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Efficacy and safety of different antiarrhythmic protocols used for rate control in dogs with secondary atrial fibrillation

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KEYWORDS
Cardiac arrhythmia;
Holter monitoring;
Diltiazem;
Digoxin;
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Abstract *Introduction/Objectives:* Studies comparing the effects of antiarrhythmic protocols used for rate control in dogs with secondary atrial fibrillation (AF) are currently limited; therefore, this study aimed to report detailed data on the efficacy and therapy-related side-effects (TRSEs) of different antiarrhythmic protocols in dogs with secondary AF.
Animals, Materials, and Methods: Dogs with secondary AF treated with combination therapy with diltiazem and digoxin ($CT_{Dilt+Digox}$), diltiazem monotherapy (MT_{Dilt}), digoxin monotherapy (MT_{Digox}), or amiodarone monotherapy (MT_{Amiod}) were retrospectively evaluated. Signalment, clinical, diagnostic, therapeutic, and outcome data were retrieved. Electrocardiographically, antiarrhythmic efficacy was defined by a reduction in the mean heart rate on Holter monitoring $\leq$125

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beats/minutes. Statistical analysis was performed to compare selected data, including the rate of efficacy and TRSEs as well as the median survival time, between dogs treated with different antiarrhythmic protocols.
Results: Fifty-four dogs were included, with 28 receiving the $CT_{Dilt+Digox}$ and 26 receiving monotherapies (MT_{Digox} = 16; MT_{Dilt} = 5; MT_{Amiod} = 5). The efficacy rate documented in dogs treated with $CT_{Dilt+Digox}$ was significantly higher than that observed in dogs from the composite monotherapy group (i.e., MT_{Dilt}+MT_{Digox}+MT_{Amiod}) (P=0.048). The rate of TRSEs documented in dogs treated with $CT_{Dilt+Digox}$ was similar to that observed in dogs from the composed monotherapy group (P=0.129). The median survival time documented in dogs treated with $CT_{Dilt+Digox}$ was significantly longer than that observed in dogs of the MT_{Digox} group (P=0.01).
Discussion: In dogs with secondary AF we included, $CT_{Dilt+Digox}$ was well tolerated and provided clinically relevant benefits compared to the use of a single antiarrhythmic drug.
Limitations: Retrospective design; heterogeneous sample size of categories analyzed; clinicopathological data available for many, but not all, dogs.
Conclusions: Our findings support the indication to generally consider $CT_{Dilt+Digox}$ as a first-line antiarrhythmic treatment in dogs with secondary AF.

Abbreviations

AF	atrial fibrillation
ALT	alanine aminotransferase
bpm	beats per minute
CHF	congestive heart failure
$CT_{Dilt+Digox}$	combination therapy with diltiazem and digoxin
LV	left ventricular
mHR	mean heart rate
MST	median survival time
MT_{Amiod}	amiodarone monotherapy
MT_{Digox}	digoxin monotherapy
MT_{Dilt}	diltiazem monotherapy
RI	reference interval
TRSEs	treatment-related side effects

Introduction

Atrial fibrillation (AF) represents the most common supraventricular tachyarrhythmia in dogs and is most frequently observed in subjects with cardiac disease associated with atrial remodeling (secondary AF) [1—5]. Once developed, AF reduces cardiac output, promotes the occurrence of congestive heart failure (CHF), and increases the risk of sudden death [5—7]. Given the high prevalence of this arrhythmia and its impact on survival, appropriate treatment is essential. In secondary AF, controlling the ventricular rate (rate control) is the most commonly used treatment strategy to prolong the survival time of affected dogs [8—12].

Although the clinical benefit of efficient rate control is well established in canine AF [10—12], the choice of antiarrhythmics aimed at achieving it is more controversial. Currently, no guidelines concerning the medical treatment of dogs with secondary AF are available, and antiarrhythmic drugs are often prescribed more on the basis of personal experience than on solid scientific evidence. Among the factors associated with the choice of these drugs are their hypothesized/perceived efficacy and safety. However, it is interesting to note that, to date, reports aimed at assessing and comparing the efficacy rates and rates of treatment-related side-effects (TRSEs) of different antiarrhythmic protocols are limited in dogs with AF [13]. This may affect our treatment choices in clinical practice.

Therefore, the aims of this study were to retrospectively evaluate a population of dogs with secondary AF that had been treated with different antiarrhythmic protocols and to provide a detailed description of selected data with emphasis on antiarrhythmic efficacy and safety.

