Journal of Veterinary Cardiology (2015) 17, S306—S317

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Journal of Veterinary Cardiology
ESVC

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Secondary prevention of cardiogenic arterial thromboembolism in the cat: the double-blind, randomized, positive-controlled feline arterial thromboembolism; clopidogrel vs. aspirin trial (FAT CAT)

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Received 17 November 2014; received in revised form 9 September 2015; accepted 7 October 2015

These data were presented at the American College of Veterinary Internal Medicine Scientific Forum, 2013.

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http://dx.doi.org/10.1016/j.jvc.2015.10.004

KEYWORDS
Thromboprophylaxis;
Thrombosis;
Antithrombotics;
Infarction;
Cardioembolic

Abstract *Objectives:* To determine if clopidogrel administration is associated with a reduced likelihood of recurrent cardiogenic arterial thromboembolism (CATE) in cats compared to aspirin administration. Secondary aims were to determine if clopidogrel administration had an effect on the composite endpoint of recurrent CATE and cardiac death and to identify adverse effects of chronic clopidogrel or aspirin therapy.
Animals: Seventy-five cats that survived a CATE event.
Methods: Multicenter, double-blind, randomized, positive-controlled study. Cats were assigned to clopidogrel (18.75 mg/cat PO q 24 h) or aspirin (81 mg/cat PO q 72 h). Kaplan–Meier survival curves were created for each endpoint and the log rank test performed to compare treatment groups with respect to time to event and the likelihood of the event occurring.
Results: The mean age of all cats was 8.0 ± 3.5 yr and 57/75 (76%) were male ($p < 0.001$); 62/75 (83%) were mixed breed with the remainder including Persian, Abyssinian, American Shorthair, Bengal, Birman, Himalayan, Maine Coon, Ragdoll, Snowshoe, and Sphynx breeds. Only 15% (11/75) of cats had a history of heart disease recorded prior to the CATE event. Clopidogrel administration was associated with significantly reduced likelihood of recurrent CATE compared to aspirin ($p = 0.024$) and had a longer median time to recurrence [443 (95% CI 185–990) days vs. 192 (95% CI 62–364) days, respectively]. Clopidogrel was also associated with a significantly reduced likelihood of the composite endpoint of recurrent CATE or cardiac death ($p = 0.033$) with a longer median time to event [346 (95% CI 146–495) days vs. 128 (95% CI 58–243) days].
Conclusions: Clopidogrel administration significantly reduces the likelihood of recurrent CATE compared with aspirin in cats; both drugs were well tolerated.

Abbreviations

ADP	adenosine diphosphate
ALP	alkaline phosphatase
ALT	alanine aminotransferase
CATE	cardiogenic arterial thromboembolism
CHF	congestive heart failure
DCM	dilated cardiomyopathy
GGT	gamma-glutamyl transpeptidase
HCM	hypertrophic cardiomyopathy
HOCM	hypertrophic obstructive cardiomyopathy
RCM	restrictive cardiomyopathy
SAM	systolic anterior motion of the mitral valve
UCM	unclassified cardiomyopathy

Introduction

Cardiogenic arterial thromboembolism (CATE) is a well-recognized and devastating clinical morbidity with feline cardiomyopathy. When fragments of an intracavitary thrombus gain access to the systemic circulation, they may obstruct distant arterial segments which can result in tissue injury or organ infarction. Distal aortic occlusion or "saddle thrombus" occurs in approximately 90% of cases[1] while right brachial, renal, splanchnic, and cerebral infarction occur less commonly.[1,2] The underlying mechanisms of CATE are distinctly different from arterial thrombosis with the most appropriate human corollary being cardioembolic disease secondary to atrial fibrillation.[3,4] Previous retrospective studies have reported that 6%–17%[5–7] of cats with underlying cardiac disease go on to develop CATE with mortality rates of 61%–67%.[1,8–10] Euthanasia, similar in frequency to natural death, is often selected in part because of lack of evidence for management strategies that might prevent recurrent CATE.

Antithrombotic drugs are the standard of care for cardioembolic prevention in humans[11,12] and this has been incorporated into clinical protocols for cats. However, there have been no prospective clinical trials in cats evaluating antithrombotic therapy for primary (initial CATE) or secondary (recurrent CATE) prevention. A number of retrospective studies have reported recurrent CATE rates of 17%–75%[1,8–10,13] in cats receiving antithrombotic therapy with one year recurrence rates of 25%–61%.[9,10] Aspirin, the most commonly used antithrombotic in cats, is an antiplatelet drug

which exerts a mild antithrombotic effect through inhibition of cyclooxygenase with reduction of thromboxane A_2 production. Clopidogrel is an irreversible antagonist of the platelet adenosine diphosphate $(ADP)_{2Y12}$ receptor which inhibits primary and secondary platelet aggregation as well as inhibiting the ADP-induced conformational change of the glycoprotein IIb/IIIa receptor complex.[14,15] Clopidogrel has been shown to induce a more potent antiplatelet effect than aspirin in humans,[16] but the comparative effect between clopidogrel and aspirin to limit CATE recurrence has not been reported in the cat.

The primary objective of this study was to determine if clopidogrel administration is associated with a reduced likelihood of recurrent CATE in cats compared to aspirin administration. Secondary aims were to determine if clopidogrel administration had an effect on the composite endpoint of recurrent CATE and cardiac death and to identify adverse effects of chronic clopidogrel or aspirin therapy. Our hypothesis was that cats receiving clopidogrel would have a decreased likelihood of recurrent CATE compared to cats receiving aspirin.

