

RVC OPEN ACCESS REPOSITORY – COPYRIGHT NOTICE

This is the peer-reviewed, manuscript version of the following article:

M.J. Mattin, A. Boswood, D.B. Church, P.D. McGreevy, D.G. O'Neill, P.C. Thomson, D.C. Brodbelt, Degenerative mitral valve disease: Survival of dogs attending primary-care practice in England, *Preventive Veterinary Medicine*, Available online 30 May 2015, ISSN 0167-5877, <http://dx.doi.org/10.1016/j.prevetmed.2015.05.007>.

The final version is available online via <http://dx.doi.org/10.1016/j.prevetmed.2015.05.007>.

© 2015. This manuscript version is made available under the CC-BY-NC-ND 4.0 license <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

The full details of the published version of the article are as follows:

TITLE: Degenerative mitral valve disease: Survival of dogs attending primary-care practice in England

AUTHORS: M.J. Mattin, A. Boswood, D.B. Church, P.D. McGreevy, D.G. O'Neill, P.C. Thomson, D.C. Brodbelt

JOURNAL TITLE: *Preventive Veterinary Medicine*

VOLUME/EDITION:

PUBLISHER: Elsevier

PUBLICATION DATE: 30 May 2015 (online)

DOI: 10.1016/j.prevetmed.2015.05.007

1 DEGENERATIVE MITRAL VALVE DISEASE: SURVIVAL OF DOGS ATTENDING
2 PRIMARY-CARE PRACTICE IN ENGLAND

3 M.J. MATTIN^{a*}, A. BOSWOOD^a, D.B. CHURCH^a, P. D. MCGREEVY^b, D.G. O'NEILL^a,
4 P. C. THOMSON^b AND D.C. BRODBELT^a

5
6 ^a Royal Veterinary College, Hawkshead lane, North Mymms, Herts AL9 7TA UK

7 ^b Faculty of Veterinary Medicine, Gunn Building, University of Sydney
8 NSW 2006, Australia

9

* Madeleine Mattin, Royal Veterinary College, Hawkshead Lane, North Mymms, Hatfield, Hertfordshire, AL9 7TA, UK. 0044 1707 667168 Email: mmattin@rvc.ac.uk

10 SUMMARY

11 This study aimed to evaluate survival of dogs with degenerative mitral valve disease
12 (DMVD). A retrospective cohort study of dogs with DMVD attending primary-care practices
13 in England was undertaken. Cases of DMVD were identified within the electronic patient
14 records (EPRs) of practices sharing data with VetCompass. Kaplan-Meier curves were used to
15 explore survival and Cox regression models identified factors associated with hazard of death.

16 The EPRs from 111,967 dogs, attending 93 veterinary practices between January 2010 and
17 December 2011 identified 405 cases diagnosed with DMVD giving a prevalence of diagnosed
18 DMVD of 0.36% (95% CI: 0.29 – 0.45%). A further 3,557 dogs were classified as possible
19 cases (heart murmurs consistent with DMVD). Overall, a total of 3,962 dogs were classified as
20 heart murmur cases (possible and diagnosed DMVD), giving a prevalence of 3.54% (95% CI:
21 3.26 – 3.84%).

22 One hundred and sixteen (28.6%) of the diagnosed DMVD cases were incident, newly
23 diagnosed with DMVD. The mean age at diagnosis was 9.52 years (95% CI: 8.98 – 10.14
24 years). Fifty-eight (50.0%) of the incident cases died during the study period. The median
25 survival time (MST) for all-cause mortality was 25.4 months (95% CI: 20.4 – 34.4 months)
26 after disease detection for DMVD cases. For possible cases, 121 (29.7%) from a random
27 sample of 407 possible DMVD cases were incident cases (newly detected heart murmur
28 consistent with DMVD during the study period). The mean age at which a heart murmur was
29 first recorded in possible cases was 9.73 years (95% CI: 9.02 – 10.44 years). Forty-nine
30 (40.5%) possible cases died during the study period. The MST for all-cause mortality was 33.8
31 months (95% CI: 23.7 – 43.1 months) after a heart murmur was initially detected. In the
32 multivariable survival analysis for possible and diagnosed cases, Cavalier King Charles
33 Spaniels (CKCSs) and other purebreds had higher hazards of death than crossbreds. Dogs

34 weighing ≥ 20.0 kg and older dogs had an increased hazard of death compared with those <
35 20.0 kg and younger dogs, respectively.

36 The study highlights poorer survival for all-cause mortality in CKCSs and larger dogs. The
37 reported survival characteristics could aid veterinary surgeons' advice on the prognosis for
38 dogs with DMVD and help the assessment of the impact of the condition at a population level.

39 KEY WORDS epidemiology, primary-care practice, cardiac, survival, canine

40 INTRODUCTION

41 Degenerative mitral valve disease (DMVD) has a high prevalence in the domestic dog
42 population, with estimates ranging between 3.5% - 69.7% (Detweiler & Patterson, 1965;
43 Whitney, 1974; Thrusfield et al., 1985). The disorder is generally straightforward to diagnose
44 from the presence of a characteristic heart murmur (Borgarelli & Haggstrom, 2010). However,
45 dogs with DMVD form a heterogeneous population and only a proportion of affected animals
46 will develop congestive heart failure or die as a result of their cardiac disease (Borgarelli et al.,
47 2012). Hence a major challenge for practitioners centres on prognostication and identifying
48 patients at greater risk of death.

49 Survival times have been reported for cohorts of dogs with DMVD recruited to clinical trials
50 (Ettinger et al., 1998; The Bench Study Group, 1999; Haggstrom et al., 2008) and those
51 included in observational studies monitored by specialist veterinary cardiologists (Borgarelli
52 et al., 2008; Moonarmart et al., 2010; Borgarelli et al., 2012; Hezzell et al., 2012). Data from
53 specialist-treated populations may be poorly generalizable to wider DMVD populations
54 because referral caseloads may include complex cases requiring more advanced care (Bartlett
55 et al., 2010) and non-consent bias may occur if patients enrolled into clinical trials are not
56 representative of more general populations (Marcus, 1997). Further, the time of entry into

57 existing survival studies was generally defined as the time of referral or randomization, rather
58 than the time the disease was initially detected, limiting the application of these results to the
59 primary-care setting. The current literature on primary-care practice populations of dogs with
60 DMVD lacks median survival time (MST) estimates from the time of disease detection to time
61 of death.