Materials and methods

Study sample

Medical records of client-owned dogs seen between 2012 and 2024 with secondary AF were retrospectively evaluated in the medical databases of the authors. For the purposes of this multicenter study, dogs treated with combination

therapy with diltiazem and digoxin ($CT_{Dilt+Digox}$), diltiazem monotherapy (MT_{Dilt}), digoxin monotherapy (MT_{Digox}), or amiodarone monotherapy (MT_{Amiod}) were considered. This choice was based on previous studies from the canine literature, which showed that the four aforementioned protocols represent the most commonly prescribed ones in dogs with secondary AF [7—18]. A minimum of two evaluations was necessary for enrollment in the study, ensuring that data from at least two timepoints were available for each dog. The first timepoint was the day of diagnosis of AF that prompted the prescription of the aforesaid antiarrhythmic protocols (T0). The second timepoint corresponded to the first recheck performed after starting antiarrhythmic treatment in which Holter monitoring was performed (T1). Only dogs that underwent Holter monitoring (with a minimum of 20 h of valid data) after the start of antiarrhythmic treatment were enrolled in this study as the data provided by this test were considered essential for a precise understanding of the effects of the different antiarrhythmic protocols [9—12].

For each dog, dates of T0 and T1, selected clinical and clinicopathological findings, and electrocardiographic and echocardiographic measurements were obtained from the medical records. Further information was also collected: type of structural heart disease associated with AF; presence/absence and type of concurrent systemic disease; type and dosage of cardiovascular drugs prescribed at the time of AF diagnosis; the number of dogs in which the use of each antiarrhythmic protocol was efficacious; the number and type of possible TRSEs; and time and cause of death. Dogs were excluded if antiarrhythmic drugs different from the aforementioned were prescribed or if, after the initial diagnosis of AF, the AF converted to sinus rhythm, atrial flutter developed, or a clinically relevant bradyarrhythmia requiring a pacemaker implantation (e.g., third-degree atrioventricular block) was noted.

Electrocardiographic analysis

All electrocardiographic exams (including $\leq$5-min surface electrocardiograms and 24-h Holter recordings) from T0 and T1 were reviewed by four expert operators (G.R., P.P., H.P., and C.G.). At T0, 6-lead/12-lead surface electrocardiogram was performed according to a standard technique [19] to diagnose AF and calculate the heart rate. According to our systematic approach to dogs with AF, in the case of a baseline heart rate $\leq$150 beats per minute (bpm), Holter monitoring was recommended before prescribing antiarrhythmic drugs to ensure that rate control was necessary. Conversely, if the baseline heart rate was >150 bpm, an antiarrhythmic treatment for rate control was immediately initiated. This approach was based on findings from a previous study, indicating that a heart rate >150 bpm on electrocardiogram in dogs with AF is typically associated with a mean heart rate (mHR) >140 bpm on Holter monitoring [20].

At recheck, dogs underwent Holter monitoring only if there were no signs of ongoing decompensated heart failure. Otherwise, medical therapy for CHF was first optimized, and Holter monitoring was performed only once the aforementioned signs resolved. Three-channel Holter recordings were obtained at different institutions using different devices[e,f,g] but the same standardized technique [16]. Holter recordings were conducted in the dogs' home environment during their daily routines, and the owners were instructed to record all activities in a diary. Holter data were acquired with a 10-bit resolution and at a sampling frequency of 250 Hz and were then transferred to a computer for analysis. A standard protocol for semiautomatic arrhythmia analysis was performed, as previously described [16]. Initially, the operators manually checked the entire recording to assess its quality, ensure that the software triggered correctly on every complex, and label possible unidentified complexes. Based on R-R intervals, the software automatically calculated minimum, mean, and maximal heart rates. Subsequently, events marked by the software (e.g., pauses) were manually checked by the operators to confirm correct classification. On Holter recordings, confirmation of the presence of AF relied on manual analysis and was based on standard electrocardiographic criteria.

Echocardiographic analysis

As for electrocardiography, all echocardiographic exams from T0 and T1 were reviewed by the same operators. In light of the possible effects of diltiazem on left ventricular (LV) systolic function [21—23], particular attention was paid to the following measurements in dogs treated with this drug [24,25]: (a) LV end-diastolic and end-systolic diameters measured using a two-dimensionally guided M-mode leading edge-to-leading edge

[e] Cube ECG, Cardioline S.p.A., Caverano, Italy.
[f] Holter ECG Cardioline Walk400h, Cardioline S.p.A., Caverano, Italy.
[g] Dynamic ECG Systems Digital 3-lead 24-h Analyzer Recorder System, Contec Medical Systems Co., LTD, China.

technique from the right parasternal short-axis view at the level of the papillary muscles and then normalized for body weight, as previously described [26]; (b) LV fractional shortening using the standard formula; (c) 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 (d) LV ejection fraction calculated from LV volumes using the standard formula. For each variable, an average of five measurements was determined from five consecutive cardiac cycles within the same video loop [27,28].

