Angiotensin-converting enzyme inhibitors in preclinical myxomatous mitral valve disease in dogs: systematic review and meta-analysis

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Abstract

Objectives

To determine the efficacy and adverse events of the administration of angiotensin-converting enzyme inhibitors (ACEIs) for the management of preclinical myxomatous mitral valve disease (MMVD) in dogs.

Materials and Methods

A comprehensive search using Pubmed/MEDLINE, LILACS and CAB abstracts databases was performed. Randomized clinical trials (RCT) that assessed efficacy and adverse events of ACEIs for the management of preclinical MMVD in dogs were included. Certainty of evidence (CoE) was rated using GRADE methods.

Results

Four RCTs were included. While safe, ACEIs administration to dogs with MMVD and cardiomegaly results in little to no difference in the risk of development congestive heart failure (CHF; high CoE; RR: 1.03; 95% CI: 0.87 – 1.23) and may result in little to no difference in cardiovascular-related (low CoE; RR: 1.01; 95% CI: 0.54 – 1.89) and all-cause mortality (low CoE; RR: 0.93; 95% CI: 0.63 – 1.36). Administration of ACEIs to dogs with MMVD without cardiomegaly may result in a reduced risk of CHF development. However, the range in which the actual effect for this outcome may be, the 'margin of error', indicates it might also increase the risk of CHF development (low CoE; RR: 0.86; 95% CI: 0.54 – 1.35).

Clinical Significance

Administration of ACEIs to dogs with preclinical MMVD and cardiomegaly results in little to no difference in the risk of development of CHF and may result in little to no difference in

cardiovascular-related and all-cause mortality. The CoE of the efficacy of ACEIs administration to dogs without cardiomegaly was low.

Key words

Heart failure; mitral valve insufficiency; benazepril; enalapril; cardiac; cardiomegaly

Introduction

Myxomatous degeneration of the mitral valve is the most common cardiac disease in the dog (Haggstrom *et al.* 2004). Although this disease can be present in any breed, it is more commonly diagnosed in small-breed dogs, being the Cavalier King Charles Spaniels (CKCS) and Dachshund overrepresented (Borgarelli & Haggstrom 2010, Swenson *et al*. 1996, Olsen *et al.* 1999). Commonly referred to as myxomatous mitral valve disease (MMVD), this disease is characterized by a progressive expansion of extracellular matrix with glycosaminoglycans and proteoglycans, valvular interstitial cell alteration and attenuation or loss of the collagen-laden fibrosa layer that results in mitral valve incompetence (Haggstrom *et al.* 2004, Fox 2012). Mitral regurgitation is a common consequence of MMVD that leads to left atrium and ventricle volume overload (Fox 2012, Di Marcello *et al.* 2014) and when severe, increased left atrial pressure, pulmonary venous congestion and cardiogenic pulmonary oedema (Fox 2012, Di Marcello *et al.* 2014, López-Alvarez *et al.* 2015).

Dogs with MMVD are classified according to the American College of Veterinary Internal Medicine (ACVIM)'s consensus guidelines (Atkins *et al.* 2009). Specifically, those with preclinical MMVD are categorized as B1 or B2 whether signs of cardiac remodelling are absent or present, respectively. Recently, the ACVIM proposed updated consensus guidelines for diagnosis and treatment of MMVD in which administration of angiotensin-converting enzyme inhibitors (ACEIs) was recommended for patients in stage B2 by half of the panel members (Keene *et al.* 2019). However, a clinical trial published after the ACVIM consensus guidelines reported no clinical benefit observed on the association of ACEIs with spironolactone in dogs with MMVD in B2 stage (Borgarelli *et al.* 2020). It is controversial whether the administration of ACEIs is efficacious for the treatment of preclinical MMVD in dogs. Additionally, there are few instances in small animal veterinary

cardiovascular medicine where data exists that allows a quantitative systematic review. Therefore, a systematic review and meta-analysis of the current evidence was conducted. The aim of this systematic review and meta-analysis was to evaluate the efficacy and adverse events of the administration of ACEIs for the treatment of preclinical MMVD in dogs.

Materials and methods

A systematic literature search of randomized clinical trials (RCT) evaluating the efficacy of ACEIs was undertaken. The preferred reporting items for systematic reviews and meta-analysis (PRISMA) (Moher *et al.* 2015) guidelines were followed to report this study. A protocol for review was conducted following the Cochrane Handbook (Higgins *et al*. 2020) and is detailed in appendix A.

