

## **Literature Review**

**Article selected:** The SEISICAT study: a pilot study assessing efficacy and safety of spironolactone in cats with congestive heart failure secondary to cardiomyopathy

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### **General remarks and Introduction**

This article covers a long overdue study of the use (safety and efficacy) of spironolactone in the treatment of CHF in cats suffering from cardiomyopathy. As is state of the art nowadays, the investigation was set up as double-blinded, placebo-controlled, randomized and multicentric. Unfortunately, it represents “only” a pilot study with a relatively low number of included cases, as a power calculation for the necessary inclusion numbers was omitted. This arbitrary limitation to studying only 20 cats and therefore loosing meaningfulness diminishes it’s scientific value somewhat, but any comparative study of an additional drug with positive effects in the treatment of feline CHF represents a very welcome addition to the veterinary literature.

The group of authors consists of experienced and well respected academic cardiologists together with equally experienced representatives from the pharmaceutical company who sponsored the study. It isn’t stated anywhere if the study serves to gain additional regulatory licensure of spironolactone for the treatment of feline CHF.

The **introduction** is generally well written, but too long. Publishing in a specialized veterinary cardiology journal, the authors should realize that the entire part of the introduction dealing with the features of aldosterone, RAAS-activation and remodelling is somewhat redundant and well known by most of the readers. Starting straight away with aldosterone receptor blockade would have been sufficient. The objectives of the study are clearly stated. But at the danger of sounding petty, the reviewer would have liked to see a clear **hypothesis** of what results the authors expected to see/obtain with the way they set up the study!

### **Animals, material and methods**

That entire chapter is very well written and clear. Limiting the enrolment of cats to 3 referral centers (names not identified, suspected to be near the academic veterinary clinic of the University of Nottingham), barely satisfies the term “multicentric”, but still warrants some potential regional variety of the included cases.

The **inclusion criteria** are precise; reliance of the CHF-diagnosis on some clinical and radiographic evidence is given, but could be expanded a bit. The evidence of echocardiographic/Doppler signs of diastolic (ventricular) dysfunction is missing there, but brought in further down in the article under “parameter assessment”.

The **exclusion criteria** are again precise, but deficient. As is evident later on in the results section, two cases of atrial fibrillation were enrolled. This seems to be in violation of their exclusion criteria, as Afib almost always requires the use of antiarrhythmic medication which they clearly ruled out and stated as one of the reasons for ineligibility. It is extremely unlikely that the 2 Afib cats in CHF had low

ventricular response rates to classify them as arrhythmic, but probably not needing antiarrhythmic medication!

The **randomisation** procedure was adequate, but what can happen with low numbers of included cases unfortunately happened, see table 2: Two Afib cats ended up in the placebo group, and bias happened with respect to blood pressure (surprisingly low in the spironolactone group) and echocardiographic LA/Ao-ratio (significantly higher in the placebo group).

The information about **Study drugs, Concomittant treatments** and **Visit schedule** (supplemental table A online) was clear, precise and adequate.

### **Parameter assessment**

The usual vital parameters were recorded. Apparently, a questionnaire was to be filled out by the owners at each visit, but details about it's content are not given. Pertinent radiographic assessment was performed, as was electrocardiography, blood pressure determination (antiquated technique with Doppler) and echocardiography. The latter was exquisitely described in details, however without details about repeated measures and averaging the numbers. It would also be nice to know how many (experienced) different echocardiographers performed the examinations, and if they ever submitted themselves to an inter-observer estimation of variance. A bit more precise information about which method was used to determine the Ao-dimension and the LA/Ao-ratio would be desirable, as well as which limits were set/used for the measurement of diastolic ventricular dysfunction, i.e. venous inflow patterns and IVRT.

While details were verified about how the owners complied with respect to the consumption of the study tablets (Spironolactone or placebo), it appears unclear if the compliance of ACEI and furosemide therapy was equally verified.

The **safety assessment** of the studied drugs was clear and complete.

### **Outcome**

The definition of study endpoints is very important, and sometimes tricky.

Particularly, the occurrence of (unobserved) sudden death may pose some problems to the owner and investigator with the assignment to cardiac or non-cardiac causes.

The reviewer believes that there is/was some overlap with the DX of cardiac death into both primary endpoint and efficacy end point (the authors avoided the term secondary endpoint in that section, but used it further down in the article), as euthanasia due to cardiac causes would be a primary end point, and *combined incidence of death (spontaneous or by euthanasia) and treatment failure (cit.)* was defined as secondary efficiency endpoint. Spontaneous (cardiac) death shouldn't feature in both endpoints! Wouldn't it have been sufficient to define the primary endpoint unchanged and the secondary endpoint as treatment failure?

The safety assessments were adequate.

