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Irish wolfhounds with subclinical atrial fibrillation: progression of disease and causes of death☆

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KEYWORDS
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Abstract *Introduction:* To evaluate the frequency of dilated cardiomyopathy (DCM) and cardiac death (CD) in Irish wolfhounds (IW) with subclinical atrial fibrillation (AF) and to compare cardiac and all-cause mortality to those of a contemporaneous control group of apparently healthy IW with sinus rhythm.
Animals: Fifty-two IW with AF, but without echocardiographic evidence of DCM or other cardiac disease, and an age- and gender-matched control cohort of 52 apparently healthy IW.
Methods: Data from 1552 IW were retrospectively evaluated. Fifty-two dogs with subclinical AF were compared with 52 IW controls. Time from initial diagnosis to development of DCM was recorded, and survival data were analyzed using cumulative incidence functions.
Results: 26/52 AF dogs developed DCM. At study end, in the AF and control group each, 49/52 AF dogs had died, three remained alive. Death in the AF cohort was attributed to

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CD in 22/49 dogs (12 congestive heart failure [CHF], 10 sudden cardiac deaths [SCD]), while 27 dogs died from non-CD. In the control group, significantly fewer dogs developed DCM (11/52 dogs, p=0.004), even fewer died from CD (5/49; three CHF, two SCD; p=0.001). The odd ratios (95% confidence interval) for dogs with AF vs. controls to develop DCM was 3.7 (1.6—8.8) and to die from CD was 7.2 (2.4—21.2). Median all-cause survival for AF IWs (CD, 36.3 months; non-CD, 33.2 months) did not differ significantly from the control group (CD, 28.6 months, p=0.377; non-CD, 45.3 months, p=0.631).
Conclusion: IW with subclinical AF commonly develop DCM and die from cardiac death.

Abbreviations

AF	atrial fibrillation
CD	cardiac death
CHF	congestive heart failure
DCM	dilated cardiomyopathy
HR	heart rate
IW	Irish wolfhound dogs
MR	mitral regurgitation
SCD	sudden cardiac death

Introduction

Atrial fibrillation (AF) is the most common arrhythmia that requires treatment in veterinary medicine [1]. A retrospective, statistical review of 3,542 dogs with AF showed that giant breeds often develop AF early in life [2]. Irish Wolfhound (IW) dogs have a high prevalence of heart disease, particularly dilated cardiomyopathy (DCM) and AF, and several studies have reported an association between AF and DCM in IW [3—6]. In one study, out of 29 IW with DCM, 17 dogs were diagnosed with both DCM and AF, whereas the remaining 12 had been diagnosed with AF 2—3 three years prior to the DCM diagnosis [6]. On the other hand, AF has been described in the absence of obvious cardiovascular disease in large and giant breeds such as the IW [7]. Likely related to the greater mass of the atria, markedly increased odds ratios to develop AF have been identified in giant breeds [2]. However, there are little data available from serial, longitudinal evaluations over the lifespan of the dogs, recording causes of death in dogs with AF who appeared at least initially to be clinically unaffected by DCM.

The purpose of this study was to evaluate the frequency of development of DCM and of cardiac death (CD)—either sudden CD (SCD) or death due to progressive congestive heart failure (CHF) in IW with no obvious clinical signs from the presence of AF. Further aims included comparison of cardiac and all-cause mortality between IW with AF with that of a contemporaneous, age- and gender-matched case control group of apparently healthy IW in sinus rhythm.

Material and methods

Study population

Medical records of 1552 IW (708 males, 844 females) that had cardiovascular examinations performed in Belgium, Germany, and the Netherlands between January 1996 and October 2014 were retrospectively reviewed. This study identified and included asymptomatic dogs diagnosed with AF and left atrial enlargement, but with normal left ventricular size and function. Dogs were only selected that had longitudinal follow-up examinations performed at 3 to 12 month intervals until death occurred or until study termination. Dogs that died within the first 6 months of study inclusion but prior to reexamination were also included. Dogs were excluded from the study if they had other cardiovascular abnormalities or lost to follow-up any time. A control cohort consisted of 52 apparently healthy IW of same gender and similar age, that were not first-degree relatives, and had a cardiovascular examination performed within the same year as the matched AF case.

