Benazepril - Spironolactone

10 years of research

What’s new with aldosterone?

The story of spironolactone in human and veterinary cardiology
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<th>Description</th>
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<tr>
<td>ACEi</td>
<td>Angiotensin-converting enzyme inhibitors</td>
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<tr>
<td>ACVIM</td>
<td>American College of Veterinary Internal Medicine</td>
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<tr>
<td>AE</td>
<td>Adverse events</td>
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<td>ARB</td>
<td>Angiotensin receptor blocker</td>
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<td>CHF</td>
<td>Congestive heart failure</td>
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<td>cTnI</td>
<td>Cardiac troponin I</td>
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<tr>
<td>ECVIM</td>
<td>European College of Veterinary Internal Medicine</td>
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<td>ESC</td>
<td>European Society of Cardiology</td>
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<tr>
<td>HF</td>
<td>Heart failure</td>
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<tr>
<td>ISACHC</td>
<td>International Small Animal Cardiac Health Council</td>
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<tr>
<td>LA/Ao</td>
<td>Left atrium to aorta ratio</td>
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<tr>
<td>LV</td>
<td>Left ventricular</td>
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<tr>
<td>LVEDDN</td>
<td>Normalised left ventricular end diastolic diameter</td>
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<tr>
<td>MMVD</td>
<td>Myxomatous mitral valve disease</td>
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<tr>
<td>MR</td>
<td>Mitral regurgitation</td>
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<tr>
<td>MRA</td>
<td>Mineralocorticoid receptor antagonist</td>
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<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
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<tr>
<td>NT-proBNP</td>
<td>N-terminal pro-brain natriuretic peptide</td>
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<tr>
<td>PO</td>
<td>Per os</td>
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<tr>
<td>QOL</td>
<td>Quality of life</td>
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<tr>
<td>RAAS</td>
<td>Renin-angiotensin-aldosterone system</td>
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<tr>
<td>SID</td>
<td>Once a day</td>
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<tr>
<td>UAldo:C</td>
<td>Urinary aldosterone to creatinine ratio</td>
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Introduction

10 years ago, Ceva initiated the European procedure for the registration of spironolactone as a veterinary pharmaceutical. Spironolactone, a mineralocorticoid receptor antagonist (MRA), was a brand new active in the veterinary therapeutic arsenal.

Looking back on the history of veterinary cardiology, 4 major steps can be identified:

- 1970s: treatments based solely on digoxin and loop diuretics.
- 1990s: introduction of ACE inhibitors.
- 2007: launch of PRILACTONE®, first veterinary spironolactone, followed in 2012 by the launch of CARDALIS®, which combined benazepril and spironolactone for greater efficacy and compliance.

Since then, no new therapeutic class has been added to the veterinary arsenal.

Registration of PRILACTONE® (spironolactone) was the result of years of research at Ceva, a long history that began in 1999, just after the publication of the RALES study.

In this groundbreaking study, Bertram Pitt and Faiez Zannad revolutionised the treatment of heart failure in human patients by demonstrating the benefits of adding spironolactone to conventional therapy (Pitt et al., 1999). Historically, spironolactone was classified as a “potassium-sparing diuretic”. However, the positive effect observed in the RALES study could not be explained by the diuretic effect of the drug alone. Instead it was proven that spironolactone provided great benefit by blocking the neurohormonal response to heart failure.

Having in mind the One Health concept, Ceva undertook research that demonstrated similar results with spironolactone in dogs suffering from heart failure, caused by MMVD in the Bernay study.

This 10th anniversary is an appropriate time to look back on the exciting story of spironolactone in human and veterinary cardiology, and how it became an essential part of the management of cardiac diseases.

History is still being written today, as Ceva pursues its research on the combination of benazepril and spironolactone, to give greater convenience, enhance compliance and to improve quality of life and survival in dogs with heart failure.

In this document, we would like to share with you the latest findings and the major milestones on the fascinating subject of aldosterone and the comprehensive RAAS blockade, both in the veterinary and human fields.

