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International Collaborative Study to Assess Cardiovascular Risk and EValuate Long-term hEALth (REVEAL) in Cats with Pre-clinical Hypertrophic Cardiomyopathy and Apparently Healthy Cats

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International collaborative study to assess cardiovascular Risk and EValuate Long-term hEALth (REVEAL) in cats with pre-clinical hypertrophic cardiomyopathy and apparently healthy cats

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Abbreviations:

AH	apparently healthy cats
APCs	atrial premature complexes
ATE	arterial thromboembolism
bpm	beats per minute
CHF	congestive heart failure

DLH	domestic longhair
DLVOTO	dynamic LV outflow tract obstruction
DSH	domestic shorthair
EFS	event-free survival
HCM	nonobstructive form of hypertrophic cardiomyopathy
HOCM	obstructive form of hypertrophic cardiomyopathy
HCM/HOCM	combined HCM and HOCM cohort
IQR	interquartile range
LAFB	left anterior fascicular block
LV	left ventricular
LVOTO	LV outflow tract obstruction
NA	not estimatable
PES	post-event survival
RBBB	right bundle branch block
RV	right ventricular
SAM	systolic anterior motion of mitral valve
SD	sudden death
SBP	systolic arterial blood pressure
VPCs	ventricular premature complexes

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Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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Abstract

Background: Hypertrophic cardiomyopathy is the most prevalent heart disorder in cats and principal cause of cardiovascular morbidity and mortality. Yet, the impact of pre-clinical disease is unresolved.

Hypothesis/Objectives: Observational study to characterize cardiovascular morbidity and survival in cats with pre-clinical nonobstructive (HCM) and obstructive (HOCM) hypertrophic cardiomyopathy and in apparently healthy cats (AH).

Animals: 1,730 client-owned cats (430 pre-clinical HCM; 578 pre-clinical HOCM; 722 AH).

Methods: Retrospective multicenter, longitudinal, cohort study. Cats from 21 countries were followed through medical record review and owner or referring veterinarian interviews. Data were analyzed to compare long-term outcomes, incidence, and risk for congestive heart failure (CHF), arterial thromboembolism (ATE), and cardiovascular death.

Results:

During the study period, CHF, ATE or both occurred in 30.5% and cardiovascular death in 27.9% of 1,008 HCM/HOCM cats. Risk assessed at 1, 5, and 10 years after study entry was 7.0%/3.5%, 19.9%/9.7%, and 23.9%/11.3% for CHF/ATE, and 6.7%, 22.8%, and 28.3% for cardiovascular death, respectively. There were no statistically significant differences between HOCM compared to HCM for cardiovascular morbidity or mortality, time from diagnosis to development of morbidity, or cardiovascular survival. Cats that developed cardiovascular morbidity had short survival (mean ± standard deviation,

1.3±1.7 years). Overall, prolonged longevity was recorded in a minority of pre-clinical HCM/HOCM cats with 10% reaching 9-15 years.

Conclusions and Clinical Importance:

Pre-clinical HCM/HOCM is a global feline health problem that carries substantial risk for CHF, ATE, and cardiovascular death. This underscores the need to identify therapies and monitoring strategies that decrease morbidity and mortality.

Introduction

Cardiomyopathies are the principal cause of cardiovascular morbidity and mortality in cats,[1-6] and hypertrophic cardiomyopathy is the most common of these disorders.[6-29] Although the majority of affected cats are assumed to remain pre-clinical (i.e., free of clinical signs), a proportion experiences serious complications, chief among which are congestive heart failure (CHF), arterial thromboembolism (ATE), and sudden cardiac death (SD).[2,5,7-9,15-20,25,26,28] Certain breeds including Maine Coon, Ragdoll, British shorthair, Sphynx, Chartreux, Persian, Domestic Shorthair, and Norwegian Forest Cats are predisposed to hypertrophic cardiomyopathy, suggesting a heritable basis in these populations.[10-12,24,29,41-49] Despite the fact that this disease is widely recognized, risk of attendant cardiovascular complications is unknown, and the natural history of pre-clinical feline hypertrophic cardiomyopathy remains unresolved.

Many phenotypic and clinical characteristics of feline hypertrophic cardiomyopathy, including a highly variable disease course, closely resemble those reported in humans.[2,7-9,15,21-26,28,29] Whereas the obstructive form of the disease (HOCM) in humans is a major determinant of negative outcome including progressive cardiovascular disability,[30-39] equivalent risk has not been established in affected cats. Nevertheless, by inference drawn from data in humans, the notion has lingered that HOCM confers a similar negative prognosis in cats and, by extension, signifies a target for pharmacotherapy.[40]

Descriptions of cardiovascular complications in cats with hypertrophic cardiomyopathy have originated predominantly from single-site referral centers.[5,7,9,17-20,25,26,28,29] Although informative, such results tend to concentrate severely affected cases and are subject to tertiary center referral bias. This can lead to overstating

adverse outcomes and fosters the impression that the disease is dominated by pessimistic outcome.[37] Furthermore, combining pre-clinical and heart failure patient data limits risk estimation and prognosis for cats having only pre-clinical disease.[5,7,9,14,17,26,28]

Thus, to understand the natural history of pre-clinical hypertrophic cardiomyopathy, we conducted a long-term multicenter, epidemiologic study to evaluate large cohorts of affected and nonaffected cats in many different countries around the world. This approach permitted us to identify and compare incidence and risk for cardiovascular morbidity, mortality, and survival characteristics among these populations.

Materials and Methods

Study Design

The "international, collaborative, multicenter study to assess cardiovascular Risk and EValuate long-term hEALth (REVEAL) in feline pre-clinical hypertrophic cardiomyopathy and apparently healthy cats" was a retrospective, longitudinal, cohort study. An ethical review committee granted approval where required. Investigators were board-certified veterinary cardiologists, or in countries without a certification process, focused on specialty cardiology practice. Each study site had a searchable echocardiographic and medical record database permitting detailed review and long-term health follow-up.

Cats

Cat populations included pre-clinical obstructive (HOCM) and nonobstructive (HCM) forms of hypertrophic cardiomyopathy, and apparently healthy cats (AH). The term pre-clinical denoted a physical condition characterized by lack of clinical signs or manifestations, and would be referred to as "asymptomatic" in human medicine. All AH

were examined by echocardiography, had an unremarkable medical history, no known illness, and had a normal physical examination findings without gallop heart sounds at the point of study entry. Some had been examined by echocardiography due to presence of a systolic heart murmur, but those with a systolic heart murmur, trivial mitral or tricuspid valve regurgitation, or dynamic right ventricular (RV) outflow tract obstruction were included, provided that the echocardiogram was otherwise normal.

Inclusion Criteria. Medical records were searched for cats diagnosed with pre-clinical hypertrophic cardiomyopathy (both HCM and HOCM) as well as apparently healthy cats free of cardiomyopathy, the health outcomes of which could be ascertained for at least 5 years after initial diagnosis. Archived echocardiographic images were examined to confirm diagnosis and measurements. Study entry represented the date when echocardiographic examination was first made.

Exclusion Criteria. Cats were not included in the study if echocardiograms were of non-diagnostic quality, or if any of the following conditions were diagnosed at or before study entry: CHF, ATE, syncope, heartworm disease, systemic arterial hypertension (defined as acute neurologic signs or retinal changes consistent with systemic hypertension, or when measured systolic arterial blood pressure [SBP] ≥ 180 mmHg), hyperthyroidism, anemia, renal disease (either serum creatinine concentration above laboratory reference range, urine concentrating ability deemed to be inadequate, or proteinuria), cardiomyopathy other than hypertrophic cardiomyopathy, congenital heart disease, or any underlying medical disease judged to be capable of limiting life expectancy. All cardiovascular medications prescribed before or at study entry were recorded, but were not considered as exclusion criteria.

Study Sites

Investigators worked at 49 veterinary centers in 21 countries: 22 centers in 17 states of the United States of America (California, Colorado, Florida, Indiana, Iowa, Kansas, Louisiana, Massachusetts, Minnesota, Missouri, New York, North Carolina, Ohio, Pennsylvania, Texas, Virginia, Wisconsin); 4 in Italy; 3 in Germany; 2 each in Canada and Japan; and, 1 each in Austria, Belgium, Brazil, England, France, Hungary, Ireland, Israel, Mexico, Taiwan, Russia, Scotland, South Africa, Spain, Sweden, and Switzerland.