62 Risk stratification could improve prognosis and management of DMVD cases. For example,
63 more frequent monitoring or targeted therapy may be warranted in patients at high risk of
64 progressive disease (Hezzell et al., 2012). Previous survival studies have largely focussed on
65 the predictive value of echocardiographic and radiographic measurements (Haggstrom et al.,
66 2008; Moonarmart et al., 2010; Lord et al., 2011; Borgarelli et al., 2012; Hezzell et al., 2012;
67 Reynolds et al., 2012) and circulating concentrations of cardiac biomarkers (Fonfara et al.,
68 2010; Moonarmart et al., 2010; Hezzell et al., 2012; Eriksson et al., 2014) in dogs with DMVD.
69 However, in primary-care practice, these diagnostic tests are often omitted due to limited
70 availability of equipment, lack of clinical expertise or financial constraints. Some of these
71 studies also evaluated the prognostic value of demographic variables, such as sex, breed, age
72 and bodyweight (Haggstrom et al., 2008; Moonarmart et al., 2010; Hezzell et al., 2012;
73 Reynolds et al., 2012), which can be easily derived from primary-care data. However, the latter
74 studies yielded conflicting results and may have limited external validity as their study
75 populations were managed by specialist veterinary cardiologists, which may be subject to
76 selection bias.

77 Estimating MST and evaluating the predictive value of demographic factors in the primary-
78 care setting would be of value as these results would be relevant to the wider primary-care
79 population and could aid prognostication. The objectives of this study were to estimate the
80 MST of dogs with DMVD and to identify demographic risk factors associated with all-cause

81 mortality in affected animals attending primary-care veterinary practices in England. It was
82 hypothesised that crossbred dogs would have a lower hazard of death than purebred dogs.

83 MATERIALS AND METHODS

84 A retrospective cohort study followed cases of DMVD identified within the electronic
85 patient records (EPRs) of dogs attending veterinary practices sharing de-identified data with
86 the Veterinary Companion Animal Surveillance System database (VetCompass, 2014) between
87 1st January 2010 and 31st December 2011. The practices were primary-care companion animal
88 practices, both independent and corporate, that had been recruited via publication of letters
89 requesting participation of interested practices in the veterinary press and journals, regional
90 meeting and presentations, and in response to enquiries from practices themselves. They were
91 mainly located in central and southeast England. Data shared included demographic (date of
92 birth, sex, breed, bodyweight, insurance status, microchip number, partial postcode, veterinary
93 practice ID) and clinical data (free-text clinical notes, VeNom diagnostic terms (VeNom
94 Coding Group, 2014), and treatments prescribed). The study received ethics approval from the
95 Royal Veterinary College ethics and welfare committee.

96 Case finding was achieved by searching for EPRs containing key diagnostic terms relating
97 to DMVD (e.g. ‘mitral’, ‘valv*’, ‘MVD’, ‘murm*’) and reviewing the free text clinical notes
98 of potential cases. Two case definitions were developed to account for different levels of
99 diagnosis: diagnosed DMVD and possible DMVD cases. Diagnosed DMVD cases were
100 defined as dogs with a stated diagnosis of DMVD (or synonym) in their clinical notes or
101 VeNom diagnostic terms. Possible DMVD cases were defined as dogs over one year old with
102 a documented heart murmur consistent with DMVD without a specific cardiac diagnosis. Dogs
103 reported to have continuous or diastolic murmurs were excluded as cases. Dogs with murmurs
104 that had only been detected during pregnancy or that presented with other clinically significant

105 systemic disease (e.g. moderate to severe anaemia, pyrexia, severe hypovolaemia or
106 dehydration) were also excluded. Dogs reported to have murmurs or mitral valve regurgitation
107 due to other diagnosed cardiac disorders (e.g. aortic stenosis, ventricular septal defects etc.)
108 were additionally excluded. Where a murmur was recorded and no evidence of any of the above
109 criteria for exclusion was documented, the dog was classified as a possible DMVD case.
110 Evidence of a point of maximal intensity (thoracic location where the heart murmur is heard
111 most loudly) inconsistent with DMVD on chest auscultation was not used as an exclusion
112 criterion. Diagnosed and possible DMVD cases were combined to form a population of dogs
113 with heart murmurs consistent with DMVD for the prevalence estimates, hereafter described
114 as heart murmur cases. Incidence estimates were reported separately for possible and diagnosed
115 cases.

116 The EPRs of all diagnosed cases up to May 2014 were examined in detail. The date of the
117 first veterinary consultation, the date the disease was detected and the date, cause and modality
118 of death were extracted, where applicable. Incident cases were defined as dogs that were newly
119 diagnosed with DMVD or recorded with a heart murmur during the study period. Dogs alive
120 at the end of the study period were censored on the date of the last entry in their clinical notes.
121 Death as a result of cardiac disease (cardiac death) was defined as euthanasia or death due to
122 worsening of clinical signs associated with DMVD or when veterinary surgeons stated that
123 heart disease was the primary cause of death in the clinical notes. Cases were not classified as
124 cardiac deaths if alternative or multiple causes of death were listed, or if the cause of death was
125 not specified. Due to the large number of possible cases and the time required to review each
126 case's clinical records, a random sample of possible DMVD cases was selected from the
127 denominator of all possible cases using an electronic random number generator
128 (www.random.org) to enable comparison between the survival of diagnosed and possible cases.
129 The number of possible cases randomly selected was based on providing a similar number of

130 cases as evaluated for the diagnosed cases in order to provide a similar level of statistical power
131 to detect major risk factors. The date of murmur detection and the date, cause and modality of
132 death in incident possible cases were recorded.

133 Data were exported to a spreadsheet (Microsoft Office Excel 2010, Microsoft Corp,
134 Redmond, WA), checked, cleaned and exported to Stata Version 13 (Stata Corporation, TX)
135 for analysis. Prevalence and 95% confidence intervals (95% CI) were calculated for heart
136 murmur cases (including both diagnosed and possible cases) and for diagnosed DMVD cases
137 only. Prevalence was adjusted for clustering at the practice level using survey commands
138 (StataCorp., 2013). Further analyses relate to incident cases only.