### **Statistical methods**

They are well written, concise and clear. The argument that because of few published prospective studies citing survival in feline heart failure made sample size calculation not feasible lacks logic ! The adequate statistical tests for comparison of the two groups at enrolment did indeed reveal bias (statistically significant differences), to be found in table 2. Construction of survival curves by the Kaplan-Meier methods is an accepted way to illustrate survival differences between treatment groups in such a study.

## Results

**Introductory remark:** While a lot of data is presented in that section, no details of heart rate, respiratory rate, overall clinical assessment and radiographic results are presented. The reviewer wonders what lead to this omission, and is curious if this deleted information, plus echocardiographic details, have been saved for a later in-depth analysis and additional publication? Accepted precedents to such a procedure can be found in the veterinary literature, e.g. the QUEST study 2008 in dogs with mitral regurgitation.

The authors could enroll 9 cats in the spironolactone-treatment group, and 11 cats in the placebo group. Roughly one third of the cats, equally distributed to both treatment groups, required hospitalisation for the stabilisation of their condition. This leads to believe that the severity of heart failure couldn't have been that high, but only moderate. No application of the accepted standard classification schemes was presented. However, the evidence of 2 Afib cases as well as significantly higher La/Ao-ratios within the placebo group suggests that placebo-treated cats were more severely affected by their heart disease, see table 2.

Clinical/vital parameters and radiographic results are missing in table 2. Although possibly difficult to derive from the clinical and radiographic data, additional evidence of the severity of heart failure of the two groups may be buried in there and would have been interesting to know? The reviewer doesn't want to overinterpret the difference of body condition score between placebo-treated cats (avg. 3.3) and spironolactone-treated cats (avg. 4.3), but that fact seems to accentuate that today's felines seem all to trend towards excessive bodyweight. The average systolic blood pressure of the treatment group (115 mm/Hg) seems inappropriately low, but the average value of the placebo group (137 mmHg) more adequate for felines with CHF at initial examination. Initial average heart rates should be published in table 2. Only in the discussion and in figure 2, it was revealed that the serum potassium levels (group averages) differed significantly between the placebo group (higher, around 4mmol/l) and the spironolactone group (lower, slightly over 3 mmol/l).

## Treatment

The administered median spironolactone dose was 2.83 mg/kg/day (range 2.08 – 3.36), and this falls in the accepted recommended daily dose range. Seventeen cats had been pretreated with furosemide (avg. 5.0 +/- 2.9 mg/kg/day), and thirteen of them had received concomitant benazepril (0.6 +/- 0.4 mg/kg/day). Regrettably, a distribution of pretreatment details onto the treatment groups (spironolactone or placebo) was not given. After enrollment, all cats from both treatment groups received both benazepril and furosemide, of course.

After inclusion in the study, the time-averaged daily dosages of furosemide differed considerably, from 3.0 +/- 1.2 mg/kg in the spironolactone group versus 4.8 +/- 2.3 mg/kg in the placebo group, representing a greater than 50% difference (no calculation of statistical significance given). Unfortunately again, no indications about permitted dose adjustments of the furosemide dose in the course of the trial was given. Similar, but smaller group differences were noticed with the benazepril treatment dosages; the spironolactone-treated group received 0.4 +/- 0.2 mg/kg/day, and placebo-treated cats received 0.6 +/- 0.4 mg/kg/day.

An annotation states that 5 cats from the spironolactone group and 3 cats from the placebo group received potassium supplementations.

## Primary end point

The numbers completing the 15 month trial period were 5/9 cats (56%) in the spironolactone group and 0/11 cats (0%) in the placebo group. Calculations of mortality due to cardiac causes revealed an estimated 15 month survival rate of 78% for cats treated conventionally plus spironolactone, versus 0% for cats treated conventionally plus placebo. This difference was statistically significant ( $p=0.0110$ ), see also fig. 1 (Kaplan-Meier survival curves), and the univariate analysis of treatment revealed a significant risk reduction ( $HR=0.158$ ,  $p=0.0226$ ) for the spironolactone treated cats.

2/9 (22%) cats of the spironolactone groups reached the primary endpoint of cardiac death, while 9/11 (82%) of placebo cats succumbed for that reason. The other 2 placebo cats were rescued to non-allowed treatments, while 2 spironolactone cats died of noncardiac causes.

When LA-size was introduced as covariate into a now bivariate Cox model, the previous statistical significance disappeared:  $HR=1.53$ ,  $p=0.53$ , and  $HR=0.199$ ,  $p=0.07$ .

As HCM represented 75% of the underlying form of cardiomyopathy and was almost equally distributed in both treatment groups (Table 1: Seven cats in the spironolactone group and 8 cats in the placebo group), a post hoc survival analysis of this population (15 cats) seemed justified and was calculated. This revealed a highly significant difference in the 15 month survival rate (100% vs. 0%,  $p=0.0005$  log rank test), and in the mortality due to cardiac causes ( $p=0.0014$ ).

