed that spironolactone was not associated with an increase in adverse events compared with placebo, and that there was a reduction in cardiac-related deaths in the spironolactone group. The study was randomised and controlled. The main objective of this study was to show that spironolactone is safe and not associated with increased risk of renal disease. Whilst the authors did show improved survival in the spironolactone group, more than half of the cases in both groups were censored, with no criteria given. This considerably reduced the sizes in which survival analysis could be performed. Thus the role of spironolactone remains controversial (Atkins *et al.* 2009; Atkins & Häggström 2012; Häggström, Höglund & Borgarelli 2009). The benefits described in human studies when added to the veterinary trial may be seen to bolster the findings of the spironolactone study somewhat, but in the hierarchy of evidence studies in other species are seen as a weaker grade of evidence.

Current guidelines for medical management of myxomatous mitral valve disease

Having understood the background of the drugs used in MMVD and the strengths and weaknesses of each, veterinarians will have a better understanding as to the intention of the ACVIM consensus statement and why there is incomplete consensus on some issues and not on others. The consensus statement regarding the medical management of MMVD has provided veterinary practitioners with a valuable resource to guide them in the optimisation of the treatment of MMVD (Atkins *et al.* 2009). In addition, this document has proposed a standardised grading system for CHF which stratifies the MMVD population according to the severity of disease. This grading system is shown below, and ranges from stage A to D (Atkins *et al.* 2009):

> **Stage A:** Predisposed to MMVD
> **Stage B:** Mitral leak present
> **B1:** No radiographic or echo evidence of remodelling
> **B2:** Radiographic or echo evidence of remodelling
> **Stage C:** CHF
> **Stage D:** CHF resistant to OPTIMUM care. (p. 1143)

The consensus document supports the use of pimobendan, ACEIs and furosemide in the treatment of stages C and D. In addition, there is some evidence to support the addition of spironolactone in stage C, but there was not complete consensus regarding this recommendation (Atkins *et al.* 2009). The use of ACEIs in preclinical heart disease (stages B1 and B2) remains controversial. The most high-powered studies to date exploring the use of ACEIs in preclinical MR, namely the SVEP trial (Kvart *et al.* 2002) and the VETPROOF study (Atkins *et al.* 2007), failed to support the use of enalapril in preclinical MR. Two additional studies investigating the use of benazepril in preclinical MR suggested an improved outcome in the treated group (Kitagawa *et al.* 1997; Pouchelon *et al.* 2008). However, these studies were un-blinded and not randomised and thus have been considered to be low-powered studies, warranting a prospective placebo-controlled trial to corroborate these findings.

Drugs that have been investigated recently but whose use remains unsupported include carvedilol (Gordon *et al.* 2012; Marcondes-Santos *et al.* 2007) and atorvastatin (Cunningham, Rush & Freeman 2013). These drugs have been shown to be

safe, but have not demonstrated any quantifiable beneficial results. Practitioners are cautioned against using medication for which good evidence does not exist, given the current cost of medication and the inclination of some clients to pursue legal action against medical professionals who do not subscribe to codes of practice.

Finally, mitral valve replacement is an exciting new area of investigation and some promising results have been observed (Uechi 2012). This remains an unattainable ideal for most practitioners and pet owners alike; however, as technology advances, these techniques will become increasingly available, and may revolutionise the way in which MMVD is managed.

Furosemide and newer loop diuretics

Intractable congestion and oedema is a common feature of clinically severe CHF as a result of MMVD (Häggström *et al.* 2009; Peddle *et al.* 2012). These haemodynamic consequences accrue as a result of volume retention and concomitant increases in capillary hydrostatic pressures (Klabunde 2011). The vascular beds of the lungs are particularly susceptible to increased hydrostatic pressure (Klabunde 2011). Drugs that are able to reduce the blood volume are therefore highly effective in reducing pulmonary congestion and oedema. Furosemide is a loop diuretic that inhibits the Na^+, K^+, Cl^- symporter in the ascending loop of Henle (Peddle *et al.* 2012). Furosemide is an efficient diuretic that is associated with predictable diuresis and is highly effective at treating the congestion associated with CHF (Peddle *et al.* 2012). There are surprisingly few trials investigating the efficacy of furosemide in the veterinary literature. A PubMed search failed to return any placebo-controlled RCTs on furosemide in dogs. Notwithstanding the paucity of literature supporting its use, it cannot be denied that furosemide is highly effective in ameliorating the clinical signs of congestion. A recent study investigated the use of torsemide (a loop diuretic), which was occasioned by the observation of superior efficacy in the treatment of human CHF compared with furosemide. The study showed that both these diuretics were effective in controlling congestion (Peddle *et al*. 2012).