139 The MST for all-cause mortality and cardiac death were calculated for diagnosed and
140 possible cases, when possible. Kaplan-Meier survival curves were generated for all-cause
141 mortality and cardiac-related death and log-rank tests were used to explore survival differences
142 between diagnosed and possible cases. Univariable and multivariable Cox proportional hazard
143 models were used to evaluate associations between the following explanatory variables and
144 hazard of death (all-cause mortality): breed, sex, insurance status, maximum recorded
145 bodyweight (kg), age at diagnosis (years) and level of diagnosis (diagnosed and possible cases).
146 Breeds were categorised into ‘crossbred’, ‘Cavalier King Charles Spaniel’ (CKCS) and ‘other
147 purebred’. CKCS were evaluated as a separate group as this represented the most common
148 breed within the data and has frequently been a comparator group in the current literature
149 (Haggstrom et al., 2008). Additional analyses evaluating a binary breed variable (‘purebreds’
150 and ‘crossbreds’) were performed. Maximum bodyweight was further dichotomised based on
151 published literature (< 20.0 kg and ≥ 20.0 kg) (Borgarelli et al., 2004; Borgarelli et al., 2012).
152 Age at diagnosis (years) was categorised into four groups (< 5.0 , $5.0 - < 10.0$, $10.0 - < 15.0$,
153 and ≥ 15.0 years) and evaluated for a linear trend association. Level of diagnosis and breed

154 were forced variables in the model to account for the sampling technique and *a priori* interest,
155 respectively. Variables significant at the 20% level in univariable analyses were taken forward
156 for consideration in the mixed effects multivariable model. Manual stepwise backward
157 elimination regression was used to sequentially remove variables with a P-value > 0.05 in the
158 multivariable model (Dohoo et al., 2009). Each eliminated variable was then added to the final
159 model to assess for important confounding by the change in parameter estimates. First order
160 interactions between final model explanatory variables were evaluated. Veterinary practice was
161 evaluated as a shared frailty term to account for clustering at the practice-level. The
162 proportional hazards assumption was tested using Schoenfeld residuals and visual inspection
163 of log-cumulative hazard and Kaplan-Meier Cox plots. Goodness of fit was evaluated using
164 Cox-Snell residuals. Dogs with any missing data for the risk factors of interest were excluded
165 from the multivariable Cox proportional hazards model.

166 It was estimated that a sample size of approximately 160 individuals would be required to
167 detect a hazard ratio (HR) for all-cause mortality of two for a variable to which 75% of
168 individuals were exposed, at a confidence level of 95% and power of 80%. This calculation
169 was based on the estimated proportion of purebred dogs in the VetCompass database (O'Neill
170 et al., 2014), an accrual time of 24 months, a follow-up time of 24 months and a MST of 20
171 months for exposed individuals (PS Power and Sample Size Calculations, 2014).

172 RESULTS

173 Descriptive statistics

174 The denominator population consisted of 111,967 individual dogs attending 93 veterinary
175 practices on one or more occasions between 1st January 2010 and 31st December 2011. Four
176 hundred and five dogs were identified as having a diagnosis of DMVD, giving a prevalence,

177 adjusted for the clustering effect of practice, of 0.36% (95% CI: 0.29 – 0.45%). A further 3,557
178 dogs were classified as possible cases, having a heart murmur consistent with DMVD recorded
179 within their EPRs. Generally, the age, bodyweight and breed distributions of possible and
180 diagnosed DMVD cases were similar; with DMVD typically affecting older small- to medium-
181 sized dogs (data not shown). A total of 3,962 dogs were heart murmur cases (with possible or
182 diagnosed DMVD), giving a prevalence, adjusted for the clustering effect of practice, of 3.54%
183 (95% CI: 3.26 – 3.84%).

184

185 Survival times of incident diagnosed and possible DMVD cases

186 Incident diagnosed DMVD cases: One hundred and sixteen (28.6%) of the 405 diagnosed
187 DMVD cases were incident cases, newly diagnosed with DMVD or recorded with a heart
188 murmur during the study period. The mean age at which DMVD was diagnosed or the presence
189 of a heart murmur was first recorded in diagnosed cases was 9.52 years (95% CI: 8.98 – 10.14
190 years). The median follow-up time was 17.9 months (IQR: 6.0 – 27.9 months, range: 0.0 – 45.2
191 months). Fifty-eight (50.0%) of the 116 incident diagnosed cases died during the study period.
192 Twenty of these 58 (34.5%) deaths were primarily due to cardiac disease, 9 (15.5%) deaths
193 occurred due to multiple causes including cardiac disease and 16 (27.6%) deaths occurred due
194 to non-cardiac causes. In 13 (22.4%) cases, cause of death was not recorded. Euthanasia
195 accounted for 43 (74.1%) of the 58 deaths. The MST for all-cause mortality was 25.4 months
196 (95% CI: 20.4 – 34.4 months) after the disease was initially detected (Table 1). MST for cardiac
197 death could not be calculated for these cases as the cumulative proportion of dogs surviving
198 failed to drop below 0.5.

199 Incident possible DMVD cases: One hundred and twenty one (29.7%) from a random
200 sample of 407 possible DMVD cases were incident cases, based on the presence of a heart

201 murmur consistent with newly detected DMVD during the study period. The mean age at which
202 the presence of a heart murmur was first recorded in possible cases was 9.73 years (95% CI:
203 9.02 – 10.44 years). The median follow-up time for possible cases was 14.4 months (IQR: 2.5
204 – 27.6 months, range 0.0 – 43.5 months). Forty-nine (40.5%) possible cases died during the
205 study period. Eight (16.3%) of the 49 deaths were primarily attributed to cardiac disease, two
206 (4.1%) deaths occurred due to multiple causes including cardiac disease and 29 (59.2%) deaths
207 occurred due to non-cardiac causes. In 10 (20.4%) of the 49 cases that died, cause of death was
208 not recorded. Euthanasia accounted for 45 (91.2%) of the 49 deaths. The MST for all-cause
209 mortality was 33.8 months (95% CI: 23.7 – 43.1 months) after a heart murmur was initially
210 detected. MST for cardiac related death was 42.0 months (95% CI: 31.2 – 52.7 months). There
211 was no evidence of a significant difference in the survival functions of diagnosed and possible
212 DMVD cases for all-cause mortality (log rank test, $P = 0.63$) (Fig. 1). However, there was a
213 statistically significant reduction in survival for cardiac mortality for diagnosed compared to
214 possible cases (log rank test, $P = 0.034$) (Fig. 2).