Laboratory analysis

The same operators reviewed the medical database of each dog to note selected clinicopathological data. In light of the reported hematologic effects of oral amiodarone [14,15,18,29–32], in dogs treated with this drug, particular attention was paid to the following laboratory variables: red blood cell, white blood cell, and platelet count; alanine aminotransferase (ALT), aspartate aminotransferase, total bilirubin, thyroxine, and thyroid-stimulating hormone concentration. Moreover, to properly analyze the tolerability of digoxin, in dogs treated with this drug, attention was paid to serum concentration of potassium (as hypokalemia may enhance the risk of digoxin toxicity) and digoxin (as a high concentration may predispose to the development of signs of digoxin toxicity) [22,33–35]. Serum digoxin concentration was measured between 6–8 h after the last administration and ≥6 days after the start of treatment [23].

Antiarrhythmic efficacy

The prescribed antiarrhythmic protocol was considered effective if the mHR on Holter monitoring at T1 was ≤125 bpm. This cutoff was chosen based on the results of previous studies on canine AF, which demonstrated a significantly longer survival in dogs with a Holter-derived mHR ≤125 bpm than in dogs with a higher mHR [11,12].

Antiarrhythmic safety

Medical records were also reviewed for the occurrence of TRSEs after the prescription of diltiazem, digoxin, and amiodarone. Based on previous literature [13,21–23], TRSEs possibly attributable to diltiazem included the occurrence of depression, weakness/exercise intolerance, decreased appetite, vomiting, diarrhea, systemic hypotension (defined as a systolic arterial blood pressure <80 mmHg, measured according to the guidelines of the American College of Veterinary Internal Medicine [36,37]), and LV systolic dysfunction (defined as an LV fractional shortening <20% and an ejection fraction <40% [38]). In the case of digoxin, possible TRSEs included the occurrence of depression, restlessness, decreased appetite, vomiting, and diarrhea [21–23,35]. In the case of amiodarone, possible TRSEs included the occurrence of clinical signs such as decreased appetite, vomiting, and diarrhea; cytopenia, including anemia (i.e., red blood cell count below the internal laboratory reference interval [RI]: 5.65–8.4 $\times$ $10^6/\mu L$]), leukopenia (i.e., white blood cell count below the RI: 5–14 $\times$ $10^3/\mu L$), and thrombocytopenia (i.e., platelet count below an RI of 150–500 $\times$ $10^3/\mu L$); hepatic injury, defined by increased ALT activity (RI: 15–65 U/L), aspartate aminotransferase activity (RI: 15–52 U/L), and/or total bilirubin concentration (RI: 0.07–0.33 mg/dL); and thyroid hormones abnormalities, including decreased thyroxine concentration (RI: 13–51 nmoL/L), increased thyroid-stimulating hormone concentration (RI: 0.03–0.38 ng/mL), or both [14,15,18,29–32].

Outcome

Outcome data were evaluated by the same operators (G.R., P.P., H.P., and C.G.). Survival data were obtained from an internal database or by telephone questionnaires. For deceased dogs with available follow-up data, time in days from T0 till death (survival time) and the cause of death were noted.

Statistical analysis

Statistical analysis was performed with commercially available statistical software.[h] All continuous variables were checked graphically and tested for their distribution using the Shapiro-Wilk test. Descriptive statistics included the report of mean ± standard deviation and median and range (minimum–maximum) for normally and non-normally distributed data, respectively. The Wilcoxon signed-rank test and the paired sample *t* test were used to compare data between timepoints (i.e., T0 and T1). To compare the rate of efficacy and TRSEs related to the use of different antiarrhythmic protocols, a comparison of proportions by the Chi-square test or Fisher's exact test was performed. Survival was calculated using the Kaplan-Meier

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

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

Variable	
N. of dogs	54
Age (years)	10 (2–17)
Body weight (kg)	33.2 (3.4–72)
Sex (EM/NM/EF/NF)	31/11/4/8
Breed (no. of dogs)	Mixed breed (8) German shepherd (5) Corso, dachshund, Dogue de Bordeaux (4) Weimaraner (3) Boxer, Doberman pinscher, Dogo, golden retriever, Labrador retriever, Maremmano-Abruzzese Sheepdog, Pinscher, Spinone Italiano (2) American Staffordshire terrier, Appenzeller Sennenhund, beagle, English bulldog, English springer spaniel, Hungarian greyhound, Jack Russell terrier, Leonberger, Pointer, Saint Bernard (1)
Type of structural heart diseases (no. of dogs)	MMVD (31) (ACVIM stages: B2 = 1; C = 28; D = 2) DCM (18) (ACVIM stages: B2 = 3; C = 14; D = 1) Mitral valve dysplasia (2) PDA, SAS, tricuspid valve dysplasia (1)
Concomitant systemic diseases (Y/N)	30/24
Type of systemic diseases (no. of dogs)	Medically/dietetically controlled chronic kidney disease (IRIS stage 1 or 2) (10) Medically/dietetically controlled chronic gastrointestinal disease (5) Dermatitis (3) Medically controlled hyperadrenocorticism (2) Chronic osteoarthritis, cutaneous mast cell tumor, glioma, medically controlled hypoadrenocorticism, mild hip dysplasia, mild tracheal collapse, splenic hemangiosarcoma (1)