Clinical examination

Enrolled cases were first diagnosed between February 12, 1996 and April 4, 2014, and the study period extended to October 12, 2014. At each examination, dogs received a focused cardiovascular physical examination, a six-lead

electrocardiogram (ECG)[f] recorded in right lateral recumbency for a minimum of 3 min, and a two-dimensional and M-mode echocardiographic examination performed by one cardiologist (AV) to acquire standard images[g,h,i,j,k]

In addition, two-dimensional systolic measurements of both atria were obtained and measured at the level of their maximal diameter, parallel to each AV valve from right parasternal four-chamber views, along with diastolic measurements of the right ventricular diameter below the tricuspid valve [9]. The value for each echocardiographic variable was determined by averaging measurements made from four to six cardiac cycles in dogs with sinus rhythm and from 10 cardiac cycles in dogs with AF. In dogs with a heart murmur, spectral-Doppler and color-flow Doppler echocardiography were used to estimate pulmonary and aortic flow velocities and subjectively evaluate the severity of atrioventricular valve regurgitation.

Criteria for the diagnosis of DCM were based on breed-specific reference values for two-dimensional and M-mode echocardiographic measurements reported in IW (left ventricular end-systolic dimension >41 mm, left ventricular end-diastolic internal dimension >60 mm, left ventricular shortening fraction <25%, left atrial end-systolic diameter >56 mm, right ventricular dimension >35 mm) [8–10]. When mitral or tricuspid regurgitation developed in dogs with DCM, the severity was graded semiquantitatively by comparing the color Doppler regurgitation flow to the area of the atrium (mild <20%, moderate 20%–50%, and severe >50% regurgitation) [11,12]. Average heart rate (HR) during the echocardiographic examination was recorded from simultaneous ECG recordings. In dogs whose history and examination findings suggested CHF, a right lateral radiograph was evaluated for presence of pleural effusion and/or mixed interstitial-alveolar lung pattern consistent with cardiogenic pulmonary edema.

Treatment

Therapy when given was not standardized and changed over the course of the study years. Treatment was optimized and recorded on a case by case basis in collaboration with the owner and referring veterinarian by the attending cardiologist (AV). In dogs with AF and a sustained HR > 180 bpm during echocardiography, ECG, and or repeated auscultation, HR control was managed using methyldigoxin with verapamil up to 2002 (N = 3) and thereafter, using methyldigoxin and diltiazem (N = 2) [13]. Target HR was less than 140 beats per minute recorded at rest in the examination room or less than 100 beats per minute recorded at home. Other drugs used during the study were methyldigoxin alone (n = 12), angiotensin converting enzyme inhibitors alone (n = 8) or in combination with methyldigoxin (n = 11), and pimobendan (after 2002; n = 9). After detection of CHF, dogs received additional medications as judged to be necessary, including furosemide and spironolactone (since 2001). According to owner decision, seven dogs with AF initially received no therapy and developed DCM later. In four of these dogs, therapy was started after development of DCM. The other three dogs never received medical therapy and were euthanized when they became symptomatic based on owner request. In the five control dogs that developed DCM with AF, similar treatment choices were offered.

Deaths were classified as CD or non-CD. Cardiac death was subclassified as SCD or euthanasia due to progressive, refractory CHF. Death was defined as SCD when witnessed by the owner as a sudden collapse and death without evidence of dyspnea or when death occurred during sleep and dogs had been observed to have been healthy within 8 h before death, in absence of history or known indication of other disease or condition likely to cause acute death.

Cause of death was obtained from medical records and descriptions recorded by the owners. Postmortem examinations were performed at Utrecht University in five, and Ghent University in two of the dogs.

Statistical analysis

Statistical analyses were performed using commercially available software and freeware.[l,m,n] Normality testing for continuous data consisted of visual inspection of probability plots and the

[f] Cardiovit AT-10; Schiller AG, Switzerland.
[g] SIM 7000 CFM Challenge, Esaote Biomedica, Italy.
[h] Logiq 400, GE Healthcare, Great Britain.
[i] My Lab 30 Vet, Esaote Biomedica, Italy.
[j] My Lab 30 Vet Gold, Esaote Biometica, Italy.
[k] CX 50 Cardiac/ShS Ultrasound system, Philips GmbH Healthcare, Germany.