Animals, materials, and methods

The study protocol was approved by the IACUC at all participating institutions and informed client consent was achieved using a standard form used by all enrolling veterinarians. This double-blind, randomized, positive-controlled multicenter study recruited investigators from throughout the world. Enrollment was accomplished through an online study website (www.vin.com/fatcat). The study was advertised to veterinarians and cat owners through websites, conferences, and social media. Entry criteria required a complete medical history and physical examination, arterial thromboembolism that developed 1–3 months previously, echocardiographic confirmation of underlying cardiac disease that could support the formation of an intracardiac thrombus, clinical pathology results that included complete blood count, biochemical panel, and, in cats >7 years of age, total serum thyroxine concentration. Exclusion criteria included no evidence of cardiac disease on the echocardiogram, presence of an intracardiac thrombus, platelet count <50,000/μl, clinical evidence of bleeding, unstable congestive heart failure or presence of concurrent non-cardiac disease thought to independently make one year survival unlikely. Cats were permitted to receive any treatment, including antithrombotic drugs, during the 1–3 month run-in period deemed necessary by the attending veterinarian who did not have to be a board-certified specialist. The medical treatment during this run-in period was continued until the day the study began which was the first day the study drug (clopidogrel or aspirin) was administered.

Study enrollment

When a cat was enrolled through the study website, the principal investigator was notified and the enrolling veterinarian was contacted directly by the principal investigator to verify that an arterial event had likely occurred and to determine other concurrent medical conditions. The principal investigator (DFH) reviewed all cases submitted for enrollment to verify that they conformed to entry criteria. There was no attempt to standardize the echocardiographic technique or measurement protocol. Baseline data collection included physical examination findings, complete blood count, serum chemistry panel, and echocardiogram as well as demographic data, estimated clinical recovery from the CATE event (percent improvement from initial presentation), site of infarction, categorization of cardiac disease, and drug therapy prior to and following the CATE event. The clinical pathology tests were performed by laboratories used by the enrolling veterinarian.

Study group allocation

Enrolled cases were randomly assigned[h] to receive either clopidogrel (18.75 mg PO q 24 h) or aspirin (81 mg tablet PO q 72 h) using an online random allocation program where group allocation was pre-determined for 100 study animals. Only the study coordinator was not blinded to study group allocation and did not participate in any study decisions. The principal investigator, enrolling veterinarian, and cat owner were kept blinded to group allocation through the use of color-coded, #3 opaque gelatin capsules.[i] Cats in the clopidogrel group were given a solid yellow capsule every third day which contained the 18.75 mg of clopidogrel along with lactose powder while the other two days they received a yellow and gray capsule which also contained the 18.75 mg of clopidogrel and lactose powder. Cats in the aspirin group were given a solid pink capsule every third day which contained the 81 mg aspirin tablet along with lactose powder while the other two days they received a pink and gray capsule which contained

[h] Research Randomizer, www.randomizer.org.
[i] PCCA, Houston, TX USA.

lactose powder only. Capsules were compounded at one site by the study coordinator for cats from North America and New Zealand while the capsules were compounded at another study site for cats from Europe. The study code and group allocation were broken after the final data analysis was performed.

Concurrent cardiac therapy

There was an effort to standardize concurrent cardiac therapy based on the presence or absence of congestive heart failure (CHF) and morphologic classification of cardiac disease as follows. All cats with a history of CHF, or who developed CHF during the study, were treated with furosemide and an angiotensin-converting enzyme inhibitor. In the absence of CHF, it was suggested that cats with hypertrophic cardiomyopathy (HCM) receive no cardiac therapy, cats with restrictive (RCM) or unclassified cardiomyopathy (UCM) receive an angiotensin-converting enzyme inhibitor, and cats with dilated cardiomyopathy (DCM) receive an angiotensin-converting enzyme inhibitor and digoxin. The use of atenolol therapy in cats with systolic anterior motion of the mitral valve was left to the discretion of the veterinarian providing direct care. No antithrombotic therapy other than the study drug was allowed during the study period.

Study monitoring

During the study, owners completed a daily log sheet that recorded appetite, mental attitude, stool consistency, development of skin lesions, and the presence or absence of vomiting or bleeding. Clinical follow up of the cats was done at 1 month, 3 months, 6 months, and 12 months after beginning the study. A physical exam, complete blood count and serum chemistry panel were repeated at 1 month, a physical exam was repeated at 3 months, and the owners were contacted through phone calls at 6 and 12 months and every 6 months thereafter. If the health status changed at a time point outside of these scheduled follow up visits, an unscheduled visit could be registered through the study website by the attending veterinarian; this entry would notify the principal investigator who would contact the veterinarian and together, would make a joint decision about whether the cat should continue on the study.