Echocardiography

Investigators were instructed to enter cats that had diagnostic-quality 2-dimensional, color flow Doppler, and M-mode echocardiographic examinations performed in accordance with published standards.[8,49-51] Diagnosis was based upon information from all available tomographic views including right parasternal long-axis 4-chamber, long-axis inflow-outflow, and short-axis views, and left apical views. Cardiac measurements were made from 2-dimensional echo-guided M-mode images from right parasternal short-axis views by most investigators or, using 2-dimensional echocardiography by several investigators. Left ventricular (LV) hypertrophy was diagnosed when the thickest end-diastolic interventricular septal, LV free wall segment or both measured ≥ 6 mm.[8] The obstructive form (HOCM) was defined for this study as LV hypertrophy with systolic anterior motion of the mitral valve (SAM), coupled with diffuse LV outflow tract turbulence and peak systolic outflow velocity ≥ 2.5 m/sec. Cases were not stratified according to LV outflow tract gradient. Dynamic RV outflow tract obstruction was designated when maximal RV outflow tract velocity was > 1.6 m/sec.[52]

Data Collection and Outcomes Assessment

Cats for which first diagnosis was made between November 2001 and January 2011 were assessed during the study period which extended between January 2010 and January 2016. Data collection forms were used by investigators to record pertinent demographic and health information. This data included age at diagnosis, breed, body weight, laboratory and echocardiographic information, physical examination and laboratory findings, arrhythmias (assessed from ECG recording or from simultaneous ECG trace during echocardiographic examination), whether cardiovascular medications were prescribed, and outcomes (CHF, ATE, and cardiovascular death). Outcomes assessments were made by study investigators based upon consideration of all available clinical data. Serum thyroxine and creatinine concentrations and SBP results that were recorded closest to date of diagnosis were included, but were not available for every case. Cardiovascular mortality was designated as death associated with CHF, ATE, euthanasia because of these complications, or sudden death (SD). Sudden death was defined as unanticipated death with absence of clinical signs or illness within 24 hours of last being observed healthy, or occurring at least 7 days after resolution of CHF.[8] Morbidity and mortality dates were recorded from medical records. When this data was not available, information was obtained from the pet owner or attending veterinarian interview, assisted by a medical questionnaire with standardized questions related to cardiovascular and non-cardiac morbidity and mortality. Survival was calculated from initial diagnosis to date of death, last recorded examination, or last contact.

Statistical Analysis

Power calculation to estimate study population size was guided by results of prior studies,[7,9] and a planned 5-year minimum follow-up period. Based upon these assumptions, 250 cats with pre-clinical hypertrophic cardiomyopathy and 250 AH were considered to provide 80% power to detect a difference in survival proportions between pre-clinical cardiomyopathy compared with AH, with a significance level (alpha) of 0.05.

Baseline descriptive statistics are reported as mean and standard deviation for normally distributed variables and median (interquartile range [IQR]) for non-normally distributed variables. The normality of the residuals was judged by visual inspection. Between-groups analyses of baseline variables were performed using analysis of variance (ANOVA) or Kruskal-Wallis tests as appropriate according to the distribution of residuals, using Holm-Sidak or Dunn's test post-hoc analyses, respectively, when indicated. Analyses for proportions of categorical variables were performed using a Chi-Square or Fisher's Exact analysis, as appropriate. Univariate time-to-event survival analyses were performed using Kaplan Meier product limit estimates where survival range was presented if median survival was not reached and statistical differences among strata were determined by log-rank test. Time-to-event survival time analyses represented time from diagnosis to end-date. End-date was defined as first instance of death, cardiovascular morbidity, or being lost to follow-up, depending upon the analysis. Patients remaining alive or lost to follow-up at study completion were right-censored. A generalized linear model was used to calculate incidence for the entire population and cohort level by age quartile expressed as rates as per 1,000 cat years, employing a Poisson distribution. Proportion at risk was calculated using Kaplan Meier analysis. Patient population survival variables were clinically defined and survival time was further assessed at 1, 5, and 10

years after initial diagnosis, respectively. Death type or comorbidity type was censored after 1, 5, and 10 years, respectively, allowing for a cross-sectional view of the respective time points. Duration of event-free survival (EFS) comprised the time interval from the date of study entry to the date of first cardiac morbidity (CHF or ATE). Post-event survival (PES) comprised the time from the date of first CHF or ATE morbidity to cardiac death from CHF, ATE, or SD. Additional analyses included stratification at age quartile determined by age at diagnosis. Due to varied study enrollment and study end dates, mean between-cohort survival times estimated by univariate Kaplan Meier method were used to calculate time to event for EFS and PES, and compared by ANOVA. All analyses were carried out with SAS 9.4 (Cary, NC 2016) and deemed significant at $P<0.05$.

Results

Population Characteristics at Time of Diagnosis

One-thousand seven-hundred thirty cats fulfilled entry criteria; 1,008 (58.3%) had hypertrophic cardiomyopathy comprising 430 (24.9%) HCM and 578 (33.4%) HOCM; and, 722 (41.7%) were AH (Table 1). Apparently healthy cats were younger (median, 4.9 years; range, 0.5-21 years) than HCM (median, 7.4 years; range, 0.5-20 years; $P<0.001$) and HOCM (median, 5.7 years; range, 0.5-19 years; $P<0.013$); HOCM were younger than HCM ($P<0.001$). Ages recorded in 1,006 of 1,008 HCM/HOCM cats clustered predominantly at 1-5 years and 5-11 years, but the proportion markedly decreased after 11 years of age (Figure 1). Twenty-seven percent were ≥ 10 years of age and 10 % were 13-20 years of age. Body weight in HCM and HOCM cats did not differ ($P=0.095$), but was slightly higher compared to AH cats (both $P<0.001$; Table 1). The overall study population included 34 breeds, most commonly Domestic Shorthair,

Main Coon Cat, Persian, Domestic Longhair, and Norwegian Forest Cat (Table 1, Figure 2). Less commonly represented breeds included Abyssinian, American Shorthair, Bengal, Birman, Bombay, British Shorthair, Burmese, Chartreux, Cornish Rex, Devon Rex, Egyptian Mau, European Shorthair, Exotic Shorthair, Havana Brown, Himalayan, Manx, Oriental Shorthair, Pixie-bob, Ragdoll, Russian Blue, Scottish Fold, Selkirk Rex, Siamese, Somali, Sphynx, Turkish Angora, and Turkish Van. The prevalence of both intact and neutered males was significantly higher in HCM and HOCM than AH. Comparing HCM and HOCM cohorts, the proportions of intact males and neutered males did not differ significantly (P = 0.303 and P = 0.589, respectively). The proportion of neutered females did not differ significantly between HCM and HOCM (P = 0.480). Intact females represented a very small proportion of HCM and HOCM compared with AH cats (Table 1).

Systolic heart murmurs were detected commonly (Table 2). Murmur prevalence was higher in HCM/HOCM (82.4%) than AH (46.4%; P<0.001). Moderate to loud (grade 3-5/6) systolic murmurs were more common in HCM/HOCM (58.8%) than AH (14.8%; P<0.001), and in HOCM (74.9%) compared to HCM (37.2%) cats (P<0.001), respectively. Soft systolic murmurs (grades 1-2/6) were more common in AH (31.6%) than HCM/HOCM (23.6%) cats (P<0.001). Dynamic RV outflow tract obstruction was recorded in 43 (10%) HCM cats (of which 39 had soft to moderately loud systolic murmurs), and in 80 (13.8%) HOCM cats. Gallop sounds were recorded in 48 (11.2%) HCM compared with 40 (6.9%) HOCM cats (P=0.025). Heart rate (median; IQR) during physical examination at study entry was lower in AH (180; 167-200 beats per minute [bpm]) compared to HOCM (190; 170-210

bpm; *P*=0.001), but did not differ between HCM (186; 167-202 bpm) and AH (*P*=0.676), or between HCM and HOCM (*P*=0.164).

Arrhythmias were recorded in 128/1,008 (12.7%) HCM/HOCM cats. These included supraventricular tachycardia (n=4), atrial fibrillation (n=6), atrial premature complexes (APCs, n=17), isolated ventricular premature complexes (VPCs, n=73), and 1 cat each with ventricular bigeminy and non-sustained ventricular tachycardia. Bradyarrhythmias included first-degree atrioventricular block (n=2) and high grade atrioventricular block (n=2). Conduction abnormalities detected from ECG recordings included left anterior fascicular block (LAFB) in 16 (4 HCM, 12 HOCM), right bundle branch block (RBBB; n=4) and 1 cat each with ventricular pre-excitation and left bundle branch block. Arrhythmias recorded in 30 (4.2%) AH were isolated VPCs (n=22), LAFB (n=5), and RBBB (n=3).

Systolic blood pressure (median; IQR) did not differ among AH (140; 120-150 mm Hg), HCM (140; 120-150 mm Hg), and HOCM (135; 120-150 mm Hg; *P*=0.168) cohorts.

One or more cardiovascular drugs (beta-adrenoceptor blockers, angiotensin converting enzyme inhibitors, diltiazem hydrochloride, aspirin, or clopidogrel) were prescribed in 52.3% HCM and 78.2% HOCM (*P*<0.001), but not in AH. No additional information regarding dosage, compliance, or duration was recorded.

