

Thrombolytic Therapy in the Acute Period of Aortic Thromboembolism in Cats

A Knowledge Summary by

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KNOWLEDGE SUMMARY

PICO question

Of cats that present with aortic thromboembolism, do patients that receive thrombolytic therapy in the acute phase have improved survival as compared to those who do not?

Clinical bottom line

Based on the current available evidence, the use of thrombolytic therapy in the acute phase of aortic thromboembolism (ATE) does not appear to improve survival when compared to conventional supportive therapy. Frequently reported adverse side effects further questions its merits, and large scale controlled clinical trials would be required to further evaluate any benefit in the use of this therapy.

Clinical Scenario

An 8-year-old male neutered domestic shorthair presents with acute onset bilateral hindlimb paralysis. On auscultation, a grade III/VI heart murmur is detected. Femoral pulses are absent, distal hindlimbs are cool when palpated and the hindlimb paw pads appear cyanotic. A previous diagnosis of pre-clinical hypertrophic cardiomyopathy had been confirmed on echocardiography. You are strongly suspicious of an aortic thromboembolism and the owner is keen to pursue further treatment. A repeat echocardiogram reveals enlargement of the left atrium, with atrial thrombus but no visible thrombus. A quick TFAST is absent for B-lines which may reflect left sided congestive heart failure (CHF).

In addition to supportive therapy, would additional thrombolytic treatment for clot dissolution improve outcome in the acute phase?

The evidence

Six studies were included that best answered the proposed PICO question. A number of thrombolytic therapies have been described for aortic thrombosis, however a lack of controlled studies prohibits direct comparison between those that receive conventional supportive therapy and the different thrombolytic options.

Three of the six studies were included for survival statistics of cats that did not receive a form of thrombolytic therapy and the three studies evaluating thrombolytic therapy explored the use of streptokinase, rheolytic thrombectomy and tissue plasminogen activator (tPA).

The three studies included for the survival statistics were all retrospective case series ranking low in evidence hierarchy.

Summary of the evidence

Schoeman, J.P. (1999)	
Population:	<ul style="list-style-type: none"> • Cats presenting to a first opinion veterinary hospital over an 8 year period with clinical signs of distal aortic thromboembolism • Episodes classified as: <ul style="list-style-type: none"> ○ Complete 34/49(69%): absent bilateral femoral pulses; cold limbs; cyanosis of the nailbeds and hindlimb paralysis ○ Partial 19/49 (39%): reduced femoral pulses; proprioceptive deficits and unilateral or bilateral hindlimb paresis • Cats had CHF in 51% of episodes
Sample size:	44 cats (49 episodes of ATE)
Intervention details:	<ul style="list-style-type: none"> • Full data of the emergency treatment was available for 32/49 episodes. • Treatment and number of cases: <ul style="list-style-type: none"> ○ Aspirin (75 mg EOD) - 21 ○ Furosemide (1–4 mg/kg) - 19 ○ Heparin (500–200 iu/kg 3–4 times daily) - 12 ○ Acepromazine (ACP) [0.05–0.2 mg/kg twice daily (BID)] - 10 ○ Nine cats received a combination of furosemide, heparin, aspirin and buprenorphine ○ Eight cats received cyproheptadine (2 mg BID) ○ Other treatments included oxygen therapy, diltiazem, non-steroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting-enzyme (ACE) inhibitors
Study design:	Retrospective case series
Outcome studied:	Evaluation of records of cats presenting to a first opinion veterinary hospital with clinical signs of distal aortic thromboembolism.
Main findings:	<ul style="list-style-type: none"> • Overall, cats survived 39% (19/49) of the episodes <ul style="list-style-type: none"> ○ Cats survived 93% (14/15) of the partial episodes ○ Cats survived 15% (5/34) of the complete episodes • Similar to other studies, ATE seemed associated with decompensation of pre-existing heart disease