Ceva Cardio-Nephrology team
Preface

In the 1980’s, pharmacological blockade of the renin-angiotensin-aldosterone-system (RAAS) came with great promise to the veterinary profession. But with the angiotensin converting enzyme inhibitors (ACEi), also came the belief that the ACEi’s major function was vasodilation and, with that, came concerns for renal safety, both of which proved to be largely unfounded. We now know that the ACEi are more important for their blunting of the neurohormonal (RAAS and sympathetic nervous system [SNS]) adaptations to cardiac disease and failure, the major driving force behind disease progression, than simply, their vasodilatory characteristics. Furthermore, ACEi are today known to be not only safe in the presence of kidney disease, but have become important therapeutic agents in the management of proteinuric renal disease.

At that time, spironolactone was considered an unimportant, antiquated, and weak diuretic, with possible utility in multi-diuretic, multicentric nephron targeting to enhance diuresis and for use in circumstances where hypokalaemia was problematic. This too turned out to be an untruth. Today spironolactone and similar drugs are considered a major component in the pharmacological arsenal for treating heart failure.

We have learned only in recent years that, while the ACEi have been shown over and over to be effective in treating cardiac disease, hypertension and proteinuric renal disease in both man and animals, their true potential has not been reached. The upside to this is that this drug class can be rendered even more effective, if accompanied by a drug such as spironolactone. This is because, for reasons not fully understood, ACEi may not remain effective in all patients, leading to a recrudescence of aldosterone secretion, with its harmful effects, termed “aldosterone breakthrough” (ABT). This concept was brought to the forefront in the “practice-changing” RALES study (Pitt et al., 1999), which demonstrated that the aldosterone or mineralocorticoid receptor antagonist (MRA), spironolactone, provided substantial survival benefit, when added to standard therapy for the treatment of human heart failure patients. The RALES study was “duplicated” in a placebo-controlled, double-blind trial in dogs with heart failure, published in the Journal of Veterinary Internal Medicine in 2010 (Bernay et al., 2010). A safety study, using the same dogs, showed that spironolactone (PRILACTONE®) was not only safe, but provided a superior safety profile to that experienced in the placebo group (standard therapy plus placebo) (Lefebvre et al., 2013).

Our laboratory has carried out a number of experimental and clinical studies, documenting and evaluating canine ABT. We have shown that it occurs in 30-50% of clinical canine patients, receiving ACEi, and from our experimental model, it appears that it often occurs very early in the course of therapy (Lantis et al., 2015 a&b). From these data, we conclude that spironolactone is required in a substantial number of dogs, treated with an ACEi. In fact, the percentage of dogs experiencing ABT and our observation of early onset ABT, has led us to conclude that, in lieu of specific testing of RAAS-activation, an MRA (spironolactone) is indicated whenever an ACEi is prescribed. This need is conveniently filled by the combination of spironolactone and benazepril, which has been approved in the E.U., since 2012 as CARDALIS®. These two agents are particularly suited for use in combination because: both have a wide margin of safety, so if necessity dictates increasing the dosage of benazepril, one is highly unlikely to experience problems with spironolactone over-dosing; spironolactone works as a preemptory “bandage” to ABT, being in place in the combination product, no matter how early or late ABT occurs; and lastly, there is great experience of these agents being used concurrently, with prospective blinded studies showing an actual benefit in the safety profile, as compared to placebo plus standard therapy.

Clarke Atkins

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WHAT’S NEW WITH ALDOSTERONE?

New data on aldosterone breakthrough in dogs and in humans

The harmful effects of the renin-angiotensin-aldosterone system (RAAS) activation are evident in veterinary cardio-renal patients. ACE inhibitors (ACEi) are beneficial in dogs with chronic heart failure, improving haemodynamics, clinical signs and survival. However, neither angiotensin nor aldosterone are consistently suppressed by ACEi, as was shown in 1996 by Häggström and coworkers, who reported what we now know as aldosterone breakthrough, after 6 months of enalapril treatment (Häggström et al., 1996). Aldosterone breakthrough (also termed aldosterone escape) is the failure of ACEi to continue adequate long-term suppression of RAAS, with the ultimate breakthrough of aldosterone, a highly “toxic” compound for the heart, vessels and kidneys, when secreted chronically at high levels.