Incidence and Risk for Cardiovascular Morbidity and Mortality

Cardiovascular morbidities were recorded in 307 (30.5%) of 1,008 HCM/HOCM cats comprising 361 events and in 7 (0.97%) AH (Table 3). The proportion of CHF events did

not differ between HCM (106/430) and HOCM (138/578; *P*=0.834), nor did ATE events differ in HCM (41/430) compared to HOCM cats (76/578; *P*=0.094). Similarly, HCM and HOCM did not differ with respect to time from study entry to development of CHF (*P*=0.216) or ATE (*P*=0.188; Figure 3). The proportion of syncopal events was not different between HCM (n=9, 2.1%) and HOCM (n=14, 2.4%; *P*=0.838). Syncope was recorded in 2 (0.28%) AH.

Incidence. The incidence of CHF, ATE, SD and all-cardiovascular death events per 1,000 cat years for each cohort was delineated by quartiles corresponding with age at the time when events occurred (group 1, < 2.5 years; group 2, 2.5-5.6 years; group 3, > 5.6-10 years; group 4, >10 years; Table 4). In the HCM/HOCM population, CHF incidence was 24.8% higher in cats > 10 years of age compared to cats < 2.5 years of age (68.1 events versus 51.2 events per 1,000 cat years, respectively). The incidence of ATE increased from the first to the third age quartile (from 22.5 to 32.7 events per 1,000 cat years, respectively), and then decreased sharply to 18.4 events per 1,000 cat years in cats > 10 years of age. Incidence of cardiovascular death was 57.1 events per 1,000 cat years for cats < 2.5 years of age, and was unchanged (57.7 events per 1,000 cat years) between 2.5 to 5.6 years of age. A higher incidence of cardiovascular death was recorded in older age quartiles. In contrast, the overall incidence of CHF or ATE in AH at initial diagnosis was 1.6 and 1.3 events per 1,000 cat years, respectively.

Risk. The risk of cardiovascular morbidity and mortality for HCM, HOCM, and HCM/HOCM cohorts increased progressively at 1, 5, and 10-year intervals after study entry, as well over age quartiles (Table 5, Figure 4). Of the 1,008 cats with pre-clinical HCM/HOCM, the risk for CHF and ATE morbidity and all-cardiovascular death was

approximately 3 times greater at 5 years compared with 1 year after initial diagnosis. Overall, the risk of all-cardiovascular death for HCM/HOCM was approximately 1 in 15, 1 in 4.4, and 1 in 3.5 as calculated at 1, 5, and 10-year time points, respectively. Overall risk of all cardiovascular death in AH was 1 in 100 (Table 5, Figure 4).

Survival Analyses- Mortality

Cardiovascular death was recorded in 281 (27.9%) of 1,008 HCM/HOCM cats (115 of 430 with HCM [26.7%], 166 of 578 with HOCM [28.7%]; Table 3). Sudden death comprised 22 of these 281, a 2.2% prevalence in the 1,008 cats. Seven deaths were attributed to cardiovascular death in the 722 AH (1.0%). Cardiovascular survival (median, range) was significantly shorter in HCM/HOCM (10.9 years; 3 days-3.1 years) than AH (not estimatable [NA] due to low event rate; 6 days-14.1 years; $P<0.0001$; Figure 5). The oldest 10% of surviving HCM/HOCM cats at study end were 9 to 14.7 years of age. Cardiovascular survival was not significantly different between HCM (10.9 years; 2 days-12.5 years) and HOCM (NA; 3 days-13.1 years) over time ($P=0.873$; Figure 6). Furthermore, no significant difference was found between HCM and HOCM populations for the overall proportion of cardiovascular death ($P=0.535$), proportion of cardiovascular death associated with CHF ($P=0.834$), and proportion of cardiovascular death associated with ATE ($P=0.118$). The proportions of SD did not differ between HCM and HOCM cats ($P=0.960$). Time (median, IQR) from study entry to SD did not differ significantly between HCM (1,290 days; 304-2176 days) and HOCM (1156; 457-1777 days; $P=0.676$). Furthermore, time from onset of CHF or ATE morbidity to

cardiovascular death did not differ between HCM and HOCM populations (*P*=0.489 and *P*=0.578, respectively; Figure 7). Cardiovascular survival did not differ significantly among age quartiles within HCM (*P*=0.206) or in HOCM (*P*=0.796) populations. Cardiovascular survival did not differ significantly between HCM cats that had SBP measured compared to HCM cats that did not have SBP measured (*P*=0.085); HOCM cats that had SBP measured compared to HOCM cats that did not have SBP measured (*P*=0.255); HCM compared to HOCM that had SBP recorded (*P*=0.476); or between these cohorts that did not have SBP recorded (*P*=0.609). In addition, cardiovascular survival did not differ significantly between HCM/HOCM cats that had serum thyroxine concentrations measured compared to HCM/HOCM cats that did not have serum thyroxine concentrations measured (*P*=0.263). Cardiovascular survival in HCM/HOCM cats did not differ significantly between those prescribed or not prescribed ≥ 1 cardiovascular medications at study entry (*P*=0.845).

Time to Event, Event-Free and Post-Event Survival Analysis

Time to Event. Congestive heart failure and ATE morbidities occurred individually or together. In HCM: CHF occurred without ATE in 90 cats (median, 57 days; range, 2-2,954 days); ATE occurred without CHF in 25 cats (median, 370 days; range, 5-3,993 days); and, both CHF and ATE occurred in 16 cats (concurrently in 10 cats [median, 513 days; range, 4-3,353]; ATE preceded CHF in 3 [1,775, 2,384, and 3,334 days]; and CHF preceded ATE in 3 [1,178, 1,316, and 2,409 days]). In HOCM: CHF occurred without ATE in 98 cats (median, 1,017 days; range, 4-4,029 days); ATE occurred without CHF in 36 cats (median, 1,081 days; range, 1-2,518 days); and both CHF and

ATE were recorded in 40 cats (concurrently in 20 [median, 790 days; range, 11-2,151 days]; ATE preceded CHF in 14 [median,1,184 days; range, 3-2,980 days]; and CHF preceded ATE in 6 [median, 933 days; range, 177-2,075 days]). In AH: CHF occurred without ATE in 5 cats (median,1,633 days; range, 841-2,749 days, both CHF and ATE developed in 1 cat, and ATE occurred without CHF in 4 cats (median, 1,760 days; range, 387-2,819 days). Two of the 5 AH with CHF without ATE had developed hyperthyroidism.

Event-Free Survival. Of the 1,008 HCM/HOCM cats, 307 (30.5%) developed CHF, ATE or both, whereas 281 (27.9%) experienced cardiovascular death (22 of the 281 [7.8%] were SD). Event-free survival was calculated for the 259 cats that died from CHF, ATE or both. Of these 259 cats, 140 (54.1%) died or were euthanized on the day of their first recorded CHF or ATE morbidity, whereas 119 (45.9%) cats survived past the day of recorded morbidity and subsequently died of their cardiovascular disease. Event-free survival (mean ± standard deviation) did not differ significantly between the cohort of 140 cats (2.9 ± 2.2 years) compared to the cohort of 119 cats (2.4 ± 2.11 years; P= 0.101; Figure 8).

Post-Event Survival. Post-event survival (the time from onset of CHF or ATE to cardiovascular death) calculated for the 119 cats that survived > 1 day after CHF or ATE had occurred was 1.3 ± 1.7 years, significantly shorter than both the EFS for this cohort (P<0.0001), and for EFS of the cohort of 140 cats that died on the day of their first cardiovascular morbidity (P< 0.0001; Figure 8). Moreover, PES in these 119 cats did not differ significantly with respect to age quartiles (P=0.402) or between HCM and HOCM cats that comprised this cohort (P=0.364).

DISCUSSION

REVEAL is the first international, collaborative, epidemiologic study to evaluate pre-clinical feline hypertrophic cardiomyopathy and AH. Intending to identify and compare long-term cardiovascular incidence, risk, and survival, REVEAL documented the natural history of cats living in geographically diverse environments, in 21 countries, and across 5 continents. In this population, the incidence of cardiovascular morbidity and mortality in affected cats was substantial. Of the cohort of 1,008 HCM and HOCM cats, nearly one-third developed CHF, ATE, or both and slightly more than one-quarter experienced cardiovascular death. In contrast, cardiovascular death occurred in 1% of AH. Pre-clinical hypertrophic cardiomyopathy therefore may be regarded as a global disease that confers reasonably high risk and denotes a major negative prognostic indicator for cardiovascular mortality.