ACVIM: American College of Veterinary Internal Medicine; DCM: dilated cardiomyopathy; EF: entire female; EM: entire male; IRIS: International Renal Interest Society; MMVD: myxomatous mitral valve disease; NF: neutered female; NM: neutered male; PDA: patent ductus arteriosus; SAS: subaortic stenosis.

method. Differences in median survival time (MST) between groups were determined using the log rank test. Dogs in the study that were alive at the end of the study or lost to follow-up were right censored. For the purpose of data analysis and comparison, dogs treated with a single antiarrhythmic were evaluated both collectively (thus forming a composite monotherapy group comprising dogs treated with MT_{Dilt}, MT_{Digox}, and MT_{Amiod}) and individually. P values$<$0.05 were considered statistically significant.

Results

Study sample

A total of 224 dogs with secondary AF were presented during the study period. One hundred seventy dogs were not enrolled due to incomplete data from T0 and/or T1, lack of Holter recording, and/or the use of antiarrhythmic protocols different from those analyzed in this study. Therefore, the study sample ultimately included 54 dogs, of which 28 received $CT_{Dilt+Digox}$ and 26 received a monotherapy. Among dogs treated with a monotherapy, 16 received MT_{Digox}, 5 received MT_{Dilt}, and 5 received MT_{Amiod}. Given the limited number of dogs treated with MT_{Dilt} and MT_{Amiod}, comparisons were predominantly made between $CT_{Dilt+Digox}$ and the composite monotherapy group (i.e., MT_{Dilt}+MT_{Digox}+MT_{Amiod}).

Demographic and clinical characteristics of enrolled dogs are reported in Table 1. Dogs treated with $CT_{Dilt+Digox}$ and those from the composite monotherapy group had similar age (P=0.66). Similarly, no differences were found between these two groups in terms of the number of dogs affected by systemic diseases (P=0.25), heart diseases associated with systolic dysfunction (P=0.79), and decompensated heart disease (American College of Veterinary Internal Medicine stages C and D) (P=0.23). Table 2 provides details on cardiovascular drugs aimed at treating the underlying structural heart diseases that had been prescribed before the diagnosis of AF. Table 3 provides details on antiarrhythmic drugs prescribed only after the diagnosis of AF was made.

Table 2 Cardiovascular drugs aimed at treating underlying structural heart diseases.

Drug	Dose	No. of dogs
Pimobendan	0.26 ± 0.04 mg/kg q 12 h	53
Furosemide	2.1 ± 0.67 mg/kg q 12 h	48
Benazepril		30
Used once a day	0.29 ± 0.12 mg/kg q 12 h	16
Used twice a day	0.34 ± 0.13 mg/kg q 24 h	14
Spironolactone	2.08 ± 0.59 mg/kg q 24 h	17
Hydrochlorothiazide	0.5 and 0.7 mg/kg q 12 h	2
Torasemide	0.22 and 0.34 mg/kg q 12 h	2

The diltiazem dosage used in dogs receiving $CT_{Dilt+Digox}$ did not differ from the one used in dogs treated with MT_{Dilt} (P=0.28). Similarly, the digoxin dosage used in dogs receiving $CT_{Dilt+Digox}$ did not differ from the one used in dogs treated with MT_{Digox} (P=0.14).

Electrocardiographic findings

At T0, the heart rate from the entire study population was 203 ± 39 bpm. At that time, only 4 of 54 (7.4%) dogs underwent Holter monitoring in light of the heart rate observed on surface electrocardiogram. In these dogs, the initial Holter analysis recorded an mHR of 151 bpm (133–170 bpm). Therefore, in these cases, antiarrhythmic drugs were subsequently prescribed, followed by a Holter recheck, as in all other dogs from this study. In the entire study population, the median time between T0 and T1 was 20 days (6–125 days). At T1, the median mHR documented in dogs from the $CT_{Dilt+Digox}$ group was within the optimal cutoff of ≤125 bpm (i.e., 124 bpm [74–182 bpm]); conversely, the median mHR documented in dogs from the composite monotherapy group was above it (i.e., 150 bpm [98–245 bpm]). The median mHR remained above the optimal cutoff also when considering each monotherapy group individually (i.e., MT_{Dilt}: 129 bpm [107–157 bpm]; MT_{Digox}: 151 bpm [98–172 bpm]; MT_{Amiod}: 157 bpm [130–245 bpm]).

