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International collaborative study to assess cardiovascular risk and evaluate long-term health in cats with preclinical hypertrophic cardiomyopathy and apparently healthy cats: The REVEAL Study

Philip R. Fox¹  | Bruce W. Keene² | Kenneth Lamb³ | Karsten A. Schober⁴ | Valerie Chetboul⁵ | Virginia Luis Fuentes⁶ | Gerhard Wess⁷ | Jessie Rose Payne⁶ | Daniel F. Hogan⁸ | Alison Motsinger-Reif⁹ | Jens Häggström¹⁰  | Emilie Trehieu-Sechi¹¹ | Deborah M. Fine-Ferreira¹² | Reid K. Nakamura¹³ | Pamela M. Lee¹  | Manreet K. Singh¹⁴ | Wendy A. Ware¹⁵ | Jonathan A. Abbott¹⁶  | Geoffrey Culshaw¹⁷ | Sabine Riesen¹⁸ | Michele Borgarelli¹⁹ | Michael B. Lesser²⁰ | Nicole Van Israël²¹ | Etienne Côté²² | John E. Rush²³ | Barret Bulmer²⁴ | Roberto A. Santilli²⁵  | Andrea C. Vollmar²⁶ | Maribeth J. Bossbaly²⁷ | Nadine Quick²⁸ | Claudio Bussadori²⁹ | Janice M. Bright³⁰ | Amara H. Estrada³¹ | Dan G. Ohad³² | Maria Josefa Fernández-Del Palacio³³ | Jenifer Lunney Brayley³⁴ | Denise S. Schwartz³⁵ | Christina M. Bové³⁶ | Sonya G. Gordon³⁷ | Seung Woo Jung³⁸  | Paola Brambilla³⁹ | N. Sydney Moïse⁴⁰ | Christopher D. Stauthammer⁴¹ | Rebecca L. Stepien⁴² | Cecilia Quintavalla⁴³ | Christophe Amberger⁴⁴ | Ferenc Manczur⁴⁵ | Yong-Wei Hung⁴⁶ | Remo Lobetti⁴⁷ | Marie De Swarte⁴⁸ | Alice Tamborini⁴⁸  | Carmel T. Mooney⁴⁸ | Mark A. Oyama⁴⁹  | Andrey Komolov⁵⁰ | Yoko Fujii⁵¹ | Romain Pariaut⁵² | Masami Uechi⁵³ | Victoria Yukie Tachika Ohara⁵⁴

¹Department of Cardiology and Caspary Research Institute, The Animal Medical Center, New York, New York, U.S.A.

²Department of Clinical Sciences, North Carolina State University, Raleigh, North Carolina, U.S.A.

