The longitudinal outcome of canine (K9) myxomatous mitral valve disease (LOOK-Mitral) registry: Baseline treatment characteristics

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Abstract
Objectives: To describe the medical treatment prescribed or modified by veterinary cardiologists at the enrollment visit in dogs included in the longitudinal outcome of canine (K9) myxomatous mitral valve disease (MMVD) registry (LOOK-mitral registry) and to evaluate the influence of the EPIC trial and other selected variables on cardiologist prescription habits.
Animals: The medical records of 6,102 dogs enrolled in the LOOK_mitral registry between 2015 and 2018 were retrospectively reviewed and 6,016 dogs were included.
Results: A medical treatment was prescribed by a cardiologist to 2,599 dogs (15% Stage-B1, 90% Stage-B2 and to all dogs in Stage-C). Angiotensin converting enzyme inhibitors (Ace-i) were the treatment most commonly prescribed for dogs in Stage- B1 (n 1⁄4 352, 9%). The combination of pimobendan and an Ace-i was the most common treatment in Stage-B2 dogs (n 1⁄4 367, 41%). Furosemide, an Ace-i, and pimobendan was the most common cardiac medical treatment prescribed for ACVIM Stage-C dogs (n 1⁄4 704, 57%). Within each stage, dogs with larger left atrial and left ventricular dimensions were more likely to receive Ace-i, pimobendan or spironolactone. There was a four-fold increase in pimobendan prescription in Stage-B2 dogs after the publication of the EPIC trial. Moreover, a 15% reduction in Ace-i prescription and a 30% reduction in spironolactone prescription occurred after EPIC.
In 974 dogs, a medical treatment was prescribed by the referring veterinarian. This was not changed (12%), modified (74%), or discontinued (14%) by the cardiologist.
Conclusions: The EPIC trial and the echocardiographic assessment of left atrial and ventricular dimensions influence cardiologists' prescription habits.

Introduction
Myxomatous mitral valve disease (MMVD) is a slowly progressive disease that usually affects middle-aged to geriatric dogs of small- to medium-sized breeds [1]. The rate of disease progression is extremely variable, and not all dogs affected by MMVD experience clinical signs (CS) of congestive heart failure (CHF) during their lifetime [2]. Dogs affected by this disease can be managed medically with the overall goal of prolonging survival time. Specifically, in dogs that have not had CS of CHF, medical treatment focuses on delaying the onset of CS. Conversely, medical treatment in dogs with current or past CS of CHF is focused on improving quality of life and
avoiding reoccurrence of CS. Although medical treatment is commonly used in dogs affected by MMVD, studies that have evaluated veterinary cardiologists' prescription habits in a large population of dogs affected by MMVD are currently lacking.
In 2015, we established the Longitudinal Out- come of Canine (K9) MMVD registry (LOOK-Mitral registry) with the main purposes of describing the natural history of MMVD and investigating predictors of outcomes in dogs affected by this disease.
This study aims to describe the medical treatment prescribed or modified by veterinary cardiologists at the enrollment of the 6,016 dogs entered in the LOOK-Mitral registry. Moreover, we wanted to evaluate the influence of the EPIC trial and echocardio- graphic left atrial and left ventricular dimensions on cardiologist prescription habits [3].
Material and methods
Medical records of dogs enrolled in the LOOK- mitral registry were retrospectively reviewed to evaluate the medical treatment prescribed by the cardiologist at the time of the enrollment visit. The LOOK-mitral registry enrolled dogs with echocardiographic evidence of MMVD from November 1, 2015 to October 31, 2018 from thirteen veterinary cardiology specialty services. Dogs were classified according to the modified 2019 American college of veterinary internal medicine guidelines [4]. Briefly, dogs in Stage-B1 were those that did not have concurrent left

atrial (LA) and left ventricular (LV) enlargement, and that had never exhibited CS of CHF. Dogs in Stage-B2 were dogs that had never exhibited CS but had echocardiographic evidence of cardiac remodeling as defined by the American college of veterinary internal medicine guidelines (left atrium to aortic ratio [LA:Ao] 1.6, and a normalized left ventricular end-diastolic diameter [LVIDd_N] 1.7) [4]. The results of the EPIC trial were published on September 28, 2016, during the enrollment period of the LOOK-mitral study [3]. Therefore, dogs in Stage-B2 were further divided into two groups that comprised dogs enrolled either before or after October 1, 2016 [3]. Dogs in Stage-C had current or past CS of CHF, defined as tachypnea, dyspnea, and/or cough that resolved with medical treatment, which included furosemide. Moreover, dogs in which furosemide was prescribed by the cardiologist based on physical examination and echocardiographic findings were also considered to be in Stage-C. Dogs without current or past CS of CHF in which the LA:Ao and/ or the left ventricular end-diastolic diameter, were not available for review were excluded.

For the purpose of this study, we evaluated the prescription of the following drugs, as monotherapy or in any combination: angiotensin-converting enzyme inhibitor (Ace-i) (benazepril or enalapril or lisinopril), pimobendan, furosemide, spironolactone, amlodipine, and sildenafil.

All echocardiographic measurements were per- formed at the time of enrollment by a board-certified cardiologist or by a cardiology resident under a cardiologist's supervision and were acquired as previously reported [5]. Pulmonary hypertension (PH) was defined by a peak tricuspid regurgitation peak velocity >3.0 m/s [6]. Patients with PH were further divided into those with an estimated pulmonary arterial pressure (ePAP) >55 mmHg and those with an ePAP 55 mmHg, based on the prognostic value of ePAP >55 mmHg [7].

The presence/absence of arrhythmias and type of arrhythmias, diagnosed by standard six-lead electrocardiogram or electrocardiographic trace during the echocardiogram, was assessed, by reviewing the medical records. Dogs were considered not to have arrhythmias if the electrocardiographic findings were not included in the medical records.

Since Ace-i are commonly used not only as treatment for MMVD but also for proteinuria and systemic hypertension (SHT), we focused our attention on these two concomitant conditions. The presence of SHT and proteinuria were assessed by review of medical records. When assessed by the

cardiologist at the time of the visit, systolic blood pressure was measured noninvasively with Doppler sphygmomanometry, as previously described [8].

Statistical analysis

The statistical analysis was performed using dedicated softwareh. Count and percentage were used for description of categorical variables. Visual inspection of normal quantile plots was used to assess normality of continuous variables. Continuous variables that were not normally dis- tributed were described by median and range while normally distributed continuous variables were described as mean standard deviation. Pearson's chi-squared test of independence was used to compare the proportions of dogs that were receiving pimobendan, spironolactone and Ace-i before and after the publication of the EPIC trial [3]. A ManneWhitney test was used to compare the LA:Ao ratio or the LVIDd_N among dogs that within each stage were, or were not, receiving the following drugs: Ace-i (y/n), pimobendan (y/n), and spironolactone (y/n).

Results

A total of 6,102 dogs were enrolled in the LOOK- Mitral registry. The LA:Ao and/or the LVIDd_N were not available for review in 86 dogs without current or past CS of CHF. Therefore, 6,016 dogs were included in the study and staged as previously discussed. Of these dogs, 3,891 were in Stage-B1 (65%), 889 in Stage-B2 (15%), and 1,236 Stage-C (20%). Mixed breed dog was the most commonly represented breed (n 1⁄4 1,239, 20%), followed by Cavalier King Charles Spaniel (n 1⁄4 491, 8%) and Chihuahua (n 1⁄4 483, 8%). Baseline characteristics for the dogs enrolled in the LOOK-Mitral registry are summarized in Table 1.