215 Cox proportional hazards models: In the univariable analysis, there was a non-statistically
216 significant trend for an association between breed and survival ($P = 0.083$). CKCS had a lower
217 hazard of death than crossbred dogs (HR 0.44, 95% CI 0.21 – 0.96), whereas there was no
218 difference observed between the survival of crossbreds and other purebreds. Dogs with a
219 maximum recorded bodyweight of 20.0 kg or greater had almost twice the hazard of death in
220 the univariable analysis (HR 1.87, 95% CI: 1.24 – 2.83). For each 5-year category increase in
221 age, the hazard of death increased by a factor of 2.80 (95% CI: 2.09 – 3.75). There was no
222 evidence of an association between survival and sex, insurance status or level of diagnosis
223 (diagnosed versus possible cases) (Table 2). When CKCS were combined with other purebreds,
224 no association between breed and survival was detected ($P = 0.245$). Twelve dogs had missing
225 bodyweight data and 10 dogs did not have insurance status recorded.

226

227

228 In the multivariable analysis, CKCS (HR 2.78, 95% CI: 1.05 – 7.36) and other purebred
229 dogs (HR 1.86, 95% CI: 1.07 – 3.23) had a higher hazard of death than crossbred dogs. Dogs
230 weighing ≥ 20.0 kg had almost three times the hazard of death than dogs < 20.0 kg (HR 2.81,
231 95% CI: 1.72 – 4.59). For each 5-year age category increase, hazard of death increased 3.85
232 fold (95% CI: 2.61 – 5.69). Veterinary practice was included as a shared frailty term (P =
233 0.027). No major confounding (as represented by substantial variation in hazard ratios on
234 addition of the second variable) or statistically significant interactions were identified. There
235 was no evidence that the proportional hazards assumption was violated and the model
236 diagnostics showed no evidence of lack of fit. When the breed variable with three groups
237 (CKCS, other purebreds and crossbreds) was substituted for the binary breed variable
238 (purebreds and crossbreds) in the multivariable model, the association between breed and
239 survival persisted; with purebreds having approximately double the hazard of death compared
240 with crossbred dogs (HR 1.84, 95% CI: 1.06 – 3.18).

241

242 DISCUSSION

243 This study identified a prevalence of diagnosed DMVD of 0.36% (95% CI: 0.29 – 0.45%)
244 and a substantially greater proportion of dogs with heart murmurs consistent with DMVD
245 (3.54%, 95% CI: 3.26 – 3.84%). The MST following detection of the disease was
246 approximately 2 – 3 years in both diagnosed and possible DMVD cases. Purebreds, older dogs
247 and those weighing ≥ 20.0 kg had a higher hazard of death compared with crossbreds, younger
248 and lighter dogs, respectively.

249 The MSTs for all-cause mortality were 25.4 (95% CI: 20.4 – 34.4) and 33.8 (23.7 – 43.1)
250 months for diagnosed and possible cases, respectively. Considering that the disease was
251 initially detected in older dogs (mean age 9.52 and 9.73 years in diagnosed and possible cases,
252 respectively) and the MST was relatively long, DMVD appeared to have minimal impact on
253 longevity in many dogs. Further, the median age of death in our DMVD cohort was 12.2 years
254 (IQR: 10.5 – 14.3 years), similar to median longevity reported for 5,095 dogs with confirmed
255 deaths within the VetCompass population (12.0 years, IQR 8.9 – 14.2 years) (O'Neill et al.,
256 2013). The median age of death of crossbreeds (14.3 years, IQR: 12.3 – 15.2), purebreds (11.7
257 years, IQR: 10.0 – 13.6) and CKCS (10.0 years, IQR 8.6 – 10.7) in the current DMVD cohort
258 were similar to those reported within the overall VetCompass population (13.1 years, IQR:
259 10.1 – 15.0; 11.9 years, IQR 8.4 – 14.0 and 9.9 years, IQR 8.1 – 12.3, respectively) (O'Neill et
260 al., 2013). However, 34.5% of deaths among dogs with diagnosed DMVD were primarily due
261 to their cardiac disease, emphasising that dogs with DMVD are a heterogeneous population
262 and that it is therefore important to identify those most at risk of progressive disease and death.
263 When only cardiac related deaths were considered, dogs with diagnosed DMVD had shorter
264 survival times than possible cases. Given the age at detection of murmurs and disease in
265 possible and diagnosed cases respectively were very similar and the shorter survival times of
266 diagnosed DMVD cases, it would appear that dogs with more advanced cardiac disease may
267 be more likely to receive a diagnosis and be classified as diagnosed DNVD and die sooner due
268 to their more severe state of disease.

269 The estimated MST in the current study was generally longer than those reported in the
270 literature. Two studies evaluating survival in dogs presenting to Italian referral centres reported
271 MST of approximately 20 months for all-cause mortality (Borgarelli et al., 2008, Borgarelli et
272 al., 2012). A cohort of dogs with DMVD enrolled to a research clinic in the UK had a MST of
273 11.1 months (range 0.1 – 32.7 months) (Moonarmart et al., 2010). Randomised controlled trials

274 evaluating different interventions in dogs with heart failure due to DMVD have reported MST
275 from the time of randomisation until cardiac death or treatment failure. In the BENCH study,
276 MST was 14.5 months in the intervention group and 5.0 months in the placebo group (The
277 Bench Study Group, 1999). MST for dogs recruited to the LIVE and QUEST studies were
278 approximately 5 - 6 months (Ettinger et al., 1998; Haggstrom et al., 2008). The discrepancies
279 between the MST reported in the current study and those published in the literature may be due
280 to differing inclusion criteria and primary end-points. The current study included dogs at all
281 stages of the disease and the primary-end point was death, whereas some previous studies
282 focused only on dogs with congestive heart failure and, for ethical reasons, included treatment
283 failure among their primary end-points. A delay between disease detection by the primary-care
284 practitioner and subsequent referral for inclusion into survival studies may also account for
285 MST differences. Moreover, referral populations may be prone to preferentially select dogs
286 with more advanced disease (Bartlett et al., 2010) than the entire canine DMVD population.
287 The MSTs reported by the current study may thus be of greater relevance to primary-care
288 practitioners, who manage most DMVD cases.