[l] SPSS 23.0, IBM Company, Chicago, Illinois 60606, USA.
[m] R Studio 0.99.99.902, The R Foundation for Statistical computing, Institute for Statistics and Mathematics, Wirtschaftsuniversität Wien, 1020 Vienna, Austria.
[n] R 3.3.0, The R Foundation for Statistical computing, Institute for Statistics and Mathematics, Wirtschaftsuniversität Wien, 1020 Vienna, Austria.

Shapiro—Wilk test. Continuous variables that were normally distributed are reported as mean ± standard deviation and variables without normal distribution of data as median and interquartile range (IQR). Categorical variables are summarized by frequencies and percentages. Each death was attributed to one cause exclusively. The frequencies of development of DCM and the frequencies of CD of the dogs with AF vs. controls were compared by Fisher's exact test. As many IW with AF died from non-cardiac causes, for survival analysis, we used the cumulative incidence function recommended by Austin et al. and Oyama et al. and which in our setting allowed for estimation of the incidence of the occurrence of the event CD while taking non-CD as competing risks into account [14,15]. Survival curves by cumulative incidence function for CD vs. non-CD were calculated for IW with AF and for controls. The median survival times of the four groups were compared using the generalized linear model for comparisons within the AF-group and using the generalized estimating equations for comparing the matched pairs. Four comparisons were carried out: (1) IW with AF and CD vs. non-CD; (2) IW with AF and CD vs. control IW with CD; (3) IW with AF and non-CD vs. control IW with non-CD; (4) control IW with CD vs. control IW with non-CD. For the more common causes of non-CD as variables, univariate analysis was applied to test for an influence on survival times, and survival times were compared by an unpaired, two-tailed t-test. Correlation between two variables was specified by Spearman's rho correlation coefficient. Age at diagnosis, HR at diagnosis, and HR after therapy of the different groups were compared by one-way analysis of variance with post hoc Bonferroni correction. Data measured at the initial echocardiographic examination were analyzed for important differences between the matched pairs of IW with AF and the corresponding control IW by using the Wilcoxon test. A value of $p < 0.05$ was considered statistically significant.

Results

Of 1552 IWs (708 males, 844 females) examined between January 1996 and October 2014, 52 AF dogs (24 males, 28 females) and 52 controls (24 males, 28 females) were included in the study. At the time of AF diagnosis, males were significantly younger (mean, 3.8 ± 1.7 years) than females (mean, 5.0 ± 2.2 years, p=0.023). Mean bodyweight of males (71.1 ± 6.9 kg) was 8.5 kg (12%) higher than that of females (62.6 ± 5.8 kg, p<0.001). The age difference between each AF dog and its control dog was mean: 0.24 ± 4 months. The maximal age difference in one pair was 9.6 months.

Echo measurements at initial diagnosis

Echocardiographic measurements of left ventricular internal dimensions and left ventricular shortening fraction were within reference ranges for all IW with AF, and for control dogs, while all IW with AF but no control dog had increased left atrial end-systolic diameters (Fig. 1). Compared with control dogs, IW with AF had greater left ventricular end-systolic dimension, left atrial end-systolic diameter, and end-diastolic right ventricular diameter. In addition, shortening fraction was significantly lower in IW with AF vs. control dogs (Table 1). There was no statistically significant difference between IW with AF and controls in left ventricular free wall and interventricular septal measurements.

Development of dilated cardiomyopathy

IW with AF developed DCM (26/52, 50%) more frequently than controls (11/52 dogs, 21%; p=0.004; Table 2). The odds ratio (95% confidence interval) for dogs with AF vs. controls to develop DCM was 3.7 (1.6—8.8). Median time to development of DCM was not significantly different for IW with AF (30.8 months; IQR 16.3—44.2 months) compared with control dogs (17.7 months; IQR 10.8—31.2 months; p=0.192). In IW with AF, 46% of males (11/24) and 54% of females (15/28) developed DCM. Of the 26 dogs that developed DCM, 19 later developed clinical signs of CHF. In 17/26 AF