Conclusion

The current body of evidence serves as a valuable guideline to guide veterinarians in the medical management of MMVD. Future research is needed to fully elucidate the role of spironolactone in the management of MMVD. Veterinarians should understand and apply EBM when making recommendations to clients in the treatment of MMVD.

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Competing interests

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Authors' contributions

R.K.B. (University of Pretoria) read the reference material and wrote the review. J.S. (University of Pretoria) read the reference material, collated key literature and envisioned the review, recognising the need for a paper to summarise and interpret the current literature.

References

Amberger, C., Chetboul, V., Bomassi, E., Rougier, S., Woehrlé, F. & Thoulon, F., 2004, 'Comparison of the effects of imidapril and enalapril in a prospective, multicentric randomized trial in dogs with naturally acquired heart failure', *Journal of Veterinary Cardiology* 6, 9–15. http://dx.doi.org/10.1016/S1760-2734(06)70053-4

Antoniades, C., Tousoulis, D., Koumallos, N., Marinou, K. & Stefanadis, C., 2007, 'Levosimendan: Beyond its simple inotropic effect in heart failure', *Pharmacology and Therapeutics* 114, 184–197. http://dx.doi.org/10.1016/j.pharmthera.2007.01.008

Atkins, C.E., Keene, B.W., Brown, W.A., Coats, J.R., Crawford, M.A., DeFrancesco, T.C. *et al*., 2007, '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', *Journal of the Veterinary Medical Association* 231, 1061–1069. http://dx.doi.org/10.2460/javma.231.7.1061

Atkins, C., Bonagura, J., Ettinger, S., Fox, P., Gordon, S., Häggstrom, J. *et al.*, 2009, 'Guidelines for the diagnosis and treatment of canine chronic valvular heart disease', *Journal of Veterinary Internal Medicine* 23, 1142–1150. http://dx.doi.org/10.1111/j.1939-1676.2009.0392.x

Atkins, C.E. & Häggström, J., 2012, 'Pharmacologic management of myxomatous mitral valve disease in dogs', *Journal of Veterinary Cardiology* 14, 165–184. http://dx.doi.org/10.1016/j.jvc.2012.02.002

Atkins, C.E., Lantis, A.C., Ames, M.K. & Gardner, S.Y., 2012, 'Utility of urinary aldosterone measurement in quantitating RAAS activation', *Journal of Veterinary Pharmacology and Therapeutics* 35, 512–515. http://dx.doi.org/10.1111/jvp.12011

Bartel, S., Stein, B., Eschenhagen, T., Mende, U., Neumann, J., Schmitz, W. *et al.*, 1996, 'Protein phosphorylation in isolated trabeculae from nonfailing and failing human hearts', *Molecular and Cellular Biochemistry* 157, 171–179. http://dx.doi.org/10.1007/BF00227896

Benavente, D., Chue, C.D. & Ferro, C.J., 2010, 'The importance of renin-angiotensin blockade in patients with cardio-renal disease', *Journal of Renal Care* 36, 97–105. http://dx.doi.org/10.1111/j.1755-6686.2010.00166.x

BENCH Study Group, 1999, 'The effect of benazepril on survival times and clinical signs of dogs with congestive heart failure: Results of a multicenter, prospective, randomized, double-blinded, placebo-controlled, long-term clinical trial', *Journal of Veterinary Cardiology* 1, 7–18. http://dx.doi.org/10.1016/S1760-2734(06)70025-X

Bernay, F., Bland, J.M., Häggström, J., Baduel, L., Combes, B., Lopez, A. *et al.*, 2010, 'Efficacy of spironolactone on survival in dogs with naturally occurring mitral regurgitation caused by myxomatous mitral valve disease', *Journal of Veterinary Internal Medicine* 24, 331–341. http://dx.doi.org/10.1111/j.1939-1676.2009.0467.x

Bonagura, J.D. & Schober, K.E., 2009, 'Can ventricular function be assessed by echocardiography in chronic canine mitral valve disease?', *Journal of Small Animal Practice* 50, 12–24. http://dx.doi.org/10.1111/j.1748-5827.2009.00803.x