## Safety

A total of **39 adverse events** were recorded (16 events in 7 cats from the spironolactone group, 23 in 11 cats of the placebo group). None of the previously recorded (MacDonald 2008, ref 14 of the manuscript) affections of the skin and muzzle were observed. Details about the recorded events are found in supplemental table C and in the text. They appeared to be minor and didn't seem to affect the trial significantly.

## Blood and urine parameters

In supplemental Table D, isolated low values of haematocrit, packed cell volume, platelet and red and white counts were recorded in single cats, without further calculations, evaluations, or recognizable trends reported. It would have been helpful to have clear indications of lowest acceptable values for these blood parameters as well as electrolytes during the present trial !

## Blood pressure

The reviewer has already commented about a surprisingly low group average of systolic blood pressure for the spironolactone group at enrolment. As the range for the group is presented, an incredibly low value for at least one cat (85 mmHg) was given, which is difficult to believe, as no therapeutic measures were taken and/or reported. The supplemental table F confirmed continued low values at some visits (e.g. V7, 96 mmHg), raising some doubts about the measurement techniques that were used and the validity of the BP-results. The oscillometric method of BP-measurement, allowing pulse wave analysis (PWA with HDO), would likely have shed light into this dilemma of BP-interpretation and is nowadays accepted as a superior technique.

## Discussion

This entire subchapter is well written, clear and addresses the pertinent findings of the trial precisely. Some discussion points about pathophysiology of heart failure and about aldosterone effects and blockade add more general information and round off the discussion. The reference list appears pertinent, without too many perceived embellishments through unnecessary citations.

The authors rightly plead with the reader about a cautious interpretation of the apparent superiority of adding spironolactone to feline CHF-therapy, because of the low numbers of cats in both treatment groups, i.e. the lack of power of the study. A combination of low patient numbers, bad luck with the randomization process and an apparent protocol violation (Afib enclosure) lead to considerable inequality/ statistically significant differences (\*) of several important values at enrolment:

Value	Spironolactone group	Placebo group
Syst. blood pressure	115 mmHg	137 mmHg *
Body conform. score	4.3	3.3 *
Atrial fibrillation	none	2 cases
Aortic diameter	9.0 mm	8.0 mm *
LA/Ao-ratio	1.9	2.5 *
Potassium levels	lower	higher *
ALT	lower	higher *
Albumin	higher	lower *
Furosemide dose	3.0 +/- 1.2	4.8 +/- 2.3
Benazepril dose	0.4 +/- 0.2	0.6 +/- 0.4

- The asterisk \* indicates statistically significant difference ( $p < 0.05$ )

Exclusion of the falsely included two cats with Afib however would have reduced the case numbers even further and diminished the value of any statistical assessment even more. On the other hand, it is generally accepted that Afib in cats carries a poor clinical prognosis and a severe reduction of the survival outlook. So, the influence of these 2 cats on the already shortened survival of the placebo group added to the negative bias, but how much remains speculative.

The trial had a high event rate, illustrated by the fact that only 5 cats (all of them in the spironolactone group) completed the 15 month trial period. This makes for clear evidence of difference in the Kaplan-Meier survival curve (fig. 1). But only when calculating a univariate analysis of treatment in the mortality due to cardiac causes, a statistically significant reduction of the hazard ratio became evident (HR= 0.033,  $p=0.0335$ ).

Two cats from the placebo group had to be withdrawn because of worsening heart failure and application of rescue drug that weren't allowed in the trial, while 2 cats from the spironolactone group exited the trial due to apparent unrelated cardiac deaths (no specific details given). This difference intuitively strengthens the impression of the superiority of additional spironolactone therapy with respect to event free improved survival, but of course without statistical evidence to prove that point. It would be very interesting to know what happened to the 2 cats with Afib, especially if they exited the trial early due to their cardiac arrhythmia.

Most cats of the present study suffered from HCM, and were almost evenly distributed onto the two treatment groups (7 in the spironolactone group, 8 in the placebo group). The authors correctly warn readers from generalising the positive

effect of spironolactone addition to the treatment of other forms of cardiomyopathy. The low numbers of enrolled cats simply wouldn't support such a belief or recommendation.

With respect to safety, the authors underline the nearly even distribution of adverse events onto both groups and highlight the low clinical importance of the recorded events that covered just about all organ systems. They also underline the absence of facial dermatitis (4/13 cats) that had been observed in the previous spironolactone trial from MacDonald et al (2008, JVIM, ref. 14). The small numbers of cats receiving spironolactone in both (the former and the present) trials however should beware any reader from believing in the total safety of the drug, before any larger trial with a greater number of cats clears this uncertainty completely.

The authors suggest that a larger trial (with the necessary power calculation) should be repeated with the same hypothesis, but with the inclusion of only HCM-cases and some stratification of severity of their cardiac disease by correcting for left atrial enlargement. This is entirely supported by the reviewer. It is unfortunate that the meaningfulness or weight of this article is somewhat reduced by the mentioned problems. It remains however a very welcome addition to the veterinary literature about the combined therapy of feline CHF.

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