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Pacemaker-lead-associated thrombosis in dogs; a multicenter retrospective study

Pacemaker-lead-associated thrombosis

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72 **Introduction/objectives**

73 Pacemaker implantation is recommended for the treatment of bradyarrhythmias
74 causing clinical signs in dogs unresponsive to medical treatment. The most common
75 canine arrhythmias requiring pacemaker implantation include high-grade second- and
76 third-degree atrioventricular block and sick sinus syndrome [1-5]. Most permanent
77 pacing leads are placed transvenously into the right ventricular apex because of the
78 relative ease of placement and high success rates [2-4, 6]. Negative prognostic
79 indicators include age, presence of concurrent cardiac disease, presence of congestive
80 heart failure (CHF), presence of complications, presence of severe azotemia, using a
81 secondhand pacemaker unit and increased troponin I levels [1, 2, 4, 5, 7]. Potential
82 contraindications for transvenous pacing include small patient size or comorbidities,
83 including pyoderma over the jugular vein insertion site, and epicardial pacing may serve
84 as a suitable alternative [8]. Specific considerations for the method of cardiac pacing
85 and treatment with anti-thrombotic therapy is often made by the clinician for patients in
86 which a comorbidity causing a hypercoagulable state is suspected or diagnosed [9].
87 Diseases strongly associated with a hypercoagulable state in dogs include immune-
88 mediated hemolytic anemia, protein-losing nephropathy (PLN) and protein-losing
89 enteropathy, with weaker associations with a variety of conditions including severe
90 pancreatitis, glucocorticoid administration and hyperadrenocorticism [9, 10].

91 Humans with intravascular foreign bodies including transvenous pacing leads are
92 at increased risk of thromboembolic disease [11], and it is also recognized that dogs
93 with transvenous pacing leads are at increased risk of thrombosis [9]. Pacemaker-lead-
94 associated thrombosis (PLAT) is a well described phenomenon in people, with PLAT

95 documented in up to 45% of people following permanent transvenous pacemaker
96 implantation and occurring either on the lead within the heart or on the lead within the
97 venous system [12-18]. Although the majority of people with PLAT are asymptomatic,
98 serious thrombotic and embolic complications are reported in 0.6%-3.5% [19], including
99 risk of sudden death [20].

100 Existing literature on the occurrence and clinical importance of PLAT in dogs is
101 scant and is limited to individual case reports or small case series [21-23] or recorded
102 as a complication in the outcomes of larger studies on transvenous pacing [1, 6, 7, 24].
103 Previous experimental studies have identified thrombi associated with pacing leads in
104 33.7% of dogs at necropsy [25], however there are no studies specifically investigating
105 PLAT in clinical dogs. Treatment modalities following diagnosis of PLAT in humans
106 include medical management with anti-thrombotic medications or thrombolysis, or
107 interventional procedures including thrombectomy or lead extraction [19]. Treatments
108 reported in case reports in dogs following PLAT diagnosis include medical management
109 with unfractionated heparin, rivaroxaban, local infusion of recombinant tissue-
110 plasminogen activator, and balloon venoplasty [21-23]. There is no treatment
111 consensus in humans or dogs with PLAT. The prognosis for dogs following identification
112 of a thrombus is unknown.

113 The aim of this study was to identify the proportion of dogs developing PLAT
114 following permanent transvenous pacemaker implantation, describe the treatment
115 received and clinical outcome in these dogs, and to identify potential risk factors for the
116 development of thrombi.

117

118 **Animals, materials and methods**

119 Data collection

120 A retrospective medical search was performed in seven referral centers^{a-g} for all
121 dogs with a permanent pacemaker implanted between January 2012 and January 2019.
122 Ethical approval was granted at the primary investigator's center (VIN/19/013). A
123 proportion of dogs from one center have been previously described [5]. Dogs were
124 divided into three groups: group one: dogs with a transvenous pacemaker with at least
125 one follow-up echocardiogram performed, group two: dogs with a transvenous
126 pacemaker without follow-up echocardiography performed, and group three: dogs with
127 an epicardial pacemaker. Dogs in group one were subdivided into dogs positive or
128 negative for PLAT. Dogs were deemed positive for PLAT if a mobile or immobile mass-
129 like vegetative lesion was identified within the venous lumen or within the right heart
130 associated with a pacemaker lead on follow-up imaging (Fig. 1), with a lack of clinical
131 signs supportive of endocarditis at the time of identification.

132 For all groups, data collected included signalment, rhythm diagnosis,
133 comorbidities and echocardiographic findings at the time of pacemaker implantation.
134 The rhythm diagnosis was based on the medical records and dogs were grouped into
135 one of: 'atrioventricular block', 'atrial standstill', 'sinus arrest', 'sinus node
136 dysfunction/sick sinus syndrome' and 'vagally mediated'. Comorbidities were classified
137 based on organ system involved rather than individual disease process.
138 Echocardiography was performed by a board-certified specialist or resident in
139 cardiology under the supervision of a board-certified Diplomate. Echocardiographic data
140 included 2D short axis left atrial to aortic ratio [26], M-mode end-diastolic left ventricular

141 internal diameter normalized for body weight [27], M-mode left ventricular fractional
142 shortening, a subjective assessment of right atrial size (compared to left atrial size,
143 being reported as either '<50%', '50-100%' or '>100%' of left atrial size), a subjective
144 assessment of right ventricular size (compared to left ventricular size, being reported as
145 either '<50%', '50-100%' or '>100%' of left ventricular size) and information on any other
146 echocardiographic abnormalities. Where available, results of serum albumin, urine
147 protein:creatinine ratio (UPCR) and thromboelastography (TEG) analysis performed
148 within 30 days of pacemaker implantation were collected. Hypoalbuminemia was
149 defined as a serum albumin below the reference interval as defined by each center, or,
150 in the absence of access to blood results, as a medical record reporting
151 hypoalbuminemia. Proteinuria was defined as a UPCR >0.5, or, in the absence of
152 access to urine results, as a medical record reporting proteinuria. A hypercoagulable
153 TEG was based on the interpretation of the clinician in charge of the case. For dogs
154 with transvenous leads, additional data on active versus passive lead and single versus
155 dual chamber pacing was collected, as was data on anti-thrombotic medications
156 prescribed during hospitalization and at discharge. For dogs with epicardial leads, the
157 reason for choosing an epicardial pacemaker was collected. For all dogs, pacemaker
158 related complications, including suspected thromboembolic events, survival time from
159 pacemaker implantation and reason for death were recorded.

160 For dogs diagnosed with PLAT, comorbidities and, where available, serum
161 albumin and UPCR at the time of PLAT diagnosis were collected. Details on the
162 treatment of each dog following PLAT diagnosis, clinical signs related to the thrombus

163 and findings on follow-up echocardiography (presence or absence of PLAT), if
164 performed, were recorded. Survival time from PLAT diagnosis was calculated.