The very recent work of Lantis et al. (2014) and Ames et al. (2015) completely changes this vision of aldosterone breakthrough. In fact, breakthrough can be identified in many patients as soon as an ACEi is initiated, thus much sooner than previously suspected.

This leads Marisa Ames to state that: “It may then be that [...] a MRA is indicated whenever an ACEi is initiated.” (Ames, 2016)

The same authors (Lantis et al., 2015 a&b; Ames et al., 2015) also demonstrated that doubling the dosage of benazepril and enalapril does not prevent furosemide-induced RAAS activation even though plasma ACE activity was diminished, suggesting that higher ACEi dosages will unlikely eradicate aldosterone breakthrough.

In humans, equal rates of breakthrough are observed among subjects treated on ACEis, ARBs, or a combination of the two. Patients who show aldosterone breakthrough have a worse clinical prognosis than those who do not (Schrier, 2010). As per the definition of aldosterone breakthrough, these patients show plasma elevated aldosterone levels, despite therapy.
Similarly, in dogs with mitral valve disease, serum aldosterone levels and urinary aldosterone-to-creatinine concentration ratio (UAldo:C) increase during ventricular remodeling, and UAldo:C appears to be negatively associated with survival (Hezzell et al., 2010; Hezzell et al., 2012a).

New clinical results in humans

Results of the EMPHASIS-HF clinical trial were recently published by Zannad et al. (2011).

This study evaluates the effect of eplerenone* in patients with mild symptoms (NYHA class II heart failure) (McMurray 2011). It is the logical extension of the pioneering RALES trial on patients with severe heart failure (see pp. 12) (Pitt et al., 1999).

*Eplerenone is an MRA that lacks the hormonal adverse effects (e.g. gynecomastia) associated with spironolactone in humans but not in dogs.

Main results of the study

The addition of the MRA eplerenone to recommended medical therapy, including ACEi, in patients with systolic heart failure and mild symptoms (NYHA class II heart failure) reduces mortality (relative risk reduction in death of 24%) and morbidity (relative risk reduction in events, cardiovascular death or hospitalisation for heart failure of 37%).

Together, the RALES and EMPHASIS-HF trials clearly demonstrate that the combination of MRAs with ACEis reduces mortality and morbidity in people, irrespective of the severity of heart failure and regardless of aldosterone concentration (Guglin et al., 2011).

Major consequences

In the words of the Heart Failure Society of America Guidelines Committee, “The efficacy of eplerenone in patients with mild heart failure symptoms translates into a unique opportunity to reduce morbidity and mortality earlier in the course of the disease”. (Funder, 2013)

Right after the publication of this groundbreaking trial, the ESC (European Society of Cardiology) amended the guidelines to take these results into account: an ACEi, a beta-blocker, and an MRA should at least be considered in every human patient with systolic HF.

In these guidelines, ARBs are recommended only as an alternative in human patients who cannot tolerate ACEi (ESC Guidelines, 2012).
WHAT’S NEW WITH SPIRONOLACTONE IN CANINE CARDIOLOGY?

A recent paper describes safety of spironolactone in dogs suffering from MMVD and HF and treated with conventional therapy including an ACEi and furosemide, evaluated in the clinical field study (Lefebvre et al., 2013). The median duration of treatment was 217 days.

**Main results of the study**

- Spironolactone, given in addition to an ACEi did not alter serum variables (creatinine, urea, potassium, or sodium levels). The risk of renal dysfunction or hyperkalaemia was similar in both groups. This is in agreement with plasma/serum sodium and potassium concentrations, recorded in healthy dogs and dogs with MMVD, without congestive HF (CHF) or azotaemia, and treated with spironolactone (Elliott et al., 2009; Thomason et al., 2007; Coussanes et al., 2012).