At least one medication was prescribed in 43% (n 1⁄4 2,599) of the dogs. Specifically, in 15% (n 1⁄4 566) of the dogs in Stage-B1, in 90% (n 1⁄4 797) of the dogs in Stage-B2 and in all dogs in Stage-C (n 1⁄4 1,236). Medical treatments, according to the stage, are summarized in Tables 2e4. In 974 (16%) dogs, a cardiac treatment was prescribed by the referring veterinarian prior to enrollment in this study, consisting of 259 dogs in Stage-B1 (7%), 108 dogs in Stage-B2 (12%), and 607 dogs in Stage-C (50%) (Tables 2e4). Medical treatment was left unchanged by the cardiologist in 116 dogs (12%), was modified in 720 dogs (74%), and was dis- continued in 138 dogs (14%). Specific changes according to the stage are reported in Table 5. Among the 138 dogs in which medical treatment was discontinued, 137 (99%) were in Stage B1 while one dog was in Stage B2. Furosemide was dis- continued by the cardiologist in 182 dogs (14%), and in 25 of those dogs, the presence of cough in association with a left apical systolic murmur was identified as the main reason for furosemide prescription.

Stage-B1 dogs

Among the 3,891 dogs in Stage-B1, 1,180 dogs (30%) had evidence of either LA or LV enlargement. In particular, 217 dogs (5%) had only LA enlargement while 963 dogs (25%) had only LV enlargement. Out of 566 dogs that were receiving a medical treatment, an Ace-i was prescribed for 352 dogs (62%) without evidence of proteinuria or STH. Of these 352 dogs, 287 (82%) had evidence of either LA or LV enlargement. Dogs in which Ace-i, pimobendan, or spironolactone were prescribed had a greater LA:Ao ratio ($P < 0.001$) or LVIDd_N ($P < 0.001$) than dogs in which these drugs were not prescribed (Table 6).

Five-hundred-eighty-eight dogs in this group had evidence of PH. The ePAP was >55 mmHg in 57 dogs (1%), and nine dogs (0.2%) had a history of syncopal episodes. The etiology of PH in dogs with ePAP >55 mmHg was considered by the cardiologist to be respiratory disease in 31 dogs (54%), pulmonary thromboembolism in one dog (2%), and previous heartworm disease in one dog (2%). In the remaining 24 dogs (42%), the etiology was unknown. Sildenafil was prescribed in 35 dogs with PH (6%), and 29 of those (83%) had ePAP >55 mmHg. Out of 35 dogs in which sildenafil was prescribed, PH was considered secondary to respiratory disease in 22 dogs (63%) while in the other 13 dogs (37%), the etiology was open but unlikely to be secondary to MMVD. Four dogs with an ePAP >55 mmHg in which sildenafil was prescribed had a history of syncopal episodes.

Systemic hypertension was diagnosed in 169 dogs in this stage (4%), and amlodipine was pre-scribed alone in 28 dogs (17%) or in combination with Ace-i in 25 dogs (15%). Proteinuria was diagnosed by the referring veterinarian in 30 dogs (0.8%), and an Ace-i was prescribed in nine of those dogs (30%). Two dogs that were diagnosed with both SHT and proteinuria were receiving Ace-i and amlodipine. Arrhythmia was identified in 296 dogs in this stage (8%) with ventricular premature complexes (n 1⁄4 107, 3%) and atrial premature complexes (n 1⁄4 92, 2%) being the most common rhythm abnormalities. Antiarrhythmic drugs were prescribed in 24 dogs (Table 7).

Stage-B2 dogs

A total of 797 dogs out of the 889 in this stage were receiving a medical treatment (90%). Dogs in which Ace-i, pimobendan, or spironolactone was prescribed had greater LA:Ao ($P < 0.001$) and LVIDd_N ($P < 0.001$) than dogs in which these drugs were not prescribed (Table 8). One dog was receiving furosemide due to concomitant syringomyelia.
Pulmonary hypertension was diagnosed in 265 dogs in this stage (30%), and 49 dogs had ePAP >55 mmHg (6%). In 22 of these dogs with ePAP >55 mmHg, PH was considered secondary to MMVD (45%), in eight dogs secondary to respira- tory disease (15%), in one dog secondary to pul- monary thromboembolism (2%), while in the remaining 18, the etiology was open (38%). His- tory of syncopal episodes was reported in five out of the 49 dogs with ePAP >55 mmHg (10%). Sil- denafil was prescribed in 12 dogs (1%), all of which had ePAP >55 mmHg, and three also had a history of syncopal episodes. In five dogs in which sildenafil was prescribed, PH was considered to be secondary to respiratory disease (42%); in four, secondary to MMVD (33%); in two, the etiology was unknown (17%); in one, secondary to pulmonary thromboembolism (8%). Systemic hypertension was diagnosed in 37 dogs (4%), and amlodipine as sole therapy was prescribed in six of these dogs (16%). Proteinuria was diagnosed by the referring veterinarian in three dogs (0.3%), but Ace-i were not prescribed before the cardiologist visit. Arrhythmias were identified in 81 dogs in this group (9%) with ventricular premature complexes (n 1⁄4 35, 4%) and atrial premature complexes (n 1⁄4 30, 3%) being the most common rhythm abnormalities. Antiarrhythmic drugs were prescribed in seven dogs (Table 6).
Two hundred and forty dogs in Stage-B2 (27%) were enrolled before the publication of the EPIC trial, while 649 dogs were enrolled after (73%) [3]. Medical treatments before and after the publication of the EPIC trial in Stage-B2 dogs are summarized in Table 9 [3]. The most common medical treatment in these patients before the EPIC trial was represented by Ace-i (n 1⁄4 78, 33%) while the most common medical treatment after the EPIC trial was a combination of Ace-i and pimobendan (n 1⁄4 334, 51%) [3]. A difference was found in the proportion of dogs pre-scribed pimobendan ($P < 0.001$), Ace-i ($P < 0.001$), and spironolactone ($P < 0.001$) before and after the publication of the EPIC trial (Figs. 1e3). In particular, there was a four-fold increase in pimobendan prescription and, respectively, 30% and 15% reductions in prescriptions of spironolactone and Ace-i after publication of the EPIC trial [3].

Stage-C dogs

A cardiac treatment was prescribed in all dogs in Stage-C (Table 4). In one dog, torsemide was chosen as a diuretic due to documented lack of response to furosemide (reoccurrence of CS of CHF despite a daily dose of 10.5 mg/kg of furosemide). Dogs for which Ace-I, pimobendan or spironolactone were prescribed had greater LA:Ao ($P < 0.001$) and LVDd_N ($P < 0.001$) compared to dogs in which these drugs were not prescribed (Table 10).
Pulmonary hypertension was diagnosed in 714 dogs in this stage (58%), and 279 had ePAP >55 mmHg (31%). In 30 of these dogs (11%), a concomitant respiratory disease was reported. Sildenafil was prescribed in 63 dogs (7%), and 57 (90%) of them had ePAP >55 mmHg. Twenty-two of these dogs (35%) had a history of syncopal episodes, while 13 presented with ascites (20%). In 10 dogs in which sildenafil was prescribed a concomitant respiratory disease was also diagnosed. Thirty-six dogs (57%) were already receiving a medical treatment which included furosemide at the time of sildenafil prescription.
A diagnosis of SHT was made in 38 dogs (3%), and in 17 (45%), amlodipine was prescribed. Proteinuria was diagnosed in four dogs (0.3%), and benazepril was prescribed as treatment in one dog (25%) before the onset of CHF. Arrhythmias were identified in 204 dogs (17%) with atrial

premature complexes (n 1⁄4 90, 7%) and ventricular premature complexes (n 1⁄4 55, 5%) being the most common rhythm abnormalities.
Antiarrhythmic treatment was prescribed in 44 of these dogs (22%) (Tables 1 and 5).