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 estimable; 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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- ³Lamb Consulting, Minneapolis, Minnesota, U.S.A.
- ⁴Department of Veterinary Clinical Sciences, The Ohio State University, Columbus, Ohio, U.S.A.
- ⁵Alfort Cardiology Unit, Ecole Nationale Vétérinaire d'Alfort, Maisons-Alfort Cedex, France
- ⁶Department of Veterinary Clinical Sciences and Services, The Royal Veterinary College, Hatfield, Hertfordshire, United Kingdom
- ⁷Clinic of Small Animal Medicine, Ludwig-Maximilians University, Munich, Germany
- ⁸Department of Veterinary Clinical Sciences, Purdue University, West Lafayette, Indiana, U.S.A.
- ⁹Department of Statistics, North Carolina State University, Raleigh, North Carolina, U.S.A.
- ¹⁰Department of Clinical Sciences, Swedish University of Agricultural Sciences, Uppsala, Sweden
- ¹¹Alfort Cardiology Unit, Ecole Nationale Vétérinaire d'Alfort, Maisons-Alfort Cedex, France
- ¹²Department of Veterinary Medicine and Surgery, University of Missouri, Columbia, Missouri, U.S.A.
- ¹³Advanced Veterinary Care Center, Lawndale, California, U.S.A.
- ¹⁴William R. Pritchard Veterinary Medical Teaching Hospital, University of California-Davis, Davis, California, U.S.A.
- ¹⁵Department of Veterinary Clinical Sciences, Iowa State University, Ames, Iowa, U.S.A.
- ¹⁶Department of Small Animal Clinical Sciences, Virginia-Maryland College of Veterinary Medicine, Blacksburg, Virginia, U.S.A.
- ¹⁷Royal (Dick) SVS Hospital for Small Animals, The University of Edinburgh, Roslin, Midlothian, United Kingdom
- ¹⁸Department for Companion Animals and Horses, University of Veterinary Medicine, Vienna, Austria
- ¹⁹Department of Clinical Sciences, Kansas State University, Manhattan, Kansas, U.S.A.
- ²⁰Advanced Veterinary Care Center, Lawndale, California, U.S.A.
- ²¹Animal CardioPulmonary Consultancy, Masta, Stavelot, Belgium
- ²²Department of Companion Animals, Atlantic Veterinary College, University of Prince Edward Island, Charlottetown, Prince Edward Island, Canada
- ²³Department of Clinical Sciences, Tufts University, Cummings School of Veterinary Medicine, North Grafton, Massachusetts, U.S.A.
- ²⁴Tufts Veterinary Emergency Treatment & Specialties, Walpole, Massachusetts, U.S.A.
- ²⁵Department of Cardiology, Clinica Veterinaria Malpensa, Varese, Italy
- ²⁶Fachtierärztin für Kleintiere, Wissen und Bonn, Germany
- ²⁷Veterinary Specialty and Emergency Center, Levittown, Pennsylvania, U.S.A.
- ²⁸Clinic of Small Animal Medicine, Ludwig-Maximilians University, Munich, Germany
- ²⁹Department of Cardiology, Clinica Veterinaria Gran Sasso, Milan, Italy
- ³⁰Department of Clinical Sciences, Colorado State University, Fort Collins, Colorado, U.S.A.
- ³¹Department of Small Animal Clinical Sciences, University of Florida, Gainesville, Florida
- ³²Department of Clinical Sciences, The Koret School of Veterinary Medicine, Rehovot, Israel
- ³³Departamento de Medicina y Cirugía Animal, Universidad de Murcia, Murcia, Spain
- ³⁴Veterinary Medical Specialists of Houston, Houston, Texas, U.S.A.
- ³⁵Department of Internal Medicine, University of São Paulo, São Paulo, Brazil
- ³⁶Department of Clinical Studies, University of Guelph, Guelph, Ontario, Canada
- ³⁷Department of Small Animal Clinical Sciences, Texas A&M University, College Station, Texas, U.S.A.
- ³⁸William R. Pritchard Veterinary Medical Teaching Hospital, University of California-Davis, Davis, California, U.S.A.
- ³⁹Department of Veterinary Medicine, University of Milan, Milan, Italy
- ⁴⁰Department of Clinical Sciences, Cornell University, Ithaca, New York, U.S.A.
- ⁴¹Department of Veterinary Clinical Sciences, University of Minnesota, St. Paul, Minnesota, U.S.A.
- ⁴²Department of Medical Sciences, University of Wisconsin School of Veterinary Medicine, Madison, Wisconsin, U.S.A.
- ⁴³Department of Veterinary Sciences, University of Parma, Parma, Italy
- ⁴⁴Cabinet Vétérinaire et Centre d'Imagerie, Geneva, Switzerland
- ⁴⁵Department of Internal Medicine, University of Veterinary Medicine, Budapest, Hungary
- ⁴⁶Cardiospecial Veterinary Hospital, Taipei, Taiwan
- ⁴⁷Bryanston Veterinary Hospital, Bryanston, South Africa
- ⁴⁸University College Dublin Veterinary Hospital, University College Dublin, Dublin, Ireland
- ⁴⁹Department of Clinical Studies, University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.
- ⁵⁰Veterinary Clinic Belyi Klyk, Moscow, Russia
- ⁵¹Azabu University, Sagami, Kanagawa, Japan

⁵²Department of Veterinary Clinical Sciences, Louisiana State University, Baton Rouge, Louisiana, U.S.A.

⁵³Jasmine Animal Cardiovascular Center, Yokohama, Kanagawa, Japan

⁵⁴Department of Medicine, Surgery and Zootechnics for Small Species, Universidad Nacional Autónoma de México, Mexico City, Mexico

Correspondence

P. R. Fox, Department of Cardiology,
Caspary Research Institute, The Animal
Medical Center, 510 E. 62nd Street, New
York 10065.
Email: philip.fox@amcn.org

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

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

Animals: One thousand seven hundred and thirty client-owned cats (430 preclinical HCM; 578 preclinical 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 1008 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 with 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 $\pm$ standard deviation, 1.3 ± 1.7 years). Overall, prolonged longevity was recorded in a minority of preclinical HCM/HOCM cats with 10% reaching 9–15 years.

Conclusions and Clinical Importance: Preclinical HCM/HOCM is a global health problem of cats that carries substantial risk for CHF, ATE, and cardiovascular death. This finding underscores the need to identify therapies and monitoring strategies that decrease morbidity and mortality.