- No difference in the number of adverse events (AE) was observed between treatment groups.

- The percentage of cardiac, renal, or cardio-renal deaths was actually significantly higher in the placebo versus the spironolactone group (30.7% versus 13.7%, p=0.0043; see figure 2).

**Major conclusions**

In conclusion, long-term treatment with spironolactone (at 2 mg/kg once daily), in addition to an ACEi, is well tolerated in dogs with chronic HF. Treated dogs are not at greater risk of AEs, hyperkalaemia, azotaemia, or death due to cardiac disease, renal disease or both.

The addition of spironolactone to ACEi treatment significantly reduced the number of deaths caused by cardiac disease, renal disease, or both.

**Figure 2.** Kaplan-Meier survival curves for MMVD dogs randomised to receive spironolactone or placebo in addition to conventional therapy (including at least an ACEi). The endpoint was death (spontaneous or euthanasia) due to cardiac/renal causes (Lefebvre et al., 2013).
Pilot study on asymptomatic dogs

To date, no drug has been proven adequately effective in delaying the onset of clinical signs in asymptomatic MMVD. Therapies aimed at the asymptomatic stage of MMVD have incredible potential, but success in discovery and proving efficacy has been elusive. Indeed, at this stage, a dog can live a normal life with its owners, without showing clinical signs for years. However, once HF develops, quality of life for the family decreases with the advent of exercise intolerance, fatigue, and respiratory difficulties for the pet, and hospital visits, medicating and financial outlay for the owner. Duration of life is reduced at this point, varying from acute death at the first onset of CHF to survival for several years. With adequate therapy, the average dog with HF due to MMVD survives approximately a year. Therefore, drugs extending the length of the asymptomatic stage could increase lifespan while maintaining quality of life.

The rationale for investigating the effect of spironolactone on the asymptomatic stage of MMVD is linked to its action on the RAAS, which is activated as cardiac disease progresses. Preliminary data showed that plasma aldosterone levels are significantly elevated in asymptomatic dogs with MMVD, as compared with healthy dogs (Borgarelli, 2011). Chronic RAAS activation, particularly aldosterone production, has been shown in many human and animal studies to be harmful to the cardiovascular and renal systems. Taking these data together, the indication is that RAAS activation early in MMVD plays a role in its progression.

A pilot study of spironolactone in dogs with compensated MMVD by Dr. Hezzell and co-workers at the Royal Veterinary College provided promising results, encouraging further investigation (Hezzell et al., 2012b). Furthermore, these investigators demonstrated that the increase in urinary aldosterone concentration in affected dogs was associated with a poorer outcome, similar to the findings in human studies (Hezzell et al., 2010).

Objective and study design

The study evaluated the effect of spironolactone in dogs with compensated MMVD with one or more risk factors (enlargement of LA/Ao and LVEDDN, and elevation of serum NT-proBNP and cTnI concentrations), all of which are associated with decreased survival times. The goal was to determine whether spironolactone reduced the rate of cardiac remodelling, associated with progressive MMVD.

Dogs with ACVIM stage B MMVD, which had not received medication for cardiac disease, were recruited in a randomised, blinded, placebo-controlled pilot study. Twenty dogs of various breeds were enrolled and randomised to receive either spironolactone (2 mg/kg, p.o., n=10) or placebo (n=10) SID for 6 months. Of the risk factors mentioned above, 10 dogs exhibited 3, 7 dogs exhibited 2, and 3 dogs had 1 risk factor.

Main results of the study

The most reliable cardiac biomarker (NT-proBNP) and echocardiographic parameters (LA/Ao and LVEDDN), used to follow progression of cardiac disease, significantly increased over time in the placebo group, but not in the spironolactone group.

Major conclusions of the study

Treatment with spironolactone slowed the rate of increase in cardiac size, as evaluated echocardiographically, in dogs with ACVIM stage B MMVD presenting risk factors for poor outcome.

