Journal of Veterinary Cardiology (2024) **53**, 20—35

ELSEVIER

Journal of Veterinary Cardiology
ESVC

www.elsevier.com/locate/jvc

Efficacy and safety of antiarrhythmic therapy in dogs with naturally acquired tachyarrhythmias treated with amiodarone or sotalol: a retrospective analysis of 64 cases

G. Romito*, N. Gemma, F. Dondi, C. Mazzoldi, S. Fasoli, M. Cipone

Department of Veterinary Medical Sciences, Alma Mater Studiorum - University of Bologna, via Tolara di Sopra 50, 40064, Ozzano dell'Emilia, Italy

Received 22 July 2023; received in revised form 13 March 2024; accepted 15 March 2024

KEYWORDS
Arrhythmias;
Holter monitoring;
Atrial fibrillation;
Supraventricular tachycardia;
Ventricular tachycardia

Abstract *Introduction/objective:* Studies on the use of amiodarone or sotalol are limited in dogs. Therefore, this study aimed to provide data on the efficacy and safety of these drugs in dogs with ventricular tachyarrhythmia (VT) and/or supraventricular tachyarrhythmia (SvT).
Animals, materials, and methods: Dogs with VT and/or SvT treated with amiodarone or sotalol as a first-line therapy were retrospectively evaluated. Signalment, clinical, diagnostic, therapeutic, and outcome data were retrieved. For VT, efficacy was demonstrated through a decrease of the Lown-Wolf grade to less than five or a reduction of at least 85% in the number of ventricular premature complexes observed on Holter monitoring. For SvT, efficacy was represented by cardioversion or a reduction in the mean heart rate on Holter monitoring $\leq$140 beats/min. Treatment-related side effects (TRSEs) were classified as clinically relevant and irrelevant. Statistical analysis was performed to compare data before and after antiarrhythmic prescription.
Results: Sixty-four dogs were included. Amiodarone and sotalol were efficacious in treating both VT (85.7% and 90.0% of cases, respectively) and SvT (75% and 71.4% of cases, respectively). No significant differences were found when comparing their efficacy rates in dogs with VT and SvT (P=0.531 and 0.483, respectively). Clinically relevant TRSEs were rare with both amiodarone and sotalol (8.3% and 5% of cases,

* Corresponding author.
E-mail address: giovanni.romito2@unibo.it (G. Romito).

https://doi.org/10.1016/j.jvc.2024.03.002

respectively), while clinically irrelevant TRSEs occurred more frequently with amiodarone (29.2%) than with sotalol (10%).
Discussion: In dogs with tachyarrhythmias, amiodarone and sotalol are generally efficacious and safe, as clinically relevant TRSEs seem rare.
Conclusions: This study provides novel data on the effects of amiodarone and sotalol in dogs with tachyarrhythmias.

Abbreviations

AF	atrial fibrillation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bpm	beats per minute
CBC	complete blood count
HR	heart rate
LV	left ventricular
QTc	QT interval corrected for the heart rate
RBC	red blood cells
RI	reference interval
SD	sudden death
SvPC	supraventricular premature complexes
SvTs	supraventricular tachyarrhythmias
TSH	thyroid stimulating hormone
T4	thyroxine
TRSEs	treatment-related side effects
VPC	ventricular premature complex
VTs	ventricular tachyarrhythmias
WBC	white blood cell

Introduction

Tachyarrhythmias are common in dogs and can be caused by a wide range of different cardiac and extracardiac conditions [1—5]. Supraventricular tachyarrhythmia (SvT) and ventricular tachyarrhythmia (VT) often contribute to morbidity and mortality in affected dogs if not properly treated. Although several therapeutic strategies are currently available to treat canine arrhythmias (e.g. electrical cardioversion in the case of lone atrial fibrillation [AF] [6] or radiofrequency catheter ablation in the case of accessory pathways [7]), the use of antiarrhythmic medications remains the most widespread in veterinary medicine [2,8,9]. Among the most commonly used antiarrhythmics in dogs with VT and SvT are class III medications (according to the Vaughan-Williams classification system), primarily amiodarone and sotalol [2,4,5,8,9]. Amiodarone shares the properties of all four classes of antiarrhythmic drugs as it has powerful class III and class I activity and ancillary class II and class IV activity [10]. Sotalol is a racemic mixture of dextro(-rotary) and levo(-rotary) isomers which combines potassium channel-blocking properties and a mild β-blocking effect [10]. Their multifaceted action explains why both amiodarone and sotalol are able to prolong the refractory period in cardiac tissues and slow the atrioventricular conduction [2,10]. Although it is generally assumed that these drugs are useful for the treatment of canine tachyarrhythmias, it is interesting to note that reports aimed at systematically assessing the rate of control of naturally acquired VT and SvT in dogs are limited for both oral amiodarone [11—13] and sotalol [14—16].

When selecting a drug in clinical practice, not only its efficacy but also its safety should be considered. This is particularly important in the case of amiodarone and sotalol, considering the list of possible treatment-related side effects (TRSEs) reported in humans for these drugs [10,17—19]. In this context, it is crucial to emphasize that only a few prior veterinary reports have explored possible TRSEs in dogs treated with oral amiodarone [11—13,20—24] and sotalol [16,25]. It should also be noted that only some of the available reports included tachyarrhythmic dogs [11—13,16,20,21], while many others exclusively enrolled healthy subjects [23—25]. This inevitably limits our perception of the clinical safety of amiodarone and sotalol in dogs with tachyarrhythmias.

Therefore, the aims of this study were to retrospectively evaluate a population of dogs with tachyarrhythmias that had been treated with amiodarone or sotalol and to provide a detailed

description of selected data with emphasis on antiarrhythmic efficacy and safety.

Materials and methods

Study population

Cases of client-owned dogs seen between 2014 and 2023 that received amiodarone or sotalol as a first-line antiarrhythmic therapy for naturally acquired VT and SvT were retrospectively evaluated in our database. For the purposes of this study, we considered only dogs with a complete case record for which the diagnosis of tachyarrhythmia, the prescription of the aforementioned antiarrhythmics, and subsequent cardiac evaluations occurred at our institution. It is worth noting that a minimum of two evaluations were necessary for enrollment in the study, ensuring that complete data from at least two time points were available for each dog. The first time point was the day of diagnosis of the tachyarrhythmia that prompted the prescription of amiodarone or sotalol (T_0). The second time point corresponded to the recheck performed after prescription of amiodarone or sotalol that was purposefully considered for analysis of antiarrhythmic efficacy and TRSEs (T_1). More in detail, for dogs subjected to a single recheck following the prescription of amiodarone or sotalol, the time of that examination was designed as T_1. In cases where dogs underwent multiple rechecks after antiarrhythmic prescription, the first time point at which a possible TRSE had occurred was designated as T_1. In cases where no apparent TRSEs manifested over time, the last available time point was designated as T_1. These criteria were chosen with the aim of optimizing the detection of TRSEs effects, including those that may develop long after the antiarrhythmic prescription (as some TRSEs have been reported in dogs even after several weeks/months [13,20,21]). The choice to use amiodarone or sotalol to treat VT and SvT was based, in each case, on the personal judgment and experience of the treating cardiologist.