Echocardiographic findings

All dogs treated with diltiazem (n = 33, including dogs treated with $CT_{Dilt+Digox}$ and MT_{Dilt}) underwent echocardiographic analysis at T0 and T1. No difference was documented after diltiazem prescription (Table 4). Moreover, no dogs with a normal LV systolic function at T0 developed echocardiographic signs of LV systolic dysfunction at T1, either among subjects treated with $CT_{Dilt+Digox}$ or among those treated with MT_{Dilt}.

Clinicopathological findings

Among dogs treated with digoxin (n = 44, including dogs treated with $CT_{Dilt+Digox}$ and MT_{Digox}), data on the serum concentration of this drug were available in 23 of 44 (52.3%) cases. The mean concentration documented at T1 was 1.4 ± 0.6 ng/ml (RI: 0.9–3 ng/ml). Serum digoxin concentration was abnormal in four cases. In all these cases, it was below the RI concentration (i.e., 0.52 ng/ml, 0.58 ng/ml, 0.69 ng/ml, and 0.84 ng/ml). No differences were found when comparing serum digoxin concentration between dogs treated with $CT_{Dilt+Digox}$ and dogs receiving MT_{Digox} (P=0.8). Data on serum potassium concentration were available in 35 of 44 (79.6%) cases. At T0, the mean concentration of potassium was 4.4 ± 0.49 mEq/L (RI: 3.8–5 mEq/L). Serum potassium concentration was above and below the RI in nine and six cases,

Table 3 Antiarrhythmic treatments prescribed at the time of atrial fibrillation diagnosis.

Combination therapy	Dose	No. of dogs
Diltiazem (SR) + digoxin	2.5 mg/kg (1.8–3.9 mg/kg) q 12 h + 3 μg/kg (1.7–5 μg/kg) q 12 h	28
Monotherapy	**Dose**	**No. of dogs**
Digoxin	4 μg/kg (1.6–6 μg/kg) q 12 h	16
Amiodarone (MD)	7.5 mg/kg (5–10 mg/kg) q 24 h	5
Diltiazem (SR)	2.1 mg/kg (1.6–2.9 mg/kg) q 12 h	5

MD: maintenance dose; SR: sustained release.

Table 4 Selected echocardiographic findings at the time of atrial fibrillation diagnosis (T0) and recheck (T1).

Echocardiographic parameters	T0	T1	P
LVIDDn	1.96 ± 0.27	1.93 ± 0.3	0.95
LVIDSn	1.43 ± 0.34	1.37 ± 0.29	0.82
FS (%)	29 ± 13	31 ± 11	0.44
EDVI (mL/m^2)	142 ± 42	142 ± 53	0.3
ESVI (mL/m^2)	66 ± 36	60 ± 30	0.65
EF (%)	55 ± 18	58 ± 17	0.44

EDVI: end-diastolic volume index; EF: ejection fraction; ESVI: end-systolic volume index; FS: fractional shortening; LVIDDn: left ventricular internal diameter in diastole normalized for body weight; LVIDSn: left ventricular internal diameter in systole normalized for body weight; T0: the day of diagnosis of AF that prompted the prescription of the aforesaid antiarrhythmic protocols; T1: the day when the first recheck performed after starting antiarrhythmic treatment in which a Holter monitoring was performed.

respectively. In all dogs with hyperkalemia and hypokalemia at T0, potassium abnormalities were mild (5.4 ± 0.28 mEq/L and 3.5 ± 0.13 mEq/L, respectively) [39]. At T1, the mean concentration of potassium was 4 ± 0.43 mEq/L. Serum potassium concentration was above and below the RI in two and five cases, respectively. In all dogs with hyperkalemia and hypokalemia at T1, potassium abnormalities were mild (5.9 mEq/L and 5.4 mEq/L and 3.4 ± 0.2 mEq/L, respectively) [39]. No differences were found when comparing serum potassium concentration at T0 (P=0.31) and T1 (P=0.56) between dogs treated with $CT_{Dilt+Digox}$ and dogs receiving MT_{Digox}.

Concerning clinicopathological findings in dogs treated with MT_{Amiod}, in which laboratory data were available (n = 4), abnormalities were limited to a case of mild non-regenerative anemia (red blood cell count: 5.32 × 10^6/μL) [40] and a case of mildly increased ALT (152 U/L) [41]. In these cases, anemia and ALT increase were documented from T0 (i.e., before the prescription of amiodarone) and remained mild at T1 (red blood cells: 5.32 × 10^6/μL; ALT: 215 U/L) [40,41]. In light of the clinical history of these dogs, mild anemia and mild ALT elevation were suspected to be caused by chronic kidney disease and ascites/hypoxic hepatic injury due to underlying cardiac disease, respectively, rather than amiodarone treatment.