165

166 Statistical analysis

167 Statistical analysis was performed using commercially available software^h.
168 Normality of the data was assessed using a combination of visual examination of
169 histograms, Q-Q plots and Kolmogorov-Smirnov tests. Non-normally distributed data
170 are reported as median (inter-quartile range). Comparisons of variables between two
171 groups were performed using Mann-Whitney U tests for continuous non-normally
172 distributed data. Comparisons of variables between more than two groups were
173 performed using Kruskal-Wallis tests with Dunn's post hoc analysis for non-normally
174 distributed data. Categorical variables were compared using the chi-squared test or
175 Fischer's exact test as appropriate. Post hoc analysis of the chi-squared test was
176 performed by assessing the adjusted residuals. Statistical significance was set at
177 $P < 0.05$ for all analyses, with a Bonferroni correction applied to reported P values for
178 multiple comparisons. Kaplan-Meier survival curves were generated looking at all-cause
179 mortality. Continuous variables were split into quartiles for the purposes of analysis. The
180 Log-Rank test was used to assess for the impact of baseline characteristics at the time
181 of pacemaker implantation, as well as the presence of PLAT, on survival. Survival times
182 are reported as median (range). To evaluate the effects of multiple variables on survival,
183 multivariable analysis was performed using variables significant at $P < 0.10$ using a
184 backward selection stepwise Cox regression model. Colinearity was checked using
185 Pearson correlation.

186

187 **Results**

188 *Whole population*

189 Permanent pacemakers were placed in 606 dogs from seven referral centers in
190 the UK and USA (Fig. 2, Table 1). Median age for the population was 9.7 years (7.1-
191 11.7 years) and females were the predominant sex (n=345, 56.9%). The population
192 consisted of 86 different breeds, with the most common breed being mixed breed dogs
193 (n=62, 10.2%). The most common rhythm was atrioventricular block (n=430, 71.0%),
194 and a minority of dogs (n=58, 9.6%) were in CHF at the point of pacemaker
195 implantation. Comorbidities (Fig. 3) were present in a majority of dogs (n=458, 75.6%),
196 the most common comorbidities being cardiac (n=354, 58.4%) and urinary (n=91,
197 15.0%). The most common cardiac comorbidity was myxomatous mitral valve disease
198 (n=284, 46.9%). Of the 143 dogs in which a UPCR was measured, 65 had increased
199 levels. An additional 12 dogs had proteinuria reported in their clinical notes without
200 evidence of a UPCR being measured. Three dogs (0.5%) had evidence of thrombotic
201 disease at the point of pacemaker implantation, one with a pulmonary thromboembolism
202 (PTE) and two with a splenic thrombus. The dog with a PTE had a transvenous lead
203 placed and did not develop PLAT. This dog received long-term treatment with
204 clopidogrel and enalapril for a PLN and had no further thrombotic events reported. Both
205 dogs with a splenic thrombus had epicardial leads placed. One dog had a splenectomy
206 and was treated with long-term clopidogrel, and the other dog was treated with a
207 continuous rate infusion of heparin whilst hospitalized, discharged on a 14-day tapering

208 course of subcutaneous heparin, and received long-term treatment with clopidogrel. No
209 further thrombotic events were reported in these patients.

210 Of the 606 dogs, 260 dogs (43%) had a transvenous pacemaker placed with
211 echocardiographic follow-up performed (group one), 268 dogs (44%) had a transvenous
212 pacemaker placed without echocardiographic follow-up (group two) and 78 dogs (13%)
213 had an epicardial pacemaker placed (group three). There were significant differences in
214 the distribution of groups between the centers (Fig. 4), with center five not placing any
215 epicardial pacemakers and center six placing more epicardial pacemakers than
216 average. There were some differences in baseline characteristics between the groups
217 (Table 1). Dogs with transvenous pacemakers without echocardiographic follow-up
218 were older than either of the other two groups, and dogs with epicardial pacemakers
219 weighed less than those with transvenous pacemakers that underwent
220 echocardiographic follow-up. Dogs with atrial standstill were more likely to receive
221 echocardiographic follow-up. There were statistically, but not clinically, significant
222 differences in left atrial to aortic ratio, end-diastolic left ventricular internal diameter,
223 serum albumin and length of hospitalization between groups. Dogs with epicardial leads
224 were more likely to be proteinuric compared to either of the other groups.

225 The most commonly reported indications for choosing epicardial pacing were due
226 to a protein-losing enteropathy or PLN (n=23, 29.5%) and patient size or demeanor
227 (n=16, 20.5%) (Table 2).

228 Of the 528 dogs with transvenous pacemakers, the majority received single
229 chamber pacemakers (n=477, 90.3%). More than half of leads implanted in the ventricle
230 used active fixation (n=321, 60.8%) whereas it was slightly more common for the leads

231 implanted in the atrium to use passive fixation (n=29, 58.0%) (Table 3). Of the dogs with
232 transvenous pacemakers, twenty-five (4.7%) were discharged on anti-thrombotic
233 medications. Twenty-two of the twenty-five (88.0%) dogs received one anti-thrombotic
234 medication (clopidogrel n=18 (72.0%), aspirin n=3 (12.0%), low-molecular-weight
235 heparin n=1 (4.0%)) and three (12.0%) dogs received two anti-thrombotic medications
236 (clopidogrel and aspirin n=2 (8.0%), clopidogrel and low-molecular-weight heparin n=1
237 (4.0%)). Dogs discharged on anti-thrombotic medications included both dogs identified
238 as being hypercoagulable on TEG, one of which had a PTE on pre-pacemaker
239 assessment.

240

241 *Pacemaker-lead-associated thrombosis population*

242 Pacemaker-lead-associated thrombosis was identified in 27/260 (10.4%) dogs
243 with echocardiographic follow-up. Median time from pacemaker implantation to PLAT
244 diagnosis was 175 days (6-1,853 days). Echocardiography identified the thrombus on
245 the lead in 26/27 (96.3%) dogs, whereas computed tomography was required to identify
246 the thrombus in one dog. Location of the thrombus was reported as the right atrium in
247 17/27 (63.0%), right ventricle in 6/27 (22.2%), cranial vena cava in 3/27 (11.1%), and
248 cranial vena cava and left brachiocephalic vein in 1/27 (3.7%). In two of the dogs with a
249 right atrial thrombus, the thrombus was also documented to extend into the cranial vena
250 cava. In two of the dogs with a right ventricular thrombus, a thrombus was also
251 documented in the right branch of the pulmonary artery. The PLAT was considered an
252 incidental finding in 15/27 (55.6%) dogs. Of the 12 dogs with PLAT and clinical signs,
253 six (50.0%) had a suspected PTE causing tachypnoea, two of which also had evidence

254 of right sided CHF (ascites 1/12 (8.3%), pleural effusion 1/12 (8.3%)), four (33.0%) had
255 right sided CHF (pleural effusion 2/12 (16.7%), ascites 1/12 (8.3%), pleural effusion and
256 trace ascites 1/12 (8.3%)), and two (16.7%) had biventricular CHF (pulmonary edema
257 and ascites). Two of the dogs with right sided CHF had chylothorax suspected to be
258 caused by the obstruction of the cranial vena cava by the PLAT. No dogs had any signs
259 of peripheral edema or head swelling.