Criteria for considering studies

All RCTs investigating the use of ACEIs in comparison to placebo (with a minimum follow-up time of 60 days) for the management of preclinical MMVD in dogs with and without cardiomegaly were included. Studies evaluating ACEIs in combination with other active drugs versus placebo were also included.

During initial selection process, outcome measures were not used as inclusion criterion. All articles meeting the criteria except for the outcome criterion were preliminarily included and evaluated in full text. Finally, studies that reported any of the following outcome measures were included:

Primary outcomes:

- Cardiovascular-related mortality
- Congestive heart failure

Secondary outcomes:

- All-cause mortality

- Adverse events related to renal disorders, those considered serious (which resulted in death, life-threatening or persistent disability), and those that generated the withdrawal of the dogs from the study.

Search strategy

Studies were selected using three databases from inception: Pubmed/MEDLINE, LILACS and CAB abstracts. No restrictions on language or publication status were made. All the references cited in each of the papers included were evaluated in order to search for undetected studies.

The search strategies used for Pubmed/MEDLINE and for the other databases are detailed in appendix B.

Data collection and analysis

Articles were independently selected by two researchers (**,**) using Rayyan software (Ouzzani *et al.* 2016). In case of disagreement, a third independent investigator (**) was consulted. After the pre-selection of studies based on their title and abstract, articles were read in full by two independent researchers (**,**) to decide inclusion. Again, in case of disagreement, a third independent investigator (**) was consulted.

Using standardized forms, two reviewers (**,**) extracted data independently from each included study. Information on the study design, duration of follow up, study setting, withdrawals, participant characteristics (including sex, breed, age and presence or absence of cardiomegaly), details about the administered intervention, comparison and concomitant medications (including dose and therapeutic scheme), the outcomes assessed (including their definition, method of assessment and time-points), the source of

funding of the study, the conflicts of interest disclosed by the investigators, and the risk of bias assessment for each individual study were collected.

Assessment of risk of bias

The risk of bias per outcome was assessed using the Cochrane 'Risk of Risk of bias assessment of inc tool (Higgins *et al*. 2011) and the proposed strategy by SYRCLE (Hooijmans *et al.* 2014). The following domains were assessed: sequence generation (selection bias); allocation concealment (selection bias); baseline characteristics; blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and other sources of bias. Risk of bias domains were judged as 'low risk', 'high risk' or 'unclear risk' and individual bias items were evaluated. Risk of publication bias was assessed by means of funnel plots.

Data synthesis

The Mantel-Haenszel random effects models was used for dichotomous outcomes. The estimate of treatment effect of an intervention was expressed as relative risk (RR) with 95% confidence intervals (CI). A RR with the range of the lower and upper bounds of the 95% CI not crossing one was considered to be statistically significant. A sensitivity analysis on studies with differences in the risk of bias (high and low risk of bias studies) was performed.

Investigation of heterogeneity

Heterogeneity between trials was assessed by means of I^2 and significant heterogeneity was assumed when $I^2 \geq 50\%$ (Deeks *et al.* 2019). Clinical and methodological differences in the included studies were assessed to decide if they were homogeneous enough to be

combined, which was performed using Review Manager (RevMan) software Version 5.4 2020 (Cochrane Collaboration, Denmark).

Cochrane standardised statements for reporting effects was used (Higgins *et al.* 2020).

Certainty of the evidence

The certainty of the evidence for all outcomes was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (https://gradepro.org) (Guyatt *et al.* 2008) across the domains of risk of bias, consistency, directness, precision and reporting bias. Certainty was categorized as high, moderate, low or very low.