Antiarrhythmic efficacy

Efficacy was demonstrated in 15 of 28 (53.6%) dogs from $CT_{Dilt+Digox}$ group and in 7 of 26 (26.9%) dogs from the composite monotherapy group. The efficacy rate documented in dogs treated with $CT_{Dilt+Digox}$ was higher than that documented in the composite monotherapy group (P=0.048). When MT_{Dilt}, MT_{Digox}, and MT_{Amiod} were considered individually, efficacy was documented in 4 of 16 (25%), 2 of 5 (40%), and 1 of 5 (20%) dogs, respectively.

Antiarrhythmic safety

After diltiazem prescription (n = 33 dogs, including dogs treated with $CT_{Dilt+Digox}$ and MT_{Dilt}), no dog developed systemic hypotension (median systolic arterial blood pressure = 130 mmHg [114—158 mmHg]) or systolic dysfunction, whereas 1 of the 33 (3%) dogs experienced transient weakness/exercise intolerance. After digoxin prescription (n = 44 dogs, including dogs treated with $CT_{Dilt+Digox}$ and MT_{Digox}), 4 of 44 (9.1%) dogs showed transient gastrointestinal signs, including decreased appetite (4/4), vomiting (4/4), and diarrhea (3/4). Among dogs showing TRSEs, the mean serum digoxin concentration was 1.6 ± 0.53 ng/ml (with one dog showing a value mildly below the RI [0.87 ng/ml]) and the mean serum potassium concentration was 4.3 ± 0.67 mEq/L (with one dog showing a value mildly above the RI [5.4 mqE/L]). After amiodarone prescription, TRSEs were documented in 2 of 5 dogs (40%) and included decreased appetite (2/2), vomiting (1/2), and diarrhea (1/2). No statistically significant differences were documented when comparing the rate of TRSEs developed by dogs from the $CT_{Dilt+Digox}$ group with that developed by dogs from the composite monotherapy group (P = 0.129).

Outcome

Complete long-term follow-up was available for 42 of 54 (77.8%) dogs, of which 24 were treated with $CT_{Dilt+Digox}$ and 18 were treated with monotherapies. At the end of the study, 16 of 42 (38.1%) dogs were still alive, whereas 26 of 42 (61.9%) dogs were dead. Cardiac-unrelated and cardiac-related deaths were documented in 10 of 26 (38.5%) and 16 of 26 (61.5%) dogs, respectively. Cardiac-related deaths were predominantly sudden deaths (10/16 [62.5%]); the remaining cases were attributed to CHF (1/16 [6.25%]) and euthanasia for worsening cardiac conditions (5/16 [31.25%]). Given the limited number of dogs initially enrolled in the MT_{Dilt} and MT_{Amiod} groups and the fact that some dogs with an unavailable follow-up were from these groups (thus further reducing the sample size), survival was compared exclusively between

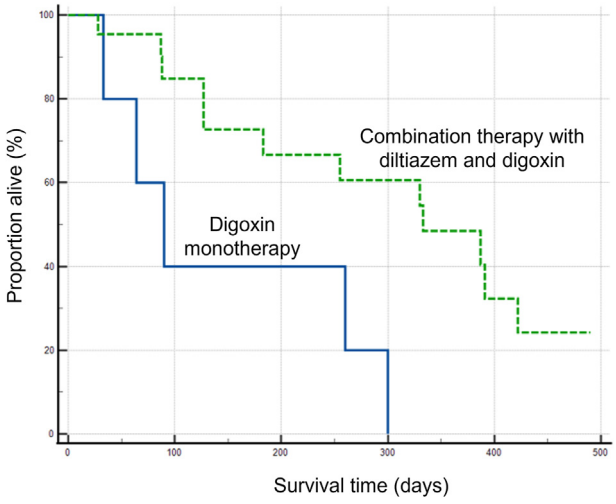

Figure 1 Kaplan-Meier survival curve displaying all-cause mortality for dogs with secondary atrial fibrillation treated with combination therapy with diltiazem and digoxin (green dotted line) and digoxin monotherapy (blue line). The median survival time of dogs treated with combination therapy was significantly longer than that of dogs treated with digoxin monotherapy (i.e., 333 days [95% confidence interval: 127—422 days] and 90 days [95% confidence interval: 33—300 days], respectively; P=0.01).

dogs treated with $CT_{Dilt+Digox}$ and those treated with MT_{Digox}. The median survival time of dogs treated with $CT_{Dilt+Digox}$ (333 days; 95% confidence interval: 127—422 days) was longer than that of dogs treated with MT_{Digox} (90 days; 95% confidence interval: 33—300 days) (P=0.01) (Fig. 1). Statistical significance was reached even when dogs with systemic diseases that can remarkably affect survival time (i.e., neoplastic diseases) were excluded from the analysis (P=0.045).