260 At pacemaker implantation, dogs that went on to be diagnosed with PLAT had a
261 higher UPCr, were more likely to be diagnosed as proteinuric and had a higher left
262 ventricular fractional shortening than those with echocardiographic follow-up that were
263 not diagnosed with PLAT. There were no other significant differences between those
264 with echocardiographic follow-up that did and did not get diagnosed with PLAT (Table
265 4). None of the dogs with PLAT had a TEG performed at pacemaker implantation.

266 Comorbidities were reported in 23/27 (85.2%) dogs at the time of PLAT
267 diagnosis. The most common comorbidities included urinary disease (PLN (n=8,
268 29.7%), chronic kidney disease and PLN (n=1, 3.7%), renal cyst (n=1, 3.7%) and
269 unspecified renal disease (n=1, 3.7%)), myxomatous mitral valve disease (n=8, 29.7%)
270 and endocrine disease (hyperadrenocorticism (n=2, (7.4%), suspected
271 hyperadrenocorticism (n=1, 3.7%) and thyroid tumor (n=1, 3.7%)). Serum albumin was
272 measured in 15/27 (55.6%) dogs, with a median (inter-quartile range) of 28.5 g/L (25.0-
273 31.0 g/L). Hypoalbuminemia was reported in 6/15 (40.0%) dogs. Urine protein:creatinine
274 ratio was performed in 12/27 (44.4%) dogs, with a median (inter-quartile range) of 2.21
275 (0.60-5.53). Proteinuria was present in 10/12 (83.3%) dogs.

276 Six dogs were receiving anti-thrombotic medications at the time of PLAT
277 diagnosis (Fig. 5), all receiving anti-platelet medications (clopidogrel and/or aspirin).
278 Indications for anti-thrombotic medications were reported in four (66.7%) of these dogs
279 and included PLN (clopidogrel n=1 (25.0%), aspirin n=1 (25.0%)), protein losing
280 enteropathy (clopidogrel n=1 (25.0%)) and suspected hyperadrenocorticism (aspirin n=1
281 (25.0%)). Five of the six (83.3%) dogs already receiving anti-thrombotics at the time of
282 PLAT had an additional anti-thrombotic added at the point of PLAT diagnosis (addition
283 of an anti-platelet n=2 (40.0%), addition of an anti-coagulant n=3 (60.0%)). Sixteen out
284 of 21 (76.2%) dogs naïve to anti-thrombotic medications at the time of PLAT diagnosis
285 started anti-thrombotics (anti-platelet n=12 (75.0%), anti-platelet and anti-coagulant n=4
286 (25.0%)) following identification of PLAT. No patients received thrombolytic medications,
287 or had any interventional procedures with thrombectomy or lead extraction.

288 Median survival time from PLAT diagnosis was 81 days (0-1,103 days). Two
289 dogs died on the day of PLAT diagnosis. One of which had a sudden cardiopulmonary
290 arrest and the other was euthanized due to suspected PTE. Follow-up
291 echocardiography was performed in 15/25 (60.0%) dogs that survived to discharge
292 following PLAT diagnosis and the thrombus resolved in 9/15 (60.0%) dogs. Seven of the
293 nine (77.8%) dogs in which the thrombus resolved were receiving anti-thrombotic
294 medication (clopidogrel n=5 (55.5%), clopidogrel and aspirin n=1 (11.1%), clopidogrel,
295 aspirin and low molecular weight heparin n=1 (11.1%)), while two out of nine (22.2%)
296 dogs had thrombus resolution without anti-thrombotic therapy. Thrombus resolution was
297 not documented on follow-up echocardiography in 6/15 (40.0%) dogs, all of which were
298 receiving anti-thrombotics (clopidogrel, aspirin and low molecular weight heparin n=2

299 (33.3%), clopidogrel and low molecular weight heparin n=2 (33.3%), aspirin n=1
300 (16.7%), clopidogrel n=1 (16.7%). There was no association between number of anti-
301 thrombotic medications prescribed and resolution of the thrombus (P=0.322). At final
302 follow-up, 22/27 (81.7%) dogs with PLAT had died and 119/232 (51.3%) non-PLAT
303 dogs had died. Dogs with PLAT had shorter survival times from implantation compared
304 to those without PLAT (Fig. 6).

305

306 *Whole population complications and outcome*

307 In 102/606 (16.8%) dogs there was at least one complication reported that was
308 considered to be directly related to the pacemaker. The complications reported were
309 lead dislodgement (n=27, 4.5%), lead thrombus (n=27, 4.5%), wound related
310 complications (n=22, 3.6%), surgical or general anesthetic related complication (n=8,
311 1.3%), development of systolic dysfunction (n=7, 1.2%), myocardial perforation (n=6,
312 1.0%), lead infection (n=4, 0.7%), exit block (n=3, 0.5%), lead fracture (n=1, 0.2%),
313 generator movement (n=1, 0.2%) and noise reversion (n=1, 0.2%).

314 In the whole population, 18/606 (3.0%) had a clinically suspected
315 thromboembolic event after pacemaker implantation. Six (33.3%) of these were
316 suspected arterial thromboembolic events (four (22.2%) with neurological signs where a
317 thromboembolic event was considered most likely, two (11.1%) to the hindlimbs) and 12
318 (66.7%) were PTEs. Of the 12 dogs with PTEs, 10 (83.3%) had transvenous leads and
319 two (16.7%) had epicardial leads. Seven of the 10 (70.0%) dogs with a transvenous

320 lead and a PTE had PLAT identified, and three (30.0%) did not, one of which had a
321 jugular vein thrombosis suspected but not confirmed.

322 Follow-up was available for 600/606 (99.0%) dogs. At final follow-up 347/600
323 (57.8%) were dead, with death being considered related to the heart or pacemaker in
324 84/347 (24.2%). Of these 84, 14 (16.7%) were sudden deaths and seven (8.3%) were
325 suspected PTEs in dogs with transvenous leads (six of whom had PLAT identified).
326 Other causes for death were neoplasia (n=56, 16.1%), neurological disease (n=23,
327 6.6%), renal disease (n=21, 6.1%), suspected PTEs in dogs with epicardial leads (n=2,
328 0.6%), hindlimb arterial thromboembolism (n=1, 0.3%), other (n=69, 19.9%) and
329 unknown (n=91, 26.2%). Overall survival time for the population was 907 days (0-2,661
330 days). Factors associated with a longer survival time on univariable analysis included
331 younger age and not being neutered. Factors associated with a shorter survival time on
332 univariable analysis included being underweight (body condition score $\leq 3/9$), presence
333 of comorbidities, being in CHF, being in the top or bottom left atrial to aortic ratio
334 quartile, right atrial enlargement, right ventricular enlargement, hypoalbuminemia,
335 experiencing pacemaker complications and having PLAT (Table 5, Fig. 6). It was not
336 possible to generate a multivariable Cox proportional hazards model as all models
337 generated violated the assumptions of the model.

338

339 **Discussion**

340 Our study documented PLAT in 27/260 (10.4%) of dogs with echocardiographic
341 follow-up. We have also identified an association between proteinuria at pacemaker

342 implantation and later development of PLAT. Finally, we have shown that those dogs
343 with PLAT have a shorter survival time from pacemaker implantation than those that
344 have not been documented to develop PLAT.