Notably, cardiovascular morbidity, mortality, and survival did not differ significantly between obstructive (HOCM) and nonobstructive (HCM) forms of feline hypertrophic cardiomyopathy, reinforcing that the clinical impression that dynamic LV outflow tract obstruction (LVOTO) is not a predictor of adverse outcome.[16,18] This finding diverges from the idea that LVOTO carries high risk for progressive heart failure and the cardiac debilitation that characterizes HOCM in human patients.[30,34-39]

Reports comparing cardiovascular survival between pre-clinical feline HCM and HOCM have been sparse, conflicting, and confined to small cohorts.[8,17] The REVEAL study demonstrated no significant difference in cardiovascular morbidity or survival between HCM and HOCM and should thus help resolve this debate. In reality, the

notion that HOCM conferred proportionately higher risk was shaped by the dominance of human literature reporting poor outcomes associated with LVOTO and increased gradients.[30-32] Echocardiography played an important role in this observation. Its introduction by the early 1970s simplified detection and characterization of cardiomyopathy in human patients, and was paralleled a decade later in veterinary medicine. In addition, echocardiography facilitated recognition of systolic anterior motion of the mitral valve (SAM) and LVOTO, characteristics of the obstructive form (HOCM) of this disease. Insofar as common clinicopathologic features shared by humans and cats hypertrophic cardiomyopathy were known,[2,4,8,15,21] and in the absence of epidemiologic data in cats, dynamic LVOTO became regarded as a target variable for therapy in veterinary medicine.[17,40] Our study contributes a fresh clinical perspective to the natural history of pre-clinical hypertrophic cardiomyopathy and counters this former perception.

One possible explanation why clinical outcomes did not differ significantly between populations with obstructive (HOCM) and nonobstructive (HCM) disease in our study is that these designations may represent more of a functional continuum than distinct, separate entities. In humans affected with the nonobstructive form (HCM), a proportion will develop LVOTO from SAM, mid-ventricular contact or both after physiologic challenge induced by drugs or exercise. This finding the concept that hypertrophic cardiomyopathy is predominantly a disease of LV outflow tract obstruction.[33] Indeed, the fact that LVOTO can be provoked in the cat[6] lends endorsement for this hypothesis. It also adds an element of ambiguity to the classification of this disease. If LVOTO was provoked as a result of stress-induced sympathetic tone during echocardiographic examination, such cats would be categorized as “obstructive” (HOCM), and yet may

have been nonobstructive (HCM) under normal or baseline living conditions. In other cases, the rapid heart rate and relatively small LV end-systolic chamber of cats can challenge the detection of SAM, or render uncertain the distinction between obstructive and nonobstructive forms of this disease. Thus, SAM could have been present but missed in some cats diagnosed with the nonobstructive (HCM) form.

The REVEAL study found that CHF incidence increased slightly from youngest to oldest age, whereas ATE incidence increased up through the third age quartile, but became less common after the age of 10 years. The incidence of cardiovascular death was highest in cats > 5.6 years of age. Risk for CHF, ATE, and cardiovascular death increased over time and age. Moreover, the risk of cardiovascular death for each age quartile was progressively higher at 5 and 10 years compared to 1 year after diagnosis for each age quartile. In AH the risk of cardiovascular death was only 1%. In pre-clinical HCM and HOCM, sudden death was substantially lower in our present study than described from mixed pre-clinical and clinical feline populations.[8,9,18,25,28] Sudden death is a well-known manifestation of hypertrophic cardiomyopathy in humans, especially in high risk sub-groups .[37-39]

Early onset of pre-clinical HCM or HOCM, defined as occurring in cats < 1 year of age was approximately 3% in the HCM/HOCM cohort in our study. Other reports of early onset vary widely based upon cut-off values used to define LV end-diastolic wall thickness.[10,12,24,28,48] Age of hypertrophic cardiomyopathy associated with cardiovascular death has been reported in certain breeds, including young, highly inbred Maine Coon cats, particularly in litters where affected individuals were mated.[24] In addition, Ragdoll cats homozygous for the MYBPC3 R820W mutation died at a

younger age and cardiovascular survival was shorter compared to heterozygous or wild types,[43] and onset of CHF before 1 year of age has been observed in this breed.[b] Others have reported that the age at which cardiovascular morbidity developed was younger in Maine Coon than Persian, DSH, Sphynx, and Chartreux breeds combined.[28]

Pre-clinical HCM/HOCM in our study was diagnosed most commonly between 1 and 11 years of age, and the proportion decreased sharply thereafter. Others have reported wide age variability from pooled pre-clinical and clinically affected populations.[7-9,12,18,25,26,53]

Of the HCM/HOCM cats that developed CHF or ATE, the mean EFS did not exceed 3 years. Also, EFS did not differ significantly between HCM and HOCM populations. Thus, once affected cats developed cardiovascular morbidity, the trajectory of PES from onset of clinical signs to cardiovascular death was rapid, averaging just 1.3 years.

Although hypertrophic cardiomyopathy has been held to presage decreased survival, REVEAL found that a proportion of affected cats survived into their second decade. Similar findings have been reported in selected pedigrees in which nearly one-third were 10 to 15 years of age and approximately 5% were > 15 years of age.[28] This finding indicates that pre-clinical hypertrophic cardiomyopathy can be compatible with normal life expectancy. Prolonged survival with this condition has been increasingly reported in affected humans.[37]

The HCM/HOCM population's high male prevalence, dominated by neutered males, was similar to previously reported male predilection rates of between 63 to 79%.[7,9,13,17,18] Heart murmurs were common in both AH as well as HCM/HOCM cats. Similar findings have been reported by others.[4,5,9,13,16-18,26-28] The true prevalence of

heart murmurs in AH is uncertain, however, because reported prevalence likely is affected by referral bias. The comparatively higher prevalence of heart murmurs and louder grades of murmurs in cats with HOCM may have provided an opportunity during physical examination to detect heart disease earlier compared to cats with HCM, accounting for the slightly younger HOCM cohort. Arrhythmias were detected at study entry in approximately 13% of pre-clinical HCM/HOCM and 4% of AH. Others have reported arrhythmias from mixed pre-clinical and decompensated cohorts.[5,7-9,13,16,25,28]

The pervasiveness of hypertrophic cardiomyopathy in the general feline population is unknown. Estimation of disease has inherent limitations including small sample size, single-site data source, selection and referral bias, skewed age and breed composition, and diagnostic verification. Additional weaknesses are imposed by lack of veterinary consensus guidelines for echocardiographic measurement technique and diagnostic cut-off values. Within this context, prevalence of feline hypertrophic cardiomyopathy has been reported. When investigators applied >5.5 mm or >6 mm diagnostic cut-off values and different measurement techniques to a cohort of 92 cats screened by echocardiography, prevalence ranged from 12%-51% in this cohort.[27] Prevalence reported by others using ≥ 6 mm cut-off was 14.7% in 780 cats screened at rehoming shelters in southeastern England,[13] 14.6% in 103 cats screened in western Virginia,[6] and 8.3% of 144 cats screened in Switzerland.[10] Two additional studies using ≥ 5.5mm cut-off reported 8.5% in 329 British shorthair cats in Denmark[12] and 25% in 53 Norwegian Forest cats screened in London.[46] Recently, echocardiographic reference ranges based upon allometric scaling have been proposed.[54]

United States pet ownership surveys identify steady growth in the feline pet population, estimating 74 million cats in 2012[c] and 94.2 million cats between 2017-2018.[d] Recently, estimates of hypertrophic cardiomyopathy prevalence in humans suggests that approximately 1 out of 200 individuals (0.5%) is genetically affected,[55] with a substantial proportion being genetically positive but phenotypically negative. If the prevalence of feline hypertrophic cardiomyopathy were conservatively extrapolated at 0.5% based upon findings reported in humans,[52] upwards of 470,000 cats could be affected in the United States of America. Alternatively, if 8% prevalence was inferred based upon the lowest reported veterinary estimate that applied an echocardiographic cut-off value ≥ 6 mm,[10] approximately 7.5 million cats could be affected in the United States of America alone.