Results

The outcome of the literature search is detailed in Fig 1. Four RCTs met inclusion criteria (Atkins *et al.* 2002, Kvart *et al.* 2002, Atkins *et al.* 2007, Borgarelli *et al.* 2020), and their main characteristics are presented in Table 1. All of the included studies were parallel randomized blinded control trials. Two of the included studies (Atkins *et al.* 2002, Atkins *et al.* 2007) evaluated the same dogs. Hwever, in Atkins *et al.* (2002) the reported outcome was renal adverse events whereas in Atkins *et al.* (2007) the efficacy of the treatment was reported. Given that the outcomes of interest were not reported in a large number of dogs withdrawn from the study, an ‘available case analysis’ (analysis of data of every participant for whom the outcome was known, Higgins *et al.* 2017) was performed. Data from the initially randomized animals (n=139) and not the ‘chronic treatment group’ (n=124) was analysed for the study of Atkins (2007), as proposed by the Cochrane’s Handbook (Higgins *et al*. 2020). Additionally, data on the number of dogs with and without cardiomegaly included in Kvart *et al.* (2002) was provided by one of the authors of the study. Therefore, the number of events and the analysed participants might not match the

primary analysis done by the original authors of the study. Primary and secondary evaluated outcomes are presented in Table 2.

Risk of bias assessment of included studies

A risk of bias summary is presented in Fig 2. Randomization was correctly described in all included studies, and therefore they were classified as with low risk of bias in this item. All included studies except for Kvart *et al.* (2002) correctly described allocation concealment and therefore, they were classified with a low and uncertain risk of bias, respectively. Baseline characteristics were similar between groups in all included studies and therefore, a low risk of bias was attributed in this item. The blinding of participants and personnel was correctly described in three studies (Atkins *et al.* 2002, Kvart *et al.* 2002, Atkins *et al.* 2007) so they were classified as low risk of bias. One study (Borgarelli *et al.* 2020) was designed to be single-blinded but interventions to maintain the owner blinded of treatment were attempted (modification of the original packaging of the treatment drugs with dedicated blister wallets) so an uncertain risk of bias was attributed. The blinding of outcome assessment was correctly described in all included studies, and therefore a low risk of bias was attributed in this item. For the incomplete outcome data item, a high risk of bias was assigned to three studies (Kvart *et al.* 2002, Atkins *et al.* 2007, Borgarelli *et al.* 2020) for cardiovascular-related mortality and all-cause mortality. A low risk of bias was assigned in all studies for the outcome congestive heart failure, and an uncertain risk of bias was attributed to one study (Atkins *et al.* 2007). A high proportion of withdrawn patients with missing outcomes were reported in all studies, but reasons for drops out were both reported and balanced across groups. Since the potential impact of missing dichotomous outcomes depends on the frequency (or risk) of the outcome (Higgins *et al.* 2017), a low risk of bias was assigned to the outcome congestive heart failure for which the numbers of events were high, and a high risk of bias was assigned to the outcomes for which the

frequency of events was low or very low (cardiovascular-related mortality and all-cause mortality). Selective reporting of outcomes was not detected in the included studies and other bias were not detected. Risk of publication bias could not be evaluated using funnel plots due to the low number of included studies.

Excluded studies

One study was excluded from this review since the follow-up period was less than 60 days and it was not an RCT (Kitagawa *et al.* 1997).

Effects of interventions

Cardiovascular-related mortality (primary outcome)

Two RCTs reported the cardiovascular-related mortality in dogs with MMVD and cardiomegaly (Atkins *et al.* 2007, Borgarelli *et al.* 2020). This study showed that administration of ACEIs may result in little to no difference in cardiovascular-related mortality (low CoE; RR: 1.01; 95% CI: 0.54 – 1.89; I^2=0%; studies=2, n=245; Fig 3).

Congestive heart failure (primary outcome)

Three RCTs evaluated the outcome congestive heart failure in dogs with MMVD and cardiomegaly (Kvart *et al.* 2002, Atkins *et al.* 2007, Borgarelli *et al.* 2020). This meta-analysis showed that administration of ACEIs results in little to no difference in the risk of development of congestive heart failure (high CoE; RR: 1.03; 95% CI: 0.87 – 1.23; I^2=0%; studies=3, n=321; Fig 4).

One RCT evaluated the outcome congestive heart failure in dogs with MMVD without cardiomegaly (Kvart *et al.* 2002) and reported that ACEIs administration may result in a slight reduction in the risk of development of congestive heart failure. However, the range in which the actual effect for this outcome may be, the ‘margin of error’, indicates that the

administration of ACEIs might also increase the also increase the risk of development of congestive heart failure (low CoE; RR: 0.86; 95% CI: 0.54 – 1.35; studies=1, n=86; Fig 5).