345 The incidence of PLAT in dogs following placement of a permanent transvenous
346 pacemaker was previously unknown, with dogs diagnosed ante-mortem with PLAT
347 described in case reports or case series [21, 22], or as complications of larger studies of
348 dogs with pacemakers, with incidence varying from 0.6-6.1% [1, 6, 7, 24]. In a post-
349 mortem study 33.7% of dogs had PLAT identified, with the thrombus most often
350 identified 10-60 days post implantation [25]. The median time to identification of PLAT in
351 our study was 175 days, however it ranged from 6-1,853 days, documenting PLAT as a
352 potential complication in both the short-term and long-term period following pacemaker
353 implantation.

354 From a post-mortem study, the most common location for PLAT in dogs was the
355 right atrium [25]. Ante-mortem reports in dogs predominantly report intra-cardiac PLAT
356 [7, 24] and, where specified, this is usually within the right atrium [6], sometimes
357 obstructing right heart inflow [21]. However, there are individual reports of thrombosis of
358 the lead as it passes through the cranial vena cava [1] and thrombosis of the lead in the
359 jugular vein and cranial vena cava as well as thrombosis of the right cephalic vein [22]
360 reported. This is in concordance with our report where 23/27 (85.2%) dogs had intra-
361 cardiac PLAT and the right atrium was the most common location. Only 4/27 (14.8%)
362 dogs had solely cranial vena cava PLAT, and two additional dogs had extension of the
363 right atrial PLAT into the cranial vena cava. One dog in our study with a PTE was
364 suspected to have jugular thrombosis but this was not confirmed and so not considered

365 to have PLAT. In the human literature PLAT has been more comprehensively reported.
366 Right atrial PLAT was initially thought to be uncommon, with a 2004 review of the
367 human literature identifying only 24 cases [16], however a more recent review suggests
368 a higher incidence of up to 38% [17]. Venographic studies in humans have documented
369 a higher incidence rate of venous thrombosis, with up to 45% people found to have a
370 venous thrombus after transvenous pacemaker placement [12-15, 18]. The apparent
371 difference in location of PLAT between dogs and people is likely due to the imaging
372 modalities used, with most dogs only undergoing echocardiography, whereas the
373 venous thrombi were identified following venographic studies which are not commonly
374 performed in dogs.

375 In our study PLAT was considered an incidental finding with no clinical signs in
376 15/27 (55.6%) dogs with the remaining dogs experiencing PTE and/or CHF. There is a
377 similar mix of clinical presentations in the veterinary literature. Some papers consider
378 PLAT to be a minor complication with no reported clinical signs [1, 6, 25] whereas
379 others report it as a major complication [7, 21, 22, 24] due to the development of PTE or
380 cranial caval syndrome. Some of the variation in the literature may represent different
381 centers approaches to follow-up in these patients – we have demonstrated that many
382 dogs do not undergo echocardiographic follow-up post pacemaker implantation and so
383 it is likely that silent PLAT will not be diagnosed in these dogs. A proportion of dogs may
384 only have undergone echocardiography because they had clinical signs of PLAT,
385 thereby selecting the most severely affected. Humans with intravascular foreign bodies
386 including transvenous pacing leads are at increased risk of thromboembolic disease
387 [11], with serious thrombotic and embolic complications reported in 0.6%-3.5% [19],

388 including risk of sudden death [20]. The majority of people with venous thrombosis are
389 asymptomatic, although up to 10% are reported to have clinical signs secondary to
390 thrombosis [12, 14, 15, 18]. Early reports suggested that more than 80% of people with
391 right atrial PLAT presented acutely or sub-acutely with signs of heart failure, shock,
392 shortness of breath, chest pain, malaise, cyanosis and oedema [16]. However, more
393 recent studies have shown an unclear relationship between intra-cardiac PLAT and PTE
394 [17]. There is concern in people about an intra-cardiac PLAT causing a paradoxical
395 embolus in those with a patent foramen ovale [17]. In our study, six dogs had suspected
396 arterial thromboembolic events and in one previous study a dog died due to an aortic
397 thromboembolism [24]. However, it is impossible to prove whether these were
398 paradoxical emboli related to PLAT or an incidental finding.

399 Studies on specific risk factors for PLAT are lacking and, where present in the
400 human literature, conflicting. One study [14] identified absence of anti-coagulant therapy
401 and multiple pacing leads as risk factors for development of thrombosis, whereas an
402 earlier study [12] did not find these associations. The presence of CHF has been
403 reported to be inversely related to the development of thrombosis in people, although
404 this was considered likely related to people with CHF receiving anti-coagulant therapy
405 rather than a direct protective effect of CHF. In our study, presence of CHF at the time
406 of pacemaker implantation or number of pacemaker leads were not associated with
407 PLAT. Results of our study show that dogs with PLAT were significantly more likely to
408 have proteinuria at the time of pacemaker implantation than dogs without PLAT.
409 Significant proteinuria was also common at the time of PLAT diagnosis. The cause of
410 proteinuria could not be determined in all dogs in our study population due to the

411 retrospective nature of the study and so full biochemical and urine analysis results were
412 not always available.

413 Risk factors for thrombosis are well described, with the CURATIVE guidelines
414 defining dogs with PLN as a 'high-risk' population and include the recommendation for
415 treatment of these dogs with anti-thrombotic therapy [10]. Despite the predisposition to
416 thromboembolic disease, the underlying cause of hypercoagulability in dogs with PLN is
417 incompletely understood. Antithrombin deficiency and increased platelet aggregation
418 secondary to hypoalbuminemia have been identified in dogs with nephrotic syndrome,
419 however plasma antithrombin activity, UPCR and serum albumin concentration are not
420 predictive of thromboembolic complications [28]. Updated CURATIVE guidelines
421 published in 2022 [9] expanded on the definition of populations at risk for thrombosis,
422 and included dogs with transvenous pacemakers. Recommendations were made that
423 antithrombotic therapy should be used in all dogs with pacemakers and prothrombotic
424 comorbidities and considered in every dog following transvenous pacemaker
425 implantation.

426 The majority of dogs in this study received treatment with anti-thrombotic drugs
427 after PLAT diagnosis, and resolution of the thrombus was seen in more than half of the
428 dogs that underwent follow-up echocardiography. However, some dogs died before
429 therapy could be initiated, and other dogs had resolution of the thrombus without anti-
430 thrombotic drugs. There is currently no consensus on treatment of PLAT in people or in
431 dogs. Therapeutic management described in people include anti-coagulation,
432 thrombectomy, thrombolysis and pacemaker lead extraction [17, 29-31], however
433 evidence-based guidance for clinicians is limited and is usually made on a case-by-case

434 basis. Intravenous administration of heparin followed by warfarin is often used as an
435 initial therapy [31]. This is in contrast to the treatment of dogs in this study, with the
436 majority of patients receiving only anti-thrombotic therapy rather than anti-coagulant
437 therapy following PLAT diagnosis. This is likely due to warfarin falling out of favor for
438 use in veterinary medicine, with recommendations to use the oral anti-coagulants
439 (rivaroxaban, apixaban) [32]. Oral anti-coagulants have been shown to be successful in
440 decreasing thrombus size in several dogs [21, 22]. Although no dogs in our study
441 received thrombolytic medications or had interventional procedures, treatment with
442 unfractionated heparin and local infusion of recombinant tissue-plasminogen activator
443 as well as interventional procedures for balloon venoplasty have been previously
444 described to be successful in treating pacemaker lead thrombosis and cranial vena
445 cava syndrome in two dogs [23].