289 Cavalier King Charles Spaniels (HR 2.78, 95% CI: 1.05 – 7.36) and other purebred dogs
290 (HR 1.86, 95% CI: 1.07 – 3.23) had a higher hazard of death than crossbred dogs in the
291 multivariable analysis. Interestingly, in the univariable analysis, CKCS had a significantly
292 decreased hazard of death (HR 0.44, 95% CI: 0.21 – 0.96) and purebreds had a similar hazard
293 of death compared with crossbreds. The differences between the results of univariable and
294 multivariable analyses were largely due to the confounding effect of age at diagnosis; CKCS
295 and other purebreds were significantly younger when they developed DMVD compared with
296 crossbred dogs and, after adjusting for age at diagnosis, the trend to reduced hazard in the
297 purebred categories disappeared and these breeds were associated with increased hazard of
298 death.

299 In the current study, dogs weighing 20 kg or more had nearly three times the hazard of death
300 compared with dogs less than 20 kg (HR 2.81, 95% CI: 1.72 – 4.59). It has been suggested that
301 heavier dogs and larger breed types with primary mitral valve disease may have a different
302 clinical course compared with smaller dogs (Borgarelli et al., 2004). An alternative explanation
303 for the association between survival and bodyweight in the current study population is that
304 heavier dogs were more likely to be misclassified as DMVD cases. It is possible that some of
305 these dogs had heart murmurs due to other causes, such as dilated cardiomyopathy, which is
306 more common in large breeds and carries a poorer prognosis than DMVD (Martin et al., 2009).
307 Finally, population-based studies consistently report that larger dogs have reduced longevity
308 compared with smaller dogs (Michell, 1999; Galis et al., 2007; Greer et al., 2007; O'Neill et
309 al., 2013). As the multivariable analysis in the current study explored only all-cause mortality,
310 the association between bodyweight and hazard of death may reflect reduced longevity in
311 general in larger dogs rather than cardiac deaths specifically.

312 In agreement with a previous study (Hezzell et al., 2012), there was strong evidence for an
313 association between age and all-cause mortality in dogs with DMVD, with hazard of death
314 increasing 3.85 fold (95% CI: 2.61 – 5.69) for each 5 year increase in age at diagnosis. In
315 addition to being an independent predictor of outcome, age at diagnosis confounded the
316 associations between breed and hazard of death, highlighting the importance of multivariable
317 analyses when interpreting the effect of explanatory variables in epidemiological studies.

318 Including veterinary practice as a shared frailty term improved model fit, suggesting that
319 practice-level factors influenced the outcome. The type of treatment administered has been
320 reported to influence survival of dogs with DMVD (The Bench Study Group, 1999; Haggstrom
321 et al., 2008), so if therapeutic management of cases within a practice are more similar than
322 between practices, the survival experience of individuals attending the same practice may be

323 more similar than those of individuals from different practices. Further, most deaths resulted
324 from euthanasia, rather than unassisted death. A poor prognosis given by the attending
325 veterinary practitioner was identified as an important factor influencing the decision to
326 euthanase dogs with congestive heart failure (Mallery et al., 1999). The timing of death may
327 therefore be influenced by human factors and highlights the importance of optimising
328 evidence-based prognostic guidelines.

329 This study had several limitations. Data were not originally recorded for research purposes
330 but for clinical and billing reasons and were analysed retrospectively. Retrospective searching
331 of the clinical records for key DMVD diagnostic terms may have missed some cases (false
332 negatives) and incorrectly classified as positive others (false positives). In relation to specificity
333 of search terms, this limitation was addressed by reviewing clinical records relating to a dog to
334 minimise misclassification of non-DMVD dogs as cases. With regard to maximising
335 sensitivity, the search strategy used was relatively broad (including use of truncated versions
336 of key terms to allow for mis-spelling) and for DMVD a limited number of clinical terms are
337 generally used by veterinary surgeons in practice, though inevitably some cases may have been
338 missed. Further, if a practitioner did not perform thoracic auscultation or transcribe the DMVD
339 diagnosis or the presence of a heart murmur into the EPR, an affected dog would fail to be
340 included as a case. In a recent study of clinical examination behaviour in practice, Robinson
341 and colleagues (2014) reported that only 59% of dogs received a full clinical examination and
342 a further 33% had focused clinical examinations only, suggesting thoracic auscultation may
343 not always be routinely performed. As such, especially where there appear to be minimal
344 clinical signs of cardiac disease, thoracic auscultation may be less likely to be performed and
345 the prevalence of disease, possible cases in particular, may have been underestimated. Equally,
346 individuals with heart murmurs due to other causes could have been misclassified as possible
347 cases, as a definitive diagnosis of DMVD requires echocardiographic confirmation (Borgarelli

348 & Buchanan, 2012). Further, based on the case definition, if excludable criteria were detected
349 by the veterinary surgeon but not recorded in the clinical records, these dogs would have been
350 misclassified as cases. However, the presence of a left apical systolic heart murmur in a dog of
351 typical signalment is highly suggestive of DMVD (Borgarelli & Haggstrom, 2010). Further,
352 the breed, age and bodyweight distributions of possible and diagnosed cases were similar,
353 suggesting that most of the possible cases were as likely to have DMVD as those diagnosed by
354 the attending veterinarian. Nonetheless, the prevalences reported must remain estimates at best,
355 of the frequency of DMVD in dogs presenting to veterinary practices. Secondly, the current
356 study evaluated only factors associated with hazard of death for all-cause mortality. However,
357 within the all-cause mortality group, based on the pre-study power calculations, the number of
358 cases identified substantially exceeded the calculation requirements, suggesting the study had
359 ample power to detect biologically meaningful associations with hazard ratios of 2 or above.
360 A higher powered study evaluating both all-cause and cardiac related mortality,
361 notwithstanding the additional resources implications of reviewing an expanded body of
362 clinical records, could help further elucidate the identified associations. Finally, it is important
363 to acknowledge that the current study was of a convenience sample of corporate and
364 independently owned, exclusively companion animal veterinary practices. Nonetheless, data
365 were from just under 100 practices distributed across England (approximately 2% of RCVS
366 registered veterinary practices), so the main conclusions are likely to be relevant for the
367 practice-attending dog population in the UK.

