



### **Study Design:**

Multi-center, double-blinded prospective study. Forty cats will be randomly assigned to receive either clopidogrel (18.75 mg PO q 24 hours) or aspirin (81 mg PO q 72 hours). The dosages chosen for the study drugs are based on the standard accepted dosing regimen for aspirin and preliminary data from clopidogrel pharmacodynamic studies.

### **Patient Selection:**

Cats of any age and sex will be eligible for study entry. Cats must have had a clinically evident cardiogenic embolic event no sooner than 1 month and no longer than 3 months previously.

“Clinically evident” is defined as objective and subjective evidence of 1) ischemic neuromyopathy (thoracic or pelvic limbs) 2) cerebrovascular accident or 3) splanchnic infarction.

Complimentary diagnostic studies, including perfusion studies (nuclear or angiographic) will be considered as supportive or definitive support but not required to make the diagnosis of an embolic event. Cats must have objective evidence (from echocardiographic studies performed or reviewed by a board-certified cardiologist) of underlying myocardial disease that would support the formation of intracardiac thrombi which fulfills the criteria for cardiogenic embolism.

Owners will complete a daily log that will record appetite, evidence for gastrointestinal or dermatologic adverse effects and evidence for bleeding.

## **Definition of Myocardial Disease:**

### **Hypertrophic cardiomyopathy (HCM):**

End-diastolic left ventricular free wall (LVFWd) and/or interventricular septum (IVSd) wall thickness  $\geq 6$  mm and normal systolic function (percent fractional shortening (%FS)  $\geq 30\%$ ).

### **Restrictive cardiomyopathy (RCM):**

Moderate to severe left atrial (LA) dilatation (left atrial end-systolic diameter (LAs)  $\geq 18$  mm) with a relatively normal left ventricle (LV) defined as normal wall thickness ( $< 6$  mm), non-dilated chamber ( $< 17$  mm) and relatively normal systolic function (%FS  $\geq 30\%$ ).

### **Ischemic cardiomyopathy/unclassified cardiomyopathy (ICM/UCM):**

Moderate to severe LA dilatation (LAs  $\geq 18$  mm) with an abnormal LV where there are areas of normal or increased wall thickness adjacent to areas of reduced wall thickness and systolic function is decreased globally (%FS  $< 30\%$ ) or regionally (discrete areas of hypokinesis, akinesis or dyskinesis).

### **Idiopathic dilated cardiomyopathy (DCM):**

Moderate to severe LA and LV dilatation (LAs  $\geq 18$  mm, LVDd  $\geq 18$  mm, respectively) with normal wall thickness (LVFWd  $\leq 6$  mm, IVSd  $\leq 6$  mm) and reduced global systolic function (%FS  $< 30\%$ ) with a normal plasma or whole-blood taurine level.

## **Concurrent Cardiac Medications:**

In an attempt to standardize concurrent cardiac therapy as much as possible, the following therapeutic protocols will be used.

- 1) Cats with a history of congestive heart failure (pulmonary venous congestion, pulmonary edema and pleural effusion or ascites with evidence of elevated venous filling pressures):**

Enalapril- 0.50 mg/kg PO daily

Furosemide- 6.25 mg PO daily (<4.0 kg), 12.5 mg PO daily ( $\geq$ 4.0 kg)

- 2) Cats without a history of congestive heart failure:**

**HCM:** no treatment except for antithrombotic agent

**RCM, ICM/UCM:** Enalapril- 0.5 mg/kg PO daily

**DCM:** Enalapril- 0.5 mg/kg PO daily, digoxin- 0.03125 mg/cat PO q 24-48 hrs determined by digoxin levels

- 3) Cats with echocardiographic evidence for SAM regardless of underlying cardiac disease:**

Atenolol- 6.25 mg PO daily (<4.0 kg), 12.5 mg PO daily ( $\geq$ 4.0 kg) can be added (not required) to treatments listed above except for DCM.

Daily medications can be given once a day or divided twice a day.

## **Study schedule:**

- 1) **Study entry**        The cat's medical record will be reviewed and an echocardiogram will be performed (or reviewed) by a board-certified cardiologist. Laboratory tests (complete blood count, chemistry panel) will be performed for baseline time point. Appropriate concurrent cardiac therapy will be initiated and the cat will be randomly assigned to receive aspirin or clopidogrel.
- 2) **Re-evaluation of renal function:**        Cats that have enalapril initiated at study entry will have renal parameters repeated within one week to evaluate for possible adverse effects.
- 3) **One month recheck:**        Cats will be re-evaluated via physical examination for evidence of bleeding tendencies (petechiae, ecchymoses) or any other abnormalities. The daily logs will be collected and evaluated and overall well-being of the cat will be discussed with the owner. Blood work (complete blood count and serum chemistries) will be performed to evaluate for possible adverse effects.
- 4) **Three month recheck:**        Identical to one month recheck except no blood work.
- 5) **Six month recheck:**        Owners will be contacted by phone to record any adverse events recorded on the daily log sheets or embolic episodes. Daily log sheets will be collected from owners. The referring veterinarian will also be contacted for any additional information or questions.
- 6) **12 month recheck:**        Identical to six month recheck.

**Primary end-point:** Clinically evident cardiogenic embolic event. This event may or may not result in death (vascular death).

**Secondary end-points:** All-cause mortality, mortality associated with cardiac disease, and development of congestive heart failure. Cats that develop congestive heart failure during the study can continue with the study. Appropriate changes to cardiac therapy will be made based on above classifications. Cats that die suddenly during the study should undergo complete necropsies to confirm the presence or absence of an embolic event.

**Exclusion Criteria:**

Exclusion criteria will include documented taurine deficiency, bleeding disorders including thrombocytopenia, thrombocytopenia without bleeding, presence of an intracardiac thrombus, unstable congestive heart failure and concurrent conditions (non-cardiac) that would likely result in death in less than 1 year. Cats with non-cardiogenic thromboembolism.

**Procedural Reimbursement:**

<b>Office calls (3/cat)</b>	<b>\$50 ea</b>
<b>Echocardiogram (1/cat)</b>	<b>\$250 ea</b>
<b>CBC (2 per cat)</b>	<b>\$35 ea</b>
<b>Serum Chemistry (3 per cat)</b>	<b>\$55 ea</b>
<b>Study Drugs (clopidogrel or aspirin)</b>	<b>supplied by principal investigator</b>