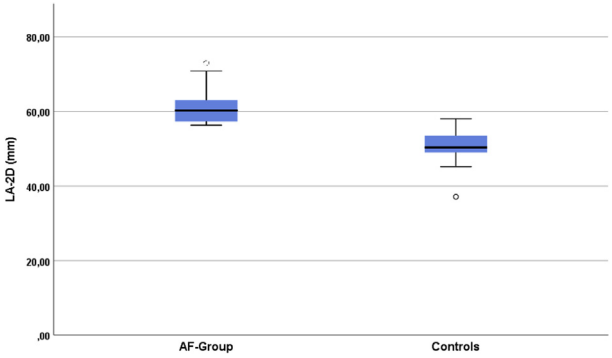

Fig. 1 Box and whisker plot depicting two-dimensional left atrial end-systolic diameter (LA-2D) of Irish wolfhound dogs with atrial fibrillation (AF) and control dogs.

Table 1 Comparison of echo measurement at diagnosis of 52 Irish wolfhounds with atrial fibrillation with those of the 52 control dogs.

Echocardiographic measurements	IW with AF	Control dogs	*p*-value
	Median (IQR)	Median (IQR)	
LVIDs (mm)	38.1 (36.1–39.3)	35.8 (31.9–37.2)	<0.001
LVIDd (mm)	52.4 (50.3–53.8)	51.6 (48.1–54.0)	0.293
FS (%)	27.4 (25.1–29.6)	30.7 (29.5–34.0)	<0.001
LA-2d (mm)	60.2 (57.2–63.0)	50.4 (48.0–53.5)	<0.001
RVIDd (mm)	33 (29.8–37.4)	30.5 (28.0–32.8)	0.007

LVIDs, end-systolic left ventricular internal diameter; LVIDd, end-diastolic left ventricular internal diameter; FS, fractional shortening; LA-2d, two-dimensional left atrial diameter; RVIDd, end-diastolic right ventricular internal diameter; IQR, interquartile range.

Table 2 Development of DCM and survival in 52 Irish wolfhounds with atrial fibrillation vs. 52 control dogs with sinus rhythm.

Outcome	IW with AF	Control dogs
Development of DCM	N = 26 (50%)	N = 11 (21.1%)
No DCM	N = 26 (50%)	N = 41 (78.8%)
Median (IQR) time to CD (days)	N = 22; 1088 (547–1718)	N = 5; 858 (595–858)
Median (IQR) time to non-CD (days)	N = 27; 997 (534–1507)	N = 44; 1360 (821–1769)
Alive at study end (days on study)	N = 3; 602 (446–1039)	N = 3; 461 (461–1039)

AF, atrial fibrillation; CD, cardiac death, DCM, dilated cardiomyopathy; IQR, interquartile range; IW, Irish wolfhounds.

IW with DCM, mild to moderate secondary mitral regurgitation (MR) developed over time. Out of the 11/52 control dogs that developed DCM, nine dogs also had AF at time of DCM-diagnosis, one male developed AF later, and another male remained in sinus rhythm until non-CD occurred. Over time, four of these nine dogs with DCM and AF developed MR, and three developed CHF later.

Survival, cardiac vs. non-cardiac death

At study termination, 49/52 AF dogs had died, 22 (44.9%) due to a cardiac, and 27 (55.1%) due to a non-cardiac cause. Three remained alive (Tables 2–4). In the control group, significantly less dogs died from CD (5/49; three CHF, two SCD; p=0.001) (Tables 2, 3, and 5). Cumulative incidence curves by cause of death and probability of overall death indicated an increased relative risk of CD for AF vs. control dogs (Fig. 2). For IW with AF, there was an approximate cumulative incidence of CD of 15% by 3.5 years from diagnosis that increased to approximately 18% by 6 years from diagnosis. For control dogs, the cumulative incidence of CD was less than 5% during the complete observation period (Fig. 2). The odds ratio (95% confidence interval) for IWs with AF to die from CD compared with control dogs was 7.2 (2.4, 21.2; p<0.001). The absolute risk to die from non-CD increased for IW with AF from approximately 14% by 3.5 years from diagnosis to 25% by 6 years from diagnosis and for the control dogs during the same time frame from 25% to approximately 40% (Fig. 2).