The date of T_0 and T_1 were noted, and clinical (including non-invasive assessment of systolic blood pressure), cardiologic (including electrocardiographic and echocardiographic evaluation), and laboratory (including complete blood count [CBC], serum chemistry, and thyroxine (T_4) and thyroid stimulating hormone [TSH] concentration) findings were retrieved at T_0 and T_1. Further data included the type of tachyarrhythmia; presence/absence and type of underlying structural heart disease and/or systemic disease concomitant with tachyarrhythmias; dosage of amiodarone and sotalol; number of dogs in which the use of amiodarone and sotalol was efficacious; number, type, and duration of possible TRSEs throughout the treatment period; and time and cause of death. For the purpose of this study, the use of antiarrhythmic drugs other than amiodarone and sotalol at T_0 was not allowed. The potential subsequent addition of another antiarrhythmic molecule during the life span of enrolled dogs (e.g. in the case of tachyarrhythmias refractory to the first-line antiarrhythmic therapy) was allowed only when its prescription occurred after T_1 (to ensure that the data collected at T_1 could not be altered by the effects of the new medication). The use of cardiovascular drugs other than antiarrhythmics (e.g. pimobendan) was allowed both at T_0 and thereafter.

Electrocardiographic analysis

All electrocardiographic exams (including both $\leq$5-min surface electrocardiograms[a] and 24-h Holter recordings[b]) from T_0 and T_1 were reviewed and used for selected measurements by a board-certified cardiologist. Electrocardiographic analysis included rhythm characterization as well as measurements of waves, segments, and intervals. Initially, the cardiac rhythm was analyzed and classified as a sinus or a pathological rhythm. On electrocardiographic tracings, the heart rate (HR) in beats per minute (bpm) was calculated manually by determining the number of QRS complexes in a three-second interval and multiplying this number by 20 at a paper speed of 50 mm/s. On Holter recordings, the software allowed the manual calculation of instantaneous HR and automatically calculated the 24-h mean HR (of note, data on patients mean HR were obtained exclusively from Holter recordings). For the purpose of this study, the classification of abnormalities of heart rhythm included the following [26]:

- supraventricular premature complex (SvPC): premature normal-appearing QRS complex not preceded by any P wave or conducted by deflections of atrial electrical activation with abnormal morphology;
- supraventricular tachycardia: four or more SvPCs at an HR greater than 160 bpm; on the

[a] Cube ECG, Cardioline S.p.A., Caverano, Italy.
[b] Cube Holter, Cardioline S.p.A., Milano, Italy.

basis of electrocardiographic characteristics, SvTs were further classified as AF, atrial flutter, and focal atrial tachycardia [2];
- ventricular premature complex (VPC): premature wide and bizarre looking QRS complex, not associated with a P wave;
- accelerated idioventricular rhythm: four or more VPCs at an HR of 60–180 bpm; and
- ventricular tachycardia: four or more VPCs at a HR > 180 bpm.

Moreover, SvPCs and VPCs were also characterized as follows [26]:

- couplet: two consecutive VPCs/SvPCs;
- triplet: three consecutive VPCs/SvPCs;
- bigeminy: a VPC/SvPC following every sinus beat; and
- trigeminy: a VPC/SvPC following every two sinus beats.

Lastly, a modified Lown-Wolf grading system was purposefully adopted for the classification of ventricular arrhythmias as follows [27]:

- grade 0: no VPCs;
- grade 1: isolated VPCs;
- grade 2: ventricular bigeminy or trigeminy;
- grade 3: accelerated idioventricular rhythm;
- grade 4: ventricular couplets or triplets; and
- grade 5: ventricular tachycardia.

The Lown-Wolf grading system was based on Holter recordings and applied to all dogs with VPCs (i.e. dogs exclusively showing VT and dogs showing VT associated with concomitant SvT). If multiple types of VT were documented in the same dog, the highest grade of arrhythmia organization was recorded for patient classification (e.g. if both ventricular bigeminy and tachycardia were documented in a dog, a grade 5 was ultimately noted).

The measurements of waves, segments, and intervals were based on the surface electrocardiogram and were done using lead II according to the standard technique [28]. In light of the previously reported possible electrocardiographic effects of oral amiodarone and sotalol [10,22,24,25], particular attention was paid to the duration of PQ interval, QT interval, and QT interval corrected for the HR (QTc). The latter electrocardiographic parameter was calculated using the logarithmic formula [$QTc = \log 600 \times QT/\log RR$] [29]). For each variable, a mean of three measurements was determined.

Echocardiographic analysis

As for electrocardiography, all echocardiographic exams[c] from T_0 and T_1 were reviewed and used for selected measures by the same operator. In light of the previously reported possible effects of oral sotalol on left ventricular (LV) systolic function [16,25], particular attention was paid to the following measurements in dogs treated with this drug [30,31]:

- LV end-diastolic and end-systolic diameters measured using a two-dimensional-guided M-mode leading edge-to-leading edge technique from the right parasternal short-axis view at the level of the papillary muscles;
- LV fractional shortening using the standard formula;
- LV end-diastolic and end-systolic volumes measured using the Simpson's method of discs from a two-dimensional right parasternal long-axis four chamber view and then indexed to body surface area; and
- LV ejection fraction calculated from LV volumes using the standard following formula.

For each variable, an average of three measurements was determined from three consecutive cardiac cycles within the same video loop when phases of sinus rhythm were available. In contrast, if only phases of tachyarrhythmia were present during the echocardiographic examination, a minimum of five consecutive cardiac cycles were considered necessary for calculating the average of echocardiographic measurements [32,33].

Laboratory analysis

The same operator reviewed the medical database of each dog to note selected laboratory data from T_0 and T_1. In light of the previously reported hematologic effects of oral amiodarone [11–13,20,21], in dogs treated with this drug, particular attention was paid on the following laboratory variables: red blood cell (RBC), white blood cell (WBC), and platelet count; and alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, thyroxine (T_4), and thyroid-stimulating hormone (TSH) concentration.

[c] iE33 ultrasound system, Philips Healthcare, Monza, Italy.

Antiarrhythmic efficacy

In dogs with ventricular arrhythmias, the administration of amiodarone and sotalol was considered electrocardiographically efficacious when runs of ventricular tachycardia were eliminated (i.e. if the Lown-Wolf grade reduced below grade 5 after antiarrhythmic prescription). When such a result could not be obtained, the antiarrhythmic therapy was considered electrocardiographically efficacious if the overall number of ventricular premature complexes (VPCs) on Holter monitoring was reduced $\geq$85% [9]. In dogs with SvTs, the administration of amiodarone and sotalol was considered electrocardiographically efficacious if it induced cardioversion or if it induced a reduction of the mean ventricular rate $\leq$140 bpm on Holter monitoring [2,34,35].

Antiarrhythmic safety

Medical records were also reviewed for the occurrence of TRSEs after the prescription of amiodarone and sotalol. Given the previous medical literature [10–13,20–22,24,36–38], TRSEs possibly attributable to oral amiodarone included the occurrence of:

- gastrointestinal signs: decreased appetite, vomiting, and/or diarrhea;
- cytopenia: anemia (i.e. RBC below the laboratory reference interval [RI]: 5.65–8.4 $\times$ 10^6/μL), leukopenia (i.e. WBC below the laboratory RI: 5–14 $\times$ 10^3/μL), and/or thrombocytopenia (i.e. platelets below the laboratory RI: 150–500 $\times$ 10^3/μL);
- hepatic injury: increased ALT activity (laboratory RI: 15–65 U/L), AST activity (laboratory RI: 15–52 U/L), and/or total bilirubin concentration (laboratory RI: 0.07–0.33 mg/dL);
- thyroid hormones abnormalities: decreased T_4 concentration (laboratory RI: 13–51 nmoL/L), increased TSH concentration (laboratory RI: 0.03–0.38 ng/mL), or both; and
- increased duration of PQ interval (RI: 60–130 ms [37]), QT (RI: 150–240 ms [39]), and/or QTc.