Decreasing the rate of cardiac enlargement (remodeling) might delay the onset of CHF. Further studies are needed to investigate this hypothesis.

PUBLICATION OF INTEREST 4

Hezzell M.J., Boswood A., Elliott J.
Treatment of Dogs with Compensated Degenerative Mitral Valve Disease (DMVD) with Spironolactone.
Oral Research communication of the 22nd ECVIM-CA Congress, Maastricht. Journal of Veterinary Internal Medicine, 2012;26:1517.
DELAY: a large scale study on asymptomatic dogs

A clinical trial, the DELAY Study ("DElay the Appearance of sYmptoms of canine degenerative mitral valve disease") is ongoing in Europe. The goal of the DELAY study is to assess the benefit of spironolactone, given in combination with benazepril, at the asymptomatic stage (ACVIM stage B2*).

The Italian Scientific Committee for the DELAY study is led by Michele Borgarelli, DVM, PhD, Dipl.ECVIM-CA (Cardiology), of Virginia Polytechnic Institute and State University, in the USA. The DELAY study involves 17 centres in Italy, 4 in the UK and 1 in the Netherlands, with a population of more than 180 dogs included. Dogs are being followed for up to 3.5 years. First results are expected in 2018.

This study is one of the largest clinical trials conducted focusing on the asymptomatic stage of MMVD.

*ACVIM stage B2 (i.e., enlarged heart but no clinical signs caused by heart failure).
In order to fill the spironolactone knowledge gap in cats, a pilot study was conducted in the UK between 2010 and 2014 in cats with CHF secondary to cardiomyopathy (hypertrophic cardiomyopathy being the most common*).

The SEISICAT (Safety and Efficacy Investigation of Spironolactone In CATs) study explored the safety and efficacy of adding spironolactone to conventional treatment with furosemide and an ACEi.

**Study design**

Dr. James and coworkers, at the University of Nottingham, led this double-blind, randomised, prospective, placebo-controlled, multicentre clinical study. Twenty cats with cardiomyopathy* were randomised to receive either spironolactone (n=11) at a dose between 1.72 to 3.33 mg/kg/day or placebo (n=9) for up to 15 months.

The primary endpoint used to assess the efficacy of adding spironolactone to furosemide and benazepril was cardiac mortality, defined as spontaneous death or euthanasia due to cardiac cause.

Mandatory concomitant treatments were furosemide and an ACEi (benazepril), while the administration of pimobendan, aspirin, and anti-arrhythmic medication, such as diltiazem, digoxin, lidocaine, beta blockers, was not allowed.

**Interim safety results** were presented at the ACVIM Congress in 2013 (James et al., 2013). No ulcerative facial dermatitis was observed in these 20 cats contrary to results previously reported, using a dosage of 4 mg/kg/day (MacDonald et al., 2008).

Results for the primary endpoint were pending.

Spironolactone was found to be well tolerated in cats with heart failure secondary to cardiomyopathy.

**PUBLICATION OF INTEREST 6**

James R.A., Guillot E., Gilmour J., Cobb M.

Efficacy of Spironolactone (SP) Following Oral Administration of SP in Cats with Heart Failure: Final Results of the SEISICAT Study.


The final efficacy results were presented at the ECVIM Congress in 2015 (James et al., 2015). A significant difference was observed between the groups in:

- Survival rate at 15 months (end of follow-up): 78% in the spironolactone group versus 12% in the placebo group (p=0.011).
- An 84% reduction in the risk of cardiac death was observed in cats treated with spironolactone.

Although this was a pilot study with a small number of cats, the data strongly suggest that spironolactone is beneficial in the treatment of cats with CHF secondary to a cardiomyopathy*, when added to standard therapy with benazepril and furosemide.