Our study has some limitations. Study cases originated from referral centers, and therefore demographics could have been subject to referral bias. However, the large study populations encompassing wide and varied geographical regions may have diminished this effect. Apparently healthy cats were significantly younger compared to HCM and HOCM cohorts. Arterial blood pressure, creatinine, and T4 data were available for a substantial number of cats with hypertrophic cardiomyopathy. Close attention was paid to the medical history and physical examination in order to exclude any cases with clinical findings indicative of systemic illness or disease. However, some cats with subclinical azotemia, increased serum thyroid hormone concentration, or increased SBP, may have been missed and inadvertently included in the HCM/HOCM cohort. In such cases, it was not possible to verify whether left ventricular hypertrophy was associated solely with hypertrophic cardiomyopathy, with abnormal loading

conditions, or was present in conjunction with comorbidities. In HCM/HOCM cats ≥10 years of age representing greater age-related risk for comorbidities, SBP and or creatinine data were available in approximately 85%, and T4 data were available in approximately half of the cases. Although the REVEAL study found that pre-clinical hypertrophic cardiomyopathy and associated cardiovascular morbidity and death are global feline health issues, it did not test for potential regional differences in cardiovascular incidence and risk. In diagnosing hypertrophic cardiomyopathy and AH, cardiac status was based upon a single initial echocardiographic examination designating the point of study entry. Potential remodeling over time was not assessed, but theoretically could have affected outcome or diagnosis in some cases, or been affected by age-related penetrance of the hypertrophic cardiomyopathic phenotype. The thickest LV wall segment was selected to diagnose LV hypertrophy, but may not by itself have represented the pathophysiologic and clinical heterogeneity of this disease. Echocardiograms were not reviewed centrally, which would have exceeded financial and logistical resources. Nonetheless, echocardiographic diagnoses were reviewed by board-certified cardiologists or veterinarians who practice cardiology. Systolic anterior motion of the mitral valve and LVOTO could have been over-diagnosed in some cats in response to stress-induced exaggerated systolic chamber function, and such cats may not have had SAM and LVOTO under normal home conditions. Response to provocative measures were not considered as a diagnostic criterion in our study, but may have induced SAM and LVOTO in some cats exposed to these measures. However, such procedures are not currently performed as part of routine, standard echocardiographic examination in cats. Cats with HOCM were not subcategorized

based upon estimated LV outflow tract gradient. Thus, it was not possible to determine whether a subset of cats with high gradients is at higher cardiovascular risk. Although we attempted to exclude cats with known underlying diseases in preclinical hypertrophic cardiomyopathy and AH cohorts, some may have had undiagnosed or pre-clinical conditions. A standardized medical questionnaire was used to aid data collection when interviewing clients and referring veterinarians, but some details may have been incorrectly remembered or missed. Assessment of treatment compliance and potential drug effects was not possible in this retrospective study.

Conclusions

Data from the REVEAL study demonstrates that pre-clinical feline hypertrophic cardiomyopathy is a global health concern that imposes considerable risk for CHF and ATE morbidity, and substantially impacts cardiovascular health over time. Indeed, cardiovascular morbidities were recorded in nearly one-third and cardiovascular-related death occurred in approximately 30% of the 1,008 cats with HCM and HOCM. There was no statistically significant difference between obstructive (HOCM) and nonobstructive (HCM) forms of hypertrophic cardiomyopathy regarding cardiovascular morbidity or mortality, time from diagnosis to development of morbidity, or cardiovascular survival. Collectively, these epidemiologic data highlight cardiovascular risks associated with pre-clinical hypertrophic cardiomyopathy, and underscore the need to identify and develop health care and treatment strategies that optimize monitoring, decrease risk, and improve outcome.

Figure Legends

Figure 1. Age distribution for 1,006 of the 1,008 cats with obstructive and nonobstructive hypertrophic cardiomyopathy recorded at the time of diagnosis. In 2 cats age was not recorded.

Figure 2. Most prevalent breeds in feline study populations. HCM, nonobstructive hypertrophic cardiomyopathy; HOCM, obstructive hypertrophic cardiomyopathy.

Figure 3. Kaplan-Meier survival curves estimating percentage of 430 cats with nonobstructive (HCM) compared to 578 cats with the obstructive (HOCM) form of hypertrophic cardiomyopathy that have not yet experienced morbidity (Y-axis) from congestive heart failure (top) or arterial thromboembolism (bottom) against time (X-axis).

Figure 4. Percentage of 1,008 cats with nonobstructive (HCM, n=430)) and obstructive (HOCM, n=578) hypertrophic cardiomyopathy at risk for cardiovascular mortality, by age quartile when diagnosed and assessed 1, 5, and 10 years following study entry. Q, age quartile; Yrs., years

Figure 5. Kaplan-Meier survival curves estimating percentage of 1,008 cats with nonobstructive (HCM, n=430) and obstructive (HOCM, n=578) forms of hypertrophic cardiomyopathy that have not yet experienced cardiovascular death (Y-axis) compared with 722 AH against time (Y-axis). NA, median not estimatable.

Figure 6. Kaplan-Meier survival curves estimating percentage of 430 cats with nonobstructive (HCM) compared to 578 cats with the obstructive form (HOCM) of

hypertrophic cardiomyopathy that have not yet experienced cardiovascular death (Y-axis) against time (X-axis). NA, median not estimatable.

Figure 7. Kaplan-Meier survival curves estimating the percentage of 430 cats with nonobstructive (HCM) compared to 578 cats with obstructive (HOCM) hypertrophic cardiomyopathy that have not yet experienced cardiovascular death (Y-axis) for congestive heart failure (A), or arterial thromboembolism (B) against time (X-axis). NA, median not estimatable.

Figure 8. Kaplan-Meier survival curves estimating the event-free survival (EFS) proportion and post-event survival (PES) proportion (Y-axis) against time (X-axis). EFS Group-A comprised a cohort of 140 cats with pre-clinical hypertrophic cardiomyopathy who died on the day of their first recorded CHF/ATE morbidity. EFS Group-B comprised a cohort of 119 cats with pre-clinical hypertrophic cardiomyopathy who survived more than one day following their first recorded CHF/ATE morbidity. PES was calculated for these 119 cats. * P=0.101; ** P<0.0001; SD, standard deviation.

Table Legends

Table 1: Demographic characteristics of feline study populations.

Table 2: Prevalence of systolic heart murmurs in feline study populations.

Table 3: Cardiovascular morbidity and mortality in feline study populations.

Table 4: Incidence of cardiovascular morbidity and mortality events per 1,000 cat years grouped by age when diagnosed.

Table 5: Risk of cardiac morbidity and death assessed at 1, 5, and 10 year intervals following study entry.

Footnotes

[a] Meurs K, Kittleson MD, Towbin J, et al. Familial systolic anterior motion of the mitral valve and/or hypertrophic cardiomyopathy is apparently inherited as an autosomal dominant trait in a family of American Shorthair cats. J Vet Intern Med 1997;11:138 (abstract).

[b] Lefbom BK, Rosenthal S, Tyrell WDJ, et al. Severe hypertrophic cardiomyopathy in 10 young Ragdoll cats. J Vet Int Med 2001;15:308 (abstract).

[c] AVMA, U.S. Pet Ownership & Demographics Sourcebook 2012.

[d] 2017-2018 APPA National Pet Owners Survey http://americanpetproducts.org/pubs_survey.asp

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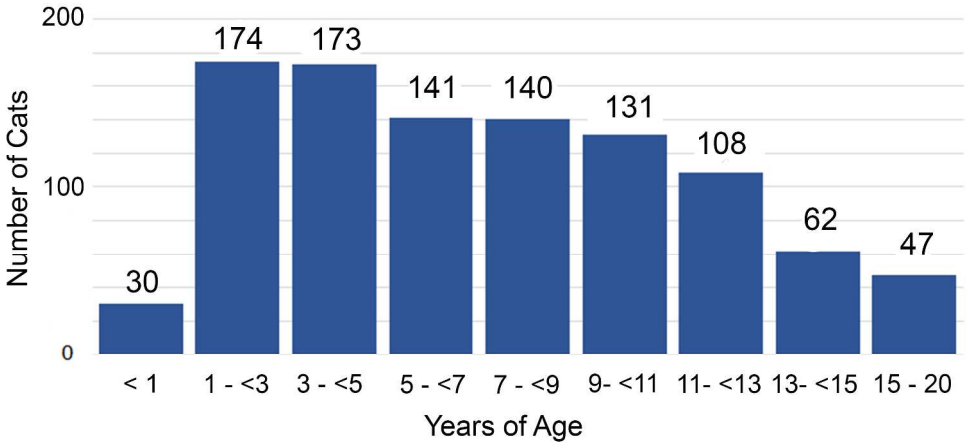

Figure 1: Demographic characteristics of feline study populations.