Concerning sotalol, in light of the previous literature [10,16,25,36–38], TRSEs possibly attributable to this antiarrhythmic included the occurrence of:

- weakness/exercise intolerance;
- systemic hypotension: defined as a systolic arterial blood pressure (measured by a high-definition oscillometric device according to the guidelines of the American College of Veterinary Internal Medicine [40]) $<$80 mmHg [41];
- LV systolic dysfunction: defined as LV fractional shortening $<$20% and ejection fraction $<$40% [42]; and
- increased duration of the PQ interval, QT, and/or QTc.

Moreover, TRSEs were classified as clinically relevant (i.e. when they were associated with overt clinical debilitation or potentially relevant clinical complications, leading to reduction of the antiarrhythmic dose or drug interruption) and clinically irrelevant (i.e. when they consisted into mild laboratory, electrocardiographic, and/or echocardiographic changes not associated with clinical deterioration so that neither a reduction of the antiarrhythmic dose nor drug interruption was considered necessary).

Outcome

Data on the outcome were evaluated retrospectively by the same operator. Dogs were classified as still alive or deceased for cardiac-related death or non-cardiac-related death. The latter was further classified as sudden death (SD), congestive heart failure (CHF), or euthanasia because of worsening cardiac condition [43]. Time in days from T_0 to death (survival time) was recorded for any dog that died of cardiac-related causes.

Statistical analysis

Statistical analysis was performed with commercially available statistical software.[d] All continuous variables were checked graphically and tested for their distribution using the Shapiro-Wilk test. Descriptive statistics included the report of mean $\pm$ standard deviation and median and range (minimum–maximum) for normally and not normally distributed data, respectively. The Wilcoxon signed-rank test and the paired sample *t*-test were used to compare data between time points (i.e. T_0 and T_1). To compare the rate of efficacy and TRSEs of amiodarone and sotalol, a comparison of proportion by chi-square test was performed. P values $<$0.05 were considered statistically significant.

[d] MedCalc Software Ltd, version 19.3.1, Ostend, Belgium.

Results

Study population

In total, 57 dogs and 85 dogs were treated with amiodarone and sotalol during the study period, respectively. However, 33 dogs treated with amiodarone and 45 dogs treated with sotalol were not included in the study because of incomplete data records or the use of concomitant antiarrhythmic drugs before T_1. Therefore, the study population ultimately included 64 dogs, of which 24 (37.5%) and 40 (62.5%) received amiodarone and sotalol, respectively. The median loading dose of amiodarone was 15 mg/kg q 24 h (12.5—18 mg/kg q 24 h). This dose was administered for seven and 14 days in 11 of 24 and 13 of 24 dogs, respectively. The loading dose was followed by a maintenance dose of 8 mg/kg q 24 h (6—11 mg/kg q 24 h). The median sotalol dose was 2 mg/kg q 12 h (1—2.8 mg/kg q 12 h). The demographic and clinical characteristics of the entire study population are reported in Table 1. Table 2 provides details on cardiovascular therapies used at T_0 in addition to amiodarone and sotalol.

Concerning diagnostic tests performed at T_0, all dogs underwent electrocardiographic and echocardiographic analyses. Moreover, at T_0, CBC and serum chemistry were performed in all dogs. Additionally, among dogs treated with amiodarone, T4 and TSH were evaluated in 12 of 24 (50%) cases.

The median number of cardiologic rechecks performed over time was three (2—6). The median

Table 1 Selected demographic and clinical data of dogs enrolled in this study.

Variable	
Number of dogs	64
Age (years)	9 (4—13)
Body weight (kg)	28.8 (6—84)
Sex (EM/NM/EF/NF)	34/7/10/13
Breed (Number of dogs)	Mixed breed (13) Boxer (10) Doberman pinscher (5) Dogue de Bordeaux, Labrador retriever, Pinscher (3) American Staffordshire terrier, basset hound, Corso, cocker spaniel, golden retriever, Jack Russel terrier, Lagotto, Saint Bernard (2) American Staffordshire terrier, Cavalier King Charles Spaniel, Czechoslovakian Wolfdog, Dogo, English setter, fox terrier, French bulldog, giant schnauzer, miniature Poodle, rottweiler, Weimaraner (1)
Concomitant structural heart diseases (Y/N)	59/5
Type of structural heart diseases (Number of dogs)	DCM (15) Acute myocardial injury (14) ACVIM stage B2 MMVD (7) ACVIM stage C MMVD (5) ACVIM stage D MMVD (3) ACVIM stage B1 MMVD, ARVC, cardiac hemangiosarcoma, cardiac tamponade, endocarditis, SAS (2) Chemodectoma, mitral dysplasia, PS (1)
Concomitant systemic diseases (Y/N)	32/32
Type of systemic diseases (Number of dogs)	Splenic hemangiosarcoma (6) Enteropathy, snake envenomation (5) Cushing syndrome, GDV (2) CKD, idiopathic epilepsy, IMHA, lymphoma, ocular neoplasia, pancreatitis, pheochromocytoma, prostatic carcinoma, pyometra, sepsis, septic arthritis, toxoplasmosis (1)

ACVIM: American College of Veterinary Internal Medicine; ARVC: arrhythmogenic right ventricular cardiomyopathy; CKD: chronic kidney disease; DCM: dilated cardiomyopathy; EF: entire female; EM: entire male; GDV: gastric dilatation-volvulus; IMHA: immune-mediated hemolytic anemia; MMVD: myxomatous mitral valve disease; NF: neutered female; NM: neutered male; PS: pulmonic stenosis; SAS: subaortic stenosis.

Table 2 Cardiovascular drugs prescribed in addition to amiodarone and sotalol.

Amiodarone	
Concomitant drugs	**Number of dogs**
Pimobendan	17
Furosemide	7
Spironolactone	7
Benazepril	3
Hydrochlorothiazide	2
Torasemide	2
Amlodipine	1
Sotalol	
Concomitant drugs	**Number of dogs**
Pimobendan	17
Furosemide	6
Benazepril	5
Hydrochlorothiazide	1
Spironolactone	1
Torasemide	1

T_1 purposefully considered for our analysis was 62 days (32—630 days). At T_1, all dogs underwent electrocardiographic and echocardiographic analyses. Moreover, at T_1, all dogs treated with amiodarone underwent a recheck for both CBC and serum chemistry. Additionally, all dogs treated with amiodarone that had an evaluation of thyroid function at T_0, also underwent T4 and TSH measurement at T_1.

Electrocardiographic analysis

Table 3 provides details on the tachyarrhythmias identified at T_0 in dogs treated with amiodarone and sotalol. Table 4 provides details on the Lown-Wolf grade assigned at T_0 and T_1 to dogs with VT (considering both dogs exclusively showing VT and dogs showing VT associated with concomitant SvT) treated with amiodarone and sotalol. In the amiodarone group, grade 5 was documented in all dogs exclusively affected by VT (14/14 [100%]), whereas grades 5, 4, and 1 were assigned to 3/7 (42.8%), 2/7 (28.6%), and 2/7 (28.6%) subjects, respectively, in dogs affected by VT associated with concomitant SvT. After the prescription of amiodarone, the Lown-Wolf grade reduced in 17/21 (81%) dogs. Specifically, such a reduction was documented in 13/17 (76.5%) grade 5 dogs, in 2/2 (100%) grade 4 dogs, and in 2/2 (100%) grade 1 dogs. All dogs without a change of the Lown-Wolf grade (4/21 [19%]) were cases in which grade 5 was originally assigned. In the sotalol group, all dogs exclusively affected by VT exhibited grade 5 (31/31 [100%]), while dogs affected by VT associated with concomitant SvT documented grades 5 and 4 in 1/2 (50%) subjects each. After the prescription of sotalol, the Lown-Wolf grade reduced in 31/33 (93.9%) dogs. Specifically, such a reduction was documented in 30/32 (93.8%) grade 5 dogs and 1/1 (100%) grade 4 dog. All dogs without a change of the Lown-Wolf grade (2/33 [6.1%]) were cases in which grade 5 was originally assigned.