Discussion

This study describes the medical treatment pre- scribed or modified by veterinary cardiologists in a large population of dogs affected by MMVD. Moreover, it analyzes the effect of the EPIC trial and selected echocardiographic variables on cardiologists' prescription habits [3].
The result of this study showed that a medical treatment for MMVD was started by the referring veterinarian in 16% of the dogs. However, in 88% of these dogs, the medical treatment was discontinued or modified by the cardiologist. This observation suggests that specialist assessment, play a central role in the prescription of medical treatment in dogs affected by MMVD.
In our population, a medical treatment was prescribed by the cardiologist in 15% of dogs in Stage-B1, and Ace-i were the most common drugs prescribed in these patients. The use of Ace-i in Stage-B1 dogs is still controversial since published literature suggest no or minimal benefit in using this class of drugs in dogs without current or past clinical signs of CHF, and no or minimal cardiac remodeling [9,10]. Interestingly, 84% of the dogs in which an Ace-i was prescribed had echocardiographic evidence of either LA or LV enlargement. Therefore, the presence of chamber enlargement may represent the reason behind the prescription of Ace-i by the cardiologists in dogs in Stage-B1 in our population. Moreover, it should also be pointed out that, although minimal, the possible benefit, the lack of major side effects, and the relatively low cost of treatment may have influenced the cardiologists' decisions not to discontinue treatment in dogs in which the referring veterinarian started an Ace-i [9].
A combination of Ace-i and pimobendan represented the most common treatment prescribed in dogs in Stage-B2 in our population. It is of interest that before the publication of the EPIC trial, the most common treatment prescribed in dogs in this stage was represented by Ace-i alone [3]. After the publication of the EPIC trial, our results showed a four-fold increase in the prescription of pimobendan, demonstrating that the results of this trial have modified cardiologists' medical treatment in dogs with MMVD [3]. Interestingly, this was also associated with a 30% reduction in the prescription of spironolactone and a 15% reduction in the prescription of Ace-i. The reason for the increase in pimobendan prescription is intuitive because benefit has been shown. An explanation for the decrease in the prescription of spironolactone and Ace-i after publication of the results of EPIC is less obvious but reasons might include: a concern that prescription of multiple medications might unhelpfully burden the pet-owner, cost and lack of data that support the hypothesis that these drugs delay the onset of CS [3].
A medical treatment was prescribed by a cardiologist for all dogs in Stage-C. This is not surprising considering that all dogs in Stage-C in our population must have had current or past clinical signs of CHF that responded to medical treatment, which included furosemide. Furosemide together with Ace-i and pimobendan was the most common medical treatment prescribed in these dogs while 30% of our dogs in Stage-C were receiving spironolactone in addition to furosemide, Ace-i, and pimobendan. The use of these drugs in these patients is foreseeable and it is in agreement with what is currently recommended by the guidelines [4].
Figure 2 Distribution of spironolactone prescription in dogs in Stage-B2 before and after the publication of the EPIC trial ($P < 0.001$).
Post capillary PH is a relatively common sequela of MMVD, particularly in dogs with chamber enlargement [7]. In our population, 588 dogs in Stage-B1 were diagnosed with PH based on the TR peak velocity. Since dogs in this stage have normal chamber dimensions, PH is more likely

to be secondary to disorders such as primary respiratory diseases rather than being post-capillary and secondary to MMVD. Therefore, it was to be expected that sildenafil would often be prescribed in these dogs [11]. However, a relatively small proportion of these dogs (6%, n 1⁄4 35) were receiving sildenafil. This can be explained by the fact that PH was mild in most dogs since only 89 dogs in this stage had ePAP >55 mmHg as well as the lack of a clear effect on outcome of sildenafil in dogs that do not have clinical signs secondary to PH [12]. Additionally, it has also been shown that estimation of systolic pulmonary artery pressure based on the TR peak velocity is an unreliable method and can lead to both underestimation and overestimation of the true systolic pulmonary artery pressure [13e15]. For this reason, the guidelines for the diagnosis of PH in dogs recommend that the diagnosis of PH is based on the presence of clinical signs and concomitant evidence of secondary changes consistent with the presence of PH such as right ventricular hypertrophy or dilation of the pulmonary artery, rather than solely on TR peak velocity, particularly in dogs without echocardiographic evidence of chamber enlargement [6]. The lack of secondary echocardiographic changes and clinical signs in the vast majority of the dogs with PH could explain why only few dogs were prescribed sildenafil.

The evaluation of cause and treatment for PH in dogs in Stage-B2 is challenging since these dogs have chamber enlargement, and PH may be secondary to MMVD. In most dogs with an ePAP >55 mmHg, PH was considered secondary to MMVD by the cardiologist; therefore, sildenafil was not prescribed. On the other hand, most dogs in which sildenafil was prescribed had evidence of con- comitant respiratory disease.

Pulmonary hypertension was identified in 58% of the dogs in Stage-C, similar to what has been previously reported [7]. The etiology of PH in these dogs is most likely to have been secondary to MMVD, although in some cases concomitant respi- ratory disease may also have played a role. Therefore, it is not surprising that most dogs with

no clinical signs secondary to PH were not receiv- ing sildenafil. On the other hand, 50% of the dogs with clinical signs of PH such as ascites and syncopal episodes were receiving sildenafil. While post-capillary PH secondary MMVD is a passive process due to an increase in left atrial pressure, over time this can lead to pathological changes in the pulmonary arteries and arterioles that leads to out of proportion PH [16]. Therefore the use of sildenafil in these patients, especially those with clinical signs, is recommended [6].

The prevalence of SHT is low in the canine population, and SHT is usually associated with other diseases such as chronic renal disease [17]. This agrees with the results of our study in which SHT was diagnosed in 4% of our population. Angiotensin-converting enzyme inhibitors are commonly used as first-line treatment in dogs with SHT [18]. However, since Ace-i have been shown to have a negligible effect in reducing systemic blood pressure, amlodipine is commonly added to control blood pressure [18]. Nevertheless, in our population, amlodipine was prescribed only in 31% of the dogs with SHT. This could be related to the fact that while a presumptive diagnosis of SHT was first made at the enrollment visit, reevaluation of the blood pressure by the referring veterinarian was recommended as a follow-up. Therefore, the decision about prescribing drugs specifically aimed to control blood pressure may have been deferred to the referring veterinarian.

Arrhythmias were relatively uncommon in our population, in agreement with what has previously been reported in dogs with MMVD [2]. In our population, most arrhythmias were represented by rhythm disturbances such as atrial premature complexes or ventricular premature complexes that occurred singly. Therefore, it is not surprising that a relatively small number of dogs were receiving antiarrhythmic treatment.

Limitations

This study has some limitations. First, our results may only reflect cardiologists' prescription habits in the thirteen referral centers, and geographic location, as well as cardiologists' training, may have also played a role. Therefore, our results cannot necessarily be generalized to all dogs affected by MMVD seen by a cardiologist.
Second, the diagnosis of concomitant disease and the execution of additional diagnostic tests was based on patient history, CS, and clinical judgment of the cardiologist or referring veterinarian. There- fore, the possibility that there were misdiagnoses of concomitant diseases cannot be excluded.
Third, the dichotomization of data in dogs enrolled before and after the EPIC trial is artificial [3]. While October first was arbitrarily chosen because the EPIC trial was published on September 28, 2016, the exact date on which cardiologists changed their prescription habits after the publication of the EPIC trial would be difficult to establish [3]. While changes in prescription habits may have occurred slightly before or slightly after the arbitrary date that was chosen, our results showed a significant change in prescription habits over the three year study period. Therefore, our results should be considered valid despite the limitation of artificial dichotomization.
Lastly, dogs in Stage-C were classified based on the presence of clinical signs of CHF or prescription of furosemide by the cardiologist based on physical examination and echocardiographic findings and thoracic radiographs were not always obtained. Therefore, the possibility that some dogs were misdiagnosed cannot be excluded. However, although thoracic radiographs are con- sidered the gold standard for the assessment of CHF in dogs, their interpretation, particularly in mild cases is subjective. Therefore, considering this limitation they are not always obtained in the everyday cardiology practice.