KEYWORDS

arterial thromboembolism, asymptomatic, congestive heart failure, epidemiology, incidence, outcome, survival

1 | 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 preclinical (ie, 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.^{10–12,24,29–38} Despite the fact that this disease is widely recognized, risk of attendant cardiovascular complications is unknown, and the natural history of preclinical 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,^{39–48} 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.⁴⁹

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.⁴⁶ Furthermore, combining preclinical and heart failure patient data limits risk estimation and prognosis for cats having only preclinical disease.^{5,7,9,14,17,26,28}

Thus, to understand the natural history of preclinical 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.

2 | MATERIALS AND METHODS

2.1 | Study design

The “International collaborative study to assess cardiovascular risk and evaluate long-term health in cats with preclinical hypertrophic cardiomyopathy and apparently healthy cats: The REVEAL Study” 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.

2.2 | Cats

Cat populations included preclinical obstructive (HOCM) and nonobstructive (HCM) forms of hypertrophic cardiomyopathy, and apparently healthy cats (AH). The term preclinical 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 unremarkable medical history, no known illness, and had 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.

2.2.1 | Inclusion criteria

Medical records were searched for cats diagnosed with preclinical hypertrophic cardiomyopathy (both HCM and HOCM) as well as AH 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.

2.2.2 | 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 mm Hg), 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.

2.3 | Study sites

Investigators worked at 50 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, and 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.

2.4 | 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.^{8,50,51} Diagnosis was based on 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 2D echo-guided M-mode images from right parasternal short-axis views by most investigators or, using 2D 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 our 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/s. 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/s.⁵²

2.5 | 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 on 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 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 noncardiac morbidity and mortality. Survival was calculated from initial diagnosis to date of death, last recorded examination, or last contact.

2.6 | 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 on these assumptions, 250 cats with preclinical hypertrophic cardiomyopathy and 250 AH were considered to provide 80% power to detect a difference in survival proportions between preclinical 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. Survival range was presented if median survival was not reached. 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 1000 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

TABLE 1 Demographic characteristics of feline study populations

Study Population Groups											
Characteristic	AH n = 722		HCM n = 430		HOCM n = 578		HCM/ HOCM n = 1008		AH versus HCM	AH versus HOCM	AH versus 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)		<.001	.013	<.001
Breed	Number	%	Number	%	Number	%	Number	%			
Domestic Shorthair	304	42.1	265	61.6	353	61.1	618	61.3	<.001	<.001	<.001
Maine Coon	145	20.1	32	7.4	26	4.5	58	5.8	<.001	<.001	<.001
Domestic Longhair	38	5.3	45	10.5	35	6.1	80	7.9	.001	.620	.038
Persian	37	5.1	27	6.3	60	10.4	87	8.6	.487	<.001	.007
Norwegian Forest Cat	30	4.2	5	1.2	5	0.9	10	1.0	<.001	<.001	<.001
Siamese	24	3.3	11	2.6	6	1.0	17	1.7	.579	.011	.041
Sphynx	21	2.9	5	1.2	8	1.4	13	1.3	.083	.095	.026
Ragdoll	14	1.9	2	0.5	2	0.3	4	0.4	.071	.020	.004
Other	109	15.1	38	8.8	83	14.4	121	12.0	.003	.769	.072
Sex											
Male Intact	97	13.4	39	9.1	41	7.1	80	7.9	.033	<.001	<.001
Male Neutered	264	36.6	268	62.3	372	64.4	640	63.5	<.001	<.001	<.001
Female Intact	159	22.0	25	5.8	21	3.6	46	4.6	<.001	<.001	<.001
Female Neutered	202	28.0	98	22.8	144	24.9	242	24.0	.061	.238	.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)		<.001	<.001	<.001

Abbreviations: IQR, interquartile range; HCM, nonobstructive hypertrophic cardiomyopathy; HOCM, obstructive hypertrophic cardiomyopathy; Other, pedigree crosses and all other nonspecified breeds.

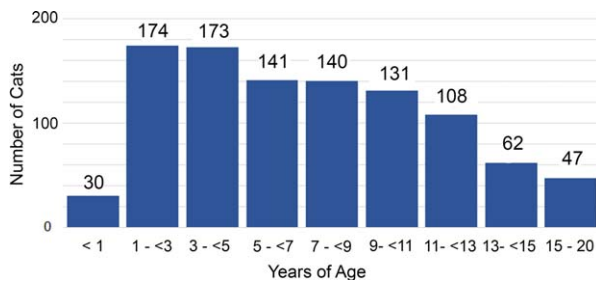


FIGURE 1 Age distribution for 1006 of the 1008 cats with obstructive and nonobstructive hypertrophic cardiomyopathy recorded at the time of diagnosis. In 2 cats, age was not recorded

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). Postevent 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. Because of 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 $P < .05$.