Discussion

This study represents one of the largest investigations on the efficacy and safety of antiarrhythmic treatments in dogs with secondary AF. Our results not only support some previous findings but also provide additional information to expand our knowledge of the effects of antiarrhythmic drugs commonly used for rate control in canine AF.

This study suggests that $CT_{Dilt+Digox}$ is generally more effective at reducing the ventricular response rate than treatment protocols based on the administration of a single antiarrhythmic drug as it allows optimal mHR to be achieved more frequently. Our results are overall consistent with previous veterinary literature. For example, a study conducted on 18 dogs affected by secondary AF treated with $CT_{Dilt+Digox}$, MT_{Dilt}, and MT_{Digox} demonstrated that $CT_{Dilt+Digox}$ allowed for a better reduction in mHR (median: 126 bpm) than did both types of monotherapy (median: ~160 bpm) [13]. Furthermore, a study conducted on 33 dogs affected by myxomatous mitral valve disease associated with CHF and AF documented a more pronounced decrease in mHR in dogs treated with $CT_{Dilt+Digox}$ (median: 144 bpm) than in dogs treated with MT_{Dilt} (median: 180 bpm) [10]. Our results also appear to be in line with human medicine. Indeed, several publications demonstrated that monotherapy based on the administration of diltiazem or digoxin is significantly less effective than the combination of these drugs for controlling heart rate in humans with AF [42—45].

Knowledge of the antiarrhythmic properties of diltiazem and digoxin and their synergistic effects is important to understand why the use of a combination of these drugs is superior to their individual use in AF. Digoxin exerts vagomimetic effects on the atrioventricular node, thereby slowing electrical conduction through the nodal tissue. Consequently, this drug reduces ventricular response during AF, particularly at rest [46,47]. However, it should be noted that the efficacy of digoxin in controlling ventricular response is reduced in patients with increased sympathetic activity (e.g., decompensated heart failure, exercise, and stress-related conditions) unless large toxic doses are administered [43,45,47,48]. Especially in sympathetic overstimulation/chronic stimulation (expected in dogs with secondary AF due to underlying advanced cardiac disease [49]), the addition of diltiazem may improve control of the ventricular response. This is because this calcium channel blocker not only further contributes to depress conduction and prolong refractory period in the atrioventricular node but also demonstrates a significant degree of non-competitive adrenergic antagonism, thus attenuating sympathetically induced increases in ventricular response [42,43,45,50,51].

The unsatisfying results we documented in dogs treated with MT_{Amiod} overall agree with some data already reported in the canine literature. Indeed, in a study of 17 dogs with secondary AF and a ventricular response of 200 bpm (180—300 bpm) at presentation, the heart rate decreased by 20—50% after prescribing amiodarone, which corresponded to an unsatisfactorily elevated median heart rate of 160 bpm at recheck [14].

An additional clinically relevant finding from the present study concerns survival as the MST documented in dogs from the $CT_{Dilt+Digox}$ group was significantly longer than that observed in dogs

from the MT_{Digox} group (i.e., 333 days and 90 days, respectively). Our findings are overall consistent with those from a previous study comprising 55 dogs with AF secondary to myxomatous mitral valve disease and dilated cardiomyopathy [17]. Specifically, in that study population, MST in dogs treated with $CT_{Dilt+Digox}$ and MT_{Digox} was 359 days and 212 days, respectively [17]. The longer MST in dogs treated with $CT_{Dilt+Digox}$ is likely primarily a consequence of the better rate control provided by combination therapy than by monotherapy.

In addition to the efficacy analysis, the present study aimed at providing data on the clinical tolerability of different antiarrhythmic protocols. The rate of TRSEs did not differ significantly between dogs treated with $CT_{Dilt+Digox}$ and dogs from the composite monotherapy group. A closer analysis of our study sample allowed us to document two other interesting findings. First, diltiazem, at the dosage reported here, was well tolerated by the enrolled dogs with secondary AF, both in those treated with $CT_{Dilt+Digox}$ and in those receiving MT_{Dilt}. Second, in our study sample, TRSEs were predominantly due to the use of digoxin.

The good clinical tolerability of diltiazem is in line with data from a previous report in dogs with secondary AF receiving diltiazem both as a monotherapy and in combination with digoxin [13]. Moreover, the lack of significant changes in echocardiographic parameters and the absence of cases developing systemic hypotension after administration of oral diltiazem are in agreement with findings from a recent study in healthy dogs treated with a standardized dose of intravenous diltiazem [52]. Collectively, these data indicate that diltiazem can be considered overall safe if used as monotherapy or in combination with digoxin in dogs. Although generally good tolerability has been reported also in humans, it should be noted that diltiazem is contraindicated in patients with myocardial failure as it may not only promote clinical worsening (e.g., fatigue, headaches) but also increase mortality [53]. This contrasts with some findings from this report as even dogs with dilated cardiomyopathy demonstrated good clinical tolerability of diltiazem. The reasons for this discrepancy are not clear. Interspecies differences could be a contributing factor. Moreover, it should be considered that the majority of dogs receiving diltiazem in our study were also on digoxin. Consequently, it cannot be conclusively excluded that the positive inotropic effect of digoxin may have counterbalanced the potentially adverse effects of diltiazem in dogs with preexisting systolic dysfunction. Further studies enrolling a larger number of dogs treated exclusively with diltiazem are therefore needed to expand on our results.