Conclusions

In conclusion, we describe the cardiac medical treatment in a large population of dogs affected by MMVD. Our results showed that the publication of the EPIC trial and echocardiographic LA and LV dimensions influenced cardiologist prescription habits [3].

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Tables and Figures

Table 1 Signalment, electrocardiographic and echocardiographic findings of the 6,016 dogs included in this study. Minimum and maximal values and 25th (Q1) and 75th (Q3) percentile are reported for continuous variables.

	Total n = 6,016	Stage-B1 n = 3,891	Stage-B2 n = 889	Stage-C n = 1,236
Age	10 (1–19) Q1: 9 Q3: 12 n = 6,016	10 (1–19) Q1: 8 Q3: 12 n = 3,891	11 (1–17) Q1: 9 Q3: 12 n = 889	11 (1–18) Q1: 9 Q3: 12 n = 1,236
Body weight	7.9 (1–82.4) Q1: 5.2 Q3: 12.4 n = 6,012	8.4 (1–71.8) Q1: 5.5 Q3: 13.7 n = 3,891	7.1 (1.7–47.2) Q1: 5 Q3: 10.6 n = 889	7.0 (1–82.4) Q1: 4.6 Q3: 10.7 n = 1,232
Sex				
Male	n = 3,163 53%	n = 2,030 52%	n = 491 55%	n = 642 52%
Sinus arrhythmia	n = 1,359 23%	n = 1,092 28%	n = 168 19%	99 8%
APCs	n = 212 4%	n = 92 2%	n = 30 3%	n = 90 7%
VPCs	n = 197 3%	n = 107 3%	n = 35 4%	n = 55 5%
II and III AVB	n = 63 1%	n = 51 1%	n = 7 1%	n = 5 0.4%
AFib	n = 61 1%	n = 5 0.1%	n = 3 0.4%	n = 53 4%
SVT	n = 39 0.6%	n = 16 0.4%	n = 2 0.2%	n = 21 2%
VT	n = 20 0.3%	n = 12 0.3%	n = 2 0.2%	n = 6 0.5%
SSS	n = 2 0.03%	n = 2 0.1%	n = 0 /	n = 0 /
LA:Ao	1.44 (0.58–4.24) Q1: 1.25 Q3: 1.8 n = 6,006	1.31 (0.58–2.37) Q1: 1.19 Q3: 1.44 n = 3,891	1.82 (1.60–3.18) Q1: 1.7 Q3: 2.0 n = 889	2.11 (1.08–4.24) Q1: 1.86 Q3: 2.42 n = 1,226
LVIDd_N	1.69 (0.74–3.36) Q1: 1.52 Q3: 1.93 n = 5,997	1.58 (0.74–3.19) Q1: 1.46 Q3: 1.69 n = 3,891	1.95 (1.70–3.10) Q1: 1.83 Q3: 2.09 n = 889	2.09 (1.04–3.36) Q1: 1.88 Q3: 2.28 n = 1,217
TR peak velocity m/s	2.78 (0.27–6.37) Q1: 2.37 Q3: 3.18 n = 4,337	2.63 (0.27–6.37) Q1: 2.23 Q3: 2.95 n = 2,589	2.83 (0.67–5.61) Q1: 2.47 Q3: 3.2 n = 692	3.26 (0.70–5.83) Q1: 2.85 Q3: 3.74 n = 1,056
PH yes (based on TR peak velocity)	n = 1,567 26%	n = 588 15%	n = 265 30%	n = 714 58%

Afib: atrial fibrillation; APC: atrial premature complex; AVB: Atrio ventricular block; LA:Ao: left atrium-aortic ratio; LVIDd_N: Left ventricle internal diameter at end-diastole indexed by body size; PH: pulmonary hypertension; Q1: 25th percentile: Q3: 75th percentile; SSS: sick sinus syndrome; SVT: supraventricular tachycardia; VPC: ventricular premature complex; TR: tricuspid regurgitation; VT: ventricular tachycardia.

Table 2 Cardiac medical treatment prescribed by referring veterinarians and by cardiologists in dogs in Stage-B1. All data are presented as median, range, 25th and 75th percentile, regardless of distribution for consistency of presentation.

	Cardiac treatment prescribed by referring veterinarians in Stage-B1 n = 3,891		Cardiac treatment prescribed by cardiologists in Stage-B1 n = 3,891	
	N	Daily dosage (mg/kg)	N	Daily dosage (mg/kg)
Cardiac treatment	n = 259, 7%		n = 566, 15%	
Loop diuretic	n = 155, 4%		n = 0	
Furosemide total	n = 155, 4%	2.6 (0.46–9.0) Q1: 1.89 Q3: 3.73 n = 131	n = 0	/
Furosemide alone	n = 53, 1%	2.14 (0.81–5.26) Q1: 1.68 Q3: 3.25 n = 45	n = 0	/
Furosemide + Ace-i	n = 45, 1%		n = 0	/
Furosemide		2.48 (0.46–9) Q1: 1.19 Q3: 3.68 n = 38		
Ace-i		0.66 (0.26–1.54) Q1: 0.44 Q3: 0.90 n = 38		
Furosemide + Pimobendan	n = 16, 0.4%		n = 0	/
Furosemide		2.91 (1.49–5.8) Q1: 2.29 Q3: 4.24 n = 15		
Pimobendan		0.44 (0.2–0.66) Q1: 0.31 Q3: 0.58 n = 15		
Furosemide + Spironolactone	n = 1, 0.03%		n = 0	
Furosemide		3.51		
Spironolactone		3.77		
Furosemide + Ace-i + Pimobendan	n = 38, 1%		n = 0	/
Furosemide		2.91 (0.5–5.62) Q1: 1.98 Q3: 4.46 n = 31		
Ace-i		0.79 (0.25–1.32) Q1: 0.6 Q3: 0.97 n = 35		
Pimobendan		0.48 (0.23–1.2) Q1: 0.37 Q3: 0.54 n = 35		
Furosemide + Ace-i + Spironolactone	n = 1, 0.03%		n = 0	
Furosemide		0.91, n = 1		
Ace-i		0.91, n = 1		
Spironolactone		1.14, n = 1		
Furosemide + Ace-i + Pimobendan + Spironolactone	n = 1, 0.03%		n = 0	/
Furosemide		3.0, n = 1		
Ace-i		0.60, n = 1		
Pimobendan		0.3, n = 1		
Spironolactone		1.0, n = 1		
Ace-i total	n = 160, 4%	0.75 (0.24–2.32) Q1: 0.54 Q3: 0.94 n = 143	n = 388, 10%	0.9 (0.12–2.1) Q1: 0.75 Q3: 1.04 n = 388
Benazepril	n = 11	0.54 (0.33–0.91) Q1: 0.49 Q3: 0.86 n = 11	n = 207 5%	0.9 (0.17–2.1) Q1: 0.76 Q3: 1.04 n = 207
Enalapril	n = 143	0.75 (0.24–2.32) Q1: 0.56 Q3: 0.96 n = 131	n = 170 4%	0.9 (0.36–1.44) Q1: 0.74 Q3: 1.03 n = 170
Lisinopril	n = 1	1.39 n = 1	n = 11 0.3%	0.76 (0.12–1.22) Q1: 0.48 Q3: 0.94 n = 11
Unspecified	n = 5	/		