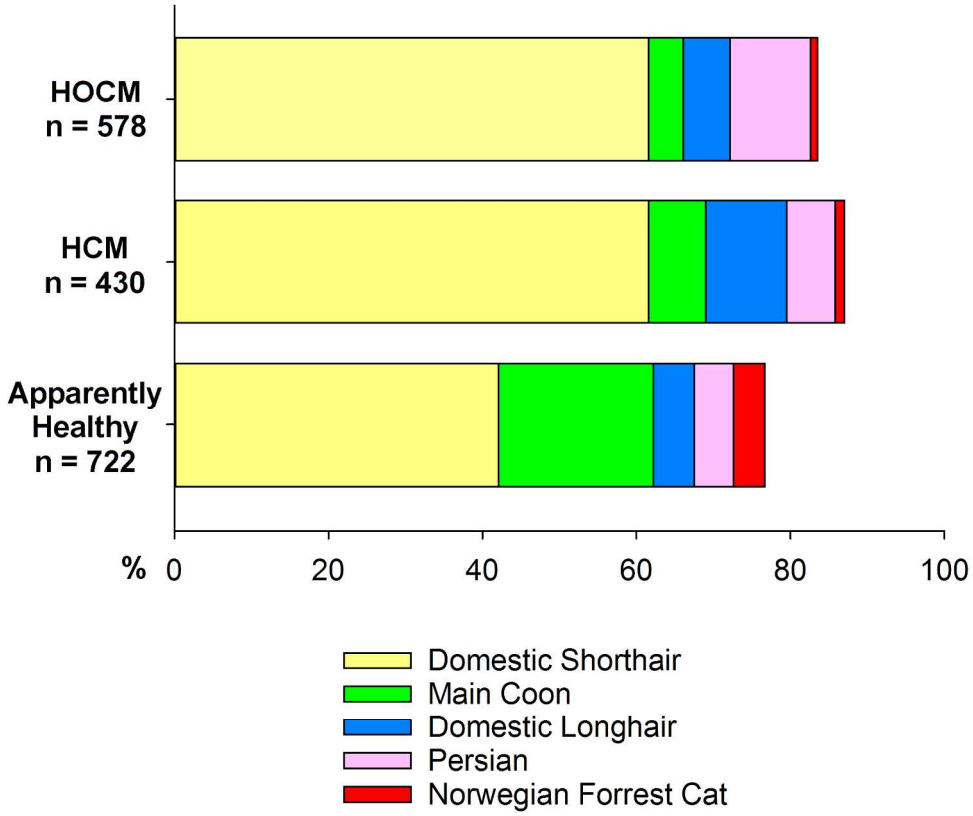

Figure 2. Most prevalent breeds in feline study populations. HCM, nonobstructive hypertrophic cardiomyopathy; HOCM, obstructive hypertrophic cardiomyopathy

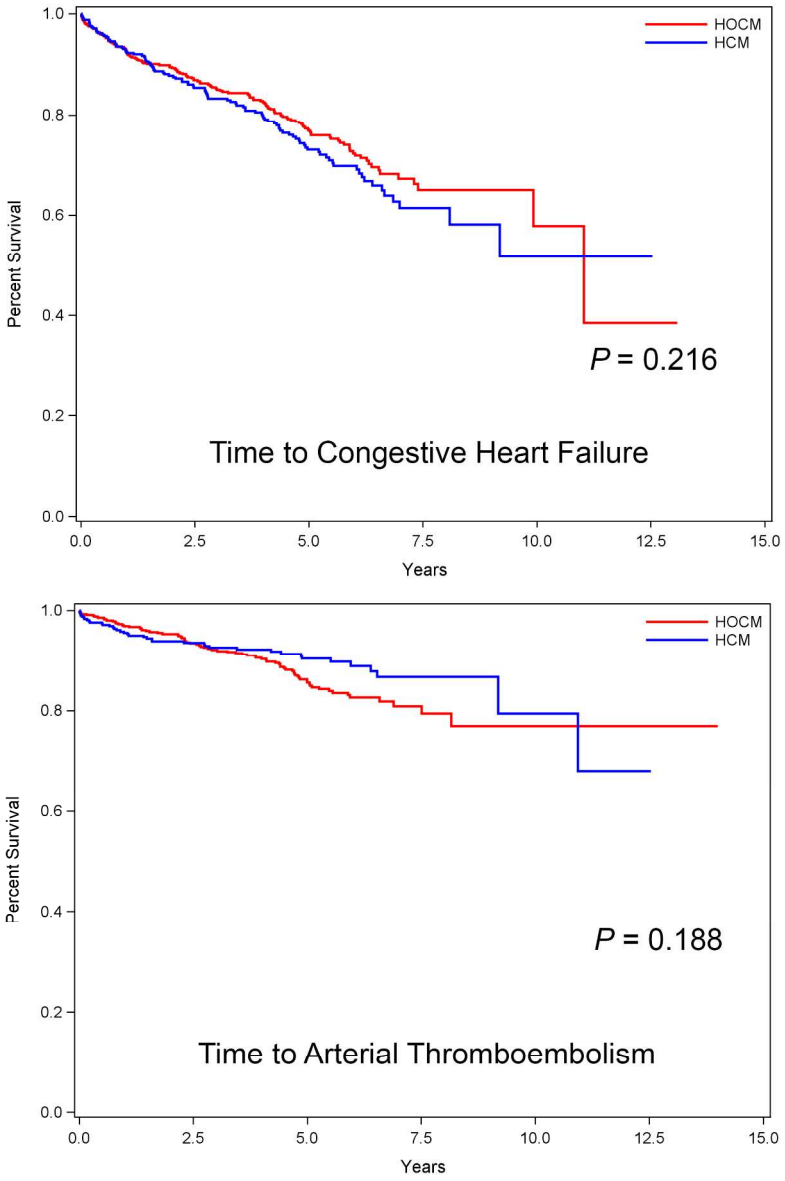

Figure 3. Kaplan-Meier survival curves estimating percentage of 430 cats with nonobstructive (HCM) compared to 578 cats with the obstructive (HOCM) form of hypertrophic cardiomyopathy that have not yet experienced morbidity (Y-axis) from congestive heart failure (top) or arterial thromboembolism (bottom) against time (X-axis).

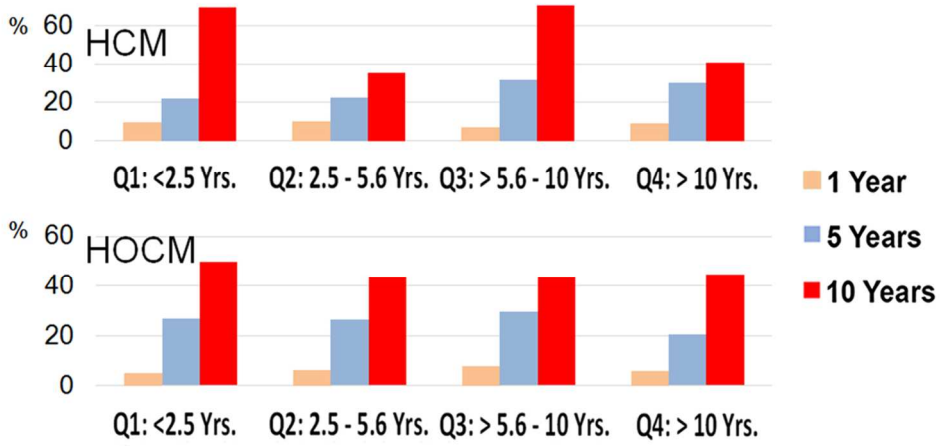

Figure 4. Percentage of 1,008 cats with nonobstructive (HCM, n=430) and obstructive (HOCM, n=578) hypertrophic cardiomyopathy at risk for cardiovascular mortality, by age quartile when diagnosed and assessed 1, 5, and 10 years following study entry. Q, age quartile; Yrs., years

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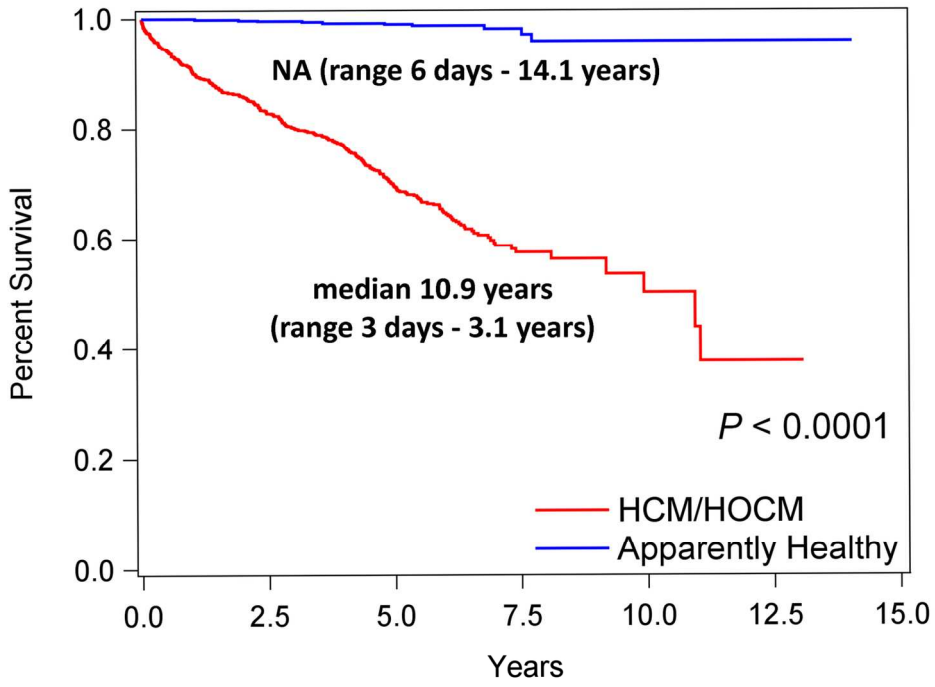

Figure 5. Kaplan-Meier survival curves estimating the percentage of 1,008 cats with nonobstructive (HCM, n=430) and obstructive (HOCM, n=578) forms of hypertrophic cardiomyopathy that have not yet experienced cardiovascular death (Y-axis), compared with 722 apparently healthy cats, against time (Y-axis). NA, median not estimatable.