The primary study endpoint of recurrent CATE was defined prospectively and determined by clinical history, physical examination and when necessary, nuclear imaging, angiography, or necropsy. Once the primary endpoint was reached, the cat was removed from the study. Secondary endpoints included cardiac death or euthanasia due to cardiovascular disease, and sudden death. In the event of sudden death, an attempt was made to obtain a necropsy to determine if sudden death was due to a CATE event. In the absence of a known CATE event, sudden death was attributed to cardiac disease. A composite endpoint of recurrent CATE or death attributed to cardiac disease was developed prospectively because cardiac death has been reported to be the second most common cause of death in cats following a CATE event[17] and the investigators wanted to see if the greater antiplatelet effects of clopidogrel compared to aspirin would have an identifiable effect on the progression of cardiac disease. The development of or worsening of congestive heart failure was not an endpoint in the study. Each attending veterinarian was permitted to add or modify CHF therapy as judged necessary for effective patient management to allow the cat to continue on the study. The number of study days was calculated from the first day of study drug administration to a study endpoint. Cats that reached a secondary endpoint were right-censored for the primary endpoint of CATE.

Statistical analysis

Statistical analyses were performed by commercially available computer software.[j] Baseline comparisons between the two treatment groups were performed on the key covariates that were known to be associated with the outcomes of interest including age, weight, gender, underlying cardiac disease category, and echocardiographic variables. T-test or Mann—Whitney test (if outliers were identified) was used to analyze continuous covariates while Pearson's chi-square test or Fisher's exact test was used for categorical covariates, and the binomial test was used for gender proportions. Paired t-test or Wilcoxon test (if outliers were identified) was used to compare clinicopathological data at baseline and after 1 month of study drug administration within each treatment group. Kaplan—Meier method was used to estimate cumulative study continuation rate and median time to event. Cox proportional hazards regression was used to adjust for any covariates found to be significantly different between the two treatment groups at baseline and also significant in the Cox regression. Adjusted hazard

[j] SPSS Statistics for Windows, Version 22.0, IBP Corp., Armonk, NY USA.

rate ratio and 95% confidence intervals were derived from the Cox regression. If no significant covariates were found, log rank test was performed to compare cumulative study continuation rates between the groups. Statistical significance was defined as $p < 0.05$.

An original power analysis suggested that 20 cats in each group would be sufficient to identify a significant difference between groups if the frequency of recurrent CATE decreased from an estimated 50% to 15% at a 95% level of confidence and 80% power. After approximately 75% of the original 40 cats had been enrolled, it was clear that the reduction in frequency of recurrent CATE between groups was not as great as assumed in the original power analysis. Therefore, the decision was made to continue the study with an aim to double the original study population from 40 cats to 80 cats. The principal investigator, enrolling veterinarian, and cat owner were kept blinded to group allocation until final data analysis had been completed.

Results

Eighty-five cats were enrolled through the study website with 42 allocated to the clopidogrel group and 43 allocated to the aspirin group (Fig. 1). Cats were enrolled at a total of 52 sites, 50 of which were from North America and 1 of each from New Zealand and Europe. Three cats were excluded from analysis in the clopidogrel group: two for noncompliance prior to study initiation and one due to death from recurrent CATE prior to study drug administration. Seven cats were excluded from the aspirin group prior to starting the study drug: three due to owner wishes (one deemed medically unstable, one due to recurrent vomiting, one due to inability to administer study medication), one due to death from recurrent CATE, one cat ran away, one euthanized due to noncardiac disease, and one who died from cardiac disease. There were 39 and 36 cats that remained in the clopidogrel and aspirin groups, respectively which were included in the final data analysis. The median time on study for all cats was 182 days (4—2034 days).

The demographic data for the cats enrolled in the study are summarized in Table 1. Mean age was 8.0 ± 3.5 yr and there was a strong male gender bias (57/75, 76%; $p < 0.001$). The majority of cats were of mixed breed (62/75; 83%) but pure breed cats were also represented including Persian (2), Himalayan (2), Abyssinian, American Shorthair, Bengal, Birman, Maine Coon, Ragdoll, Snowshoe, and Sphynx. Eleven out of 75 cats (15%) had a known history of heart disease prior to the initiating CATE event with 10/11 (91%) receiving cardiac drug therapy (Table 2). Therapy included beta-blocker (4/10, 40%), angiotensin-converting enzyme inhibitor (4/10; 40%), furosemide (3/10; 30%), aspirin (2/10; 20%), calcium channel blocker (2/10; 20%), spironolactone (2/10; 20%), clopidogrel (1/10; 10%), and low molecular-weight heparin (1/10; 10%); 7/10 (70%) received multiple drug therapy. In most cats (70/75; 93%), the initiating CATE was their first vascular event. However, 3/75 (4%) had two prior CATE events, while 2/75 (3%) had four prior CATE events. The majority of cats presented for bilateral, symmetrical pelvic limb infarction (45/75; 60%) but right thoracic limb (14/75; 19%), unilateral pelvic limb (14/75; 19%), unilateral thoracic and unilateral pelvic limb (1/75; 1%), and left thoracic limb infarction (1/75; 1%) were also reported. Owner-reported percent clinical recovery from the CATE event was high with a mean of $87.5\% \pm 16.1\%$ (range, 30%—100%). A number of underlying cardiac diseases were represented including HCM (46/75; 61%), UCM (12/75; 16%), hypertrophic obstructive cardiomyopathy (HOCM) (8/75; 11%), RCM (7/75; 9%), DCM (1/75; 1%), and congenital cardiac disease (mitral valve stenosis) (1/75; 1%).