In addition to Lown-Wolf grades, Table 4 illustrates the number of VPCs documented by Holter monitoring at T_0 and T_1 in dogs with VT (considering both dogs exclusively showing VT and dogs showing VT associated with concomitant SvT) treated with amiodarone and sotalol. In dogs treated with amiodarone ($n = 21$, including 14 dogs exclusively affected by VT and seven dogs affected by VT associated with concomitant SvT), a reduction in the number of VPCs on Holter monitoring $\geq$85% was

Table 3 Types of tachyarrhythmias in dogs in which amiodarone or sotalol was prescribed after electrocardiographic diagnosis.

Tachyarrhythmias	Amiodarone (Number of dogs)	Sotalol (Number of dogs)
SvT	3	7
Type of SvT		
FAT	1	7
AF	2	0
Aflu	0	0
VT	14	31
VT associated with concomitant SvT	7	2
Type of SvT		
FAT	4	1
AF	3	0
AFlu	0	1

AF: atrial fibrillation; Aflu: atrial flutter; FAT: focal atrial tachycardia; SvT: supraventricular tachyarrhythmia; VT: ventricular tachyarrhythmia.

Table 4 Selected electrocardiographic findings at the time of tachyarrhythmias diagnosis (T_0) and recheck (T_1) in dogs treated with amiodarone and sotalol.

	Amiodarone		P	Sotalol		P
	T_0	T_1		T_0	T_1	
Lown-Wolf grade (assigned to both dogs exclusively affected by VT and dogs affected by VT associated with concomitant SvT)						
Grade 0	0	2		0	9	
Grade 1	2	2		0	7	
Grade 2	0	1		0	3	
Grade 3	0	1		0	3	
Grade 4	2	11		1	9	
Grade 5	17	4		32	2	
Number VPCs/Holter (counted in both dogs exclusively affected by VT and dogs affected by VT associated with concomitant SvT)	1049 (130—33,259)	1880 (0—22,426)	0.65	7635 (148—30,451)	54 (0—3973)	**0.002**
Mean HR/Holter (calculated in both dogs exclusively affected by SvT and dogs affected by VT with concomitant SvT)	144 bpm (100—230 bpm)	108 bpm (60—185 bpm)	**0.003**	146 bpm (107—255 bpm)	95 bpm (79—205 bpm)	**< 0.001**
ECG parameters (measured in the entire study population)						
PQ interval	105 (70—150)	105 (80—148)	0.67	106 ± 17.5	117 ± 20	0.06
QT interval	220 ± 17.9	223 ± 23	0.47	214 (160—300)	230 (190—300)	**0.004**
QTc	227 ± 18.7	227 ± 18	0.88	222 (175—299)	230 (196—327)	0.13

Normally and not normally distributed data are reported as mean ± standard deviation and median and range (minimum—maximum), respectively. Significant P values are reported in bold. QTc: QT interval corrected for the heart rate; SvT, supraventricular tachyarrhythmia; VPCs: ventricular premature complexes; VT: ventricular tachyarrhythmia.

documented in 12/21 (57.1%) cases. Among the remaining 9/21 (42.9%) dogs, 6 showed a reduction of the Lown-Wolf grade, whereas three dogs had an unchanged Lown-Wolf grade (i.e. all dogs with grade 5). In dogs treated with sotalol (n = 33, including 31 dogs exclusively affected by VT and two dogs affected by VT associated with concomitant SvT), a reduction in the number of VPCs on Holter monitoring ≥85% was documented in 16/33 (48.5%) cases. Among the remaining 17/33 (51.5%) dogs, 14 showed a reduction in the Lown-Wolf grade, whereas three dogs had an unchanged Lown-Wolf grade (i.e. all dogs with grade 5).

Table 4 also reports the mean HR documented on Holter monitoring in dogs with SvT (considering both dogs exclusively showing SvT and dogs showing VT associated with concomitant SvT) from the amiodarone and sotalol groups at T_0 and T_1. With both drugs, a statistically significant reduction in mean HR was documented. In dogs from the amiodarone group (n = 10, including three dogs exclusively affected by SvT and seven dogs affected by VT associated with concomitant SvT), the mean HR was ≤140 bpm in 6/10 (60%) and 9/10 (90%) dogs at T_0 and T_1, respectively. In dogs from the sotalol group (n = 9, including seven dogs exclusively affected by SvT and two dogs affected by VT associated with concomitant SvT), the mean HR was ≤140 bpm in 2/9 (22.2%) and 7/9 (77.8%) dogs at T0 and T1, respectively.

Lastly, Table 4 reports the measurements of PQ interval, QT interval, and QTc obtained at T_0 and T_1 in all dogs treated with amiodarone (n = 24) and sotalol (n = 40). The only statistically significant difference was found for the QT interval duration in the sotalol group.

Table 5 provides further data on electrocardiographic measurements as it illustrates the number of dogs with PQ, QT, and QTc values within/outside the RIs at T_0 a T_1 in the amiodarone and sotalol groups. No new onset of abnormalities in PQ and QT interval were documented after amiodarone prescription; in contrast, PQ and QT interval became prolonged in two dogs each after sotalol prescription. No additional causes of PQ and QT interval prolongation other than sotalol administration were documented in these dogs.

Echocardiographic analysis

Table 6 shows the echocardiographic measurements obtained at T_0 and T_1 in dogs treated with sotalol. No statistically significant difference was documented after sotalol prescription. Further echocardiographic data are provided in Table 5 as it illustrates the number of dogs with values within/outside the RIs at T_0 and T_1 in the sotalol group. Of note, the number of dogs with LV systolic dysfunction reduces from T_0 (n = 9) to T_1 (n = 6) as three dogs initially showing acute myocardial injury experienced an echocardiographic improvement over time.

Laboratory analysis

Table 7 illustrates selected CBC and biochemistry findings obtained at T_0 and T_1 in dogs treated with amiodarone. No statistically significant differences were documented. Further laboratory data are provided by Table 5 as it illustrates the number of dogs with values within/outside the RIs at T_0 and T_1 in the amiodarone group. The only case showing abnormal RBC at T_0 as well as at T_1 was a dog with mild anemia (RBC: $5.1 \times 10^6/\mu L$ and $5.3 \times 10^6/\mu L$ at T_0 and T_1, respectively). In this case, the suspected cause of anemia was represented by an ongoing infection due to *Toxoplasma gondii*. The only case that developed an abnormality of WBC at T_1 was a dog with leukopenia (WBC: $3.1 \times 10^3/\mu L$) characterized by severe neutropenia ($0.75/mm^3$ [laboratory RI $3-10 \times 10^3/\mu L$]). In this dog, no causes of leukopenia other than amiodarone administration were documented.

