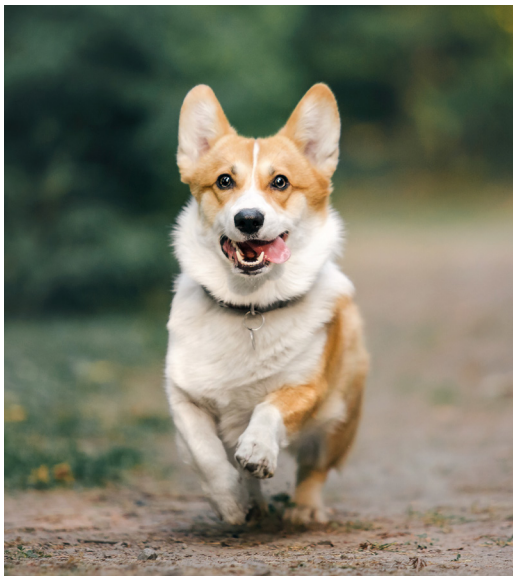
PRACTICE POINTER
conversations with a cardiologist

CARDIAC EDUCATION group

Clinical efficacy of a benazepril and spironolactone combination in dogs with congestive heart failure due to myxomatous mitral valve disease: The Benazepril Spironolactone STudy (BESST)[1]

Need-to-know summary: BESST Study

- The BESST Study was a large multicenter, prospective, randomized, double-blinded, comparator clinical trial of dogs in congestive heart failure (CHF) due to myxomatous mitral valve disease (MMVD).
- **Key Findings:** When compared to therapy with furosemide and benazepril for the management of CHF due to MMVD in dogs, use of furosemide plus a combination of spironolactone + benazepril reduced the percentage of dogs experiencing events at one year. The risk of dying or experiencing an event in the first year following initiation of therapy was also decreased. Adverse events were rare in both groups.
- **Key Unanswered Question:** Pimobendan was not permitted in the study. Given the importance of pimobendan therapy in the management of CHF due to MMVD (link to ABCDs of MMVD), it is unclear whether the benefit conferred by the combination of spironolactone + benazepril in this study would remain significant if the combination was used concurrently with pimobendan therapy.



What was the main objective of the BESST Study?

- The BESST study compared the time to the primary endpoint in dogs with CHF due to MMVD with two treatment regimens. The groups were treated with furosemide plus benazepril alone or furosemide plus a fixed dose combination of spironolactone + benazepril (Cardalis®).
- The primary endpoint was reached when the patient experienced any of the following:
  - cardiac death/euthanasia
  - recurrence or worsening of pulmonary edema
  - development of cardiogenic ascites
  - worsening or new cardiac clinical signs requiring therapy with a nonauthorized cardiac drug or furosemide at doses > 8 mg/kg every 24 hours.

Which dogs were enrolled in the BESST Study?

- Five hundred and sixty-nine client-owned dogs (> 2.5 kg) with ACVIM Stage C MMVD whose CHF was medically stabilized within the previous 10 days.
- To be enrolled, dogs must have had the following:
  - ≥ 3/6 left-sided systolic murmur
  - clinical signs of CHF (dyspnea, exercise intolerance) within the previous 10 days
  - radiographic evidence of pulmonary edema within the previous 10 days
  - echocardiographic evidence of significant left atrial enlargement (left atrium-to aorta ratio ≥1.6)
- Which other cardiac medications were allowed?
  - Furosemide: ***allowed*** furosemide dose on day of enrollment < 6 mg/kg/d.
  - Heart rate control medications (digoxin, calcium channel blockers) ***allowed.***
  - Pimobendan use was ***not allowed*** during the study.

What were the baseline characteristics of the dogs enrolled in the BESST study?

- The mean age of dogs at inclusion was 11.0 years (range, 3.4-19.2 years). Dogs were primarily small breeds and had a median (IQR) body weight of 6.9 kg (4.8-10.2 kg). Common dog breeds included Cavalier King Charles Spaniel, Chihuahua, Shih Tzu, Maltese, and Dachshund breeds. These dogs were a good representation of dogs commonly affected by MMVD.
- Study dogs were enrolled and evenly randomized to receive either the combination of spironolactone + benazepril (n = 284) or benazepril (n = 285) in addition to their baseline furosemide therapy. 187 dogs were excluded (equal numbers from the study groups) for various reasons, resulting in available data from **382** dogs followed for 360 days.

What were the main results of the BESST Study?

- The combination of furosemide, spironolactone + benazepril reduced the risk of cardiac death/euthanasia and worsening of heart failure by 27% at 360 days (p = .002) compared to furosemide and benazepril.
- Fewer dogs (p = .04) treated with the combination of spironolactone + benazepril reached the primary endpoint at day 360.
- Adverse events were rare and not different between the study groups.

What other interesting findings arose from the BESST study?

- The mean total daily dose of benazepril was 0.37 mg/kg and 0.36 mg/kg in the combination product and benazepril alone groups, respectively. This benazepril dose is lower than often recommended (link to canine formulary); the potential benefit of ACE inhibitor therapy may not have been fully achieved.
- The fixed dose ratio of the spironolactone + benazepril combination product is 8:1. The tablet doses for the spironolactone:benazepril combination are: 20mg:2.5 mg; 40mg:5mg; 80mg:10mg.

Clinical relevance of the BESST Study

- The BESST study results support the safety and benefit of the combination of spironolactone + benazepril when added to furosemide in the management of dogs with stabilized Stage C MMVD to reduce or delay recurrence of CHF.
- Because pimobendan was not included in the study design, the true benefit of the combination spironolactone + benazepril as typically used in clinical practice to treat CHF due to MMVD has not been evaluated.

How should veterinarians apply these results to their clinical practice?

- The Cardiac Education Group and the ACVIM consensus statement[2] (link to ACVIM consensus) recommends use of spironolactone, ACE inhibitor, pimobendan and loop diuretic for the optimal chronic management of dogs with Stage C MMVD.
- The fixed dose spironolactone + benazepril combination product provides convenience and may facilitate medication administration in some dogs.

References

1. Coffman M, Guillot E, Blondel T, et al. Clinical efficacy of a benazepril and spironolactone combination in dogs with congestive heart failure due to myxomatous mitral valve disease: the BEnazepril Spironolactone Study (BESST). J Vet Intern Med. 2021;35(4):1673-1687.
2. Keene BW, Atkins CE, Bonagura JD, et al. ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs. J Vet Intern Med. 2019;33(3):1127-1140.

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