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*Types of cardiomyopathy (number of cats): hypertrophic (n=15), dilated (n=2), unclassified (n=2) and arrhythmogenic right ventricular (n=1).
ACEi were first used to treat human heart failure in the late 1980s, largely in response to the findings of the CONSENSUS and SOLVD trials (CONSENSUS 1987, Domanski et al., 2003). Thereafter it was recognised that neither angiotensin II nor aldosterone were fully suppressed by ACEi, termed aldosterone breakthrough. Consequently, this concept led to the exploration of whether adding spironolactone to an ACEi in human heart failure would produce benefits.

Aldosterone blockade was then shown to markedly reduce total mortality in both the RALES and EMPHASIS-HF studies. The timeline below shows the main findings of 4 ground-breaking trials on ACEis and MRAs (figure 5).

Figure 6 illustrates the pathophysiological pathways where MRAs have an action during progression of HF.

Allan Struthers : “The results of the RALES and EMPHASIS-HF studies allow us to conclude that aldosterone blockade reduces mortality in both mild and severe heart failure.” (Struthers, 2011)
Therefore, in human patients with heart failure due to left ventricular dysfunction, aldosterone blockade is strongly indicated, irrespective of both the patient’s aldosterone levels and heart failure severity.

**Figure 6.** The direct deleterious effects of mineralocorticoid receptor activation in the heart and kidneys and the common pathophysiological mechanisms involved. The beneficial effects of MRA-mediated interruption of these pathways are also illustrated (Bauersachs et al., 2015).
THE STORY OF SPIRONOLACTONE IN VETERINARY CARDIOLOGY

The pivotal study: the Bernay study

The clinical value of combining spironolactone with an ACEi in dogs with MMVD was demonstrated in more than 190 dogs recruited into a European multicentre double-blind study published in the Journal of Veterinary Internal Medicine (Bernay et al., 2010).

**PUBLICATION OF INTEREST 7**

Efficacy of Spironolactone on Survival in Dogs with Naturally Occurring Mitral Regurgitation Caused by Myxomatous Mitral Valve Disease

**Bernay F., Bland J.M., Hagström J., Baduell., Combes B., Lopez A. and Kaltsatos V.**

*Journal of Veterinary Internal Medicine.*


**Background:** Spironolactone, an aldosterone antagonist, has been demonstrated to decrease mortality in human patients when added to other cardiac therapies.

**Hypothesis:** Spironolactone in addition to conventional therapy increases survival compared with conventional therapy in dogs with naturally occurring myxomatous mitral valve disease (MMVD).

**Animals:** Between February 2003 and March 2005, 221 dogs were recruited in Europe. Nine dogs were excluded from analysis, leaving 212 dogs with moderate to severe mitral regurgitation (MR) caused by MMVD (International Small Animal Cardiac Health Council classification classes II [n = 190] and III [n = 21]).

**Methods:** Double-blinded field study, conducted with dogs randomised to receive either spironolactone (2 mg/kg once a day) or placebo, in addition to conventional therapy (angiotensin converting enzyme inhibitor, plus furosemide and digoxin, if needed). Primary endpoint was a composite of cardiac-related death, euthanasia, or severe worsening of MR.

**Results:** Primary endpoint reached by 11/102 dogs (10.8%) in the spironolactone group (6 deaths, 5 worsening) versus 28/110 (25.5%) in control group (14 deaths, 8 euthanasia, 6 worsening). Risk of reaching the composite endpoint significantly decreased by 55% (hazard ratio [HR] = 0.45; 95% confidence limits [CL], 0.22–0.90; log rank test, *P* = .017). Risk of cardiac related death or euthanasia was significantly reduced by 69% (HR = 0.31; 95% CL, 0.13–0.76; *P* = .0071).

Number of dogs not completing the study for cardiac and other miscellaneous reasons similar in spironolactone (67/102) and control groups (66/110).

**Conclusion and Clinical Importance:** Spironolactone, added to conventional cardiac therapy, decreases the risk of reaching the primary endpoint (i.e., cardiac-related death, euthanasia, or severe worsening) in dogs with moderate to severe MR caused by MMVD.