Concerning cases with abnormalities of transaminases at T_0, these were dogs with mildly increased ALT (n = 8) and AST (n = 4) activity in which no primary liver diseases were documented. In light of their clinical history, the increased transaminases were presumed to originate from the underlying heart disease (as these dogs had either a stage C myxomatous mitral valve disease [44] or a stage C dilated cardiomyopathy [45], two conditions that can induce increased ALT and AST due to hypoxic injury [46]). At T_1, 6/8 of dogs that initially exhibited elevated ALT activity at T0 and 4/4 dogs that initially exhibited elevated AST activity at T0 demonstrated normal levels of these transaminases. Only 2/8 of dogs showing an elevated ALT activity at T_0 maintained an increased value also at T_1. Moreover, two dogs originally showing normal ALT activity at T_0 and one dog originally showing normal AST activity at T_0 subsequently developed an elevated activity of these transaminases at T_1. Amiodarone was considered a plausible cause of increased ALT and AST levels. The T4 concentration was mildly decreased at T1 in four dogs. In these cases, no additional causes of decreased T4 concentration other than amiodarone administration were documented. The same three dogs that showed a mildly increased TSH

Table 5 Selected electrocardiographic, echocardiographic, and laboratory findings at the time of tachyarrhythmias diagnosis (T_0) and recheck (T_1) in dogs treated with amiodarone and sotalol.

	Amiodarone			Sotalol		
	Number of dogs within/outside RI at T_0	Number of dogs within/outside RI at T_1	Number of dogs with new onset of abnormalities	Number of dogs within/outside RI at T_0	Number of dogs within/outside RI at T_1	Number of dogs with new onset of abnormalities
ECG parameters (measured in the entire study population)						
PQ interval	22/2	22/2	0/24	39/1	37/3	2/38
QT interval	22/2	22/2	0/24	36/4	34/6	2/38
Echocardiographic parameters (measured exclusively in the sotalol group)						
FS	—	—	—	31/9	34/6	0/40
EF	—	—	—	31/9	34/6	0/40
EDVI	—	—	—	31/9	34/6	0/40
ESVI	—	—	—	31/9	34/6	0/40
Laboratory variables (measured exclusively in the amiodarone group)						
RBC	23/1	23/1	0/24	—	—	—
WBC	24/0	23/1	1/24	—	—	—
PTL	24/0	24/0	0/24	—	—	—
ALT	16/8	20/4	2/24	—	—	—
AST	20/4	23/1	1/24	—	—	—
Bil	24/0	24/0	0/24	—	—	—
T4	24/0	20/4	4/24	—	—	—
TSH	21/3	21/3	0/24	—	—	—

ALT: alanine aminotransferase; AST: aspartate aminotransferase; Bil: total bilirubin; EDVI: end-diastolic volume index; EF: ejection fraction; ESVI: end-systolic volume index; FS: fractional shortening; PTL: platelet count; RBC: red blood cell; RI: reference interval; T4: thyroxine; TSH; thyroid stimulating hormone; WBC: white blood cell.

Table 6 Selected echocardiographic findings at the time of tachyarrhythmia diagnosis (T_0) and recheck (T_1) in dogs treated with sotalol.

Echocardiographic parameters	T_0	T_1	P
FS (%)	27.5 (11–49)	27 (7–71)	0.75
EF (%)	52.2 (19.2–74)	50 (15–81)	0.51
EDVI (mL/m^2)	79 (18–245)	72 (27–316)	0.33
ESVI (mL/m^2)	37 (16–120)	33 (15–137)	0.79

Data are reported as median and range (minimum–maximum) due to their not normal distribution. P values are not reported in bold as they are not significant. EDVI: end-diastolic volume index; EF: ejection fraction; ESVI: end-systolic volume index; FS: fractional shortening.

value at T_0 also showed a mildly elevated TSH concentration at T_1.

Antiarrhythmic efficacy

Amiodarone was considered electrocardiographically efficacious in 18/21 (85.7%) dogs with VT (considering both dogs showing exclusively VT and dogs showing VT associated with concomitant SvT); in contrast, 3/21 (14.3%) dogs showed neither a reduction in the Lown-Wolf grade <5 nor a reduction in the VPCs on Holter monitoring $\geq$85% after amiodarone prescription. In these dogs, mexiletine (6–8 mg/kg q 8 h) or omega-3 fatty acids (eicosapentaenoic acid 24–26 mg/kg/die; docosahexaenoic acid 16–18 mg/kg/die) were subsequently introduced. Sotalol was considered efficacious in 30/33 (90.9%) dogs with VT (considering both dogs showing exclusively VT and dogs showing VT associated with concomitant SvT); in contrast, 3/33 (9.1%) dogs showed neither a reduction in the Lown-Wolf grade <5 nor a reduction in the VPCs on Holter monitoring $\geq$85% after sotalol prescription. In these dogs, mexiletine (6–8 mg/kg q 8 h) was subsequently introduced.

In dogs with SvT (considering both dogs showing exclusively SvT and dogs showing VT associated with concomitant SvT), amiodarone and sotalol efficacy was determined exclusively on the number of dogs that developed a mean HR $\leq$ 140 bpm on Holter monitoring, since no subject experienced cardioversion after antiarrhythmic prescription. Amiodarone was considered electrocardiographically efficacious in the management of SvT in 3/4 (75%) dogs that had a mean HR $>$ 140 bpm at T0, since their mean HR at T1 was $\leq$140 bpm; in contrast, the remaining 1/4 (25%) dog maintained a mean HR $>$ 140 bpm also at T1. In this dog, sustained-release diltiazem (2 mg/kg q 12 h) was subsequently added to amiodarone. Sotalol was considered efficacious for the management of SvT in 5/7 (71.4%) subjects that had a mean HR $>$ 140 bpm at T_0, since their mean HR at T_1 was $\leq$140 bpm; in contrast, the remaining 2/7 (28.6%) dogs maintained a

Table 7 Selected laboratory findings at the time of tachyarrhythmia diagnosis (T_0) and recheck (T_1) in dogs treated with amiodarone.

Laboratory variables	T_0	T_1	P
RBC ($\times 10^6/\mu$L)	6.9 $\pm$ 0.7	6.7 $\pm$ 0.9	0.24
WBC ($\times 10^3/\mu$L)	9.8 (6.6–13.4)	9.9 (3.1–13.9)	0.31
PTL ($\times 10^3/\mu$L)	289.7 $\pm$ 116.8	311.7 $\pm$ 100.6	0.42
ALT (U/L)	50 (20–173)	65 (21–226)	0.67
AST (U/L)	50 (20–175)	35 (23–178)	0.3
Bil (mg/dL)	0.23 $\pm$ 0.07	0.23 $\pm$ 0.06	0.94
T4 (nmoL/L)	24.4 $\pm$ 7.6	16.7 $\pm$ 10.4	0.13
TSH (ng/mL)	0.22 (0.12–0.99)	0.19 (0.1–0.8)	0.84

Normally and not normally distributed data are reported as mean $\pm$ standard deviation and median and range (minimum–maximum), respectively. P values are not reported in bold as they are not significant. ALT: alanine aminotransferase; AST: aspartate aminotransferase; Bil: total bilirubin; PTL: platelet count; RBC: red blood cell; T4: thyroxine; TSH: thyroid stimulating hormone; WBC: white blood cell.

mean HR > 140 bpm also at T_1. In these dogs, sustained-release diltiazem (2–3 mg/kg q 12 h) was subsequently added to sotalol.