There was no significant difference in age, weight, gender, or underlying cardiac disease (HCM vs. non-HCM) between the clopidogrel and aspirin groups. Echocardiographic measurements were recorded in 31/39 (80%) cats in the clopidogrel group and 28/36 (78%) cats in the aspirin group (Table 1). There were significantly more cats with reported systolic anterior motion of the mitral valve (SAM) in the clopidogrel treated group (10/31, 32%) than the aspirin treated group (2/28, 7%) ($p = 0.024$). The presence of SAM was included as a covariate in the Cox regression model for event with regard to the primary endpoint of recurrent CATE, the composite endpoint of recurrent CATE or cardiac death, and all-cause mortality. However, SAM did not have a significant effect in this model so it was not included in the final data analysis. The median follow up period was 185 days (4—2034 days) for the clopidogrel treated group and 122 days (6—883 days) for the aspirin treated group.

With regard to the primary endpoint of recurrent CATE, clopidogrel was associated with a significantly reduced likelihood ($p = 0.024$) and longer median time to event than aspirin [443 (95% CI 185—990) days vs. 192 (95% CI 62—364) days, respectively] (Fig. 2). Recurrent CATE occurred in 19/39 (49%) cats receiving clopidogrel with 14/39

(36%) occurring within the first year. In comparison, recurrent CATE occurred in 27/36 (75%) cats receiving aspirin with 23/36 (64%) occurring within the first year. Most of the cats that experienced a recurrent CATE event did so within the first year of starting the study (14/19; 74% and 23/27; 85% for clopidogrel and aspirin, respectively) with a median time to recurrence of 146 days (7—990 days) for clopidogrel and 83 days (6—883 days) for aspirin. The cumulative frequency for recurrent CATE increased most rapidly over the first 6 months of the study in cats receiving clopidogrel with 8/19 (42%) cats experiencing a recurrent CATE event within the first 3 months of the study. In comparison, the cumulative frequency for recurrent CATE increased most rapidly over the first 9 months of the study in cats receiving aspirin with 14/27 (52%) cats similarly experiencing a recurrent CATE event within the first 3 months of the study.

When the primary endpoint of recurrent CATE was combined with death due to cardiac disease into a composite endpoint, clopidogrel was also associated with a significantly reduced likelihood ($p = 0.033$) and longer median time to event than aspirin [346 (95% CI 146—495) days vs. 128 (95% CI 58—243) days, respectively] (Fig. 3). Death due to CHF occurred in 3/39 (8%) clopidogrel treated cats and 3/36 (8%) in aspirin treated cats. Sudden death occurred in 4/39 (10%) clopidogrel treated cats with three of those cats undergoing a full necropsy confirming lack of recurrent CATE. There were 2/36 (6%) cats in the aspirin group that died suddenly, with neither receiving a necropsy.