**Main results of the study**

- Spironolactone combined with cardiac therapy, including an ACEi, significantly reduces the risk of cardiac morbidity and mortality in dogs with MMVD as compared with conventional cardiac therapy alone.

All dogs were undergoing treatment with an ACEi (mainly benazepril, n=111 dogs). The findings demonstrate the benefit of adding spironolactone to this treatment regimen, as compared with ACEi treatment alone.

- This study is one of the largest field trials to measure survival in dogs with moderate to severe mitral regurgitation, due to MMVD. Most of the participating dogs (89.6%) were in ISACHC* stage II.

**Major conclusions**

- This study supports the inclusion of spironolactone in treatment protocols for dogs with MMVD.

- The beneficial effects of spironolactone on survival cannot be explained exclusively by the diuretic effect of the drug, and may be related to a counteractive effect of spironolactone on the arterial changes and cardiac replacement fibrosis, described in dogs with naturally occurring MMVD (Falk et al., 2010; Lee et al., 2015).
The story of spironolactone in veterinary cardiology

Reminder: ISACHC (Fox et al., 1999) stages II and III

**4mg not licensed dose for spironolactone**

**Stage II:** Mild-to-moderate heart failure (HF)
Clinical signs of HF are evident at rest or with mild exercise and adversely affect the quality of life. Typical signs of HF include exercise intolerance, cough, tachypnoea, mild respiratory distress (dyspnoea), and mild to moderate ascites. Hypoperfusion at rest is generally not present. Home treatment is often indicated at this stage.

**Stage III:** Advance HF
Clinical signs of advanced congestive HF are immediately obvious. These signs could include respiratory distress (dyspnoea), marked ascites, profound exercise intolerance or hypoperfusion at rest. In the most severe cases, the patient is moribund and suffers from cardiogenic shock. Death or severe debilitation is likely without therapy. Patients with advanced HF may be divided into two categories:

- **Stage IIIA.** Home care is possible
- **Stage IIIB.** Hospitalisation is mandatory (cardiogenic shock, life-threatening pulmonary oedema or a large pleural effusion is present)

**Main results of the study**

- Survival was significantly increased in dogs treated with benazepril plus spironolactone, as compared with the reference group (p=0.011). The risk of mortality from cardiac causes was decreased by 89% in the benazepril plus spironolactone group as compared with those treated with benazepril alone (p=0.036).
- Analysis on quality of life revealed that benazepril plus spironolactone significantly accelerated the improvement of cough and activity, and delayed the worsening of cough, heart sounds, and appetite.

**Figure 7. Speed of onset of combination of benazepril + spironolactone versus benazepril alone.**

Improvement of clinical signs appears faster with combination of benazepril + spironolactone

Improvement of heart failure symptoms: difference between the time-to-improvement observed in dogs treated with benazepril alone versus dogs treated with combination of benazepril + spironolactone (significant difference, p<0.05).

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*Reminder: ISACHC (Fox et al., 1999) stages II and III
**4mg not licensed dose for spironolactone
The consensus statement was prepared before publication of the Bernay study (see page 14).

After publication of these ACVIM guidelines, several authors reviewed data on the treatment of dogs with MMVD (Borgarelli and Häggström, 2010; Atkins, 2011; Atkins and Häggström, 2012) and, in particular, the results of successive clinical trials investigating the efficacy of the different available drugs (see figure 8).

**Clarke Atkins:** “The ACVIM consensus panel has unanimously indicated that chronic pharmacologic management of heart failure in dogs caused by Mitral Regurgitation should include furosemide, pimobendan, and an ACE inhibitor, with the majority of panelists also recommending a Mineralocorticoid Receptor Antagonist (such as spironolactone).”

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**Figure 8.** Timeline of all clinical trials on MMVD, adapted from Atkins and Häggström 2012.