140x110mm (300 x 300 DPI)

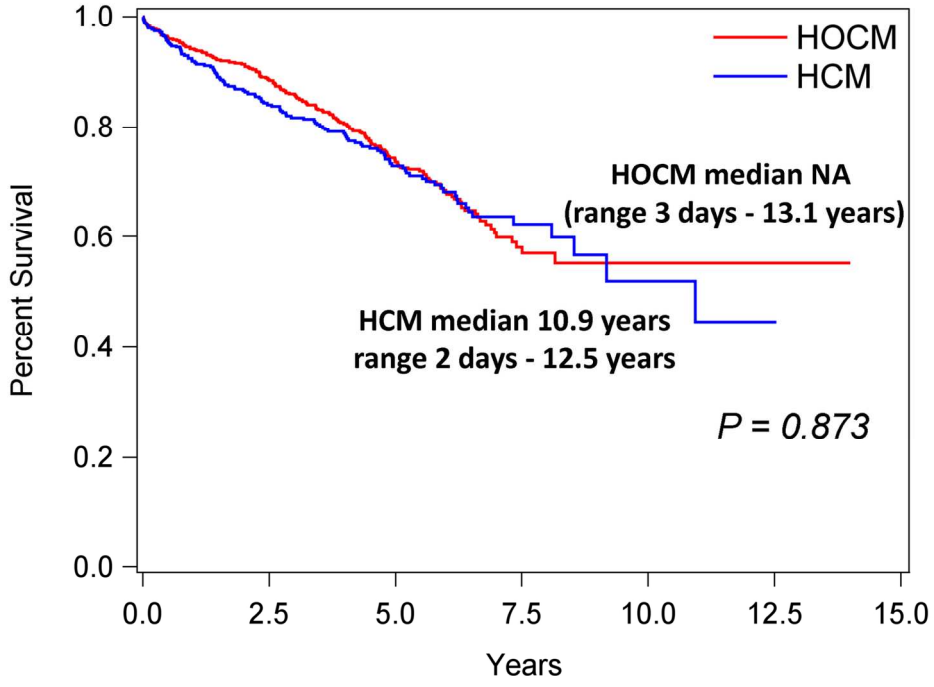

Figure 6. Kaplan-Meier survival curves estimating the percentage of 430 cats with nonobstructive (HCM) compared to 578 cats with obstructive (HOCM) forms of hypertrophic cardiomyopathy that have not yet experienced cardiovascular death (Y-axis), against time (Y-axis). NA, median not estimatable.

147x122mm (300 x 300 DPI)

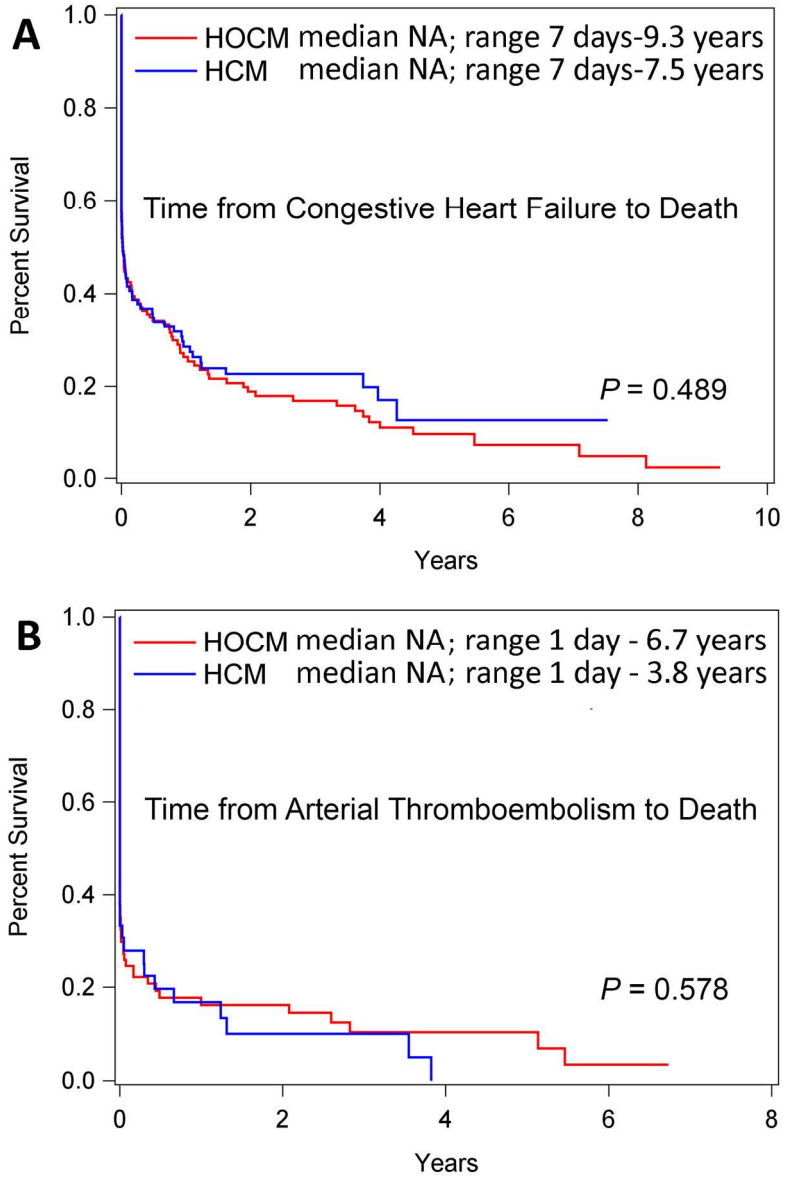

Figure 7. Kaplan-Meier survival curves estimating the percentage of 430 cats with nonobstructive (HCM) compared to 578 cats with obstructive (HOCM) hypertrophic cardiomyopathy that have not yet experienced cardiovascular death (Y-axis) for congestive heart failure (A), or arterial thromboembolism (B) against time (X-axis). NA, median not estimatable

177x220mm (300 x 300 DPI)

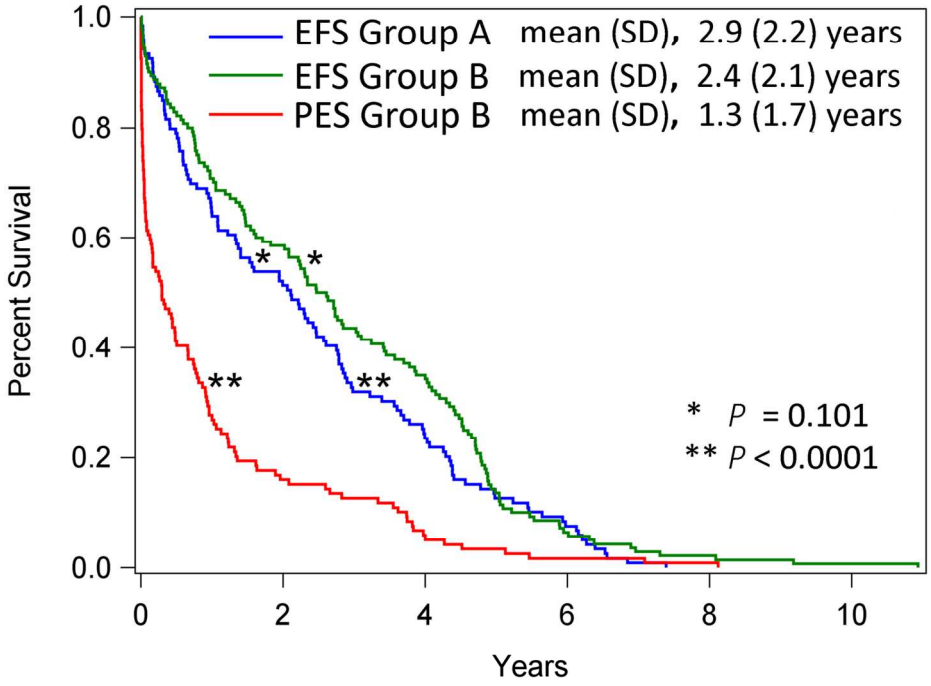

Figure 8. Kaplan-Meier survival curves estimating the event-free survival (EFS)$_{\top}$ proportion and post-event survival (PES) proportion (Y-axis) against time (X-axis). EFS Group-A comprised a cohort of 140 cats with pre-clinical hypertrophic cardiomyopathy who died on the day of their first recorded CHF/ATE morbidity. EFS Group-B comprised a cohort of 119 cats with pre-clinical hypertrophic cardiomyopathy who survived more than one day following their first recorded CHF/ATE morbidity. PES was calculated for these 119 cats. * P=597 0.101; ** P<0.0001; SD, standard deviation.$_{\top}$

140x111mm (300 x 300 DPI)

Table 1: Demographic characteristics of feline study populations.