In IW with AF, the median survival time to non-CD was significantly shorter (p=0.004) than in control IW, whereas the median survival time to CD was not significantly different (p=0.458, generalized estimating equations). Within the AF group, survival times to either CD or non-CD were not statistically different (p=0.207). Likewise, within the control group, survival times to CD vs. non-CD were not statistically different (p=0.246, generalized linear model).

Out of the 10 IW with AF that died from SCD, SCD occurred during subclinical AF in three and after development of DCM in seven dogs. Two of

Table 3 Causes of death in 49 Irish Wolfhounds with atrial fibrillation and in 49 control dogs with sinus rhythm.

Group	Death from CHF	SCD	Non-CD	Alive
AF (n = 52)	12 (23.1%)	10 (19.2%)	27 (51.9%)	3 (5.8%)
Controls (n = 52)	3 (5.8%)	2 (3.8%)	44 (84.6%)	3 (5.8%)

AF, atrial fibrillation; CD, cardiac death; CHF, congestive heart failure; SCD, sudden cardiac death.

Table 4 Causes of death in 49 Irish wolfhounds with atrial fibrillation.

Cause of death	n	%
Cardiac	22	44.9
Sudden cardiac death	10	20.4
Days from diagnosis (median; IQR)	956 (582—1294.8)	
Median (IQR) age at death (years)	6.1 (4.7—7.7)	
Congestive heart failure	12	24.5
Days from diagnosis (median; IQR)	1274 (656—1983)	
Median (IQR) age at death (years)	7.5 (5.5—9.0)	
Non-cardiac death	27	55.1
Median (IQR) age at death (years)	7.3 (6.9—8.0)	
Bone cancer		10.2
Gastric torsion	5	10.2
Paraparesis	4	8.2
Pneumonia	3	6.1
Non-orthopedic neoplasia	5	10.2
Pyometra	1	2.0
Thromboembolism hind leg	1	2.0
Liver failure and uncontrolled diabetes	1	2.0
Gastric and splenic torsion	1	2.0
Inability to eat or drink	1	2.0

IQR, interquartile range.

Table 5 Causes of death in 49 apparently healthy Irish wolfhounds (control group).

Causes of death in 47 control dogs	n	%
Median (IQR) age at death (years)	7.0 (6.0—8.5)	
Sudden cardiac death	2	4.1
Congestive heart failure	3	6.1
Bone cancer	15	30.6
Non-orthopedic neoplasia	5	10.2
Paraparesis	6	12.2
Back problems	1	8.5
Renal failure	1	6.4
Pneumonia	4	8.2
Old age	2	4.1
Gastric torsion	2	4.1
Pyometra	3	6.1
Anaphylactic shock	1	2.0
Intoxication	1	2.0
Immune disease	1	2.0
Unexplained sudden death	1	2.0
Unknown	1	2.0

IQR, interquartile range.

these also had developed CHF. In nine of these dogs, death was witnessed by the owners as sudden collapse and death; whereas, death was unwitnessed in one dog, occurring during sleep with the dog having been observed to be asymptomatic 3 h before dying, with no history of other conditions likely to cause sudden death. Dogs with AF that died from SCD were slightly younger (mean, 6.6 $\pm$ 2.4 years) than dogs with AF that died from CHF (mean, 7.3 $\pm$ 2.4 years, p=0.469) or from non-cardiac causes (mean, 7.5 $\pm$ 1.6 years), but differences were not statistically significant. In the control group, one dog which had later developed DCM with AF subsequently suffered a SCD during a walk. Another control dog died unexpectedly during mating with a bitch, a death that was classified as sudden unexplained death because he had an unremarkable cardiac examination carried out 3 days before.

For all dogs (AF group and control group), age at study entry was negatively correlated with survival time (Spearman rho = 0.522, $p<0.001$), while bodyweight was not significantly correlated with survival time (Spearman rho = 0.123, p=0.226). In addition, survival of both genders was not statistical significantly different for all dogs (males, 1039.0 days; IQR 586.3—1682.5 days; females, 1107.5 days; IQR 604.5—1653.8 days, p=0.096).