Concerning the relatively limited clinical tolerability of digoxin, it is important to note that we have excluded the presence of major factors known to increase the risk of digoxin toxicity (i.e., elevated serum digoxin concentration and moderate/severe hypokalemia). Moreover, we prescribed conventional dosages of digoxin [9–12,23]. Therefore, we believe that our results can represent a reliable picture of the actual clinical tolerability of digoxin in dogs with AF. Intriguingly, our findings are consistent with those from human literature as digoxin causes TRSEs more often than other antiarrhythmics commonly used for rate control in patients with AF [54].

Regarding the clinical tolerability of MT_{Amiod}, our analysis is limited by the small number of dogs treated with this protocol and the variable timing of rechecks after its prescription (as a TRSE associated with the use of amiodarone can be time-dependent) [18].

Limitations

This study has some limitations. First, the retrospective design precluded the standardization of timing of diagnostic procedures and therapeutic interventions. Second, similar to many other previous studies on canine AF [7,11–13], we enrolled dogs affected by various heart conditions, which could have partially influenced some of our analyses (e.g., the echocardiographic assessment of systolic function, due to differences in loading conditions and myocardial function between dogs with myxomatous mitral valve disease and those with dilated cardiomyopathy). Moreover, some dogs in this study were also affected by systemic disorders. However, the vast majority of these were mild and/or properly medically controlled at the time of the study inclusion. Moreover, our statistical analysis demonstrated that the aforesaid conditions were similarly distributed among dogs treated with $CT_{Dilt+Digox}$ and monotherapy. Third, the heart rate at T0 was based on electrocardiographic analysis, not Holter recording, as we do not systematically use Holter monitoring in dogs with AF at the time of the first presentation. This choice is based on the following reasons: a) the diagnosi of AF is straightforward based on electrocardiogram alone; b) although the mHR assessed by electrocardiogram over a few minutes may overestimate that documented by Holter monitoring, a heart rate on electrocardiogram $>$150 bpm can be considered predictive of an mHR

>140 bpm on Holter monitoring in dogs with AF (therefore, it can be useful in terms of prognostic and therapeutic considerations despite the possible overestimation) [20]; and c) we considered it unethical to delay prescribing antiarrhythmic therapy in dogs manifesting a fast AF-related mHR at presentation while waiting for Holter results. Notably, this approach is consistent with that described by other authors [12]. Fourth, our results may have been partially influenced by the way we determined antiarrhythmic efficacy, the dosages of drugs we administered, and the time at which Holter monitoring was performed. At the same time, it should be noted that we adopted an efficacy criterion validated and used by various authors [9,11,12]. Moreover, the dosages of diltiazem, digoxin, and amiodarone that we used are within the ranges reported by several authors in veterinary literature [9–15,18,23]. Lastly, the median time at which Holter control was performed in our study population (i.e., 20 days) is similar to that reported in many other studies on canine AF (i.e., 1–3 weeks [11–13]). This timing is considered appropriate by many veterinary cardiologists, also because digitalization and amiodaronization (steady-state drug effect) are expected to occur in most dogs within the above-mentioned time period [21,55,56]. Fifth, not all categories were equally represented (e.g., $CT_{Dilt+Digox}$ and MT_{Digox} groups overnumbered MT_{Dilt} and MT_{Amiod} groups). Sixth, clinicopathological data were available in many, but not all, dogs treated with digoxin and amiodarone. However, it should be noted that these last two limitations have also affected numerous previous studies on the use of the antiarrhythmic drugs investigated here [7,12,14,15,17,18,32]. Lastly, we did not evaluate the potential role of digoxin in the development or worsening of concomitant ventricular arrhythmias.

Conclusions

In conclusion, this study provides detailed data on the efficacy and safety of different antiarrhythmic protocols used for rate control in dogs with secondary AF. Our findings support the indication to generally consider $CT_{Dilt+Digox}$ as a first-line antiarrhythmic treatment in dogs with secondary AF. In contrast, the use of a single antiarrhythmic such as diltiazem, digoxin, and amiodarone appears to be a more flawed approach, which consequently should generally be discouraged. Further studies are needed to provide information on dogs with secondary AF treated with different antiarrhythmic protocols.

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Conflict of Interest Statement

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

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