Ace-i alone	n = 57, 2%	0.76 (0.23–2.32) Q1: 0.6 Q3: 1.06 n = 53	n = 266, 7%	0.90 (0.12–2.1) Q1: 0.76 Q3: 1.04 n = 266
Ace-i + Pimobendan	n = 15, 0.4%		n = 96, 3%	
Ace-i		0.67 (0.39–1.39) Q1: 0.47 Q3: 0.79 n = 12		0.87 (0.27–1.28) Q1: 0.72 Q3: 1.0 n = 96
Pimobendan		0.52 (0.2–0.69) Q1; 0.44 Q3: 0.59 n = 14		0.50 (0.24–0.78) Q1: 0.44 Q3: 0.56 n = 96
Ace-i + Spironolactone	n = 2, 0.05%		n = 20, 0.5%	
Ace-i		0.84 (0.81–0.86) Q1 0.81 Q3: 0.86 n = 2		0.94 (0.38–1.36) Q1: 0.77 Q3: 1.13 n = 20
Spironolactone		2.09 (2.02–2.16) Q1: 2.02 Q3: 2.16 n = 2		2.00 (1.38–3.94) Q1: 1.8 Q3: 2.9 n = 20
Ace-i + Pimobendan + Spironolactone	n = 1, 0.03%		n = 6, 0.2%	
Ace-i		0.49, n = 1		0.93 (0.72–1.26) Q1: 0.77 Q3: 1.22 n = 6
Pimobendan		0.49, n = 1		0.51 (0.26–0.8) Q1: 0.37 Q3: 0.68 n = 6
Spironolactone		4.9, n = 1		2.33 (1.81–4.02) Q1: 1.88 Q3: 3.38 n = 6
Pimobendan total	n = 99, 3%	0.46 (0.2–1.2) Q1: 0.37 Q3: 0.55 n = 88	n = 230, 6%	0.5 (0.22–1.08) Q1: 0.44 Q3: 0.56 n = 230
Pimobendan alone	n = 28, 0.7%	0.43 (0.21–0.73) Q1: 0.35 Q3: 0.52 n = 22	n = 123, 3%	0.5 (0.22–1.08) Q1: 0.45 Q3: 0.56 n = 123
Pimobendan + Spironolactone	n = 0		n = 5, 0.1%	
Pimobendan		/		0.50 (0.42–0.56) Q1: 0.43 Q3: 0.55 n = 5
Spironolactone		/		2.09 (1.38–2.66) Q1: 1.72 Q3: 2.56 n = 5
Spironolactone total	n = 7, 0.2%	2.04 (1–4.09) Q1: 1.14 Q3: 3.77 n = 7	n = 32, 0.8%	2.06 (1.38–4.02) Q1: 1.84 Q3: 2.77 n = 32
Spironolactone alone	n = 1, 0.03%	2.04, n = 1	n = 1, 0.03%	2.08, n = 1

Ace-i: angiotensin converting enzyme inhibitors; Q1: 25th percentile; Q3: 75th percentile.

Table 3 Cardiac medical treatment prescribed by referring veterinarians and by cardiologists in dogs in Stage-B2. All data are presented as median, range, 25th and 75th percentile, regardless of distribution for consistency of presentation.

	Cardiac treatment prescribed by referring veterinarians in Stage-B2 n = 889		Cardiac treatment prescribed by cardiologists in Stage-B2 n = 889	
	N	Daily dosage (mg/kg)	N	Daily dosage (mg/kg)
Cardiac treatment	n = 108, 12%		n = 797, 90%	
Loop diuretic	n = 36, 4%		n = 1, 0.1%	
Furosemide total	n = 36, 4%	2.29 (0.58–7.14) Q1: 1.85 Q3: 3.64 n = 36	n = 1, 0.1%	1.58
Furosemide alone	n = 13, 2%	2.40 (1.04–5.94) Q1: 1.67 Q3: 3.12 n = 12	n = 1, 0.1%	1.58
Furosemide + Ace-i	n = 12, 1%		n = 0	/
Furosemide		3.21 (0.8–5.56) Q1: 1.70 Q3: 4.86 n = 10		
Ace-i		0.62 (0.32–1.66) Q1: 0.47 Q3: 1.04 n = 12		
Furosemide + Pimobendan	n = 5, 0.6%		n = 0	/
Furosemide		2.08 (1.3–7.14) Q1: 1.65 Q3: 5.38 n = 5		
Pimobendan		0.50 (0.40–0.71) Q1: 0.41 Q3: 0.68 n = 5		
Furosemide + Ace-i + Pimobendan	n = 5, 0.6%		n = 0	/
Furosemide		2.16 (0.58–5.40) Q1: 0.97 Q3: 4.59 n = 4		
Ace-i		0.67 (0.43–1.0) Q1: 0.44 Q3: 0.97 n = 4		
Pimobendan		0.43 (0.40–0.47) Q1: 0.41 Q3: 0.46 n = 4		
Furosemide + Ace-i + Pimobendan + Spironolactone	n = 1, 0.1%		n = 0	/
Furosemide		16.3, n = 1		
Ace-i		0.74, n = 1		
Pimobendan		0.55, n = 1		
Spironolactone		3.68, n = 1		
ACE-I total	n = 78, 9%	0.73 (0.18–1.66) Q1: 0.5 Q3: 0.95 n = 73	n = 569, 64%	0.94 (0.2–1.92) Q1: 0.82 Q3: 1.04 n = 568
Benazepril	n = 4 0.4%	0.72 (0.54–0.96) Q1: 0.56 Q3: 0.92 n = 4	n = 287 32%	0.94 (0.32–1.92) Q1: 0.82 Q3: 1.02 n = 287
Enalapril	n = 73 8%	0.73 (0.18–1.66) Q1: 0.49 Q3: 0.95 n = 69	n = 263 30%	0.93 (0.2–1.66) Q1: 0.82 Q3: 1.04 n = 262
Lisinopril	n = 1 0.1%	/	n = 19 2%	0.9 (0.4–1.2) Q1: 0.76 Q3: 1.06 n = 19
Ace-i alone	n = 44, 5%	0.70 (0.29–1.39) Q1: 0.5 Q3: 0.90 n = 40	n = 93, 11%	0.98 (0.32–1.92) Q1: 0.82 Q3: 1.5 n = 93
Ace-i + Pimobendan	n = 13, 2%		n = 367, 41%	
ACE-I		0.83 (0.18–1.09) Q1: 0.61 Q3: 0.95 n = 13		0.92 (0.20–1.66) Q1: 0.82 Q3: 1.04 n = 366
Pimobendan		0.52 (0.22–0.68) Q1: 0.44 Q3: 0.57 n = 12		0.50 (0.26–1.2) Q1: 0.46 Q3: 0.55 n = 366
Ace-i + Spironolactone	n = 0	/	n = 69, 8%	