Considering dogs with AF and controls together, tests by univariate analysis for a potential influence of individual non-cardiac causes of death on survival times revealed a statistically significantly shorter survival time in seven dogs that died from pneumonia (28.7 months; IQR 11.4—36.2 months) compared with all non-cardiac causes of death (38.4 months; IQR 22.5—55.2 months; p=0.034). Compared with all non-cardiac causes of death, survival was not significantly different for 20 dogs with osteosarcoma (48.6 months; IQR 20.8—55.9 months; p=0.792), for 10 dogs with soft tissue tumor disease (31.6 months; IQR 11.4—56.8 months; p=0.323), and for 10 dogs with paraparesis (40.6 months; IQR 19.2—65.5 months; p=0.665).

Heart rate

Heart rate at time of initial diagnosis recorded during echocardiography was significantly higher in dogs with AF (144 $\pm$ 35 bpm) compared with control dogs with sinus rhythm (118.5 $\pm$ 16 bpm; $p<0.001$). Eight dogs (AF group) had tachycardia 180-233bpm. However, the initial HR did not correlate with survival (Spearman rho = 0.097, p=0.342). Under various medical treatments, HR of dogs with AF decreased to 129 $\pm$ 24 bpm and

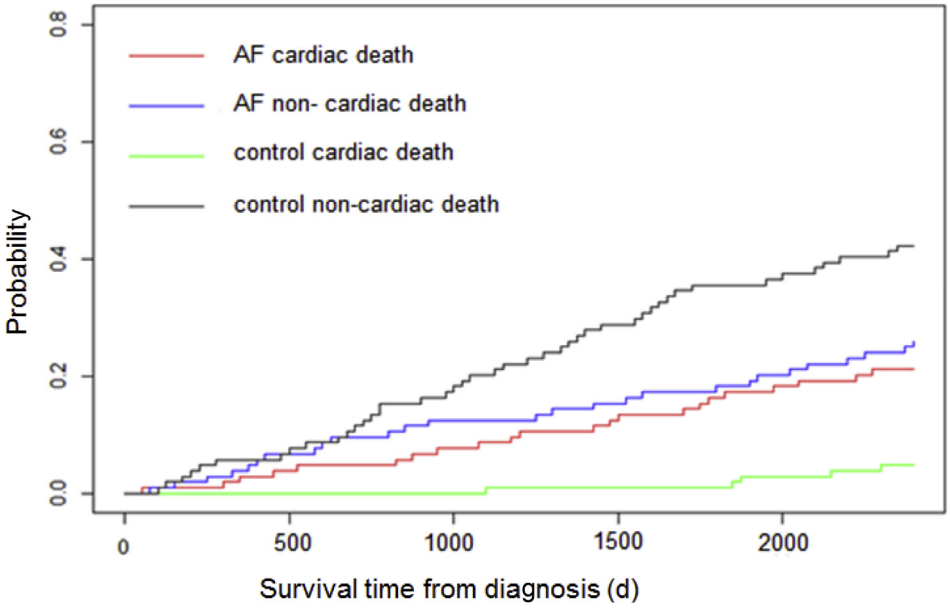

Fig. 2 Cumulative incidence functions comparing survival from diagnosis by cause of death (cardiac vs. non-cardiac) in 52 Irish wolfhounds with atrial fibrillation (AF) and in 52 apparently healthy Irish wolfhounds (control dogs) with sinus rhythm.

was significantly different from pretreatment HR (p=0.024) but not significantly different from controls (p=0.23) at their inclusion.

Discussion

In this study of IWs, we evaluated the time to event, defined as time from first detection of AF in dogs that did not meet echocardiographic criteria for DCM, to the time that DCM was detected, and its relationship to cardiac and all-cause mortality. These findings were compared with a contemporaneous, apparently healthy control group that had sinus rhythm and no echocardiographic evidence of DCM at first presentation, but might have developed DCM, CHF, or CD later in life.

As the establishment and maintenance of AF is related to the mass of the atria, large dogs have a greater predisposition to develop AF [2]. Although AF has been reported most commonly associated with DCM in large and giant breed dogs, AF has been observed in otherwise healthy dogs in the absence of obvious cardiovascular disease [2,7]. In people, AF sometimes develops in younger individuals without any evident of cardiac or other disease. However, growing insights into the pathophysiology of AF suggest subclinical alterations in cardiac function or structure or genetically determined subtle alterations do occur at cellular levels in some young patients with lone AF [16]. Several studies have reported an association between AF and DCM in IW, and AF has been suggested as a precursor of DCM [3–6]. In this study, at time of diagnosis, there were statistically significant differences in some echocardiographic measurements (left ventricular end-systolic dimension, shortening fraction, and end-diastolic right ventricular diameter) between IW with AF and controls. However, all echocardiographic measurements were within reference ranges [8–10], except the left atrial end-systolic diameter that was increased in all IW with AF but not in control dogs. The range of reference values is influenced by interindividual variations of cardiac measurements and might be too wide to identify influences of AF on cardiac size and function and development of DCM in an individual dog.