3 | RESULTS

3.1 | Population characteristics at time of diagnosis

One-thousand seven-hundred thirty cats fulfilled entry criteria; 1008 (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; $P < .001$) and HOCM (median, 5.7 years; range, 0.5–19 years; $P < .013$); HOCM were younger than HCM ($P < .001$). Ages recorded in 1006 of 1008 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

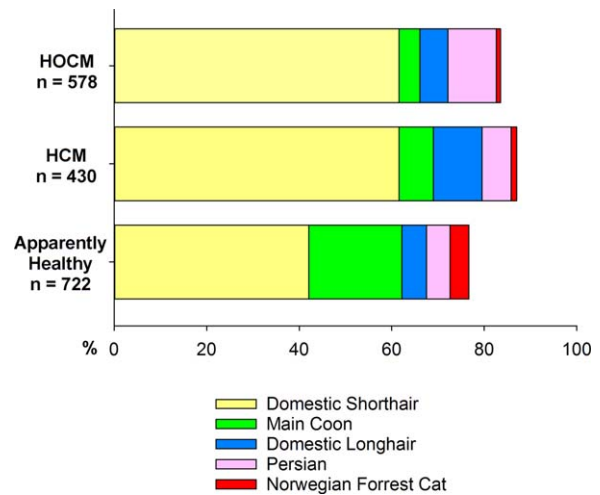


FIGURE 2 Most prevalent breeds in feline study populations. HCM, nonobstructive hypertrophic cardiomyopathy; HOCM, obstructive hypertrophic cardiomyopathy

not differ ($P = .095$), but was slightly higher compared with AH (both $P < .001$; 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 ($P = .303$ and $P = .589$, respectively). The proportion of neutered females did not differ significantly between HCM and HOCM ($P = .480$). 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%; $P < .001$). Moderate to loud (grade 3–5/6) systolic murmurs were more common in HCM/HOCM (58.8%) than AH (14.8%; $P < .001$), and in

TABLE 2 Prevalence of systolic heart murmurs in feline study populations

	Study Population (n = 1730)								P values		
Number of cats with heart murmurs	AH (n = 722)		HCM (n = 430)		HOCM (n = 578)		HCM/HOCM (n = 1008)		AH versus HCM	AH versus HOCM	AH versus 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	.028	<.001	<.001
2	168	23.3	109	25.3	91	15.7	200	19.8	.465	.007	.078
3	91	12.6	120	27.9	271	46.9	391	38.8	<.001	<.001	<.001
4	16	2.2	39	9.1	157	27.2	196	19.4	<.001	<.001	<.001
5	0	0.0	1	0.2	5	0.9	6	0.6	.195	.012	.038

Abbreviations: HCM, nonobstructive hypertrophic cardiomyopathy; HOCM, obstructive hypertrophic cardiomyopathy.

TABLE 3 Cardiovascular morbidity and mortality in feline study populations

Study Population Groups								
Cardiovascular morbidity	AH n = 722		HCM n = 430		HOCM n = 578		HCM/HOCM n = 1008	
	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

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

HOCM (74.9%) compared with HCM (37.2%) cats ($P < .001$), respectively. Soft systolic murmurs (grades 1–2/6) were more common in AH (31.6%) than HCM/HOCM (23.6%) cats ($P < .001$). 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 ($P = .025$). Heart rate (median; IQR) during physical examination at study entry was lower in AH (180; 167–200 beats per minute [bpm]) compared with HOCM (190; 170–210 bpm; $P = .001$), but did not differ between HCM (186; 167–202 bpm) and AH ($P = .676$), or between HCM and HOCM ($P = .164$).

Arrhythmias were recorded in 128/1008 (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 nonsustained 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; $P = .168$) 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 ($P < .001$), but not in AH. No additional information regarding dosage, compliance, or duration was recorded.

3.2 | Incidence and risk for cardiovascular morbidity and mortality

Cardiovascular morbidities were recorded in 307 (30.5%) of 1008 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; $P = .834$), nor did ATE events differ in

HCM (41/430) compared with HOCM cats (76/578; $P = .094$). Similarly, HCM and HOCM did not differ with respect to time from study entry to development of CHF ($P = .216$) or ATE ($P = .188$; 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.