446 The clinical importance and outcome of dogs with PLAT was previously
447 unknown. Our study identified that dogs with PLAT had significantly shorter survival
448 times when compared to those without PLAT. Whether this difference was due to the
449 presence of PLAT, or due to an underlying disease process causing a hypercoagulable
450 state is unknown, however prompt diagnosis and treatment as well as screening for risk
451 factors may help improve the outcome in these dogs. In the entire population 14 dogs
452 died suddenly, including one dog that died following a cardiopulmonary arrest on the
453 day of PLAT diagnosis, nine dogs died due to PTEs and one died due to an arterial
454 hindlimb thromboembolism. However, it is unknown whether the PLAT was the cause of
455 death in these dogs, particularly in the absence of necropsies being performed and
456 because concurrent disease was common.

457 This study is the largest study looking at dogs with permanent pacemakers. As in
458 previous studies, atrioventricular block and sick sinus syndrome were the most common
459 indications for pacemaker implantation in our study [1-6, 8, 33, 34]. The patient
460 population reported here was similar to previous studies, with older dogs [1-8, 34], a
461 slight predominance of female dogs [1, 2, 4, 5, 8] and a large variety of breeds [1-5, 7,
462 8, 33, 34] being included. The proportion of dogs with concurrent cardiac disease [1, 2,
463 5, 7, 8] and CHF [1-3, 5-7] in our population is similar to that which has been reported in
464 previous studies. One study [4] had a lower proportion of both concurrent cardiac
465 disease and CHF, implying that although a bradyarrhythmia alone can cause CHF, the
466 presence of underlying cardiac disease is an important determinant for the development
467 of CHF in dogs with bradyarrhythmias.

468 The majority of publications focus on transvenous pacemaker implantation [2-4,
469 6, 7, 33, 34]. In our study 78/606 (12.9%) of pacemakers were epicardial, and in other
470 studies epicardial pacemakers accounted for 11.7-32.7% [1, 5] of pacemakers placed.
471 Based on our data, we can see that there are differences between centers as to
472 whether epicardial pacemakers are used. This may reflect the availability of a surgeon
473 to place the epicardial lead or the cardiologist's assessment of other patient factors.
474 Small patient size, the need for abdominal surgery and concurrent dermatological
475 disease have all been previously reported as reasons to place an epicardial lead system
476 [8]. While these were also reported as reasons for choosing an epicardial lead system in
477 our population, the most common reason reported in our study was the presence of
478 protein losing conditions, with other reasons including the presence of a
479 hypercoagulable state. The decision to place an epicardial pacemaker in these cases

480 was potentially due to the concern about these dogs developing PLAT. Although only
481 proteinuria was associated with PLAT in our study, the small number of cases and the
482 retrospective nature mean that we cannot say that other conditions that cause a
483 hypercoagulable state do not predispose dogs to PLAT.

484 In our study, 50/606 (9.5%) of transvenous pacemakers were dual chamber but
485 dual chamber pacemakers have represented 0% [2, 3, 7, 34], 0.7% [1], 2.7% [5], 4.8%
486 [4], 48.1% [33] and 100% [6] of transvenous pacemakers placed in other studies. There
487 were slightly more active fixation than passive fixation leads in this study which is similar
488 to a previous study [2], although in another study it was approximately even [1]. These
489 differences in single versus dual chamber and active versus passive fixation are likely to
490 reflect clinician preference and the availability of pacing systems. Rates of
491 complications in this study (102/606, 16.8%) were slightly lower than in many previous
492 studies (25-82%) [1-4, 6-8, 33, 34], but higher than in one study (11.8%) [5]. This may
493 simply reflect the variable definition of complication used in each study and that
494 reporting of other complications was not the primary aim of this study.

495 Median survival time from pacemaker implantation in our study (approximately 30
496 months) was similar to that previously reported in other studies [1, 6-8, 33], although
497 some studies report slightly shorter (median survival 14-22 months) [3, 34] or longer
498 (median survival 35 months; 55-65% of dogs alive at 36 months) [2, 4, 5] survival times.
499 As with previous studies, the majority of dogs with pacemakers in our study did not die
500 due to the pacemaker or due to cardiac disease [1-5, 34], likely reflecting the older age
501 and high levels of comorbidities of the population at pacemaker implantation. In our
502 study, younger age at implantation was associated with a better outcome. Age has been

503 previously associated with outcomes in dogs with pacemakers [1, 2], although one of
504 these studies [2] reported that dogs that were middle aged at implantation lived longer
505 than young or older dogs. In this study and one other study [1] CHF was a negative
506 prognostic indicator, but this was not reported in another study [2]. As with a previous
507 study [7], the presence of a pacemaker-related complication in our study resulted in a
508 poorer outcome. Our study reported that the presence of comorbidities was associated
509 with a poorer outcome, and this is in agreement with another study that reported the
510 presence of concurrent cardiac disease was associated with a worse outcome [4].

511 This study has several limitations in addition to those reported above that should
512 be considered. The echocardiographic appearance of lead-attached thrombi and
513 endocarditis may be very similar and differentiation by echocardiographic means alone
514 is not possible, however a lack of clinical signs associated with endocarditis at the time
515 of thrombus diagnosis or during follow-up in our dogs makes endocarditis less likely.
516 Transthoracic echocardiography identified thrombi in 26/27 of dogs in our study but in
517 the other dog a large thrombus obstructing the cranial vena cava was only identified on
518 computed tomography. Three dogs had a suspected PTE and a PLAT was not
519 identified. Using alternative imaging modalities may therefore be beneficial in dogs in
520 which thrombotic disease is suspected without evidence of PLAT on echocardiography.
521 As it is a retrospective study, clinical data including screening for risk factors for
522 hypercoagulability was not available for all dogs and may have been more likely to be
523 performed in those considered 'at risk' by the clinician. Follow-up examinations
524 including the timing of rechecks and diagnostics performed, were not standardized
525 among the study dogs. As some dogs did not show clinical signs associated with their

526 PLAT, this may have led to an overall under diagnosis of silent PLAT. It may have also
527 introduced bias as follow-up echocardiography may have been more likely to be
528 recommended in dogs with known risk factors for thrombosis or clinical signs of
529 thrombosis, increasing the likelihood of identifying PLAT in these dogs. We can
530 therefore can only conclude an association between proteinuria and PLAT. Further
531 prospective studies with standardized screening for risk factors, timing of follow-up
532 echocardiography and treatment groups would be required to investigate this
533 association further as well as optimal management strategies.