No statistically significant differences were documented when comparing the efficacy rates of amiodarone and sotalol in dogs with VT (P=0.531) and SvT (P=0.483).

Antiarrhythmic safety

After amiodarone prescription, 7/24 (29.2%) dogs had clinically irrelevant TRSEs, including two dogs with mildly increased ALT activity, one dog with mildly increased AST activity, and four dogs with decreased T4 concentration not associated with additional laboratory or clinical signs consistent with hypothyroidism. Moreover, 2/24 (8.3%) dogs showed clinically relevant TRSEs, including one dog with gastrointestinal signs (decreased appetite and diarrhea) and one dog with leukopenia characterized by severe neutropenia (developed 11 days and 150 days after amiodarone prescription, respectively). In both cases, amiodarone was discontinued. After amiodarone interruption, both gastrointestinal signs and leukopenia resolved (within 7 days and 28 days, respectively).

After sotalol prescription, 4/40 (10%) dogs showed clinically irrelevant TRSEs, including two dogs with prolonged PQ interval and two dogs with prolonged QT interval. Moreover, 2/40 (5%) dogs showed clinically relevant TRSEs represented in both cases by weakness/exercise intolerance (developed 2 days and 42 days after sotalol prescription, respectively). In one of them, the clinical condition was further complicated by systemic hypotension. In one case (the one with systemic hypotension), sotalol was interrupted, while sotalol dose was halved in the remaining dog. After sotalol interruption and halving, clinical signs resolved within 2 days and 7 days, respectively.

A statistically significant difference was documented when comparing the overall rates of TRSEs (considering both clinically irrelevant and clinically relevant TRSEs) of amiodarone and sotalol; specifically, overall TRSEs were more frequent in dogs treated with amiodarone (P=0.0024).

Outcome

Complete long-term follow-up was available for 30/64 (46.9%) dogs (13 treated with amiodarone and 17 treated with sotalol). Cardiac-unrelated and cardiac-related deaths were documented in 19/30 (63.3%) and 11/30 (33.7%) dogs, respectively. In all cases, cardiac-related death was represented by SD. At T_0, all of these dogs had VT on electrocardiographic examination and an underlying structural heart disease on echocardiography (i.e. 8/11 dogs had dilated cardiomyopathy, 1/11 dog had a stage D myxomatous mitral valve disease, 1/11 dog had a severe subaortic stenosis, and 1/11 dog had arrhythmogenic right ventricular cardiomyopathy). Additionally, 2/11 (18.2%) of these dogs developed prolonged QT interval at T_1. The median survival time in dogs with cardiac-related death was 183 days (87–645 days).

Discussion

This study represents the largest investigation on the efficacy and safety of two largely used class III antiarrhythmic drugs, namely amiodarone and sotalol, in dogs with naturally acquired tachyarrhythmias.

Concerning efficacy, we demonstrated that both drugs were efficacious in the majority of dogs with VT (85.7% and 90.0% of cases, respectively) and SvT (75% and 71.4%, respectively). Moreover, no statistically significant differences were documented when directly comparing the efficacy rates of these drugs. These results may rely on several factors, including our way to determine the electrocardiographic efficacy, the type of tachyarrhythmias treated, and the dosages administered. Although specific guidelines on the use of antiarrhythmics are not available in veterinary literature, we adopted efficacy criteria used by many veterinary cardiologists [2,9,34,35]. According to these criteria, the lack of efficacy for the management of VT was observed only in 3/24 (12.5%) and 3/40 (7.5%) dogs treated with amiodarone and sotalol, respectively. Intriguingly, these results are in line with human literature as an efficacy in suppressing VT up to 86% and 89% has been documented in people treated with amiodarone and sotalol, respectively [47,48]. Concerning SvT, we based our results on dogs that developed a mean HR ≤ 140 bpm on Holter monitoring (since no dog with SvT experienced cardioversion after antiarrhythmic prescription). According to this criterion, a lack of efficacy was only observed in 1/4 (25%) and 2/7 (28.6%) dogs treated with amiodarone and sotalol, respectively. These results partially agree with the findings from a previous study on the use of amiodarone in dogs with AF, where only 24% of

dogs showed no relevant reduction of HR after antiarrhythmic prescription [11]. It should be noted that we treated tachyarrhythmias following previous indications from veterinary textbooks and manuscripts as the use of both drugs have been reported for VT [9,12,13,16,36,37,49] as well as SvT, including focal atrial tachycardia, AF, and atrial flutter [2,11,13]. Moreover, our median dosages are within the ranges reported by many veterinary cardiologists [9,36,37].

In the few dogs with VT in which amiodarone and sotalol were considered not efficacious, strategies to improve VT management included the introduction of omega-3 fatty acids [50] and mexiletine [15]. Despite this, some dogs experienced SD. As none of these dogs had Holter monitoring during SD, it is impossible to conclusively establish the cause of death. However, in these dogs, an underlying arrhythmogenic structural heart disease (e.g. dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy) associated with VT was diagnosed at T_0; moreover, a prolongation of QT interval was documented at T_1 in ~1/5 of them. Therefore, VT degenerating into ventricular fibrillation could be hypothesized as a likely cause of SD [51,52]. This finding highlights the importance of maintaining a conservative approach even after the prescription of apparently appropriate treatments.

Although the overall rate of TRSEs (i.e. considering both clinically irrelevant and clinically relevant TRSEs) was statistically higher in dogs treated with amiodarone than in those treated with sotalol, in our opinion, both drugs can be considered generally safe and well tolerated at the dosage reported here, at least when monitored within the timelines described by us. This consideration is mainly based of the fact that, in our study population, clinically relevant TRSEs were rare (~8% and 5% in dogs treated with amiodarone and sotalol, respectively) and reversible after antiarrhythmic interruption/dose reduction. In the case of amiodarone, clinically relevant TRSEs included gastrointestinal signs and leukopenia with neutropenia. While the first type of TRSE has been previously reported with relative frequency both in humans (up to 25%) [10] and dogs (~7–45%) [12,13], the second one has never been documented in dogs and seems to be extremely rare in people [53]. Direct bone marrow toxicity represents the main mechanism of amiodarone-induced neutropenia [53]. In the case of sotalol, clinically relevant TRSEs included weakness/exercise intolerance and systemic hypotension. Although studies purposefully designed to evaluate the frequency of such signs in dogs under sotalol are lacking, it is interesting to note that fatigue develops in up to 20% of humans treated with this drug [10]. These TRSEs are likely secondary to the negative inotropic and chronotropic effects of sotalol [10].