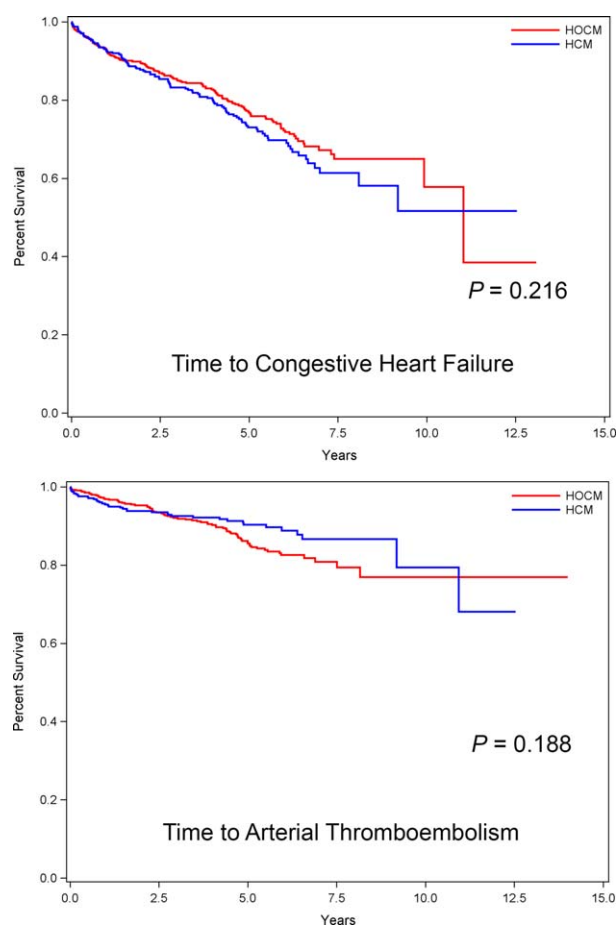


FIGURE 3 Kaplan-Meier survival curves estimating percentage of 430 cats with nonobstructive (HCM) compared with 578 cats with the obstructive (HOCM) form of hypertrophic cardiomyopathy that have not yet experienced morbidity (Y-axis) from CHF (top) or ATE (bottom) against time (X-axis)

TABLE 4 Incidence of cardiovascular morbidity and mortality events per 1000 cat years grouped by age at study entry

Age group	Population cohorts	CHF morbidity	ATE morbidity	Sudden death	All-cardiovascular death
Total Population	AH	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)	AH	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)	AH	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)	AH	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)	AH	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

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

3.2.1 | Incidence

The incidence of CHF, ATE, SD, and all-cardiovascular death events per 1000 cat years for each cohort was delineated by quartiles corresponding with age at the time of study entry (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 1000 cat years, respectively). The incidence of ATE increased from the first to the third age quartile (from 22.5 to 32.7 events per 1000 cat years, respectively), and then decreased sharply to 18.4 events per 1000 cat years in cats > 10 years of age. Incidence of cardiovascular death was 57.1 events per 1000 cat years

TABLE 5 Risk of cardiac morbidity and death assessed at 1, 5, and 10 year intervals after study entry

Risk	CHF		ATE		Sudden Death		All-Cardiovascular Death	
	% 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								
AH	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								
AH	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								
AH	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

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

for cats <2.5 years of age, and was unchanged (57.7 events per 1000 cat years) between 2.5 and 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 1000 cat years, respectively.

3.2.2 | 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 1008 cats with preclinical 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 and Figure 4).

3.3 | Survival analyses-mortality

Cardiovascular death was recorded in 281 (27.9%) of 1008 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 1008 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 estimable [NA] due to low event rate; 6 days-14.1 years; $P < .0001$; Figure 5). The oldest 10% of surviving HCM/HOCM cats at study end were 9–14.7 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 ($P = .873$; Figure 6). Furthermore, no significant difference was found between HCM and HOCM populations for the overall proportion of cardiovascular death ($P = .535$), proportion of cardiovascular death associated with CHF ($P = .834$), and proportion of cardiovascular death associated with ATE ($P = .118$). The proportions of SD did not differ between HCM and HOCM cats ($P = .960$). Time (median, IQR) from study entry to SD did not differ significantly between HCM (1290 days; 304–2176 days) and HOCM (1156 days; 457–1777 days; $P = .676$). Furthermore, time from