368 In summary, this study has highlighted a high prevalence of heart murmurs consistent with
369 DMVD in primary-care practices in England, with DVMD diagnosed less frequently. Survival
370 following detection appeared good for both possible and diagnosed cases, although purebreds,
371 larger and older dogs tended to have a less favourable prognosis. Further studies evaluating

372 cardiac related mortality and the predictive value of other factors including clinical and
373 biochemical variables in primary-care practice are warranted.

374 ACKNOWLEDGEMENTS

375 The authors are grateful to the Medivet group and other veterinary practices and their clients
376 who participated in this project. We also thank Peter Dron, Noel Kennedy and James
377 Hoontrakul (Royal Veterinary College) for database development and management.

378 REFERENCES

379 Bartlett, P.C., Van Buren, J.W., Neterer, M. and Zhou, C., (2010). Disease surveillance and
380 referral bias in the veterinary medical database. *Prev. Vet. Med.* 94, 264-271

381 Borgarelli, M. and Buchanan, J.W., (2012). Historical review, epidemiology and natural
382 history of degenerative mitral valve disease. *J. Vet. Cardiol.* 14, 93-101

383 Borgarelli, M., Crosara, S., Lamb, K., Savarino, P., La Rosa, G., Tarducci, A. and Haggstrom,
384 J., (2012). Survival characteristics and prognostic variables of dogs with preclinical
385 chronic degenerative mitral valve disease attributable to myxomatous degeneration. *J. Vet.*
386 *Intern. Med.* 26, 69-75

387 Borgarelli, M. and Haggstrom, J., (2010). Canine degenerative myxomatous mitral valve
388 disease: natural history, clinical presentation and therapy. *Vet. Clin. North. Am. Small*
389 *Anim. Pract.* 40, 651-663

390 Borgarelli, M., Savarino, P., Crosara, S., Santilli, R.A., Chiavegato, D., Poggi, M., Bellino, C.,
391 La Rosa, G., Zanatta, R., Haggstrom, J. and Tarducci, A., (2008). Survival characteristics
392 and prognostic variables of dogs with mitral regurgitation attributable to myxomatous
393 valve disease. *J. Vet. Intern. Med.* 22, 120-128

394 Borgarelli, M., Zini, E., D'Agnolo, G., Tarducci, A., Santilli, R.A., Chiavegato, D., Tursi, M.,
395 Prunotto, M. and Haggstrom, J., (2004). Comparison of primary mitral valve disease in
396 German Shepherd dogs and in small breeds. *J. Vet. Cardiol.* 6, 27-34

397 Detweiler, D.K. and Patterson, D.F., (1965). The prevalence and types of cardiovascular
398 disease in dogs. *Ann. N. Y. Acad. Sci.* 127, 481-516

399 Dohoo, I.R., Martin, S.W. and Stryhn, H., (2009). *Veterinary epidemiologic research*. 2nd edn.
400 VER Inc. Charlottetown, P.E.I.

401 Eriksson, A.S., Haggstrom, J., Pedersen, H.D., Hansson, K., Jarvinen, A.K., Haukka, J. and
402 Kwart, C., (2014). Increased NT-proANP predicts risk of congestive heart failure in

- 403 Cavalier King Charles spaniels with mitral regurgitation caused by myxomatous valve
404 disease. *J. Vet. Cardiol.* 16, 141-54
- 405 Ettinger, S.J., Benitz, A.M., Ericsson, G.F., Cifelli, S., Jernigan, A.D., Longhofer, S.L.,
406 Trimboli, W. and Hanson, P.D., (1998). Effects of enalapril maleate on survival of dogs
407 with naturally acquired heart failure. The Long-Term Investigation of Veterinary Enalapril
408 (LIVE) Study Group. *J. Am. Vet. Med. Assoc.* 213, 1573-1577
- 409 Fonfara, S., Loureiro, J., Swift, S., James, R., Cripps, P. and Dukes-McEwan, J., (2010).
410 Cardiac troponin I as a marker for severity and prognosis of cardiac disease in dogs. *Vet.*
411 *J.* 184, 334-339
- 412 Galis, F., Van der Sluijs, I., Van Dooren, T.J., Metz, J.A. and Nussbaumer, M., (2007). Do
413 large dogs die young? *J. Exp. Zool. B Mol. Dev. Evol.* 308, 119-126
- 414 Greer, K.A., Canterberry, S.C. and Murphy, K.E., (2007). Statistical analysis regarding the
415 effects of height and weight on life span of the domestic dog. *Res. Vet. Sci.* 82, 208-214
- 416 Haggstrom, J., Boswood, A., O'Grady, M., Jons, O., Smith, S., Swift, S., Borgarelli, M.,
417 Gavaghan, B., Kresken, J.G., Patteson, M., Ablad, B., Bussadori, C.M., Glaus, T.,
418 Kovacevic, A., Rapp, M., Santilli, R.A., Tidholm, A., Eriksson, A., Belanger, M.C.,
419 Deinert, M., Little, C.J., Kvart, C., French, A., Ronn-Landbo, M., Wess, G., Eggertsdottir,
420 A.V., O'Sullivan, M.L., Schneider, M., Lombard, C.W., Dukes-McEwan, J., Willis, R.,
421 Louvet, A. and DiFruscia, R., (2008). Effect of pimobendan or benazepril hydrochloride
422 on survival times in dogs with congestive heart failure caused by naturally occurring
423 myxomatous mitral valve disease: the QUEST study. *J. Vet. Intern. Med.* 22, 1124-1135
- 424 Hezzell, M.J., Boswood, A., Chang, Y.M., Moonarmart, W., Souttar, K. and Elliott, J., (2012).
425 The combined prognostic potential of serum high-sensitivity cardiac troponin I and N-
426 terminal pro-B-type natriuretic peptide concentrations in dogs with degenerative mitral
427 valve disease. *J. Vet. Intern. Med.* 26, 302-311
- 428 Lord, P.F., Hansson, K., Carnabuci, C., Kvart, C. and Haggstrom, J., (2011). Radiographic
429 heart size and its rate of increase as tests for onset of congestive heart failure in Cavalier
430 King Charles Spaniels with mitral valve regurgitation. *J. Vet. Intern. Med.* 25, 1312-1319
- 431 Mallery, K.F., Freeman, L.M., Harpster, N.K. and Rush, J.E., (1999). Factors contributing to
432 the decision for euthanasia of dogs with congestive heart failure. *J. Am. Vet. Med. Assoc.*
433 214, 1201-1204
- 434 Marcus, S.M., (1997). Assessing non-consent bias with parallel randomized and
435 nonrandomized clinical trials. *J. Clin. Epidemiol.* 50, 823-828
- 436 Martin, M.W., Stafford Johnson, M.J. and Celona, B., (2009). Canine dilated cardiomyopathy:
437 a retrospective study of signalment, presentation and clinical findings in 369 cases. *J. Small*
438 *Anim. Pract.* 50, 23-29
- 439 Michell, A.R., (1999). Longevity of British breeds of dog and its relationships with sex, size,
440 cardiovascular variables and disease. *Vet. Rec.* 145, 625-629
- 441 Moonarmart, W., Boswood, A., Luis Fuentes, V., Brodbelt, D., Souttar, K. and Elliott, J.,
442 (2010). N-terminal pro B-type natriuretic peptide and left ventricular diameter