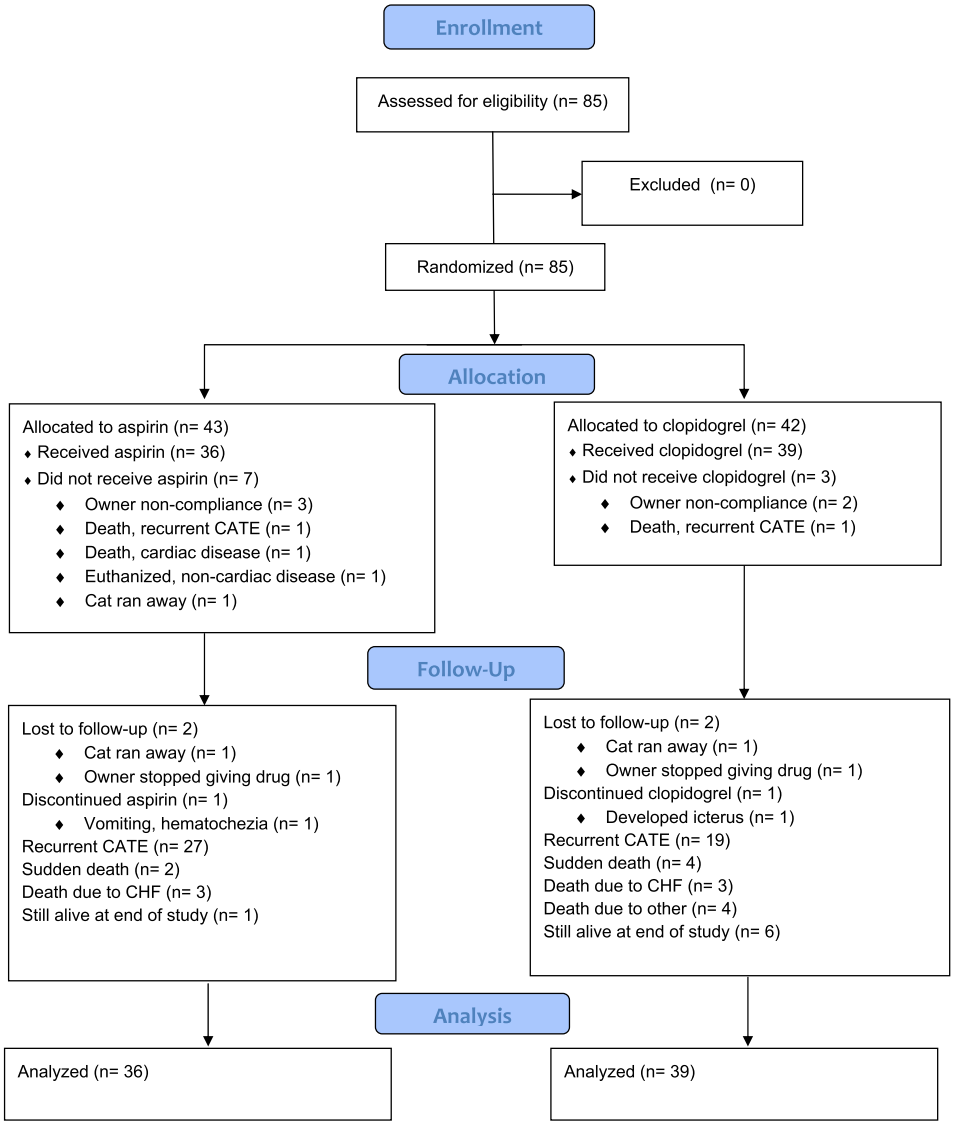

Figure 1 Flow diagram for animal enrollment, allocation, and outcome on study.

Table 1 Demographic and echocardiographic data from cats that were enrolled onto the study.

Parameter	Aspirin	Clopidogrel	Between groups
Age (yr)	8.5 ± 3.3	7.5 ± 3.6	p = 0.187
Weight (kg)	5.3 ± 1.7	4.8 ± 1.5	p = 0.144
Gender (MN/FN)	27/9	30/9	p = 0.840
Breed	DSH (29), DLH (2), Abyssinian, Bengal, Himalayan, Persian, Snowshoe	DSH (24), DLH (7), Persian (2), ASH, Birman, Himalayan, Maine Coon, Ragdoll, Sphynx	
Cardiac disease	HCM (19), RCM (7), UCM (6), HOCM (2), DCM, congenital	HCM (27), HOCM (6), UCM (6)	
Echocardiogram	n = 28	n = 31	
IVSDd (mm)	6.18 ± 1.45	6.63 ± 1.60	p = 0.257
LVFWd (mm)	7.04 ± 2.12	6.58 ± 1.72	p = 0.401
LA/Ao	2.22 ± 0.44	2.10 ± 0.52	p = 0.207
LVIDd (mm)	14.21 ± 2.54	15.27 ± 2.78	p = 0.133
LVIDs (mm)	7.89 ± 2.90	8.57 ± 2.81	p = 0.360
FS (%)	44.52 ± 16.67	44.52 ± 11.26	p = 0.998
SAM (Y)	2	10	***p = 0.024***
Spontaneous contrast (Y)	10	8	p = 0.573

ASH = American shorthair; DLH = domestic longhair; DSH = domestic shorthair; FN = female neutered; FS = fractional shortening; IVSDd = interventricular septal diameter at end-diastole; LA/Ao = left atrial to aortic ratio; LVFWd = left ventricular free wall diameter at end-diastole; LVIDd = left ventricular internal diameter at end-diastole; LVIDs = left ventricular internal diameter in systole; MN = male neutered; SAM = systolic anterior motion of the mitral valve; Y = yes; see abbreviation table for the remainder of the abbreviations.
Bold and italic data represents significantly different between the groups identified.

There was no significant difference (p = 0.105) in the likelihood of all-cause mortality between clopidogrel and aspirin treated cats; the median survival time for clopidogrel was 248 days (95% CI 137—431) and 128 days (95% CI 58—243) for aspirin.

There was one cat in each group that was removed from the study for a possible adverse effect from study drug administration. Icterus and elevated liver enzymes developed in a clopidogrel treated cat at 40 days and persistent vomiting and hematochezia occurred in an aspirin treated cat at 70 days.

Clinical pathology parameters did not differ significantly between treatment groups at baseline or at 1 month (Table 3). Within the aspirin group, there was a significant increase in alkaline phosphatase (ALP) and a significant decrease in gamma-glutamyl transpeptidase (GGT) at 1 month compared to baseline, although none of the parameters for the individual animals fell outside of reference ranges. Total white blood cell count decreased and serum alanine aminotransferase (ALT) increased significantly at 1 month compared to baseline for the clopidogrel group, although none were outside of the reference range. The

Table 2 Concurrent cardiac medications before and after enrolling embolic event.

Cardiac drug	Pre-CATE		Post-CATE	
	Aspirin	Clopidogrel	Aspirin	Clopidogrel
ACE inhibitor	1	3	18	25
Aspirin	1	1	36	NA
Atenolol	2	2	5	7
Clopidogrel	1	0	NA	39
Digoxin	0	0	1	0
Diltiazem	1	1	2	3
Furosemide	0	3	14	17
LMWH	1	0	NA	NA
Spironolactone	1	1	1	1
Multiple	2	3	14	18

CATE: cardiogenic arterial thromboembolism; LMWH: low molecular-weight heparin; NA: not allowable.

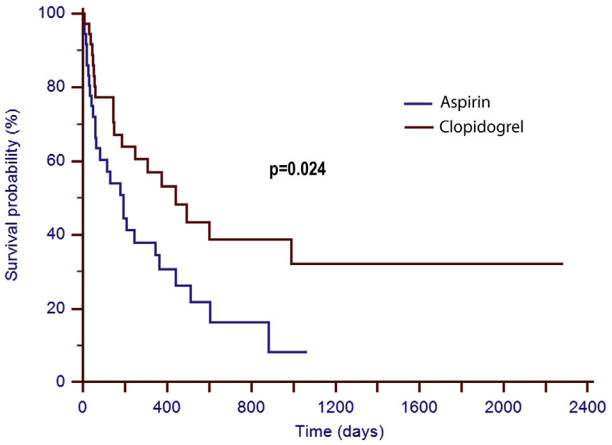

Figure 2 Kaplan—Meier event curve for the primary endpoint of recurrent cardiogenic arterial thromboembolism for the aspirin (blue line) and clopidogrel (brown line) groups.

clopidogrel treated cat that developed icterus and elevated liver enzymes had normal ALT, ALP, and GGT values recorded 1 month after starting clopidogrel administration.