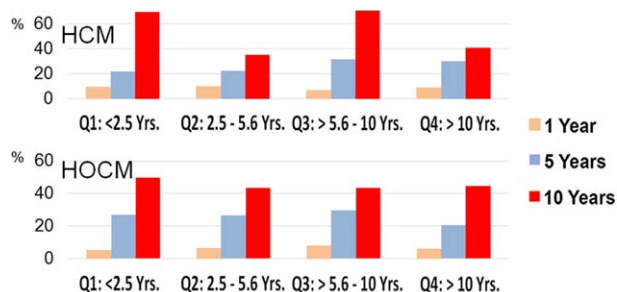


FIGURE 4 Percentage of 1008 cats with nonobstructive (HCM, $n = 430$) and obstructive (HOCM, $n = 578$) hypertrophic cardiomyopathy at risk for cardiovascular mortality, by age quartile when diagnosed and assessed 1, 5, and 10 years after study entry. Q, age quartile; yrs., years

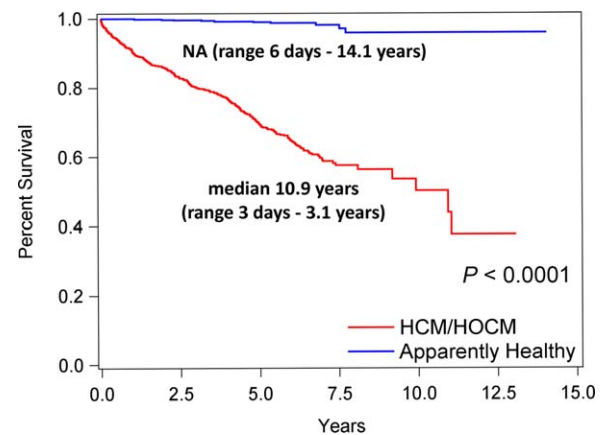


FIGURE 5 Kaplan-Meier survival curves estimating percentage of 1008 cats with nonobstructive (HCM, $n = 430$) and obstructive (HOCM, $n = 578$) forms of hypertrophic cardiomyopathy that have not yet experienced cardiovascular death (Y-axis) compared with 722 AH against time (X-axis). NA, median not estimable

onset of CHF or ATE morbidity to cardiovascular death did not differ between HCM and HOCM populations ($P = .489$ and $P = .578$, respectively; Figure 7). Cardiovascular survival did not differ significantly among age quartiles within HCM ($P = .206$) or in HOCM ($P = .796$) populations. Cardiovascular survival did not differ significantly between HCM cats that had SBP measured compared with HCM cats that did not have SBP measured ($P = .085$); HOCM cats that had SBP measured compared with HOCM cats that did not have SBP measured ($P = .255$); HCM compared with HOCM that had SBP recorded ($P = .476$); or between these cohorts that did not have SBP recorded ($P = .609$). In addition, cardiovascular survival did not differ significantly between HCM/HOCM cats that had serum thyroxine concentrations measured compared with HCM/HOCM cats that did not have serum thyroxine concentrations measured ($P = .263$). Cardiovascular survival in HCM/HOCM cats did not differ significantly between those prescribed or not prescribed ≥ 1 cardiovascular medications at study entry ($P = .845$).

3.4 | Time to event, event-free, and PES analysis

3.4.1 | 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, 2–2954 days); ATE occurred without CHF in 25 cats (median, 370 days; range, 5–3993 days); and, both CHF and ATE occurred in 16 cats (concurrently in 10 cats [median, 513 days; range, 4–3353]; ATE preceded CHF in 3 [1775, 2384, and 3334 days]; and CHF preceded ATE in 3 [1178, 1316, and 2409 days]). In HOCM: CHF occurred without ATE in 98 cats (median, 1017 days; range, 4–4029 days); ATE occurred without CHF in 36 cats (median, 1081 days; range, 1–2518 days); and both CHF and ATE were recorded in 40 cats (concurrently in 20 [median, 790 days; range, 11–2151 days]; ATE preceded CHF in 14 [median, 1184 days; range, 3–2980 days]; and CHF preceded ATE in 6 [median, 933 days; range, 177–2075 days]). In AH: CHF occurred without ATE in 5 cats (median, 1633 days; range, 841–2749