534 **Conclusion**

535 Pacemaker-lead-associated thrombosis is common on echocardiography in the
536 short- and long-term follow-up period of dogs following permanent transvenous
537 pacemaker lead implantation. In more than half of dogs, the thrombi are considered an
538 incidental finding, however PLAT can cause significant morbidity in some dogs and is
539 associated with reduced survival time from pacemaker implantation. Proteinuria at the
540 time of pacemaker implant is associated with PLAT, and significant proteinuria at the
541 time of thrombus diagnosis is a common finding. Anti-thrombotic medications are
542 frequently prescribed when PLAT is diagnosed and, in some dogs, resolution of the
543 thrombus can be identified at follow-up assessments. Based on our data, we
544 recommend screening for proteinuria prior to pacemaker implantation and regular
545 echocardiographic monitoring of patients with transvenous pacemakers. We would also
546 recommend considering the use of anti-thrombotics in patients with transvenous
547 pacemakers that are diagnosed with proteinuria.

548

549 **Conflict of Interest**

550 The authors have no conflicts of interest to disclose.

551

552 **Footnotes**

553 ^h IBM® SPSS® Statistics for Windows Version 27, IBM Corp, Armonk, NY, USA

554

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644

645 Table 1: Population characteristics of whole population, and comparisons between the three groups. AV: atrioventricular;
 646 CHF: congestive heart failure; LA:Ao: left atrial to aortic ratio; LV FS: left ventricular fractional shortening; N/A: not
 647 applicable; nLVIDd: end-diastolic left ventricular internal diameter normalized for body weight; SND: sinus node
 648 dysfunction; SSS: sick sinus syndrome; TEG: thromboelastography; UPCR: urine protein:creatinine ratio; WHWT: West
 649 Highland White Terrier.

	Whole population	Group 1 (transvenous pacemaker with echocardiographic follow up)	Group 2 (transvenous pacemaker without echocardiographic follow up)	Group 3 (epicardial pacemaker)	P value	Post hoc comparison P value (Bonferroni correction applied)
Number of dogs	606	260	268	78		
Age (years)	9.7 (7.1-11.7) (n=606)	9.3 (6.4-11.3) (n=260)	10.1 (8.0-12.0) (n=268)	8.9 (7.0-11.0) (n=78)	0.003	Group 1 vs 2: 0.011 Group 2 vs 3: 0.025

Sex					0.477	
Male	261 (43.1%)	113 (43.5%)	110 (41.0%)	38 (48.7%)		
Female	345 (56.9%)	147 (56.5%)	158 (59.0%)	40 (51.3%)		
Neuter status					0.403	
Neutered	526 (86.8%)	224 (86.2%)	237 (88.4%)	65 (83.3%)		
Entire	79 (13.0%)	36 (13.8%)	30 (11.2%)	13 (16.7%)		
Unknown	1 (0.2%)	0 (0.0%)	1 (0.4%)	0		
Breed (top 6)	Cross-breed 62 (10.2%) Labrador 54 (8.9%) Schnauzer 49 (8.1%) WHWT 48 (7.9%)	Labrador 32 (12.3%) Cross-breed 31 (11.9%) WHWT 20 (7.7%) Schnauzer 17 (6.5%) Cocker Spaniel 15 (5.8%)	Cross-breed 27 (10.1%) WHWT 25 (9.3%) Schnauzer 22 (8.2%) Labrador 17 (6.3%) Cocker Spaniel 15 (5.6%)	Schnauzer 10 (12.8%) Cocker Spaniel 7 (9.0%) Dachshund 7 (9.0%) Labrador 5 (6.4%)	0.058	

	Cocker Spaniel 37 (6.1%) Jack Russell Terrier 23 (4.0%)	Cavalier King Charles Spaniel 13 (5.0%)	Jack Russell Terrier 11 (4.1%)	Cross-breed 4 (5.1%) WHWT 3 (3.8%)		
Body weight (kg)	12.9 (7.9-24.8) (n=604)	16.1 (8.2-28.4) (n=260)	12.3 (7.9-22.1) (n=267)	10.1 (6.9-18.9) (n=77)	0.004	Group 1 vs 3: 0.004
Body condition score (/9)	5 (5-6) (n=549)	5 (5-6) (n=232)	5 (5-6) (n=247)	5 (4-6) (n=70)	0.377	
Comorbidities	458 (75.6%)	188 (72.3%)	211 (78.7%)	59 (75.6%)	0.229	
Rhythm diagnosis					0.007	^a 0.005
AV block	430 (71.0%)	190 (73.0%)	189 (70.5%)	51 (65.4%)		^b 0.017
Atrial standstill	21 (3.5%)	17 (6.5%) ^a	2 (0.7%) ^b	2 (2.6%)		
Sinus arrest	3 (0.5%)	2 (0.8%)	1 (0.4%)	0 (0.0%)		
SND/SSS	148 (24.4%)	49 (18.8%)	74 (27.6%)	25 (32.1%)		
Vagally mediated	4 (0.7%)	2 (0.8%)	2 (0.7%)	0 (0.0%)		

In CHF at implantation	58 (9.6%)	27 (10.4%)	28 (10.4%)	3 (3.8%)	0.184	
Underwent echo prior to implantation	594 (98.0%)	257 (98.8%)	260 (97.0%)	77 (98.7%)	0.286	
LA:Ao	1.45 (1.28-1.70) (n=567)	1.47 (1.30-1.76) (n=246)	1.42 (1.24-1.62) (n=251)	1.49 (1.36-1.73) (n=72)	0.014	Group 2 vs 3: 0.033
nLVIDd	1.65 (1.50-1.86) (n=567)	1.71 (1.52-1.90) (n=244)	1.63 (1.47-1.82) (n=253)	1.65 (1.51-1.84) (n=70)	0.043	Group 1 vs 2: 0.036
LV FS	46.5 (40.0-52.6) % (n=574)	46.6 (39.0-53.0) % (n=247)	46.2 (40.1-52.3) % (n=254)	46.0 (41.1-51.3) % (n=73)	0.953	
Right atrial size (compared to left atrial size)					0.657	
<50%	164 (27.1%)	70 (26.9%)	84 (31.3%)	10 (12.8%)		

50-100%	220 (36.3%)	108 (41.5%)	96 (35.8%)	16 (20.5%)		
>100%	15 (2.5%)	6 (2.3%)	8 (3.0%)	1 (1.3%)		
Unknown	207 (34.2%)	76 (29.2%)	80 (29.9%)	51 (65.4%)		
Right ventricular size (compared to left ventricular size)					0.465	
<50%	313 (51.7%)	150 (57.7%)	144 (53.7%)	19 (24.4%)		
50-100%	80 (13.2%)	31 (11.9%)	41 (15.3%)	8 (10.3%)		
>100%	5 (0.8%)	3 (1.2%)	2 (0.7%)	0 (0.0%)		
Unknown	208 (34.3%)	76 (29.2%)	81 (30.2%)	51 (65.4%)		
Albumin (g/L)	32.0 (29.0-36.0) (n=487)	32.0 (28.5-35.0) (n=200)	33.0 (30.0-37.0) (n=222)	32.0 (28.0-34.0) (n=65)	0.006	Group 1 vs 2: 0.018 Group 2 vs 3: 0.040
Hypoalbuminemia	41/491 (8.4%)	19/203 (9.4%)	15/223 (6.7%)	7/65 (10.8%)	0.464	