All-cause mortality (secondary outcome)

Two RCTs reported the outcome all-cause mortality in dogs with MMVD and cardiomegaly (Atkins *et al.* 2007, Borgarelli *et al.* 2020). This study showed that administration of ACEIs may result in little to no difference in cardiovascular related mortality (low CoE; RR: 0.93; 95% CI: 0.63 – 1.36; I^2=0%; studies=2, n=245; Fig 6).

Adverse events (secondary outcome)

Adverse events were reported in detail in three of the included RCT (Atkins *et al.* 2002, Borgarelli *et al.* 2020, Kvart *et al.* 2002).

In one of the studies, 11 dogs were withdrawn from the enalapril-treated group (three for neoplastic disease, one for disk herniation, one for epilepsy, one for neurological crisis, one for otitis media, one for paralysis, one for peritonitis, one for urolithiasis and one for facial paralysis/vestibular syndrome) whereas 16 were withdrawn from the placebo-treated group (three for neoplastic disease, three for disk herniation, one for Cushing disease, one for lethargy, one for unverified congestive heart failure, one for haematuria, one for joint disease, one for chronic diarrhoea, one for sudden death of unknown aetiology and one for gastric ulceration) (Kvart *et al.* 2002).

Another study reported adverse events in five dogs treated with benazepril and spironolactone (two presented neurological disorders, one presented cardiovascular abnormalities, one presented gastrointestinal disorders and one presented systemic disorders) and in 15 dogs treated with placebo (five neurological disorders, three presented cardiovascular disorders, one presented musculoskeletal disorders) (Borgarelli *et al.* 2020).

Another study reported a 35% or higher increase in creatinine serum level compared to baseline in 12 dogs treated with enalapril and in 17 dogs treated with placebo (Atkins *et al.* 2002).

The administration of ACEIs may result in little to no difference in the occurrence of adverse events in comparison to placebo (low CoE; RR: 0.65; 95% CI: 0.43 – 0.98; I^2=0%; studies=3, n=540).

Certainty of evidence

The CoE was high for the outcome congestive heart failure in dogs with MMVD and cardiomegaly, and low for the outcomes cardiovascular-related mortality, all-cause mortality, adverse events and congestive heart failure in dogs with MMVD without cardiomegaly. The main reasons for downgrading the CoE were risk of bias and imprecision. A summary of findings for the primary and secondary outcomes is presented in Table 2.

Discussion

This is the first comprehensive systematic review and meta-analysis on the efficacy and adverse events of the use of ACEIs for management of preclinical MMVD in dogs using the GRADE approach. This systematic review included a total of four RCTs. Three studies evaluated the efficacy of ACEIs randomizing a total of 551 dogs and the fourth included study only investigated potential renal adverse effects. The CoE was high for the outcome congestive heart failure and low for the outcomes cardiovascular related-mortality, all-cause mortality and adverse events. Most of the data were obtained from dogs with MMVD and cardiomegaly in which administration of ACEIs results in little to no difference in the risk of development of congestive heart failure and may result in little to no difference in cardiovascular related and all-cause mortality.

It is possible that the administration of ACEIs in dogs with MMVD without cardiomegaly may result in a reduction in the development of congestive heart failure. However, the range in which the actual effect for this outcome may be, the 'margin of error', indicates that the administration of ACEIs might also increase the risk of development of congestive heart failure. Due to the low certainty of the evidence obtained for the outcomes studied in dogs with MMVD without cardiomegaly, and the beneficial effects previously described by Borgarelli *et al.* (2020), it cannot be ruled out that the early administration of ACEIs at the initial stages of the disease may have had an impact on the clinical outcomes studied in this meta-analysis. Therefore, additional studies are required to confirm this hypothesis.

It should be noted that all evaluated dogs with MMVD without cardiomegaly were CKCS (Kvart *et al*. 2002). It has been previously suggested that this breed presents a higher prevalence and earlier onset of the disease compared with other small breed dogs (Serfass *et al*. 2006). Additionally, it has been shown in a previous study that CKCS dogs did not benefit from renin-angiotensin-aldosterone-system suppression when compared to other breeds (Pouchelon *et al*. 2008). However, the study was retrospective and included only a small number of CKCS (n = 48). On the other hand, neither in the EPIC trial (Boswood *et al.* 2016) nor in the QUEST trial (Haggstrom *et al*. 2013) it was observed that CKCS had a higher risk of presenting cardiac events. For this reason, there is no conclusive evidence to date that CKCS with MMVD have a different course of the disease or response to treatment than other dog breeds.