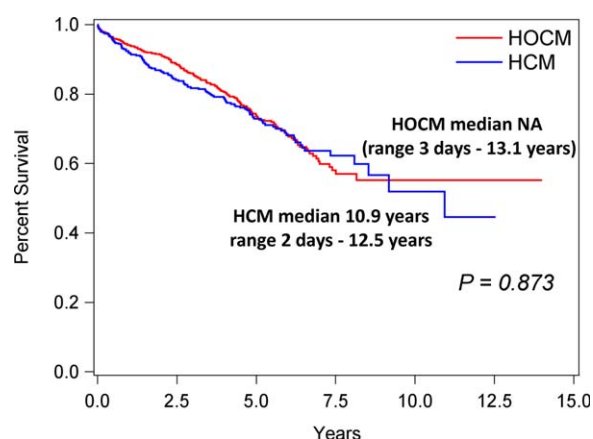


FIGURE 6 Kaplan-Meier survival curves estimating percentage of 430 cats with nonobstructive (HCM) compared with 578 cats with the obstructive form (HOCM) of hypertrophic cardiomyopathy that have not yet experienced cardiovascular death (Y-axis) against time (X-axis). NA, median not estimable

days, both CHF and ATE developed in 1 cat, and ATE occurred without CHF in 4 cats (median, 1760 days; range, 387–2819 days). Two of the 5 AH with CHF without ATE had developed hyperthyroidism.

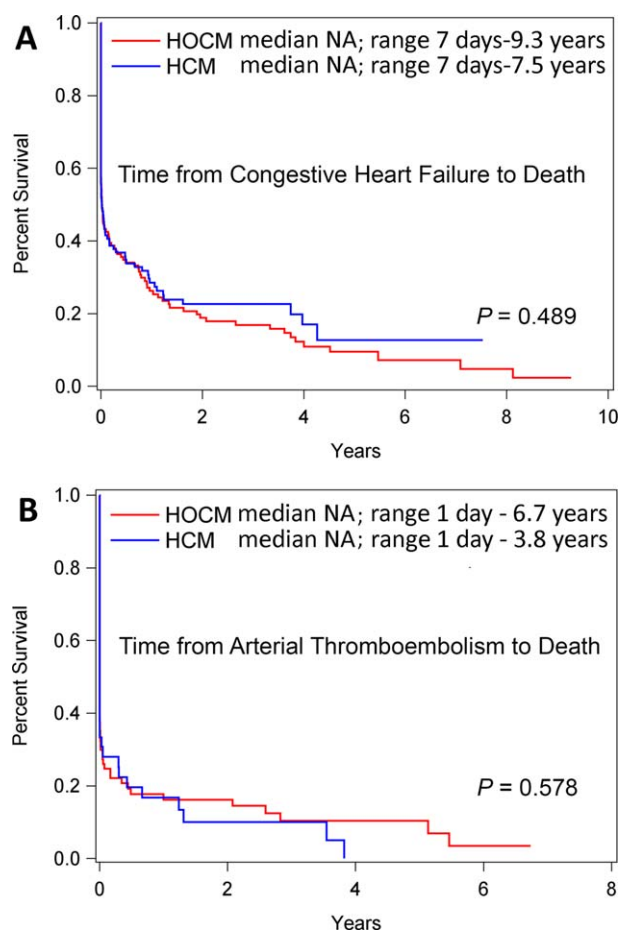


FIGURE 7 Kaplan-Meier survival curves estimating the percentage of 430 cats with nonobstructive (HCM) compared with 578 cats with obstructive (HOCM) hypertrophic cardiomyopathy that have not yet experienced cardiovascular death (Y-axis) for CHF (A), or ATE (B) against time (X-axis). NA, median not estimable

3.4.2 | Event-free survival

Of the 1008 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 $\pm$ standard deviation) did not differ significantly between the cohort of 140 cats (2.9 ± 2.2 years) compared with the cohort of 119 cats (2.4 ± 2.11 years; $P = .101$; Figure 8).

3.4.3 | 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 ($P < .0001$), and for EFS of the cohort of 140 cats that died on the day of their first cardiovascular morbidity ($P < .0001$; Figure 8). Moreover, PES in these 119 cats did not differ significantly with respect to age quartiles ($P = .402$) or between HCM and HOCM cats that comprised this cohort ($P = .364$).

4 | DISCUSSION

REAL is the first international, collaborative, epidemiologic study to evaluate populations of preclinical 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

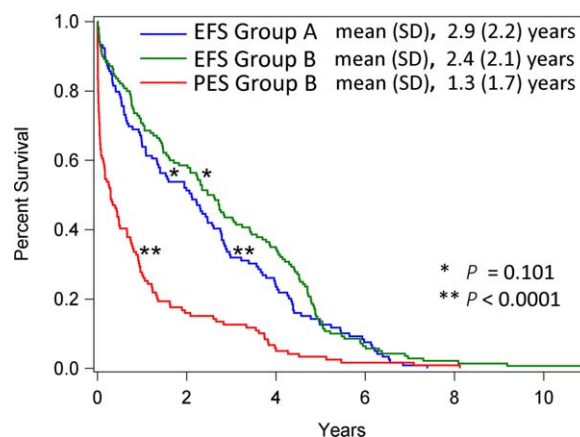


FIGURE 8 Kaplan-Meier survival curves estimating the EFS proportion and PES proportion (Y-axis) against time (X-axis). Event-free survival group-A comprised a cohort of 140 cats with preclinical hypertrophic cardiomyopathy who died on the day of their first recorded CHF/ATE morbidity. Event-free survival group-B comprised a cohort of 119 cats with preclinical hypertrophic cardiomyopathy who survived more than one day after their first recorded CHF/ATE morbidity. Postevent survival was calculated for these 119 cats. * $P = .101$; ** $P < .0001$; SD, standard deviation