443 independently predict mortality in dogs with mitral valve disease. *J. Small Anim. Pract.*
444 51, 84-96

445 O'Neill, D.G., Church, D.B., McGreevy, P.D., Thomson, P.C. and Brodbelt, D.C., (2013).
446 Longevity and mortality of owned dogs in England. *Vet. J.* 198, 638-643

447 O'Neill, D.G., Church, D.B., McGreevy, P.D., Thomson, P.C. and Brodbelt, D.C., (2014).
448 Prevalence of disorders recorded in dogs attending primary-care veterinary practices in
449 England. *PLoS ONE* 9, 1-16

450 PS Power and Sample Size Calculations, (2014). PS Power and Sample Size Calculations.
451 Available at <http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize>. Accessed May
452 20, 2014

453 Reynolds, C.A., Brown, D.C., Rush, J.E., Fox, P.R., Nguyenba, T.P., Lehmkuhl, L.B., Gordon,
454 S.G., Kellihan, H.B., Stepien, R.L., Lefbom, B.K., Meier, C.K. and Oyama, M.A., (2012).
455 Prediction of first onset of congestive heart failure in dogs with degenerative mitral valve
456 disease: the PREDICT cohort study. *J. Vet. Cardiol.* 14, 193-202

457 Robinson, N.J., Brennan, M.L., Cobb, M. and Dean, R.S. (2014) Clinical examination and
458 weighing of patients in small animal consultations. *Vet. Rec.*, doi: 10.1136/vr.102829

459 StataCorp., (2013). *Stata: Release 14. Statistical Software.* College Station, TX: StataCorp LP

460 The Bench Study Group, (1999). The effect of benazepril on survival times and clinical signs
461 of dogs with congestive heart failure: Results of a multicenter, prospective, randomized,
462 double-blinded, placebo-controlled, long-term clinical trial. *J. Vet. Cardiol.* 1, 7-18

463 Thrusfield, M.V., Aitken, C.G.G. and Darker, P.G.G., (1985). Observations on breed and sex
464 in relation to canine heart valve incompetence. *J. Small Anim. Pract.* 26, 709-717

465 VeNom coding group, (2014). VeNom Veterinary Nomenclature. Available at
466 <http://venomcoding.org> 2013. Accessed May 20, 2014

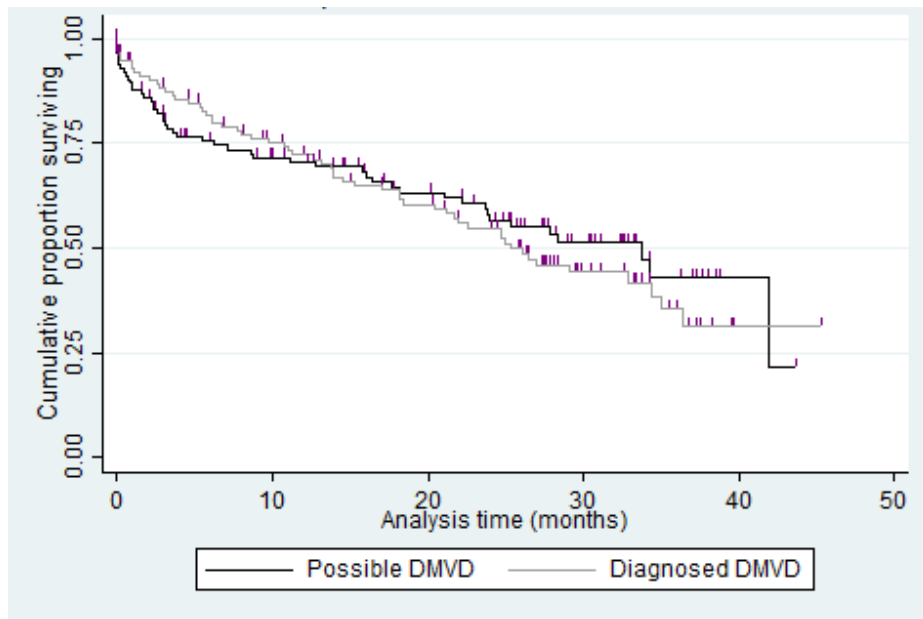
467 VetCompass, (2014). VetCompass: Health surveillance for UK companion animals. Available
468 at: <http://www.rvc.ac.uk/VetCompass>. RVC ElectronicMedia Unit; 2013. Accessed May
469 20, 2014

470 Whitney, J.C., (1974). Observations on the effect of age on the severity of heart valve lesions
471 in the dog. *J. Small Anim. Pract.* 15, 511-522