ACE_i				0.94 (0.68—1.22) Q1: 0.85 Q3: 1.04 n = 69
Spironolactone				2.16 (1.28—2.14) Q1: 1.83 Q3: 2.59 n = 69
Ace-i + Pimobendan + Spironolactone	n = 3, 0.3%		n = 40, 5%	
Ace-i		0.96 (0.88—1.1) Q1: 0.88 Q3: 1.1 n = 3		0.95 (0.44—1.38) Q1: 0.83 Q3: 1.04 n = 40
Pimobendan		0.48 (0.41—0.88) Q1: 0.41 Q3: 0.88 n = 3		0.52 (0.36—0.88) Q1: 0.46 Q3: 0.6 n = 40
Spironolactone		1.37 (1.2—4.39) Q1: 1.2 Q3: 4.39 n = 3		2.18 (1.22—4.98) Q1: 1.63 Q3: 3.09 n = 40
Pimobendan total	n = 39, 4%	0.51 (0.22—0.88) Q1: 0.43 Q3: 0.59 n = 36	n = 628, 71%	0.50 (0.26—1.02) Q1: 0.45 Q3: 0.56 n = 628
Pimobendan alone	n = 12, 1%	0.55 (0.37—0.88) Q1: 0.45 Q3: 0.61 n = 11	n = 209, 24%	0.50 (0.26—1.07) Q1: 0.44 Q3: 0.56 n = 209
Pimobendan + Spironolactone	n = 0	/	n = 12, 1%	
Pimobendan				0.49 (0.38—0.66) Q1: 0.43 Q3: 0.58 n = 12
Spironolactone				1.88 (1.04—2.36) Q1: 1.46 Q3: 2.13 n = 12
Spironolactone total	n = 4, 0.5%	2.53 (1.2—4.39) Q1: 1.24 Q3: 4.21 n = 4	n = 122, 14%	2.16 (1.04—4.98) Q1: 1.72 Q3: 2.64 n = 122
Spironolactone alone	n = 0	/	n = 1, 0.1%	3.76 n = 1

Ace-i: angiotensin converting enzyme inhibitor; Q1: 25th percentile Q3: 75th percentile.

Table 4 Cardiac medical treatment prescribed by referring veterinarians and by cardiologists in dogs in Stage-C. All data are presented as median, range, 25th and 75th percentile, regardless of distribution for consistency of presentation.

	Cardiac treatment prescribed by referring veterinarians in Stage-C n = 1,236		Cardiac treatment prescribed by cardiologists in Stage-C n = 1,236	
	N	Daily dosage (mg/kg)	N	Daily dosage (mg/kg)
Cardiac treatment	n = 607, 49%		n = 1,236, 100%	
Loop diuretic	n = 543, 44%		n = 1,236, 100%	
Furosemide total	n = 543, 44%	3.36 (0.4–12.5) Q1: 2.18 Q3: 4.47 n = 538	n = 1,235, 99.9%	3.59 (0.41–12.69) Q1: 2.54 Q3: 4.32 n = 1,235
Torsemide total	n = 0	/	n = 1, 0.08%	1.06
Furosemide alone	n = 125, 10%	3.26 (0.56–10.7) Q1: 2.23 Q3: 4.46 n = 124	n = 13, 1%	2.46 (1.46–5.16) Q1: 2.08 Q3: 3.28 n = 13
Furosemide + Ace-i	n = 130, 11%		n = 54, 4%	
Furosemide		3.05 (0.68–12.5) Q1: 1.85 Q3: 4.11 n = 128		2.19 (0.65–5.4) Q1: 1.72 Q3: 3.41 n = 54
Ace-i		0.81 (0.25–2.32) Q1: 0.56 Q3: 0.99 n = 127		0.93 (0.54–2.28) Q1: 0.82 Q3: 1.11 n = 54
Furosemide + Pimobendan	n = 94, 8%		n = 59, 5%	
Furosemide		3.50 (0.91–9.76) Q1: 2.32 Q3: 5 n = 94		3.1 (0.41–9.15) Q1: 2 Q3: 4.08 n = 59
Pimobendan		0.49 (0.18–1.0) Q1: 0.38 Q3: 0.56 n = 94		0.54 (0.24–1.29) Q1: 0.48 Q3: 0.60 n = 59
Furosemide + Ace-i + Pimobendan	n = 175, 14%		n = 704, 57%	
Furosemide		3.44 (0.84–11.7) Q1: 2.14 Q3: 4.52 n = 174		3.38 (0.66–11.4) Q1: 2.4 Q3: 4.12 n = 704
Ace-i		0.80 (0.19–1.85) Q1: 0.6 Q3: 1.20 n = 172		0.90 (0.20–2.34) Q1: 0.76 Q3: 1.02 n = 704
Pimobendan		0.49 (0.15–1.22) Q1: 0.41 Q3: 0.58 n = 174		0.52 (0.22–1.28) Q1: 0.46 Q3: 0.58 n = 704
Furosemide + Ace-i + Pimobendan + Spironolactone	n = 17, 1%		n = 370, 30%	
Furosemide		4.60 (1.2–11.01) Q1: 3.6 Q3: 5.71 n = 17		4.02 (0.74–12.79) Q1: 3.48 Q3: 4.7 n = 370
Ace-i		0.89 (0.34–1.27) Q1: 0.48 Q3: 1.07 n = 17		0.92 (0.24–1.78) Q1: 0.8 Q3: 1.04 n = 370
Pimobendan		0.55 (0.41–0.93) Q1: 0.48 Q3: 0.61 n = 17		0.54 (0.22–1.48) Q1: 0.48 Q3: 0.6 n = 370
Spironolactone		2.69 (1.2–5.88) Q1: 1.81 Q3: 4.23 n = 16		2.30 (0.92–4.800) Q1: 1.86 Q3: 2.78 n = 370
Furosemide + Ace-i + Spironolactone	n = 0	/	n = 22, 2%	
Furosemide				2.30 (0.9–4.84) Q1: 1.88 Q3: 3.86 n = 22
Ace-i				1.02 (0.7–1.78) Q1: 0.83 Q3: 1.12 n = 22
Spironolactone				2.27 (1.18–4.50) Q1: 1.83 Q3: 2.70 n = 22
Furosemide + Pimo + Spironolactone	n = 2, 0.2%		n = 13, 1%	
Furosemide		5.1 (4.88–5.32) Q1: 4.88 Q3: 5.32 n = 2		4.08 (1.8–6.14) Q1: 3.30 Q3: 5.09 n = 13
Pimobendan		0.47 (0.41–0.53) Q1: 0.41 Q3: 0.53 n = 2		0.52 (0.44–1.26) Q1: 0.46 Q3: 0.61 n = 13
Spironolactone		2.35 (0.66–4.03) Q1: 0.66 Q3: 4.02 n = 2		2.31 (1.28–3.68) Q1: 2.06 Q3: 2.45 n = 13
ACE-I total	n = 371, 30%	0.81 (0.19–2.32) Q1: 0.58 Q3: 1.0 n = 366	n = 1,150, 93%	0.92 (0.2–2.34) Q1: 0.78 Q3: 1.04 n = 1,151
Benazepril	n = 24 2%	0.80 (0.24–1.59) Q1: 0.59 Q3: 1.01 n = 24	n = 456 37%	0.91 (0.24–1.78) Q1: 0.76 Q3: 1.02 n = 456
Enalapril	n = 344 28%	0.81 (0.19–2.32) Q1: 0.58 Q3: 1.0 n = 340	n = 688 56%	0.92 (0.2–2.34) Q1: 078 Q3: 1.04 n = 686