substantial. Of the cohort of 1008 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. Preclinical 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 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.^{39,43–48}

Reports comparing cardiovascular survival between preclinical 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.^{39–41} 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 with 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 treatment in veterinary medicine.^{17,49} Our study contributes a fresh clinical perspective to the natural history of preclinical 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 supports the concept that hypertrophic cardiomyopathy is predominantly a disease of LVOTO.⁴² Indeed, the fact that LVOTO can be provoked in the cat⁶ 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. 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 with 1 year after diagnosis for each age quartile. In AH the risk of cardiovascular death was only 1%. In preclinical HCM and HOCM, sudden death was substantially lower in our present study than described from mixed preclinical 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 subgroups.^{46–48}

Early onset of preclinical 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 on cut-off values used to define LV end-diastolic wall thickness.^{10,12,24,28,37} 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,³² and onset of CHF before 1 year of age has been observed in this breed.⁵³ 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

Preclinical 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 preclinical and clinically affected populations.^{7–9,12,18,25,26,54}

Of the HCM/HOCM cats that developed CHF or ATE, the mean EFS did not exceed 3 years. In addition, 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 10–15 years of age and approximately 5% were > 15 years of age.²⁸ This finding indicates that preclinical hypertrophic cardiomyopathy can be compatible with normal life expectancy. Prolonged survival with this condition has been increasingly reported in affected humans.⁴⁶

The HCM/HOCM population's high male prevalence, dominated by neutered males, was similar to previously reported male predilection rates of between 63% and 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 with cats with HCM, accounting for the slightly younger HOCM cohort. Arrhythmias were detected at study entry in approximately 13% of preclinical HCM/HOCM and in 4% of AH. Others have reported arrhythmias from mixed preclinical 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% to 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 ≥ 5.5 mm cut-off reported 8.5% in 329 British shorthair cats in Denmark¹² and 25% in 53 Norwegian Forest cats screened in London.³⁵ Recently, echocardiographic reference ranges based on allometric scaling have been proposed.^{54,55}

United States pet ownership surveys identify steady growth in the feline pet population, estimating 74 million cats in 2012 (AVMA, U.S. Pet Ownership & Demographics Sourcebook, 2012) and 94.2 million cats between 2017 and 2018 (2017–2018 APPA National Pet Owners Survey http://americanpetproducts.org/pubs_survey.asp). Recently, estimates of hypertrophic cardiomyopathy prevalence in humans suggests that ~ 1 out of 200 individuals (0.5%) is genetically affected,⁵⁶ with a substantial proportion being genetically positive but phenotypically negative. If the prevalence of feline hypertrophic cardiomyopathy were conservatively extrapolated at 0.5% based on findings reported in humans,⁵⁶ upwards of 470 000 cats could be affected in the United States of America. Alternatively, if 8% prevalence was inferred based on 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 LV 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 preclinical 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 on 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 on 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 preclinical 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.

5 | CONCLUSIONS

Data from the REVEAL study demonstrates that preclinical 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 1008 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 preclinical hypertrophic cardiomyopathy, and

underscore the need to identify and develop health care and treatment strategies that optimize monitoring, decrease risk, and improve outcome.

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CONFLICT OF INTEREST DECLARATION

This study was funded by the Morris Animal Foundation and Winn Feline Foundation.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

ORCID

Philip R. Fox  <http://orcid.org/0000-0003-4089-0573>

Jens Häggström  <http://orcid.org/0000-0003-3402-023X>

Pamela M. Lee  <http://orcid.org/0000-0001-6003-0496>

Jonathan A. Abbott  <http://orcid.org/0000-0001-6981-8968>

Roberto A. Santilli  <http://orcid.org/0000-0001-5937-2050>

Seung Woo Jung  <http://orcid.org/0000-0002-6313-3084>

Alice Tamborini  <http://orcid.org/0000-0003-3589-203X>

Mark A. Oyama  <http://orcid.org/0000-0002-5218-9226>

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