At enrollment, there were 3/39 (8%) cats in the clopidogrel treated group that had been previously diagnosed with CHF and were receiving therapy while no cats (0%) in the aspirin group had a history of CHF prior to the initiating CATE event (Table 2). By the end of the study, 17/39 (44%) cats in the clopidogrel group and 14/36 (39%) cats in the aspirin group had received therapy for CHF. The distribution of concurrent cardiac therapies was similar between the groups with furosemide (17/39; 44%), angiotensin-converting enzyme inhibitor (25/39; 64%), beta-blocker (7/39; 18%), calcium channel blocker (3/39; 8%), and spironolactone (1/39; 3%) administered in the clopidogrel group while furosemide (14/36; 39%), angiotensin-converting enzyme inhibitor (18/36; 50%), beta-blocker (5/36; 14%), calcium channel blocker (2/36; 6%), digoxin (1/36; 3%), and spironolactone (1/36; 3%) were administered in the aspirin group. Similarly, multiple cardiac drugs were used in 18/39 (46%) in the clopidogrel group compared to 14/36 (39%) cats in the aspirin group.

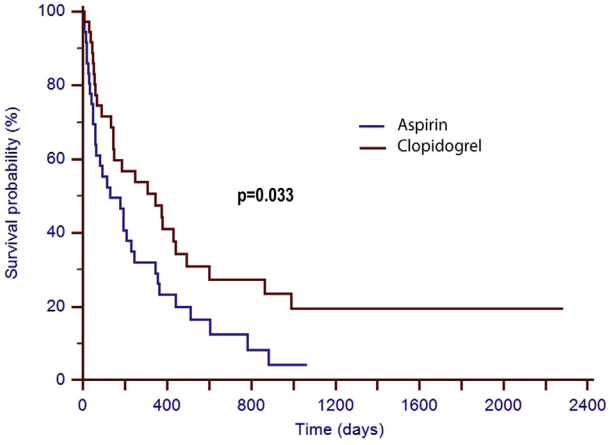

Figure 3 Kaplan—Meier event curve for the composite endpoint of recurrent cardiogenic arterial thromboembolism or cardiac death for the aspirin (blue line) and clopidogrel (brown line) groups.

Discussion

This is the first prospective, randomized, double-blind, positive-controlled antithrombotic trial in cats with underlying cardiac disease. Clopidogrel treated cats were significantly less likely to reach the primary endpoint of recurrent CATE ($p = 0.024$) and had a longer median time to event (443 days vs. 192 days) than aspirin treated cats. Given the most common forms of cardiac disease and absence of epicardial coronary arterial disease in cats, an antithrombotic drug would not be expected to have a direct impact on clinical outcomes outside of recurrent thrombotic events. However, clopidogrel treated cats were also significantly less likely to reach the composite endpoint of recurrent CATE or cardiac death ($p = 0.033$) and had a longer median time to event (346 vs. 128 days) than aspirin treated cats. Approximately twice as many cats developed congestive heart failure in the clopidogrel group compared to the aspirin group and this could be explained by the fact that cats in the aspirin group did not live long enough to develop progressive cardiac disease while the cats receiving clopidogrel were able to live longer, due to not having a recurrent CATE event.

Twenty-six percent (10/39) of the clopidogrel treated cats did not have a recurrent CATE event or die from a cardiac cause with six still alive at the end of the study (400, 505, 659, 1076, 1729, and 2034 days). Within the aspirin group, 11% (4/36) did not have a recurrent CATE event or die from a cardiac cause with one cat alive at the end of the study (715 days). The difference between groups is emphasized by the fact that 16/39 (41%) of clopidogrel treated cats were still on study after 1 year compared to 7/36 (19%) of aspirin treated cats. Published overall median survival times from retrospective studies of recurrent CATE with aspirin therapy range from 24 days to 149 days[1,10,17] which is similar to the median survival time in the aspirin group within this study [128 (95% CI 58—243) days], while the median survival time for the clopidogrel

Table 3 Clinicopathological data for aspirin and clopidogrel groups at baseline and after 1 month of study drug administration.