472

473 Figures

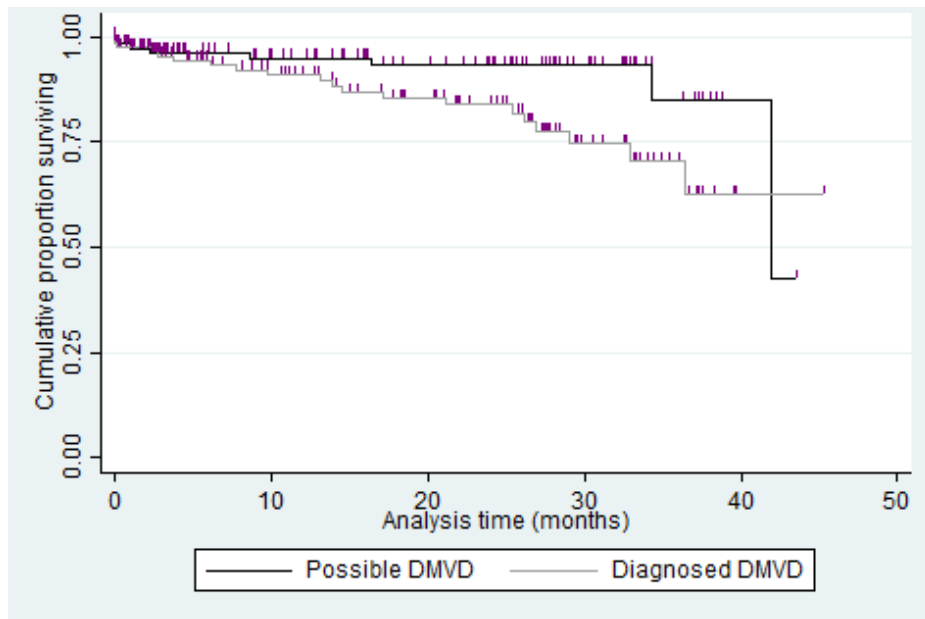
474



475

476 Fig. 1 Kaplan-Meier survival curve of all-cause mortality in incident cases of diagnosed and
477 possible degenerative mitral valve disease in dogs attending primary-care practices in
478 England. Survival time represents the time from when the disease was initially detected until
479 the time of death due to all-cause mortality.

480



481

482 Fig. 2 Kaplan-Meier survival curve of cardiac death in incident cases of diagnosed and
 483 possible degenerative mitral valve disease in dogs attending primary-care practices in
 484 England. Survival time represents the time from when the disease was initially detected until
 485 the time of death due to cardiac disease. Deaths due to other causes were censored.

486

487 Tables
 488
 489 Table 1. Mean age at diagnosis and survival characteristics of incident cases of diagnosed and
 490 a random sample of possible degenerative mitral valve disease in dogs attending primary-care
 491 practices in the UK

	Diagnosed DMVD	Possible DMVD ^a
Incident cases, number (%)	116 (28.6)	121 (29.7)
Mean age in years at DMVD diagnosis / murmur detection (standard deviation)	9.52 (3.20)	9.73 (4.01)
All-cause mortality		
Deaths, number (%)	58 (50.0)	49 (40.5)
Median survival time in months (95% CI)	25.4 (20.4 – 34.4)	33.8 (23.7 – 43.1)
Cumulative proportion surviving at 1 year (95% CI)	0.72 (0.64 – 0.80)	0.71 (0.62 – 0.79)
Cumulative proportion surviving at 2 years (95% CI)	0.55 (0.45 – 0.65)	0.57 (0.47 – 0.67)
Cardiac related death		
Cardiac deaths, number (%)	20 (17.2)	8 (6.6)
Median survival time in months (95% CI)	n/a	42.0 (31.2 – 52.7)
Cumulative proportion surviving at 1 year (95% CI)	0.91 (0.85 – 0.97)	0.95 (0.91 – 0.99)
Cumulative proportion surviving at 2 years (95% CI)	0.84 (0.76 – 0.91)	0.93 (0.88 – 0.99)

492 ^a Possible DMVD cases were defined as dogs over one year old with a documented heart
 493 murmur consistent with a diagnosis of DMVD without a specific cardiac diagnosis

494
 495
 496

497 Table 2. Descriptive statistics and univariable Cox regression analysis for risk factor
 498 association with death (all-cause mortality) among 237 incident cases with diagnosed or
 499 possible degenerative mitral valve disease attending primary-care veterinary practices. (Some
 500 variables had missing data, e.g. insurance status and bodyweight).

Variable	Number (%)	Hazard ratio	95% confidence interval	P-value
Breed				0.083
Crossbred	43 (18.1)	Baseline	~	
Cavalier King Charles Spaniel	31 (13.1)	0.44	0.21 – 0.96	
Purebred other	163 (68.8)	0.82	0.52 – 1.32	
Sex				0.403
Female	111 (46.8)	Baseline	~	
Male	126 (53.2)	0.85	0.58 – 1.24	
Insurance status				0.940
Not insured	88 (38.8)	Baseline	~	
Insured	139 (61.2)	0.98	0.65 – 1.49	
Maximum bodyweight				0.004
<20.0 kg	163 (72.4)	Baseline	~	
≥20.0 kg	62 (27.6)	1.87	1.24 – 2.83	
Age group (years)				<0.0001
<5.0 years	27 (11.4)	Baseline	~	
5.0 - <10.0 years	97 (40.9)	2.80 ^a	2.09 – 3.75	
10.0 - <15.0 years	99 (41.8)			
≥ 15.0 years	14 (5.9)			
Level of diagnosis				0.631
Possible DMVD	121 (51.1)	Baseline	~	
Diagnosed DMVD	116 (48.9)	1.10	0.75 – 1.61	

501 ^aHazard ratio relates to each 5 year increment in age

502

503 Table 3. Multivariable Cox regression analysis for risk factor association with death (all-
504 cause mortality) among incident cases with diagnosed or possible degenerative mitral valve
505 disease attending primary-care veterinary practices. Observations from 225 of the 237
506 incident cases (12 had a missing value for one of the final model variables).

Variable	Hazard ratio	95% confidence interval	P-value
Breed			0.053
Crossbred	Baseline	~	
Cavalier King Charles Spaniel	2.78	1.05 – 7.36	
Purebred other	1.86	1.07 – 3.23	
Maximum bodyweight			0.0001
<20.0 kg	Baseline	~	
≥20.0 kg	2.81	1.72 – 4.59	
Age group (years)			<0.0001
<5.0 years	Baseline	~	
5.0 - <10.0 years	3.85 ^a	2.61 – 5.69	
10.0 - <15.0 years			
≥ 15.0 years			
Level of diagnosis			0.609
Possible DMVD	Baseline	~	
Diagnosed DMVD	1.12	0.72 – 1.73	
Veterinary clinic (included as a shared frailty term)			0.027
Theta	0.23		

507 ^a Hazard ratio relates to each 5 year increment in age

508

509

510