	Cardiac treatment prescribed by referring veterinarians in Stage-C n = 1,236		Cardiac treatment prescribed by cardiologists in Stage-C n = 1,236	
	N	Daily dosage (mg/kg)	N	Daily dosage (mg/kg)
Lisinopril	n = 0	/	n = 6 0.5%	0.98 (0.56–1.14) Q1: 0.74 Q3: 1.05 n = 6
Unspecified	n = 3	/	/	/
Ace-i alone	n = 34, 3%	0.81 (0.35–1.25) Q1: 0.59 Q3: 1.0 n = 33	n = 0	
Ace-i + Pimobendan	n = 11, 0.9%		n = 0	
ACE-I		0.80 (0.3–1.4) Q1: 0.47 Q3: 1.04 n = 11		
Pimobendan		0.42 (0.24–0.66) Q1: 0.35 Q3: 0.51 n = 11		
Ace-i + Spironolactone	n = 1, 0.08%		n = 0	
ACE_i		0.45, n = 1		
Spironolactone		4.5, n = 1		
Ace-i + Pimobendan + Spironolactone	n = 3, 0.2%		n = 0	
Ace-i		0.83 (0.66–0.99) Q1: 0.66 Q3: 0.99 n = 3		
Pimobendan		0.50 (0.25–0.66) Q1: 0.25 Q3: 0.66 n = 3		
Spironolactone		1.66 (1.60–2.08) Q1: 1.60 Q3: 2.08 n = 3		
Pimobendan total	n = 316, 26%	0.49 (0.15–1.22) Q1: 0.41 Q3: 0.58 n = 315	n = 1,146, 93%	0.52 (0.22–1.48) Q1: 0.48 Q3: 0.58 n = 1.146
Pimobendan alone	n = 14, 1%	0.51 (0.22–0.70) Q1: 0.40 Q3: 0.59 n = 14	n = 0	
Spironolactone total	n = 23, 2%	2.43 (0.66–5.88) Q1: 1.70 Q3: 4.05 n = 22	n = 405, 33%	2.30 (0.92–4.8) Q1: 1.87 Q3: 2.78 n = 405

Ace-i: angiotensin converting enzyme inhibitor; Q1: 25th percentile Q3: 75th percentile.

Table 5 Modification of cardiac medical therapy by cardiologists according to stage.

	Stage-B1 n = 3,891	Stage-B2 n = 889	Stage-C n = 1,236
Loop diuretic	n = 155	n = 35	n = 320
Suspended	n = 155	n = 35	n = 0
Started	n = 0	n = 0	n = 57
Increased	n = 0	n = 0	n = 170
Decreased	n = 0	n = 0	n = 93
Ace-i	n = 111	n = 54	n = 333
Suspended	n = 81	n = 8	n = 11
Started	n = 14	n = 20	n = 218
Increased	n = 12	n = 24	n = 91
Decreased	n = 4	n = 2	n = 13
Pimobendan	n = 93	n = 58	n = 334
Suspended	n = 65	n = 0	n = 0
Started	n = 19	n = 50	n = 241
Increased	n = 7	n = 6	n = 89
Decreased	n = 2	n = 2	n = 4
Spironolactone	n = 10	n = 18	n = 195
Suspended	n = 3	n = 0	n = 0
Started	n = 6	n = 17	n = 186
Increased	n = 0	n = 1	n = 7
Decreased	n = 1	n = 0	n = 2

Ace-i: angiotensin converting enzyme inhibitor.

Table 6 Median and range of left atrium to aortic ratio (LA:Ao) and normalized left ventricular internal diastolic dimeter normalized in (LVIDd_N) in dogs in Stage-B1 in which angiotensin converting enzyme inhibitor (Ace-i), pimobendan or Spironolactone were or were not prescribed. The 36 dogs in which Ace-i were prescribed due to systemic hypertension and/or proteinuria were excluded from the Ace-i analysis.

Drug	LA:Ao	LVIDd_N
Ace-i		
Yes	1.5 (0.78—2.3)	1.70 (0.83—2.50)
n = 352	Q1: 1.36 Q3: 1.58	Q1: 1.6 Q3: 1.88
No	1.29* (0.58—2.37)	1.56* (0.74—2.38)
n = 3,503	Q1: 1.18 Q3: 1.42	Q1: 1.45 Q3: 1.68
Pimobendan		
Yes	1.56 (0.78—2.36)	1.74 (0.83—2.50)
n = 230	Q1: 1.40 Q3: 1.64	Q1: 1.64 Q3: 1.93
No	1.29* (0.58—2.37)	1.57* (0.74—2.49)
n = 3,661	Q1: 1.19 Q3: 1.42	Q1: 1.45 Q3: 1.68
Spironolactone		
Yes	1.50 (1.06—2.00)	1.81 (1.46—2.50)
n = 32	Q1: 1.34 Q3: 1.56	Q1: 1.63 Q3: 1.99
No	1.30* (0.58—2.37)	1.58* (0.74—2.49)
n = 3,859	Q1: 1.19 Q3: 1.44	Q1: 1.45 Q3: 1.69

Table 7 Antiarrhythmic treatment according to Stage. All data are presented as median, range, 25th and 75th percentile, regardless of distribution for consistency of presentation.

	Stage-B1 n = 3,891		Stage-B2 n = 889		Stage-C n = 1,236	
	N	Daily dosage (mg/kg)	N	Daily dosage (mg/kg)	N	Daily dosage (mg/kg)
Digoxin	n = 0		n = 4	0.0049 (0.0044—0.0054) Q1: 0.0045 Q3: 0.0053	n = 40	0.0068 (0.0026—0.007) Q1: 0.006 Q3: 0.0088
Digoxin + Diltiazem	n = 1		n = 0	/	n = 1	
Digoxin		0.008				0.008
Diltiazem		2.26				2.73
Diltiazem	n = 3	3.87 (1.44—7.89) Q1: 1.44 Q3: 7.89	n = 0	/	n = 3	3.36 (2.58—4.92) Q1: 2.58 Q3: 4.92
Sotalol	n = 20	1.88 (0.86—5) Q1: 1.49 Q3: 2.27	n = 3	3.46 (3.1—3.86) Q1: 3.1 Q3: 3.86	n = 0	/

Table 8 Median and range of left atrium to aortic ratio (LA:Ao) and left ventricular internal dimeter normalized in diastole (LVIDd_N) in dogs in Stage-B2 in which angiotensin converting enzyme inhibitor, pimobendan or Spironolactone were or not prescribed.

Drug	LA:Ao	LVIDd_N
Ace-i		
Yes	1.87 (1.60—2.91)	1.99 (1.70—3.10)
n = 569	Q1: 1.73 Q3: 2.06	Q1: 1.87 Q3: 2.13
No	1.75* (1.60—3.18)	1.87* (1.70—2.85)
n = 320	Q1: 1.67 Q3: 1.91	Q1: 1.78 Q3: 2.02
Pimobendan		
Yes	1.83 (1.60—3.18)	1.96 (1.70—3.10)
n = 628	Q1: 1.71 Q3: 2.00	Q1: 1.83 Q3: 2.11
No	1.79* (1.60—2.89)	1.92* (1.70—2.86)
n = 261	Q1: 1.67 Q3: 2.00	Q1: 1.81 Q3: 2.05
Spironolactone		
Yes	2.00 (1.60—2.81)	2.06 (1.71—3.10)
n = 122	Q1: 1.82 Q3: 2.20	Q1: 1.93 Q3: 2.34
No	1.80* (1.60—3.18)	1.93* (1.70—2.85)
n = 767	Q1: 1.69 Q3: 2.00	Q1: 1.81 Q3: 2.07

Table 9 Distribution of cardiac medical treatment in Stage-B2 before and after the publication of the EPIC trial. All data are presented as median, range, 25th and 75th percentile, regardless of distribution for consistency of presentation.