Aspirin	Baseline	1 month	Within group (baseline-1 month)	Between groups (baseline-1 month)
Hematocrit (%), n = 22	35.4 ± 5.0	35.4 ± 5.4	p = 0.937	p = 0.723
Platelets ($\times 10^3/\mu l$), n = 14	184.8 ± 107.8	174.0 ± 96.5	p = 0.952	p = 0.645
Total WBC ($\times 10^3/\mu l$), n = 22	13.1 ± 7.8	11.7 ± 6.5	p = 0.244	p = 0.488
Neutrophils ($\times 10^3/\mu l$), n = 22	9.6 ± 7.2	8.1 ± 5.2	p = 0.455	p = 0.321
ALT (IU/L), n = 22	85.1 ± 59.2	55.2 ± 35.7	***p = 0.005***	p = 0.062
ALP (IU/L), n = 22	26.8 ± 11.9	28.0 ± 10.8	p = 0.635	p = 0.355
GGT (IU/L), n = 17	4.1 ± 2.8	2.8 ± 2.1	***p = 0.031***	p = 0.557
Total bilirubin (mg/dl), n = 19	0.3 ± 0.3	0.2 ± 0.2	p = 0.127	p = 0.496
Clopidogrel	Baseline	1 month		
Hematocrit (%), n = 23	35.2 ± 4.3	35.6 ± 5.5	p = 0.703	
Platelets ($\times 10^3/\mu l$), n = 13	193.9 ± 63.7	225.0 ± 102.8	p = 0.340	
Total WBC ($\times 10^3/\mu l$), n = 19	11.2 ± 5.8	8.9 ± 3.6	***p = 0.014***	
Neutrophils ($\times 10^3/\mu l$), n = 19	7.6 ± 4.8	5.5 ± 2.7	p = 0.066	
ALT (IU/L), n = 24	76.3 ± 40.3	77.1 ± 62.7	p = 0.989	
ALP (IU/L), n = 24	30.0 ± 13.5	34.2 ± 13.4	***p = 0.044***	
GGT (IU/L), n = 16	3.7 ± 3.7	2.9 ± 3.4	p = 0.188	
Total bilirubin (mg/dl), n = 20	0.2 ± 0.1	0.2 ± 0.1	p = 0.677	

WBC = white blood cells; see abbreviation table for the remainder of the abbreviations.
Bold and italic data represents significantly different between the groups identified.

group was somewhat longer [248 (95% CI 137—431) days]. However, the cats in this study had a run-in period of 1—3 months which could impact the comparison to other studies.

Both aspirin and clopidogrel were well tolerated in this study but the relatively small population size potentially limits the clinical recognition of adverse events to those that occur commonly while more infrequent or episodic events would only be recognized with a larger study population. Vomiting, hematemesis, inappetance and other gastrointestinal signs have been reported in up to 22% of cats receiving aspirin at the same dose used in this study.[1] Aspirin had to be discontinued in 1 cat due to vomiting and hematochezia while one additional aspirin treated cat who died following recurrent CATE had a large gastric ulcer on necropsy. Empirical observations of vomiting and frothing at the mouth have been reported in cats receiving clopidogrel, presumably due to the bitter taste of the drug. None of the cats receiving clopidogrel in this study experienced vomiting or gastrointestinal signs attributable to clopidogrel administration. The apparent lack of gastrointestinal signs for both drugs is unexplained, but these drugs were put into an empty gelatin capsule for administration and this could have reduced oral or gastric irritation. After 1 month of study drug administration in the study reported here, there was a significant increase in ALP in the aspirin group and a significant increase in ALT in the clopidogrel group. However, none of these individual cats had values outside of the reference range. One cat in the clopidogrel group experienced elevated liver enzymes and developed icterus after 40 days of drug administration. There was a significant reduction in the white blood cell count at 1 month in the cats from the clopidogrel group (Table 2) but none were outside of the reference range. There was no identifiable bleeding noted in any of the cats in this study aside from the one cat in the aspirin group with hematochezia. In the seminal CAPRIE study evaluating clopidogrel and aspirin in humans, adverse gastrointestinal events including diarrhea, indigestion, nausea, and vomiting were reported in 19% of patients receiving clopidogrel and 21% receiving aspirin with diarrhea significantly more common with clopidogrel and indigestion, nausea, and vomiting significantly more common with aspirin.[18] A small number of patients developed elevated liver values with the incidence significantly higher for aspirin (3.15%) than clopidogrel (2.97%). Thrombocytopenia and neutropenia were rare and severe neutropenia has been reported in <1% of human patients taking clopidogrel in post-market monitoring.[k]

[k] Plavix® package insert, December 2013, Bristol-Meyers Squibb/Sanofi Pharmaceuticals Partnership, Bridgewater, NJ, USA.

Clopidogrel was associated with a significantly higher frequency of dermatologic rash than aspirin but no such occurrence was noted in the cats in the study reported here. There was no significant difference in all-cause bleeding between clopidogrel and aspirin (9.27% vs. 9.28%) although there was a significantly higher incidence of gastrointestinal bleeding associated with aspirin (2.66% vs. 1.99%).

Retrospective studies of aspirin therapy have reported recurrent CATE rates from 17% to 75%[1,10,13,17] and the recurrence rate for aspirin in this study was 75% while the recurrence rate in clopidogrel treated cats was 53%. The overall recurrence rate of CATE may not be the best marker of antithrombotic therapy in this population of cats as complete protection against recurrent thrombotic events in such animals is unlikely and unrealistic. Such a marker interprets a recurrent CATE event in a cat at 2 months in the same light as a recurrent event in another cat at 2 years. For this reason, the median time to event for the primary endpoint of recurrent CATE may provide a more objective assessment of therapeutic success.

Anticoagulant therapy with warfarin has been shown to be superior to aspirin or combined aspirin and clopidogrel therapy for the prevention of cardioembolic events in humans.[19] Similarly, clopidogrel added to aspirin is superior to aspirin alone in patients unsuitable for anticoagulant therapy.[20] Newer anticoagulant drugs have been shown to be as effective as warfarin for cardioembolic events with atrial fibrillation without the need for frequent monitoring and the same or reduced risk of bleeding.[21–23] These drugs may provide similar benefits in cats at risk for recurrent CATE and should be evaluated against clopidogrel in the future.