Tachycardia-induced cardiomyopathy is an established phenomenon, and HR control in dogs with AF may affect survival [17,18]. In the present study, eight IW with AF had tachycardia ranging from 180 to 233 bpm. Autonomic nerve activity plays an important role in the initiation and maintenance of AF, especially imbalances between the sympathetic and parasympathetic system. Simultaneous sympathovagal activity and atrial sympathetic hyperinnervation with chronic AF are important mechanisms in AF [19]. In a recently published study, in IW with DCM whose HR was

controlled, only IW with CHF due to DCM and AF had significantly elevated HR recorded during echocardiography [20]. In this study, rate-managed AF dogs did not have a significantly different HR recorded during echocardiography compared with the control dogs. These findings suggest that tachycardia-induced cardiomyopathy is not likely in this population. As suggested by Simpson et al., AF may represent a precursor to a clinical phenotype of DCM in IW [6]. This is supported by a study on cardiac pathology in IW, similar histological changes were detected in IW with AF (fibrosis and adipocytes) in atrial and in ventricular myocardium as in IW with DCM [21]. In an earlier study, out of 1018 IW, the total prevalence of DCM was higher in males (33.5%) than in females (19.4%) [22]. However, in this study of IW with AF, gender played no role in development of DCM, CHF, or CD, but IW with AF developed DCM more commonly (50%) than control dogs (21.1%). However, 50% of IW with AF did not develop DCM. As the breed is commonly affected with other fatal diseases resulting in early death or euthanasia, some dogs may not have lived long enough to develop DCM [10,20,23—25]. Median time to development of DCM from time of examination was shorter in the untreated control dogs (530 days) than in the AF dogs of this study (923 days), but the difference was not statistically significant. Although treatments were not standardized in this study and changed significantly over time, in general, early initiation of treatment in IW with preclinical AF may have contributed to the delayed onset of DCM and prolonged survival, as has been shown in an earlier study in IW with preclinical DCM or AF [26]. In that prospective, blinded, clinical trial, median time to a composite endpoint of CHF or SCD was significantly prolonged in IW treated with pimobendan monotherapy compared with dogs on monotherapy with benazepril or methyldigoxin [26]. Delayed onset of CHF or SCD has also been recorded in pimobendan treated Doberman pinscher dogs with preclinical DCM compared with placebo in a randomized, multicenter trial [27]. However, the present retrospective study was not designed to assess the effect of any administered therapies. Inasmuch as treatment was not standardized, the influence of drug therapy can only be speculative at best.

In this study, approximately 45% of the mortality in IW with AF was cardiac-related, compared with 10.2% in the control group, and the odds ratio to die from CD was 6.9 for IW with AF compared with the control dogs. These data suggest that IW with AF have a relatively high likelihood to die from SCD or CHF.

Cumulative incidence curves by cause of death and probability of overall death indicated for IW an increased absolute risk of CD, from 3.5 to 6 years from diagnosis, and an even higher risk to die from non-CD (Fig. 2). In the control dogs, the absolute risk to die from non-CD increased from 25% to 40% during the same timeframe from 3.5 to 6 years. While IW with AF were more likely to develop DCM and CD was more likely in the AF group, the presence of AF did not confer worse survival. Irish wolfhounds are commonly affected by other diseases that adversely affect life expectancy, with non-CD mortality increasing during aging [24,25]. This corresponds with findings in the present study that age was negatively correlated with survival time. Leading non-cardiac causes of death in the dogs of this study as in the studies by Brungs et al. and by Vollmar et al. were bone cancer, non-orthopedic neoplasia, paraparesis, pneumonia, and gastric torsion [10, 20]. Interestingly, one of the AF dogs developed thromboembolism in a hind-leg resulting in euthanasia. Thromboembolism is a common complication of AF in humans and has been reported in association with AF in three dogs [28].