	Stage-B2 before EPIC n = 240		Stage-B2 after EPIC n = 649	
	N	Daily dosage (mg/kg)	N	Daily dosage (mg/kg)
Cardiac treatment	n = 198 83%		n = 593 91%	
Ace-i total	n = 183 76%	0.95 (0.42—1.92) Q1: 0.82 Q3: 1.04	n = 386 60%	0.92 (0.20—1.66) Q1: 0.82 Q3: 1.04
Ace-i alone	n = 78 33%	0.98 (0.42—1.92) Q1: 0.85 Q3: 1.05	n = 15 2%	0.92 (0.32—1.58) Q1: 0.78 Q3: 1.06
Benazepril	n = 48 20%		n = 8 1%	
Enalapril	n = 38 16%		n = 7 1%	
Lisinopril	n = 2 0.8%		n = 0 /	
Ace-i + Pimobendan	n = 33 14%		n = 334 52%	
ACE-I		0.90 (0.58—1.12) Q1: 0.78 Q3: 1.04		0.92 (0.2—1.66) Q1: 0.82 Q3: 1.04
Pimobendan		0.50 (0.36—0.60) Q1: 0.42 Q3: 0.56		0.50 (0.26—1.20) Q1: 0.46 Q3: 0.54
Ace-i + Spironolactone	n = 67 28%		n = 2 0.3%	
ACE-I		0.94 (0.74—1.22) Q1: 0.86 Q3: 1.04		0.79 (0.68—0.90) Q1: 0.68 Q3: 0.90
Spironolactone		2.16 (1.28—4.14) Q1: 1.84 Q3: 2.60		1.98 (1.72—2.24) Q1: 1.72 Q3: 2.24
Ace-i + Pimobendan + Spironolactone	n = 5 2%		n = 35 5%	
Ace-i		0.82 (0.68—1.08) Q1: 0.71 Q3: 1.02		0.96 (0.44—1.38) Q1: 0.86 Q3: 1.04
Pimobendan		0.54 (0.42—0.68) Q1: 0.45 Q3: 0.64		0.51 (0.36—0.88) Q1: 0.46 Q3: 0.60
Spironolactone		2.03 (1.62—3.72) Q1: 1.65 Q3: 2.90		2.30 (1.22—4.98) Q1: 1.6 Q3: 3.12
Pimobendan total	n = 53 22%	0.52 (0.36—0.98) Q1: 0.42 Q3: 0.57	n = 575 89%	0.50 (0.26—1.20) Q1: 0.45 Q3: 0.56
Pimobendan alone	n = 14 6%	0.54 (0.36—0.98) Q1: 0.48 Q3: 0.67	n = 195 30%	0.50 (0.26—1.07) Q1: 0.44 Q3: 0.56
Pimobendan + Spironolactone	n = 1 0.4%		n = 11 2%	
Pimobendan		0.38		0.50 (0.40—0.66) Q1: 0.44 Q3: 0.58
Spironolactone		1.87		1.89 (1.04—2.36) Q1: 1.42 Q3: 2.16
Spironolactone total	n = 73 30%	2.16 (1.28—4.14) Q1: 1.83 Q3: 2.59	n = 49 8%	2.16 (1.04—4.98) Q1: 1.59 Q3: 2.86
Spironolactone alone	n = 0	/	n = 1 0.6%	3.76

Table 10 Median and range of left atrium to aortic ratio (LA:Ao) and normalized left ventricular internal diastolic dimeter (LVIDd_N) in dogs in Stage-C in which angiotensin converting enzyme inhibitor, pimobendan or Spironolactone were or not prescribed.

Drug	LA:Ao	LVIDd_N
Ace-i		
Yes	2.13 (1.10—4.24)	2.09 (1.04—3.36)
n = 1,151	Q1: 1.87 Q3: 2.43	Q1: 1.89 Q3: 2.29
No	1.87* (1.08—3.42)	1.88* (1.20—2.70)
n = 85	Q1: 1.68 Q3: 2.27	Q1: 1.69 Q3: 2.20
Pimobendan		
Yes	2.13 (1.10—4.24)	2.09 (1.20—3.36)
n = 1,147	Q1: 1.87 Q3: 2.45	Q1: 1.89 Q3: 2.29
No	1.84* (1.08—2.84)	1.94* (1.04—2.70)
n = 89	Q1: 1.67 Q3: 2.12	Q1: 1.67 Q3: 2.13
Spironolactone		
Yes	2.22 (1.30—4.24)	2.17 (1.34—3.22)
n = 405	Q1: 2.00 Q3: 2.53	Q1: 1.97 Q3: 2.36
No	2.01* (1.08—3.67)	2.04* (1.04—3.36)
n = 831	Q1: 1.82 Q3: 2.36	Q1: 1.84 Q3: 2.22

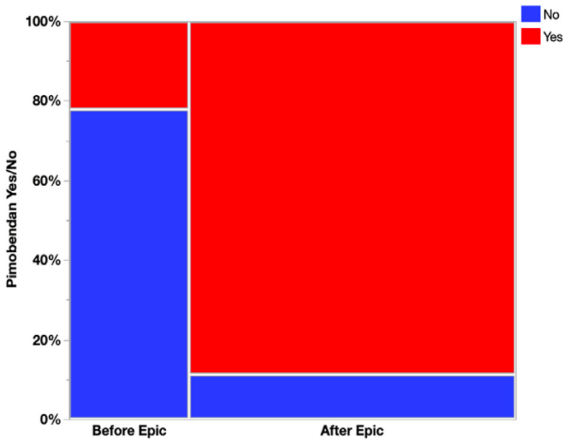

Figure 1 Distribution of pimobendan prescription in dogs in dogs in Stage-B2 before and after the publication of the EPIC trial ($P < 0.001$).

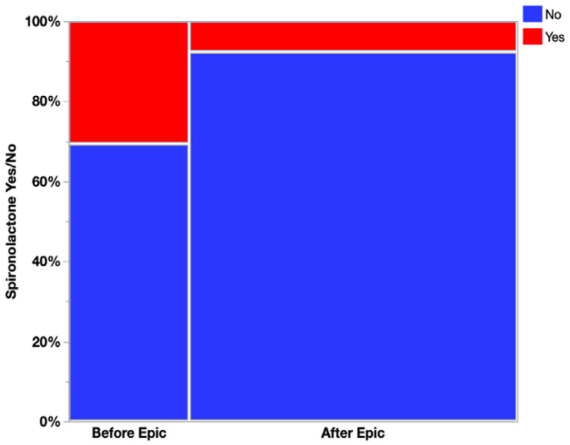

Figure 2 Distribution of spironolactone prescription in dogs in Stage-B2 before and after the publication of the EPIC trial ($P < 0.001$).

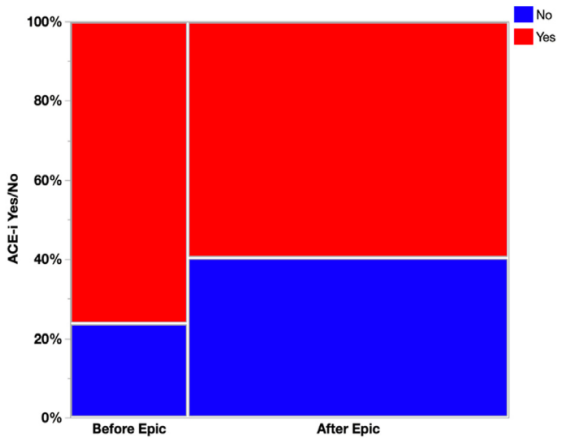

Figure 3 Distribution of angiotensin converting enzyme inhibitor (ACE-i) prescription in Stage-B2 dogs before and after the publication of the EPIC trial ($P < 0.001$).