There a number of study limitations. The overall study population size is relatively small but the survival rate for CATE is poor which limited enrollment. Despite the small study groups a significant difference was identified between the study groups with respect to the primary endpoint although this did require an increase in population size determined through a repeat power analysis during the study. The small population size does impair the ability to identify less common adverse events from the study drugs. The echocardiographic exams were performed by individuals with varied levels of expertise and precise measurements were not verified by a central site. However, diagnosis of underlying cardiac disease was always made by a board-certified cardiologist either directly from their examination or from images provided to the principal investigator. Subsequent echocardiographic exams were not included in the study design, so the assessment of progressive cardiac disease and association with recurrent CATE cannot be determined. While concurrent cardiac therapy was attempted to be standardized based on the underlying cardiac disease, this was not always possible. Adherence to a strict schedule for blood test monitoring was not possible in some cases and platelet counts were difficult to reliably obtain. Platelet function was not assessed in this study so we cannot determine if an individual cat had appropriate platelet inhibition in response to the study drug and absent or reduced responders to both aspirin and clopidogrel have been reported in humans.[24–27] The dose of aspirin used in this study could be challenged. We decided to use the standard dose of aspirin as it allowed for easier creation of study drug capsules and precluded the need to change dosing based on changing weight of the cats. Concerns have been expressed that this dose of aspirin may inhibit endothelial cells and reduce the formation of prostacyclin, which inhibits platelet aggregation. However, it has been shown that this dose of aspirin was not associated with a higher frequency of recurrent CATE compared to a lower dose of aspirin in a retrospective study.[1] Additionally, there is evidence that the dose of aspirin used in this study does not result in platelet inhibition in the cat[28] (Hogan DF, unpublished data) so the use of a lower dose of aspirin would seem unlikely to result in platelet inhibition. The use of a lower aspirin dose has been associated with reduced adverse events in cats but we did not see a high frequency of adverse events associated with aspirin administration in this study. The study drugs were put into capsules of different colors and if an investigator had two cats on different colored capsules, they could assume they were assigned to different study groups. However, the different colored capsules reduced the risk of cats accidently receiving multiple consecutive days of aspirin and the investigators and enrolling veterinarians were not informed during the study that the different colors were associated with different treatment groups. Lastly, this study was not a placebo controlled trial, but the steering committee had concerns regarding the ethics of including a placebo arm when the prognosis of CATE is so poor. We were also concerned that cat owners and enrolling veterinarians would be reluctant to enroll cats knowing that the cat may receive no prevention for a recurrent CATE event. That being said, this study is a comparative study between clopidogrel and aspirin and the possibility

that aspirin actually resulted in a worse outcome than no treatment must be considered; resulting in clopidogrel having a neutral effect on the study outcome.

In conclusion, clopidogrel was superior to aspirin for the prevention of recurrent CATE and chronic clopidogrel administration was well tolerated and bleeding was not reported. It is possible that cats who survive a CATE event are somehow different from the broader population of cats with underlying heart disease so it is unknown if the superiority of clopidogrel over aspirin is applicable to primary prevention of CATE. However, given the route of administration, good tolerability, lack of bleeding, and concern regarding the inadequate antiplatelet effect of aspirin in cats, clopidogrel would appear to be a reasonable clinical choice for primary thromboprophylaxis in cats determined to be at risk for CATE.

Conflicts of interest

D.F. Hogan: prior grant support from Bristol-Meyers Squibb/Sanofi Pharmaceuticals Partnership.

There are no other reportable potential conflicts of interest related to this study.

Acknowledgments

This study was funded by the Morris Animal Foundation (D04FE-005, D09FE-001). Additional support was provided by the VIN Foundation and private donors.

We would like to thank Kim Sederquist for her critical role as study coordinator and we would like to thank Dr. Mark Rishniw for his assistance in setting up the study website.

The steering committee would like to acknowledge the following clinicians who enrolled cats onto the study:

Leslie Ahluwalia, Eddison Barrientos, Helen Bell, Ben Beyers, Jan Bright, Sara Brown, Carol Champion, I-Ping Chan, Kevin Christiansen, Taro Cuetara, Laura DeLellis, Cathy Eastman, Amara Estrada, Scott Fausel, Nonya Fiakpui, Deb Fine, Darren Fry, Carrie Ginieczki, Jonathan Goodwin, Henry Green, Karen Hayworth, Debra Henderson, Beverly Hickman, Andonia Hsu, Herbert Hulls, Kate Jacob, Lauren Kappers, William Keatts, Mike Luethy, Aliya Magee, Rebecca Malakoff, Sue Marshall, Dawn Martin, Anne Masloski, Christopher Middleton, Lindsay Norman, Stacy O'Quinn, Jeanne Pittari, Analisa Prahl, Robert Prosek, Rebecca Reardon, Erin Reed, Evelyn Richer, Yvonne Roberts, Carl Sammarco, Karen Sanderson, Josef Schiele, Sarah Scruggs, Eryn Shipley, Eva Sikorska, Meg Sleeper, Barb Smith, Aarthi Subram, Dennis Trafny, Robert Vasilopulos, Carole Werkhoven, Elaine Wexler-Mitchell, Aaron Wey.

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