Borgarelli, M., Crosara, S., Lamb, K., Savarino, P., La Rosa, G., Tarducci, A. *et al*., 2012, 'Survival characteristics and prognostic variables of dogs with preclinical chronic degenerative mitral valve disease attributable to myxomatous degeneration', *Journal of Veterinary Internal Medicine* 26, 69–75. http://dx.doi.org/10.1111/j.1939-1676.2011.00860.x

Boswood, A., 2010, 'Current use of pimobendan in canine patients with heart disease', *Veterinary Clinics of North America: Small Animal Practice* 40, 571–580. http://dx.doi.org/10.1016/j.cvsm.2010.04.003

Boyle, K.L. & Leech, E., 2012, 'A review of the pharmacology and clinical uses of pimobendan', *Journal of Veterinary Emergency and Critical Care* 22, 398–408. http://dx.doi.org/10.1111/j.1476-4431.2012.00768.x

Chetboul, V., Lefebvre, H.P., Sampedrano, C.C., Gouni, V., Saponaro, V., Serres, F. *et al.*, 2007, 'Comparative adverse cardiac effects of pimobendan and benazepril monotherapy in dogs with mild degenerative mitral valve disease: A prospective, controlled, blinded, and randomized study', *Journal of Veterinary Internal Medicine* 21, 742–753. http://dx.doi.org/10.1111/j.1939-1676.2007.tb03016.x

Cockcroft, P.O. & Holmes, M.A., 2003, *Handbook of evidence-based veterinary medicine,* Blackwell, Oxford. http://dx.doi.org/10.1002/9780470690833

Corcoran, B., Culshaw, G., Dukes-McEwan, J., French, A., Smith, S. & Swift, S., 2008, 'Concerns about "Comparative adverse cardiac effects of pimobendan and benazepril monotherapy in dogs with mild degenerative mitral valve disease"', *Journal of Veterinary Internal Medicine* 22, 243. http://dx.doi.org/10.1111/j.1939-1676.2008.0070.x

Cunningham, S.M., Rush, J.E. & Freeman, L.M., 2013, 'Short-term effects of atorvastatin in normal dogs and dogs with congestive heart failure due to myxomatous mitral valve disease', *Journal of Veterinary Internal Medicine* 27, 985–989. http://dx.doi.org/10.1111/jvim.12123

Eisen, S.A., Miller, D.K. & Woodward, R.S., 1990, 'The effect of prescribed daily dosing frequency on patient medication compliance', *Archives of Internal Medicine* 150, 1181–1183. http://dx.doi.org/10.1001/archinte.1990.00390200073014

Ettinger, S.J., Benitz, A.M., Ericsson, G.F., Cifelli, S., Jernigan, A.D., Longhofer, S.L. *et al.*, 1998, 'Effects of enalapril maleate on survival of dogs with naturally acquired heart failure: The long-term investigation of veterinary enalapril (LIVE) study group', *Journal of the American Veterinary Association* 213, 1573–1577.

Geyman, J.P., 2000, 'Evidence-based medicine in primary care: An overview', in J.P. Geyman, R.A. Deyo & S.O. Ramsey (eds.), *Evidence based clinical practice: Concepts and approaches*, pp. 1–11, Butterworth-Heinemann, Boston.

Gordon, S.G., Saunders, A.B., Hariu, C.D., Boggess, M.M. & Miller, M.W., 2012, 'Retrospective review of carvedilol administration in 38 dogs with preclinical chronic valvular heart disease', *Journal of Veterinary Cardiology* 14, 243–252. http://dx.doi.org/10.1016/j.jvc.2012.01.007

Häggström, J., Boswood, A., O'Grady, M., Jöns, O., Smith, S., Swift, S. *et al.*, 2008, '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', *Journal of Veterinary Internal Medicine* 22, 1124–1135. http://dx.doi.org/10.1111/j.1939-1676.2008.0150.x

Häggström, J., Höglund, K. & Borgarelli, M., 2009, 'An update on treatment and prognostic indicators in canine myxomatous mitral valve disease', *Journal of Small Animal Practice* 50, 25–33. http://dx.doi.org/10.1111/j.1748-5827.2009.00800.x

Hamlin, R.L. & Nakayama, T., 1998, 'Comparison of some pharmacokinetic parameters of 5 angiotensin-converting enzyme inhibitors in normal beagles', *Journal of Veterinary Internal Medicine* 12, 93–95. http://dx.doi.org/10.1111/j.1939-1676.1998.tb02101.x

Hjørland, B., 2011, 'Evidence-based practice: An analysis based on the philosophy of science', *Journal of the American Society for Information Science and Technology* 62, 1301–1310. http://dx.doi.org/10.1002/asi.21523