UPCR	0.38 (0.09-1.93) (n=143)	0.30 (0.08-1.94) (n=58)	0.23 (0.08-0.78) (n=53)	1.89 (0.21-4.76) (n=32)	0.002	Group 1 vs 3: 0.013 Group 2 vs 3: 0.001
Proteinuria	77/155 (49.7%)	29/60 (48.3%)	24/60 (40.0%)	24/35 (68.6%) ^a	0.026	^a 0.033
TEG hypercoagulable	2/3 (66.7%)	2/3 (66.7%)	0	0	N/A	
Length of hospitalization (days)	3 (1-4) (n=596)	3 (1-4) (n=259)	2 (1-4) (n=265)	3 (3-4) (n=72)	<0.001	Group 1 vs 3: <0.001 Group 2 vs 3: <0.001

650

651 Table 2: Reason listed in the medical records for an epicardial lead system being
 652 chosen. PLE: protein-losing enteropathy; PLN: protein-losing nephropathy; *included
 653 four patients with suspected/confirmed hyperadrenocorticism, and one patient with each
 654 of immune-mediated hemolytic anemia, splenic thrombus and diffuse spontaneous echo
 655 contrast on echocardiography.

Reason epicardial system chosen	Number (%)
PLN/PLE	23 (29.5%)
Patient size/demeanour	16 (20.5%)
Dermatologic disease	8 (10.3%)
Suspected hypercoagulable state*	7 (9.0%)
Complications from previous pacemaker	6 (7.7%)
Need for concurrent surgery	6 (7.7%)
Concurrent disease	4 (5.1%)
Structural cardiac disease	2 (2.6%)
PLN and patient size	1 (1.3%)
PLN and dermatologic disease	1 (1.3%)
Suspected hypercoagulable state* and need for concurrent surgery	1 (1.3%)
Unknown	3 (3.8%)

656

657 Table 3: Details of the chambers paced and lead fixation type in patients with a
 658 transvenous pacemaker system.

Chamber paced and lead type	Number (%)	
Single chamber – active lead	294 (55.7%)	477 (90.3%)
Single chamber – passive lead	168 (31.8%)	
Single chamber – unknown lead fixation	15 (2.8%)	
Dual chamber – active atrial lead, active ventricular lead	14 (2.7%)	50 (9.5%)
Dual chamber – active atrial lead, passive ventricular lead	7 (1.3%)	
Dual chamber – passive atrial lead, active ventricular lead	13 (2.5%)	
Dual chamber – passive atrial lead, passive ventricular lead	16 (3.0%)	
Dual chamber – unknown lead fixation	0 (0.0%)	
Unknown number of chambers paced and unknown lead fixation	1 (0.2%)	1 (0.2%)

659

660 Table 4: Comparison of characteristics at pacemaker implantation between patients that did and did not develop
 661 pacemaker-lead-associated thrombosis. AV: atrioventricular; CHF: congestive heart failure; LA:Ao: left atrial to aortic ratio;
 662 LV FS: left ventricular fractional shortening; N/A: not applicable; nLVIDd: end-diastolic left ventricular internal diameter
 663 normalized for body weight; SND: sinus node dysfunction; SSS: sick sinus syndrome; UPCR: urine protein:creatinine
 664 ratio; WHWT: West Highland White Terrier.

	Pacemaker-lead-associated thrombosis	No pacemaker-lead-associated thrombosis	P value
Number of dogs	27	233	
Center			0.077
Center 1	2 (7.4%)	22 (9.4%)	
Center 2	7 (25.9%)	28 (12.0%)	
Center 3	7 (25.9%)	40 (17.2%)	
Center 4	6 (22.2%)	31 (13.3%)	
Center 5	3 (11.1%)	40 (17.2%)	
Center 6	2 (7.4%)	52 (22.3%)	
Center 7	0 (0.0%)	20 (8.6%)	

Age (years)	8.9 (4.1-12.2)	9.4 (6.6-11.3)	0.677
Sex			0.153
	Male	8 (29.6%)	105 (45.1%)
	Female	19 (70.4%)	128 (54.9%)
Neuter status			0.553
	Neutered	22 (81.5%)	202 (86.7%)
	Entire	5 (18.5%)	31 (13.3%)
Breed (top 6)	WHWT 5 (18.5%) Cross-breed 4 (14.8%) Cocker spaniel 2 (7.4%) Jack Russell terrier 2 (7.4%) Dogue de Bordeaux 2 (7.4%) Yorkshire terrier 2 (7.4%)	Labrador 31 (13.3%) Cross-breed 27 (11.6%) Schnauzer 17 (7.3%) WHWT 15 (6.4%) Cocker spaniel 13 (5.6%) Cavalier King Charles Spaniel 12 (5.2%)	0.438
Body weight (kg)	10.2 (6.8-20.0)	17.0 (8.4-28.8)	0.071
Body condition score (/9)	5 (5-6) (n=24)	5 (5-6) (n=208)	0.779

Comorbidities	17 (63.0%)	171 (73.4%)	0.261
Rhythm diagnosis			0.950
AV block	19 (70.4%)	171 (73.4%)	
Atrial standstill	2 (7.4%)	15 (6.4%)	
Sinus arrest	0 (0.0%)	2 (0.9%)	
SND/SSS	6 (22.2%)	43 (18.5%)	
Vagally mediated	0 (0.0%)	2 (0.9%)	
In CHF	1 (3.7%)	26 (11.2%)	0.329
LA:Ao	1.49 (1.34-1.86) (n=25)	1.47 (1.30-1.73) (n=221)	0.444
nLVIDd	1.60 (1.40-1.84) (n=24)	1.72 (1.52-1.90) (n=220)	0.054
LV FS	52.5 (45.3-57.5) % (n=24)	46.3 (38.8-52.3) % (n=223)	0.010
Right atrial size (compared to left atrial size)			0.156
<50%	10 (37.0%)	60 (25.8%)	
50-100%	10 (27.0%)	98 (42.1%)	
>100%	2 (7.4%)	4 (1.7%)	

Unknown	5 (18.5%)	71 (30.5%)	
Right ventricular size (compared to left ventricular size)			0.805
<50%	18 (66.7%)	132 (56.7%)	
50-100%	4 (14.8%)	27 (11.6%)	
>100%	0 (0.0%)	3 (1.3%)	
Unknown	5 (18.5%)	71 (30.5%)	
Albumin (g/L)	29.0 (26.5-35.5) (n=17)	32.0 (29.0-35.0) (n=183)	0.082
Hypoalbuminemia	4/18 (22.2%)	15/185 (8.1%)	0.072
UPCR	2.38 (0.68-6.75) (n=6)	0.20 (0.06-1.63) (n=52)	0.022
Proteinuria	6/6 (100.0%)	21/52 (40.4%)	0.007
TEG hypercoagulable	0	2/3 (66.7%)	N/A
Single vs dual chamber			0.740
Single chamber	24 (88.9%)	210 (90.1%)	
Dual chamber	3 (11.1%)	23 (9.9%)	