Characteristic	Study Population Groups: Apparently Healthy n=722		HCM n=430		HOCM n=578		HCM/HOCM n=1,008		Apparently Healthy *vs* HCM	Apparently Healthy *vs* HOCM	Apparently Healthy *vs* HCM/HOCM
									Group Comparison *P* Values		
Age, years (Median; IQR)	*4.9 (1.9-9)*		*7.4 (4-11)*		*5.7 (3-9)*		*6.5 (3-10)*		***<0.001***	***0.013***	***<0.001***
Breed	**Number**	**%**	**Number**	**%**	**Number**	**%**	**Number**	**%**			
Domestic Shorthair	*304*	*42.1*	*265*	61.6	*353*	*61.1*	*618*	61.3	**<0.001**	**<0.001**	**<0.001**
Maine Coon	*145*	*20.1*	*32*	7.4	*26*	*4.5*	*58*	5.8	**<0.001**	**<0.001**	**<0.001**
Domestic Longhair	*38*	*5.3*	*45*	10.5	*35*	*6.1*	*80*	7.9	**0.001**	**0.620**	**0.038**
Persian	*37*	*5.1*	*27*	6.3	*60*	*10.4*	*87*	8.6	**0.487**	**<0.001**	**0.007**
Norwegian Forest Cat	*30*	*4.2*	*5*	*1.2*	*5*	*0.9*	*10*	*1.0*	**<0.001**	**<0.001**	**<0.001**
Siamese	*24*	*3.3*	*11*	2.6	*6*	*1.0*	*17*	*1.7*	**0.579**	**0.011**	**0.041**
Sphynx	*21*	*2.9*	*5*	1.2	*8*	*1.4*	*13*	*1.3*	**0.083**	**0.095**	**0.026**
Ragdoll	*14*	*1.9*	*2*	0.5	*2*	*0.3*	*4*	*0.4*	**0.071**	**0.020**	**0.004**
Other	*109*	*15.1*	*38*	8.8	*83*	*14.4*	*121*	*12.0*	**0.003**	**0.769**	**0.072**
Sex											
Male Intact	*97*	*13.4*	*39*	*9.1*	*41*	*7.1*	*80*	*7.9*	**0.033**	**<0.001**	**<0.001**
Male Neutered	*264*	*36.6*	*268*	*62.3*	*372*	*64.4*	*640*	*63.5*	**<0.001**	**<0.001**	**<0.001**
Female Intact	*159*	*22.0*	*25*	*5.8*	*21*	*3.6*	*46*	*4.6*	**<0.001**	**<0.001**	**<0.001**
Female Neutered	*202*	*28.0*	*98*	*22.8*	*144*	*24.9*	*242*	*24.0*	**0.061**	**0.238**	**0.057**
Body weight, kg (Median, IQR)	*4.5 (3.6-5.4)*		*5.2 (4.2-6.0)*		*5 (4.2-6.0)*		*5 (4.2-6.0)*		*<0.001*	*<0.001*	*<0.001*

IQR, interquartile range; HCM, nonobstructive hypertrophic cardiomyopathy; HOCM, obstructive hypertrophic cardiomyopathy; Other, pedigree crosses and all other non-specified breeds.

Table 2: Prevalence of systolic heart murmurs in feline study populations.

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	Study Population (n=1,730)								*P* values		
Number of cats with heart murmurs	Apparently Healthy (n=722)	%	HCM (n=430)	%	HOCM (n=578)	%	HCM/HOCM (n=1,008)	%	Apparently Healthy *vs* HCM	Apparently Healthy *vs* HOCM	Apparently Healthy *vs* HCM/HOCM
	335	46.4	294	68.4	537	92.9	831	82.4			
Heart murmur grade											
1	60	8.3	25	5.8	13	2.3	38	3.8	0.028	<0.001	<0.001
2	168	23.3	109	25.3	91	15.7	200	19.8	0.465	0.007	0.078
3	91	12.6	120	27.9	271	46.9	391	38.8	<0.001	<0.001	<0.001
4	16	2.2	39	9.1	157	27.2	196	19.4	<0.001	<0.001	<0.001
5	0	0.0	1	0.2	5	0.9	6	0.6	0.195	0.012	0.038

HCM, nonobstructive hypertrophic cardiomyopathy; HOCM, obstructive hypertrophic cardiomyopathy

Table 3: Cardiovascular morbidity and mortality in feline study populations.

	Study Population Groups							
	Apparently Healthy n=722		HCM n=430		HOCM n=578		HCM/HOCM n=1008	
Cardiovascular Morbidity	Number Events	% Normal	Number Events	% HCM	Number Events	% HOCM	Number. Events	% HCM/HOCM
CHF	6	0.83	106	24.7	138	23.9	244	24.2
ATE	5	0.69	41	9.5	76	13.2	117	11.6
Sudden death	0	0	9	2.1	13	2.3	22	2.2
All cardiovascular death	7	0.97	115	26.7	166	28.7	281	27.9

HCM, nonobstructive hypertrophic cardiomyopathy; HOCM, obstructive hypertrophic cardiomyopathy; CHF, congestive heart failure; ATE, arterial thromboembolism

Table 4: Incidence of cardiovascular morbidity and mortality events per 1,000 cat years grouped by age when diagnosed.

Age Group	Population Cohorts	CHF Morbidity	ATE Morbidity	Sudden Death	All-Cardiovascular Death
Total Population	Apparently Healthy	1.6	1.3	0	1.8
	HCM	62.9	22.2	4.6	64.8
	HOCM	54.2	29.5	5.3	62.5
	HCM/HOCM	57.6	26.6	5.0	63.4
Group 1 (<2.5 years)	Apparently Healthy	0.7	0.7	0	0
	HCM	52.6	11.7	2.9	46.7
	HOCM	50.4	28.3	6.3	62.7
	HCM/HOCM	51.2	22.5	5.1	57.1
Group 2 (2.5 - 5.6 years)	Apparently Healthy	2.3	0	0	1.1
	HCM	55.1	22.8	8.2	55.5
	HOCM	57.8	31.0	3.6	59.1
	HCM/HOCM	56.8	28.0	5.3	57.7
Group 3 (>5.6 -10 years)	Apparently Healthy	2.4	2.4	0	4.7
	HCM	62.6	33.1	1.8	78.8
	HOCM	53.4	32.4	6.1	69.9
	HCM/HOCM	57.1	32.7	4.4	72.7
Group 4 (>10 years)	Apparently Healthy	2.0	3.9	0	3.9
	HCM	81.4	15.3	5.0	75.1
	HOCM	54.4	21.7	5.3	53.6
	HCM/HOCM	68.1	18.4	5.1	64.7

HCM, nonobstructive hypertrophic cardiomyopathy; HOCM, obstructive hypertrophic cardiomyopathy; CHF, congestive heart failure; ATE, arterial thromboembolism

Table 5: Risk of cardiac morbidity and death assessed at 1, 5, and 10 year intervals following study entry.

	CHF		ATE		Sudden Death		All-Cardiovascular Death	
Risk	% Population Remaining at-Risk	% Population Affected	% Population Remaining at-Risk	% Population Affected	% Population Remaining at-Risk	% Population Affected	% Population Remaining at-Risk	% Population Affected
1-year post diagnosis								
Apparently Healthy	100	0.0	100	0.0	100	0.0	100	0.0
HCM	93.3	6.7	95.8	4.2	99.3	0.7	92.3	7.7
HOCM	92.7	7.3	97.1	2.9	99.1	0.9	94.1	5.9
HCM/HOCM	93.0	7.0	96.5	3.5	99.2	0.8	93.3	6.7
5-years post diagnosis								
Apparently Healthy	99.6	0.4	99.6	0.4	100	0.0	99.3	0.7
HCM	79.5	20.5	92.3	7.7	98.1	1.9	77.7	22.3
HOCM	80.4	19.6	88.7	11.3	96.7	3.3	76.8	23.2
HCM/HOCM	80.1	19.9	90.3	9.7	97.3	2.7	77.2	22.8
10-years post diagnosis								
Apparently Healthy	99.2	0.8	99.3	0.7	100	0.0	99.0	1.0
HCM	75.6	24.4	91.2	8.8	97.4	2.6	73.3	26.7
HOCM	76.5	23.5	86.8	13.2	96.0	4.0	70.6	29.4
HCM/HOCM	76.1	23.9	88.7	11.3	96.6	3.4	71.7	28.3

HCM, nonobstructive hypertrophic cardiomyopathy; HOCM, obstructive hypertrophic cardiomyopathy; CHF, congestive heart failure; ATE, arterial thromboembolism.