The rationale for the administration of ACEIs is based on a reduced afterload, a decreased volume of the left ventricle, a decreased size of the regurgitant orifice and an anti-fibrotic effect in later stages of cardiac disease (Ames *et al.* 2019, Tischler *et al.* 1998). However, controversy surrounding the benefits of ACEIs administration for the treatment of preclinical chronic mitral valve disease exist both in human and veterinary medicine (Dell'italia *et al.* 1997, Harris *et al.* 2005, Keene *et al.* 2019). Guidelines of human

American and European cardiology associations do not recommend its use in patients with preclinical chronic mitral valve disease (Nishimura *et al.* 2014, Baumgartner *et al.* 2017). In dogs, the ACVIM consensus does not recommend its use in B1 stage and only half of the panel members recommended it for dogs in B2 stage (Keene *et al.* 2019). The results of this meta-analysis do not support ACEIs administration, with a high CoE, for dogs with preclinical MMVD with cardiomegaly. However, it should be noted that the dosages used in the included RCTs are in the lower range of the current clinical recommendation. Therefore, the results obtained in this meta-analysis are only applicable to the range of doses of ACEIs used in the included RCTs.

This meta-analysis has several limitations. Firstly, the low number of included studies hindered evaluation of risk of publication bias using funnel plots. Secondly, a low number of dogs included had MMVD without cardiomegaly and therefore, that results should be interpreted with caution. Finally, the fact that the only breed included in this category were CKCS, precludes from extrapolation to dog population. These factors should be taken into account when interpreting the results of this meta-analysis.

Conclusion

This meta-analysis shows that the administration of ACEIs results in little to no difference in the risk of development of congestive heart failure and may result in little to no difference in cardiovascular-related and all-cause mortality in dogs with MMVD and cardiomegaly. Angiotensin-converting enzyme inhibitors administration may result in a reduced risk of congestive heart failure development in dogs with MMVD without cardiomegaly. However, the range in which the actual effect for this outcome may be, the 'margin of error', indicates that the administration of ACEIs might also increase the also increase the risk of development of congestive heart failure. Due to the small number of dogs included with MMVD without cardiomegaly, and due to the fact that they were of a

single breed, additional studies are required to draw definitive conclusions about the efficacy of ACEIs in this stage of the disease.

No conflicts of interest have been declared.

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Figure legends

Fig 1. Study flow diagram. CAB, Commonwealth Agricultural Bureaux; LILACS, Latin American and Caribbean Health Sciences Literature.

Fig 2. Risk of bias assessment of included trials using the Cochrane's Collaboration tool. ?, unclear risk; –, high risk; +, low risk.

Fig 3. Forest plot of the outcome 'cardiovascular-related mortality' showing the number of dogs with myxomatous mitral valve disease with cardiomegaly treated with angiotensin-converting enzyme inhibitors versus placebo. A Mantel-Haenszel (M-H) random effects model was used for this meta-analysis. The results of the relative risk with a 95% confidence interval (95% CI) are shown. ACE: angiotensin-converting enzyme.

Fig 4. Forest plot of the outcome 'congestive heart failure' showing the number of dogs with myxomatous mitral valve disease with cardiomegaly treated with angiotensin-converting enzyme inhibitors versus placebo. A Mantel-Haenszel (M-H) random effects model was used for this meta-analysis. The results of the relative risk with a 95% confidence interval (95% CI) are shown. ACE: angiotensin-converting enzyme.

Fig 5. Forest plot of the outcome 'congestive heart failure' showing the number of dogs with myxomatous mitral valve disease without cardiomegaly treated with angiotensin-converting enzyme inhibitors versus placebo. A Mantel-Haenszel (M-H) random effects model was used for this meta-analysis. The results of the relative risk with a 95% confidence interval (95% CI) are shown. ACE: angiotensin-converting enzyme.

Fig 6. Forest plot of the outcome 'all-cause mortality' showing the number of dogs with myxomatous mitral valve disease with cardiomegaly treated with angiotensin-converting enzyme inhibitors versus placebo. A Mantel-Haenszel (M-H) random effects model was used for this meta-analysis. The results of the relative risk with a 95% confidence interval (95% CI) are shown. ACE: angiotensin-converting enzyme.