Ventricular lead passive vs active			1.000
Passive	9 (33.3%)	78 (33.5%)	
Active	17 (63.0%)	151 (64.8%)	
Unknown	1 (3.7%)	4 (1.7%)	

665

666 Table 5: Median survival time for the overall population and comparisons in survival times (log-rank test) for different
 667 factors. AV: atrioventricular; CHF: congestive heart failure; LA:Ao: left atrial to aortic ratio; LV FS: left ventricular fractional
 668 shortening; nLVIDd: end-diastolic left ventricular internal diameter normalized for body weight; PLAT: pacemaker-lead-
 669 associated thrombosis; SND: sinus node dysfunction; SSS: sick sinus syndrome; UPCR: urine protein:creatinine ratio.

	n	Survival time	P value
Overall	600	907 days (0-2661 days)	
Center			0.091
Center 1	33	1,056 days (70-1,469 days)	
Center 2	52	817 days (0-2,286 days)	
Center 3	86	828 days (0-2,661 days)	
Center 4	123	972 days (0-2,658 days)	
Center 5	115	733 days (4-2,120 days)	
Center 6	141	1,090 days (0-2,282 days)	
Center 7	50	1,625 days (1-2,232 days)	
Age			<0.001
≤7.0 years	146	>2,661 days (0-2,661 days)	

	7.1-9.6 years	150	828 days (0-2,472 days)	
	9.7-11.6 years	151	865 days (0-2,186 days)	
	≥11.7 years	153	696 days (2-2,450 days)	
Sex				0.100
	Male	260	842 days (0-2,658 days)	
	Female	340	907 days (0-2,661 days)	
Neuter status				0.029
	Neutered	522	877 days (0-2,658 days)	
	Entire	78	1,070 days (0-2,661 days)	
Body weight				0.937
	≤7.8 kgs	147	936 days (0-2,661 days)	
	7.9-12.8 kgs	150	909 days (0-2,450 days)	
	12.9-24.6 kgs	150	841 days (0-2,472 days)	
	≥24.7 kgs	150	949 days (0-2,658 days)	
Body condition score (/9)				<0.001
	Underweight (≤3/9)	34	491 days (0-1,477 days)	

	Ideal weight (4-5/9)	288	1,018 days (0-2,658 days)	
	Overweight ($\geq 6/9$)	221	882 days (0-2,450 days)	
Comorbidities				<0.001
	Yes	452	795 days (0-2,661 days)	
	No	148	1,324 days (0-2,658 days)	
Rhythm diagnosis				0.533
	AV block	426	949 days (0-2,658 days)	
	Atrial standstill	21	653 days (0-1,988 days)	
	Sinus arrest	3	>1,353 days (507-1,353 days)	
	SND/SSS	146	801 days (0-2,661 days)	
	Vagally mediated	4	603 days (68-1,054 days)	
In CHF at implantation				<0.001
	Yes	55	551 days (0-1948 days)	
	No	545	963 days (0-2,661 days)	
LA:Ao				0.009
	≤ 1.28	143	842 days (0-2,658 days)	

	1.29-1.45	140	1,194 days (2-2,232 days)	
	1.46-1.69	139	1,102 days (1-2,661 days)	
	≥1.70	141	797 days (0-2,472 days)	
nLVIDd				0.546
	≤1.49	141	828 days (0-2,661 days)	
	1.50-1.65	141	949 days (0-2,472 days)	
	1.66-1.85	140	984 days (0-2,186 days)	
	≥1.86	139	895 days (0-2,658 days)	
LV FS				0.608
	≤40.0%	144	808 days (0-2,279 days)	
	40.1-46.3%	139	1,018 days (0-2,472 days)	
	46.4-52.4%	142	979 days (0-2,658 days)	
	≥52.5%	143	842 days (1-2,661 days)	
Right atrial size (compared to left atrial size)				0.034
	<50%	164	828 days (4-2,658 days)	
	50-100%	219	1,033 days (0-2,661 days)	

	>100%	15	386 days (0-1,650 days)	
Right ventricular size (compared to left ventricular size)				0.048
	<50%	312	907 days (1-2,661 days)	
	50-100%	80	777 days (0-2,450 days)	
	>100%	5	461 days (0-505 days)	
Albumin (g/L)				0.054
	≤28.9	109	801 days (0-1,922 days)	
	29.0-31.9	98	801 days (0-2,661 days)	
	32.0-34.9	121	826 days (1-2,472 days)	
	≥35.0	154	1,142 days (0-2,658 days)	
Hypoalbuminemia				0.010
	Yes	41	797 days (0-1,906 days)	
	No	445	912 days (0-2,661 days)	
UPCR				0.337
	≤0.10	37	941 days (0-2,279 days) days	
	0.11-0.49	38	701 days (29-2,071 days)	

	0.50-1.99	30	805 days (0-2,472 days)	
	≥2.00	34	924 days (12-1,892 days)	
Proteinuria				0.625
	Yes	76	801 days (0-2,472 days)	
	No	75	865 days (0-2,279 days)	
Pacemaker				0.064
	Transvenous	522	842 days (0-2,661 days)	
	Epicardial	78	1,206 days (0-2,472 days)	
Single vs dual chamber				0.632
	Single chamber	471	842 days (0-2,661 days)	
	Dual chamber	50	1,018 days (4-2,120 days)	
Ventricular lead passive vs active				0.240
	Passive	188	791 days (0-2,658 days)	
	Active	318	907 days (0-2,661 days)	
Pacemaker complications				0.021
	Yes	102	795 days (0-2,128 days)	

	No	498	963 days (0-2,661 days)	
PLAT				0.003
	Yes	27	677 days (9-1,988 days)	
	No	232	1,105 days (1-2,661 days)	

670

671 Figure legends

672

673 Figure 1: Echocardiographic image of a pacemaker-associated-lead thrombosis. LA: left
674 atrium; RA: right atrium; *: pacemaker-associated-lead thrombosis.

675

676 Figure 2: Flow chart showing enrolment and grouping of dogs in the study.

677

678 Figure 3: Comorbidities in the population. Figure 3a: Comorbidities in the whole
679 population, divided by organ system. Figure 3b: Cardiac comorbidities in the whole
680 population. ARVC: arrhythmogenic right ventricular cardiomyopathy; MMVD:
681 myxomatous mitral valve disease; SPAVF: systemic to pulmonary arteriovenous fistula.

682

683 Figure 4: Percentage of dogs in groups 1, 2 and 3. Comparison of the percentages of
684 dogs in each group across the seven centers. *Statistically significant difference
685 compared to expected value.

686

687 Figure 5: Anti-thrombotic medications that the 27 dogs that developed pacemaker-lead-
688 associated thrombosis were receiving before and following their diagnosis. LMWH: low
689 molecular weight heparin.

690

691 Figure 6: Survival curve (all cause mortality): dogs that developed pacemaker-lead-
692 associated thrombosis had shorter survival times from pacemaker implantation (677
693 days (9-1,988 days)) than those that didn't develop pacemaker-lead-associated
694 thrombosis (1,105 days (1-2,661 days)) (P=0.003).