Ishikawa, T., Tanaka, R., Suzuki, S., Miyaishi, Y., Akagi, H., Iino, Y. *et al.*, 2010, 'The effect of angiotensin-converting enzyme inhibitors of left atrial pressure in dogs with mitral valve regurgitation', *Journal of Veterinary Internal Medicine* 24, 342–347. http://dx.doi.org/10.1111/j.1939-1676.2009.0455.x

Kanno, N., Kuse, H., Kawasaki, M., Hara, A., Kano, R. & Sasaki, Y., 2007, 'Effects of pimobendan for mitral valve regurgitation in dogs', *Journal of Veterinary Medical Science* 69, 373–377. http://dx.doi.org/10.1292/jvms.69.373

Kitagawa, H., Wakamiya, H., Kitoh, K., Kuwahara, Y., Ohbha, Y., Isaji, M. *et al.*, 1997, 'Efficacy of monotherapy with benazepril, an angiotensin converting enzyme inhibitor, in dogs with naturally acquired chronic mitral insufficiency', *Journal of Veterinary Medical Science* 59, 513–520. http://dx.doi.org/10.1292/jvms.59.513

Kittleson, M.D. & Bonagura, J.D., 2010, 'Letter to the editor', *Journal of Veterinary Internal Medicine* 24, 1245–1246. http://dx.doi.org/10.1111/j.1939-1676.2010.0622.x

Klabunde, R., 2011, *Cardiovascular physiology concepts*, Lippincott Williams and Wilkins, Philadelphia.

Kvart, C., Häggström, J., Pedersen, H.D., Hansson, K., Eriksson, A., Järvinen, A. *et al.*, 2002, 'Efficacy of enalapril for prevention of congestive heart failure in dogs with myxomatous valve disease and asymptomatic mitral regurgitation', *Journal of Veterinary Internal Medicine* 16, 80–88. http://dx.doi.org/10.1111/j.1939-1676.2002.tb01610.x

Lefebvre, H.P., Ollivier, E., Atkins, C.E., Combes, B., Concordet, D., Kaltsatos, V. *et al.*, 2013, 'Safety of spironolactone in dogs with chronic heart failure because of degenerative valvular disease: A population-based, longitudinal study', *Journal of Veterinary Internal Medicine*. http://dx.doi.org/10.1111/jvim.12141

Ma, T.K., Kam, K.K., Yan, B.P. & Lam, Y.Y., 2010, 'Renin-angiotensin-aldosterone system blockade for cardiovascular diseases: Current status', *British Journal of Pharmacology* 160, 1273–1292. http://dx.doi.org/10.1111/j.1476-5381.2010.00750.x

Marcondes-Santos, M., Tarasoutchi, F., Mansur, A.P. & Strunz, C.M., 2007, 'Effects of carvedilol treatment in dogs with chronic mitral valvular disease', *Journal of Veterinary Internal Medicine* 21, 996–1001. http://dx.doi.org/10.1111/j.1939-1676.2007.tb03055.x

Mochel, J.P., Peyrou, M., Fink, M., Strehlau, G., Mohamed, R., Giraudel, J.M. *et al.*, 2013, 'Capturing the dynamics of systemic renin-angiotensin-aldosterone system (RAAS) peptides heightens the understanding of the effect of benazepril in dogs', *Journal of Veterinary Pharmacological Therapy* 36, 174–180. http://dx.doi.org/10.1111/j.1365-2885.2012.01406.x

Ouellet, M., Bélanger, M.C., Difruscia, R. & Beauchamp, G., 2009, 'Effect of pimobendan on echocardiographic values in dogs with asymptomatic mitral valve disease', *Journal of Veterinary Internal Medicine* 23, 258–263. http://dx.doi.org/10.1111/j.1939-1676.2008.0239.x

Papp, Z., Édes, I., Fruhwald, S., De Hert, S.G., Salmenperä, M., Leppikangas, H. *et al.*, 2012, 'Levosimendan: Molecular mechanisms and clinical implications: Consensus of experts on the mechanisms of action of levosimendan', *International Journal of Cardiology* 159, 82–87. http://dx.doi.org/10.1016/j.ijcard.2011.07.022

Peddle, G.D., Singletary, G.E., Reynolds, C.A., Trafny, D.J., Machen, M.C. & Oyama, M.A., 2012, 'Effect of torsemide and furosemide on clinical, laboratory, radiographic and quality of life variables in dogs with heart failure secondary to mitral valve disease', *Journal of Veterinary Cardiology* 14, 253–259. http://dx.doi.org/10.1016/j.jvc.2012.01.003

Pitt. B., Zannad, F., Remme, W.J., Cody, R., Castaigne, A., Perez, A. *et al.*, 1999, 'The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators', *New England Journal of Medicine* 341, 709–717. http://dx.doi.org/10.1056/NEJM199909023411001

Popper, K., 1963, *Conjectures and refutations,* Routledge & Keagan Paul, London.