In this study, approximately 45% of the mortality in IWs with AF was cardiac-related, compared with10.2% in the control group. Median survival in the dogs with AF of this study was 35.8 months for CD and 32.8 months for non-cardiac death compared with a study for 17 dogs of different breeds with AF without structural and functional disease (40 months) and the median survival of giant breed dogs with AF with and without heart disease, reported in the analysis of the Veterinary Medical Data Base (20 months) [2,7].

In another study of dogs with AF and advanced heart disease, digoxin-diltiazem combination therapy provided a better ventricular rate control ($<$140 bpm for 85% of the Holter recording period) than either drug alone [13]. In addition, a retrospective evaluation of the effect of HR on survival in dogs with structural heart disease and AF based on 24-hour Holter recordings showed a significantly longer survival time of dogs with mean HR $<$ 125 bpm than for dogs with mean HR $\geq$ 125 bpm [18]. For every 10 bpm increase in mean HR, the risk of all-cause mortality increased by 35%. In IW with subclinical AF, HR is usually only mildly elevated. A 24-hour Holter ECG study comparing HR of 13 IW with lone AF in the home environment with data obtained from 13 healthy IW of similar age and gender showed that peak hourly HRs did not differ significantly in IW with AF (164.6 bpm) compared with normal IW (159 bpm), but the average hourly

HR was significantly higher in AF dogs (98.6 bpm) vs. normal dogs (72.5 bpm)[°]. After treatment with digoxin, the average hourly HR of the IW with AF was not significantly different from normal dogs in that study. Heart rate data from the present study showed similar trends, the mean HR of the dogs with AF during echocardiography and ECG recordings at time of first diagnosis was about 26 bpm higher (143.8 ± 34.6 bpm) than that of the control group (117.5 ± 15.6 bpm) and decreased to about 130 bpm with therapy. However, HR of both studies are not directly comparable, as the Holter study reported 24 h average HR, while in this study, for HR assessment, mean HR during echocardiography was used.

In this study, mild to moderate MR was observed in 21 dogs with chronic AF and DCM, developing over time secondary to dilation of the mitral annulus. Although in a previous study, pathologic evaluation of hearts of 26 IW revealed mild degenerative mitral valve changes in most older IW, more pronounced degenerative changes were seen in dogs with secondary MR due to chronic AF or DCM [21].

This study has several limitations. Dogs were included in the study from the time of detection of AF, and follow-up for detection of DCM or CHF was attempted semi-annually but depended on recognition of signs by the dog owners. Thus, the time recorded for the duration of AF prior to the detection of DCM or CHF was potentially influenced by the timing of the follow-up examination. While medications used to treat AF or DCM might have influenced time of development of DCM or CHF, the study was retrospective and not designed or powered to address this question. Another limitation is that tests for the presence of potentially concurrent diseases (e.g. hypothyroidism, myocarditis, hypertension, other underlying systemic diseases, or nutritional or metabolic problems) were not consistently performed in this population.

We used color flow Doppler imaging to assess MR severity, but the color flow may be affected by many technical and haemodynamic factors, such as increased left atrial pressure and size, and eccentric vs. centrally directed jets. For the estimation of MR severity, the European Association of Echocardiography recommends measuring the vena contracta width or visualization of the proximal isovelocity area [29]. In addition, newer ultrasound techniques, including tissue Doppler imaging, strain and strain rate imaging, and speckle tracking echocardiography, provide additional information to assess regional and global myocardial performance [30].

Furthermore, the cause of death was obtained from descriptions of the owners or clinical notes of veterinary practices, with only few dogs undergoing postmortem examinations. While in general a clear reason of death was given by the owner or practice, misclassifications might have occurred. Finally, the HR of dogs with AF was not measured by 24-hour monitoring, which would permit the best assessment [13,18].

The major conclusion from the longitudinal follow-up examinations in IWs with subclinical AF is that a large percentage of dogs will progress to develop DCM and CHF or die from SCD. Therefore, IWs with AF should be closely monitored for development of DCM and related cardiac complications.

Conflict of Interest Statement

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

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