Approximately 29% and 10% of dogs receiving amiodarone and sotalol developed clinically irrelevant TRSEs, respectively. In the case of amiodarone, these TRSEs consisted of mild changes of the activity of ALT, AST, or both (without concomitant signs of liver insufficiency) and of thyroid hormone concentration (without concomitant clinical or clinicopathological signs of thyroid dysfunction). These findings are in line with previous human and canine studies documenting an asymptomatic increase of transaminase activity in 15–30% of people [10] and many dogs under amiodarone [11–13,21,24]. The mechanism of hepatic injury appears to be direct damage to lipid bilayers and disturbance of lysosomal and/or mitochondrial function [10]. The effects of amiodarone on levels of thyroid hormones depend on the structure of this molecule and its content in iodine [10]. In humans, although fluctuations in T4 concentration levels may develop over time, amiodarone-induced hypothyroidism/hyperthyroidism is rare (up to 6%) [10]. Similarly, in dogs treated with amiodarone, the development of clinically relevant thyroid dysfunction occurs infrequently [13,24]. It is also interesting to note that we observed no case of PQ or QT interval prolongation after amiodarone prescription. This finding disagrees not only with previous human data [10] but also with a previous study in healthy dogs where PQ, QT, and QTc prolonged within the first 4 weeks of drug administration [24]. Such a difference may be explained by the different amiodarone dosages as we employed a median maintenance dose of 8 mg/kg q 24 h, whereas a maintenance dose of 30 mg/kg q 24 h was used in that previous study [24]. Contrary to amiodarone, all clinically irrelevant TRSEs documented in dogs treated with sotalol included electrocardiographic changes, namely PQ and QT prolongation. Although no study has previously assessed the frequency of these changes in dogs with naturally acquired tachyarrhythmias under sotalol, they seem relatively common in experimental canine models [54] and humans [10] treated with this drug. Interestingly, no dog treated with sotalol had a significant reduction in LV systolic function. This finding disagrees with two recent studies on the effects of sotalol on echocardiographic parameters in healthy dogs and dogs with

VT as a mild reduction in LV systolic function was documented in both reports [16,25].

This study has some limitations. First, the retrospective design precluded the standardization of timing of diagnostic procedures and therapeutic interventions. Second, data on thyroid function were only available for half of the dogs treated with amiodarone. Third, not all categories were equally represented (e.g. sotalol and VT groups overnumbered amiodarone and SvT groups, respectively). Fourth, the median time of T_1 was relatively short (~2 months). However, it should be noticed that the aforementioned limitations also affected the majority of previous studies on the use of class III antiarrhythmics in dogs [11—13]. Another potential limitation could be associated with the timing of rechecks considered for our statistical analysis as our criteria for selecting T_1 could have introduced a possible source of bias. Last, dogs treated with amiodarone did not undergo the assessment of serum amiodarone concentration. This was primarily due to the fact that no validated canine RIs exist. Indeed, previous veterinary studies performing such a measurement used RIs from human medicine [12,13].

In conclusion, this study provides detailed data on the efficacy and safety of amiodarone and sotalol in dogs with naturally acquired tachyarrhythmias. Based on our results, these drugs can generally be considered efficacious for the treatment of canine VT and SvT, showing a similar efficacy rate. Moreover, they also appear to be generally well tolerated, at least when prescribed at the dosage used in this study and monitored within the timelines described here, as clinically relevant TRSEs were rare and reversible in our population.

Funding

This research did not receive any grants from funding agencies in the public, commercial or not-for-profit sectors.

Conflict of Interest Statement

The authors do not have any conflicts of interest to disclose.

Acknowledgments

Part of the study was presented as an oral communication at the 33rd Congress of the European Society of Veterinary Internal Medicine — Companion Animals, Barcelona, Spain, 21st—23rd September 2023.

References

[1] Buchanan JW. Spontaneous arrhythmias and conduction disturbances in domestic animals. Ann N Y Acad Sci 1965; 127:224—38.
[2] Pariaut R, Santilli RA, Moïse NS. Supraventricular tachyarrhythmias in dogs. In: Bonagura JD, Twedt DC, editors. Kirk's Current Veterinary Therapy. XV ed. St. Louis: Elsevier Saunders; 2014. p. 737—44.
[3] Noszczyk-Nowak A, Michałek M, Kałuza E, Cepiel A, Pasławska U. Prevalence of arrhythmias in dogs examined between 2008 and 2014. J Vet Res 2017;61:103—10.
[4] Romito G, Guglielmini C, Poser H, Baron Toaldo M. Lorenz plot analysis in dogs with sinus rhythm and tachyarrhythmias. Animals (Basel) 2021;11:1645.
[5] Hellemans A, Schittekatte M, Covents M, Smets P. Diagnosis and management of arrhythmias in dogs: a cross-sectional online survey among Flemish veterinary practitioners. Vet Rec Open 2022;9:e35.
[6] Pariaut R. Atrial fibrillation: current therapies. Vet Clin North Am Small Anim Pract 2017;47:977—88.
[7] Wright KN, Connor CE, Irvin HM, Knilans TK, Webber D, Kass PH. Atrioventricular accessory pathways in 89 dogs: clinical features and outcome after radiofrequency catheter ablation. J Vet Intern Med 2018;32:1517—29.
[8] DeFrancesco TC. Management of cardiac emergencies in small animals. Vet Clin North Am Small Anim Pract 2013; 43:817—42.
[9] Oyama MA, Reynolds CA. Ventricular arrhythmias in dogs. In: Bonagura JD, Twedt DC, editors. Kirk's Current Veterinary Therapy. XV ed. St. Louis: Elsevier Saunders; 2014. p. 745—8.
[10] Nattel S, Gersh BJ, Opie LH. Antiarrhythmic drugs and strategies. In: Opie LH, Gersh BJ, editors. Drugs for the Heart. 8th ed. Philadelphia: Elsevier Saunders; 2013. p. 272—331.
[11] Saunders AB, Miller MW, Gordon SG, Van De Wiele CM. Oral amiodarone therapy in dogs with atrial fibrillation. J Vet Intern Med 2006;20:921—6.
[12] Kraus MS, Thomason JD, Fallaw TL, Calvert CA. Toxicity in Doberman Pinchers with ventricular arrhythmias treated with amiodarone (1996-2005). J Vet Intern Med 2009;23: 1—6.
[13] Pedro B, López-Alvarez J, Fonfara S, Stephenson H, Dukes-McEwan J. Retrospective evaluation of the use of amiodarone in dogs with arrhythmias (from 2003 to 2010). J Small Anim Pract 2012;53:19—26.
[14] Meurs KM, Spier AW, Wright NA, Atkins CE, DeFrancesco TC, Gordon SG, Hamlin RL, Keene BW, Miller MW, Moise NS. Comparison of the effects of four antiarrhythmic treatments for familial ventricular arrhythmias in Boxers. J Am Vet Med Assoc 2002;221: 522—7.
[15] Gelzer AR, Kraus MS, Rishniw M, Hemsley SA, Moïse NS. Combination therapy with mexiletine and sotalol suppresses inherited ventricular arrhythmias in German shepherd dogs better than mexiletine or sotalol monotherapy: a randomized cross-over study. J Vet Cardiol 2010;12:93—106.