Pouchelon, J., Jamet, N., Gouni, V., Tissier, R., Serres, F., Sampedrano, C. *et al.*, 2008, 'Effect of benazepril on survival and cardiac events in dogs with asymptomatic mitral valve disease: A retrospective study of 141 cases', *Journal of Veterinary Internal Medicine* 22, 905–914. http://dx.doi.org/10.1111/j.1939-1676.2008.0105.x

Sackett, D.L., Straus, S.E. & Richardson, W.S., 2000, 'Introduction', in D.L. Sackett, S.E. Straus, W.S. Richardson, W. Rosenberg & R.B. Haynes (eds.), *Evidence-based medicine: How to practice and teach EBM*, 2nd edn., pp. 1–12, Churchill-Livingstone, Philadelphia.

Sisson, D.D., 1995, 'Acute and short-term hemodynamic, echocardiography, and clinical effects of enalapril mealeate in dogs with naturally acquired heart failure: Results of the invasive multicenter prospective veterinary evaluation of enalapril study: The IMPROVE study group', *Journal of Veterinary Internal Medicine* 4, 234–242. http://dx.doi.org/10.1111/j.1939-1676.1995.tb01074.x

Sisson, D.D., 2010, 'Pathophysiology of heart failure', in S.J. Ettinger & C. Feldman (eds.), *Textbook of veterinary internal medicine*, pp. 1143–1158, Elsevier Health Sciences, New York.

Summerfield, N.J., Boswood, A., O'Grady, M.R., Gordon, S.G., Dukes-McEwan, J., Oyama, M.A. *et al.*, 2012, 'Efficacy of pimobendan in the prevention of congestive heart failure or sudden death in Doberman pinschers with preclinical dilated cardiomyopathy (the PROTECT Study)', *Journal of Veterinary Internal Medicine* 26, 1337–1349. http://dx.doi.org/10.1111/j.1939-1676.2012.01026.x

Suzuki, S., Fukushima, R., Ishikawa, T., Hamabe, L., Aytemiz, D., Huai-Che, H. *et al.*, 2011, 'The effect of pimobendan on left atrial pressure in dogs with mitral valve regurgitation', *Journal of Veterinary Internal Medicine* 25, 1328–1333. http://dx.doi.org/10.1111/j.1939-1676.2011.00800.x

Suzuki, S., Ishikawa, T., Hamabe, L., Aytemiz, D., Huai-Che, H., Fukushima, R. *et al.*, 2011, 'The effect of furosemide on left atrial pressure in dogs with mitral valve regurgitation', *Journal of Veterinary Internal Medicine* 25, 244–250. http://dx.doi.org/10.1111/j.1939-1676.2010.0672.x

Suzuki, S., Fukushima, R., Ishikawa, T., Yamamoto, Y., Hamabe, L., Kim, S. *et al.*, 2012, 'Comparative effects of amlodipine and benazepril on left atrial pressure in dogs with experimentally-induced mitral valve regurgitation', *BMC Veterinary Research* 8, 166. http://dx.doi.org/10.1186/1746-6148-8-166

Uechi, M., 2012, 'Mitral valve repair in dogs', *Journal of Veterinary Cardiology* 14, 185–192. http://dx.doi.org/10.1016/j.jvc.2012.01.004

Woodfield, J.A., 1995, 'Controlled clinical evaluation of enalapril in dogs with heart failure: Results of the cooperative veterinary enalapril study group (the COVE study group)', *Journal of Veterinary Internal Medicine* 9, 243–252. http://dx.doi.org/10.1111/j.1939-1676.1995.tb01075.x

Yokoshiki, H., Katsube, Y., Sunagawa, M. & Sperelakis, N., 1997, 'Levosimendan, a novel Ca2+ sensitizer, activates the glibenclamide-sensitive K+ channel in rat arterial myocytes', *European Journal of Pharmacology* 333, 249–259. http://dx.doi.org/10.1016/S0014-2999(97)01108-4