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LETTER TO THE EDITOR

Letter regarding "Efficacy of adding ramipril (VAsotop) to the combination of furosemide (Lasix) and pimobendan (VEtmedin) in dogs with mitral valve degeneration: The VALVE trial"

Dear Editors,

The recent article on the efficacy of ramipril in combination with furosemide and pimobendan in dogs with degenerative mitral valve disease (VALVE study)[1] reported absence of survival benefit associated with the combination of ramipril, furosemide, and pimobendan (ie, triple treatment) as compared to treatment with furosemide and pimobendan (ie, double treatment). This finding has potential implications for many dogs with heart failure. As stated by the authors, existing treatment guidelines,[2] which recommend triple treatment along with mineralocorticoid blockers, primarily are based on expert opinion. Development of evidence-based treatment guidelines rely on results of randomized clinical trials such as the VALVE study, and the more fully the trial design, execution, administration, and reporting are understood, the more reliable the resultant guidelines. In this spirit, additional clarification and details of the VALVE study would be useful.

In the VALVE study, the association of baseline variables with survival was first examined using univariable and then multivariable Cox regression analysis. Unlike other randomized clinical trials in dogs with heart disease,[3-6] the VALVE manuscript does not include full results of these analyses. The variables' magnitude of effect and confidence intervals will help increase understanding, regardless of whether or not they were statistically significant. One striking feature of the VALVE study was the high dose of furosemide that was administered to the study population. The median dose at study entry was approximately 8.0 mg/kg/d, and in response to worsening signs, doses up to 15 mg/kg/d without recourse for any additional treatments other than the small proportion of dogs (~10%) that received spironolactone or an increased dose of ramipril were permitted. These doses exceeded both the baseline and maximum permitted dose of furosemide, the former by almost 2 times, as compared to the clinical trial upon which VALVE was based.[3] During the VALVE study, clinical guidelines recommended that upon achievement of furosemide in excess of 12 mg/kg/d, additional treatment in the form of vasodilators, spironolactone, chronic parenteral dosing of furosemide, and other classes of diuretics be instituted.[7] As such, the pharmacotherapy of the patient cohort in the VALVE study both at entry and throughout the duration of the study does not represent typical clinical practice. Adverse events are an important result of clinical trials[3-6] but are not reported in the VALVE study. A fuller understanding of adverse events, particularly in light of the study's high diuretic doses, would be helpful. There are administrative features of the VALVE study that would benefit from further clarification, including description of study execution as following Good Clinical Practice, which involves well-defined, comprehensive, stringent, and verifiable practices on both the part of the investigator and sponsor, including data auditing by independent monitors, reporting of all adverse events, and preservation of records, to name a few.[8] Performing clinical trials in veterinary medicine is extremely challenging and the authors are congratulated on tackling an important clinical question. I hope the study investigators will consider addressing the queries and provide the veterinary community with the requested information.

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