### Follow-up
- 21 days
- 28 days
- 87 days
- 151 days
- 1150/1130 days

### Severity of MMVD
- NYHA III-IV
- NYHA III-IV
- NYHA III-IV
- ISACHC II-III
- NYHA I-II

### Number of patients with MMVD
- 22 dogs
- 141 dogs
- 67 dogs
- 61 dogs
- 229 dogs

### Drug
- Enalapril
- Enalapril
- Enalapril vs placebo
- Benazepril vs placebo
- Enalapril vs placebo

### Endpoint/Outcome vs placebo or drug

- **1995 IMPROVE**
  - Improved:
    - mobility
    - pulmonary oedema score
    - NYHA Class
    - PWP

- **1995 COVE**
  - Improved:
    - clinical signs
    - QOL

- **1998 LIVE**
  - Improved survival or removal from study for worsening signs

- **1999 BENCH**
  - Improved:
    - survival or removal from study for worsening signs
    - QOL

- **2002 SVEP**
  - No benefit in preventing/delaying CHF

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*Drug tested, plus standard therapy except for SVEP and VETPROOF studies, which evaluated enalapril only.

*All findings refer only to the MR dogs in this study, except for QOL score, which was improved for the combination of MR and DCM, but the data were not stratified further.

*Mobility scores were significantly improved in MR dogs; other significant findings were for the whole group (DCM + MMVD + AI).

*Improvement NYHA class was significant for all (DCM + MR) dogs, but $P = 0.52$ for MR subgroup. The MR subgroup showed significant improvement in overall evaluation and activity and mobility scores.
According to Borgarelli and Häggström (2010): “the results of several clinical trials together with clinical experience suggest that dogs with overt CHF can be managed with acceptable quality of life for a relatively long time period, with medical treatment including furosemide, an ACEi, pimobendan, and spironolactone”.

12 months
NyHA II-IV
93 dogs
Imidapril vs enalapril
Similar to enalapril:
• QOL
• survival

56 days
Asymptomatic
76 dogs
Pimobendan vs benazepril
Improved heart insufficiency score

895/778 days
NyHA III
124 dogs
Enalapril vs placebo
1º endpoint (delay CHF by 3 mos; not significant), significant benefit in number of CHF-free dogs at 500 and 1500 days and in all-cause mortality

267/140 days
NyHA III
252 dogs
Pimobendan vs benazepril
Improved time to:
• cardiac-related death
• euthanasia for cardiac disease
• or treatment failure

12-15 months
IsACHC II-III
194 dogs
Spironolactone
Reduced risk for:
• reaching cardiac-related death/euthanasia
• or severe worsening of CHF

2006
VETSCOPE
2007
VETPROOF
2008
QUEST
2010
BERNAY

**Endpoints were not stratified by disease; so results are for DCM and MR dogs, though the strong majority (83%) of dogs had MMVD.**

Abbreviations: PWP = pulmonary wedge pressure; MR = mitral regurgitation, AI = aortic insufficiency, Asympt = asymptomatic, CHF = congestive heart failure; DCM = dilated cardiomyopathy; QOL = quality of life; NYHA = Modified New York Heart Association Heart Disease score (I-IV); ISACHC = International Cardiac Health Council score (I-III).
CONCLUSION

This literature review, covering the most recent data on spironolactone, as well as major milestones in understanding the role of aldosterone, leads to two major conclusions.

First, a considerable body of literature indicates a detrimental role of aldosterone in cardiovascular disease. Accumulating evidence supports the use of a combination of spironolactone and an ACEi, such as benazepril, in the treatment of MMVD in dogs to block the negative effects of aldosterone.

Second, the remaining areas of interest for further investigation are numerous, and include benefits of spironolactone in other species (e.g. cats) and the role of aldosterone in the disease of other organs, such as vascular and kidney disease. Now that the mode of action is better understood, spironolactone clearly has therapeutic actions beyond its diuretic effects. Ongoing research will certainly provide us with new pieces of the puzzle that will hopefully find clinical application in the coming years.

Ceva is committed to continuing exciting work in this area and looks forward to presenting the next major advances.

REFERENCES


16. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. European Heart Journal, 2012;33(14):1787–1847.