[16] Visser LC, Kaplan JL, Nishimura S, Gunther-Harrington CT, Bélanger C, Oldach MS, Stern JA, Mueller MS. Acute echocardiographic effects of sotalol on ventricular systolic function in dogs with ventricular arrhythmias. J Vet Intern Med 2018;32:1299—307.
[17] Zanetti LA. Sotalol: a new class III antiarrhythmic agent. Clin Pharm 1993;12:883—91.
[18] Zimetbaum P. Amiodarone for atrial fibrillation. N Engl J Med 2007;356:935—41.
[19] Vassallo P, Trohman RG. Prescribing amiodarone: an evidence-based review of clinical indications. JAMA 2007; 298:1312—22.
[20] Calvert CA, Sammarco C, Pickus C. Positive Coombs' test results in two dogs treated with amiodarone. J Am Vet Med Assoc 2000;216:1933—6.
[21] Jacobs G, Calvert C, Kraus M. Hepatopathy in 4 dogs treated with amiodarone. J Vet Intern Med 2000;14:96—9.
[22] Bicer S, Nakayama H, Nakayama T, Strauch SM, Hamlin RL. Effects of chronic, oral amiodarone on left ventricular pressure, electrocardiograms, and action potentials from myocardium in vivo and from Purkinje fibers in vitro. Vet Therapeut 2001;2:325—33.
[23] Bicer S, Fuller GA, Wilkie DA, Yamaguchi M, Hamlin RL. Amiodarone-induced keratopathy in healthy dogs. Vet Ophthalmol 2002;5:35—8.
[24] Bicer S, Nakayama T, Hamlin RL. Effects of chronic oral amiodarone on left ventricular function, ECGs, serum chemistries, and exercise tolerance in healthy dogs. J Vet Intern Med 2002;16:247—54.
[25] Treseder JR, LeBlanc NL, Scollan KF. Inotropic and chronotropic effects of sotalol in healthy dogs. J Vet Cardiol 2019;25:14—24.
[26] Romito G, Castagna P, Sabetti MC, Ablondi M, Cipone M. Evaluating the accuracy of a six-lead smartphone-based electrocardiographic device compared with standard electrocardiography in brachymorphic dogs. Vet Rec 2023: e2879.
[27] Matthews DJ, Saunders AB, Meyers AC, Gordon SG, Hamer SA. Cardiac diagnostic test results and outcomes in 44 dogs naturally infected with Trypanosoma cruzi. J Vet Intern Med 2021;35:1800—9.
[28] Tilley LP. The approach to the electrocardiogram. In: Tilley LP, editor. Essentials of Canine and Feline Electrocardiography: Interpretation and Treatment. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1992. p. 40—55.
[29] Matsunaga T, Mitsui T, Harada T, Inokuma M, Murano H, Shibutani Y. T corrected for heart rate and relation between QT and RR intervals in beagle dogs. J Pharmacol Toxicol Methods 1997;38:201—9.
[30] Boon JA. Evaluation of size, function, and hemodynamics. In: Boon JA, editor. Veterinary Echocardiography. 2ed. Ames: Wiley-Blackwell; 2011. p. 153—266.
[31] Bonagura JD, Visser LC. Echocardiographic assessment of dilated cardiomyopathy in dogs. J Vet Cardiol 2022;40: 15—50.
[32] Kim TS, Youn HJ. Role of echocardiography in atrial fibrillation. J Cardiovasc Ultrasound 2011;19:51—61.
[33] Constantinos H, Papadopoulos CH, Oikonomidis D, Lazaris E, Nihoyannopoulos P. Echocardiography and cardiac arrhythmias. Hellenic J Cardiol 2018;59:140—9.
[34] Gelzer AR, Kraus MS, Rishniw M, Moïse NS, Pariaut R, Jesty SA, Hemsley SA. Combination therapy with digoxin and diltiazem controls ventricular rate in chronic atrial fibrillation in dogs better than digoxin or diltiazem monotherapy: a randomized crossover study in 18 dogs. J Vet Intern Med 2009;23:499—508.
[35] Gelzer AR, Kraus MS, Rishniw M. Evaluation of in-hospital electrocardiography versus 24-hour Holter for rate control in dogs with atrial fibrillation. J Small Anim Pract 2015; 56:456—62.
[36] Kittleson M. Drugs used in the treatment of cardiac arrhythmias. In: Kittleson M, Kienle RD, editors. Small Animal Cardiovascular Medicine. St. Louis: Mosby; 1998. p. 502—24.
[37] da Silva JF. Anti-arrhythmic drugs. In: Willis R, Oliveira P, Mavropoulou, editors. Guide to Canine and Feline Electrocardiography. Oxphord: John Wiley & Sons; 2018. p. 241—54.
[38] Santilli RA, Moïse NS, Pariaut R, Perego M. Electrocardiographic changes secondary to systemic disorders and drugs. In: Santilli RA, Moïse NS, Pariaut R, Perego M, editors. Electrocardiography of the Dog and Cat - Diagnosis of Arrhythmia. 2nd ed. Milan: Edra; 2018. p. 293—312.
[39] Santilli RA, Moïse NS, Pariaut R, Perego M. Formation and interpretation of the electrocardiographic waves. In: Santilli RA, Moïse NS, Pariaut R, Perego M, editors. Electrocardiography of the Dog and Cat - Diagnosis of Arrhythmia. 2nd ed. Milan: Edra; 2018. p. 35—70.
[40] Acierno MJ, Brown S, Coleman AE, Jepson RE, Papich M, Stepien RL, Syme HM. ACVIM consensus statement: guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. J Vet Intern Med 2018;32:1803—22.
[41] Waddell LS. Systemic hypotension. In: Ettinger SJ, Feldman EC, Côté E, editors. Textbook of Veterinary Internal Medicine. 8th ed. St. Louis: Elsevier; 2017. p. 671—5.
[42] Boon JA. Dilated cardiomyopathy. In: Boon JA, editor. Veterinary Echocardiography. 2nd ed. Ames: Wiley-Blackwell; 2011. p. 381—95.
[43] Baron Toaldo M, Romito G, Guglielmini C, Diana A, Pelle NG, Contiero B, Cipone M. Prognostic value of echocardiographic indices of left atrial morphology and function in dogs with myxomatous mitral valve disease. J Vet Intern Med 2018;32:914—21.
[44] Keene BW, Atkins CE, Bonagura JD, Fox PR, Häggström J, Fuentes VL, Oyama MA, Rush JE, Stepien R, Uechi M. ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs. J Vet Intern Med 2019;33:1127—40.
[45] Wess G. Screening for dilated cardiomyopathy in dogs. J Vet Cardiol 2022;40:51—68.
[46] Chong A, Appleton M, Casamián-Sorrosal D, Raheb S, O'Sullivan ML, Pires A, Fonfara S. Total bilirubin is an independent predictor of death in dogs with degenerative valvular disease and dilated cardiomyopathy. J Vet Cardiol 2022;43:10—26.
[47] Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. Circulation 1999;100:2025—34.
[48] Anderson JL, Askins JC, Gilbert EM, Miller RH, Keefe DL, Somberg JC, Freedman RA, Haft LR, Mason JW, Lessem JN. Multicenter trial of sotalol for suppression of frequent, complex ventricular arrhythmias: a double-blind, randomized, placebo-controlled evaluation of two doses. J Am Coll Cardiol 1986;8:752—62.
[49] Côté E, Ettinger SJ. Cardiac arrhythmias. In: Ettinger SJ, Feldman EC, Côté E, editors. Textbook of Veterinary Internal Medicine. 8th ed. St. Louis: Elsevier; 2017. p. 1176—200.
[50] Smith CE, Freeman LM, Rush JE, Cunningham SM, Biourge V. Omega-3 fatty acids in Boxer dogs with arrhythmogenic right ventricular cardiomyopathy. J Vet Intern Med 2007;21:265—73.

[51] Ware WA, Reina-Doreste Y, Stern JA, Meurs KM. Sudden death associated with QT interval prolongation and KCNQ1 gene mutation in a family of English Springer Spaniels. J Vet Intern Med 2015;29:561—8.
[52] Santilli R, Saponaro V, Carlucci L, Perego M, Battaia S, Borgarelli M. Heart rhythm characterization during sudden cardiac death in dogs. J Vet Cardiol 2021;38:18—30.
[53] Patel H, Peace D. Isolated neutropenia: an unexplored side effect of amiodarone. J Med Cases 2020;11:1—5.
[54] Vormberge T, Hoffmann M, Himmel H. Safety pharmacology assessment of drug-induced QT-prolongation in dogs with reduced repolarization reserve. J Pharmacol Toxicol Methods 2006;54:130—40.