Limitations:	<ul style="list-style-type: none"> • Retrospective - diagnostics, treatment and population not standardised • Complete emergency data was only available for 32 of the cases • Limb assessment subjective • Diagnosis of heart failure questionable from available information • Each episode of ATE survived was included in the overall survival figure. This means a single cat surviving multiple episodes could skew the result of the overall population. ATE severity and prognosis is dependent on multiple factors which include episode severity, treatments provided and co-morbidity. These factors should be considered in individuals that went on to survive multiple episodes • Incomplete records
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Moore, K.E. et al. (2000)	
Population:	<ul style="list-style-type: none"> • Cats with clinical signs of ATE presenting to two hospitals between 1992–1998 (one university) treated with streptokinase (SK) <ul style="list-style-type: none"> ○ Definition: dysfunction in one or two limbs and lack of arterial pulse in affected limb • Limbs affected: <ul style="list-style-type: none"> ○ 89% hindlimb paresis or paralysis ○ 9% monoparesis hindlimb ○ 2% monoparesis forelimb • 33/43 (77%) cats presented hypothermic (43/46 had temperature recorded) • 21/32 (66%) were in CHF (32/46 cats had thoracic radiographs on admission) • 36/36 (100%) had echocardiographic evidence of structural heart disease (echocardiography was performed on 36/46 cats)
Sample size:	46 cats
Intervention details:	<ul style="list-style-type: none"> • Streptokinase dosed on u/kg basis • Duration of infusion ranged from 1–28 hours (median 4 hours) • 35% (16/46) cats received ACP • Cats also received nitroglycerin (dose not stated), heparin (50–232 u/kg four times daily (QID) subcutaneous (S/C)) and other unspecified therapies
Study design:	Retrospective case series

Outcome studied:	<ul style="list-style-type: none"> To identify complications and outcomes of cats treated with SK following ATE Whether time administered following clinical signs altered outcome Prognostic indicators
Main findings:	<ul style="list-style-type: none"> 18/46 (39%) died in hospital 13/46 (28%) were euthanised due to poor response to treatment or complications 15/46 (33%) were discharged 25/46 (54%) regained arterial pulses within 2–24 hours post streptokinase 14/46 (30%) regained motor function 18/46 (39%) developed evidence of clinical bleeding or had measurable coagulation abnormalities following SK Higher rectal temperature was associated with survivors No significant difference between survivors and nonsurvivors and time of SK administration Hyperkalaemia post SK administration (40/46 had serum potassium levels measured following SK administration): <ul style="list-style-type: none"> 14/40 (35%) of cats Two suspected based on electrocardiogram (ECG) changes 11/16 (69%) of these cats died in hospital, four were euthanised and one discharged. Hyperkalaemia was associated with longer infusion time Cats who received heparin were more likely to survive (P = 0.052)
Limitations:	<ul style="list-style-type: none"> Retrospective: sample population; treatment and diagnostics performed were not standardised Incomplete clinical records No control group Highly variable range in administration time of SK

Smith, S.A. et al. (2003)

Population:	<ul style="list-style-type: none"> Cats presenting to the University of Minnesota Veterinary hospital over a 10 year period with clinical signs of ATE Cats with clinical signs >2 days were excluded Limbs affected: <ul style="list-style-type: none"> 72% bilateral hindlimbs 2% bilateral hindlimb and one forelimb 13% one hindlimb 12% one forelimb 2% other body system affected 55/125 (44%) had CHF on presentation (125/250 had thoracic radiographs or post-mortem)
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	<ul style="list-style-type: none"> 72/110 (65%) presented hypothermic (110/250 had records of rectal temperature)
Sample size:	127 cats
Intervention details:	<ul style="list-style-type: none"> Supportive therapy: n41 – fluid therapy; heat – n24; physical therapy – n14; oxygen – n34; analgesia – n53 Streptokinase infusion (dose not stated): n4 Anticoagulant therapy: unfractionated heparin (75–500 u/kg I/V single dose; 10–300 u/kg S/C q6–12 hours) – n67; aspirin – n46 Aspirin dose: <ul style="list-style-type: none"> High (HDA) ≥ 40 mg/cat q72h – n35 (27 in conjunction with heparin) Low (LDA) 5 mg/cat q72h – n12 (six in conjunction with heparin)
Study design:	Retrospective case series
Outcome studied:	<ul style="list-style-type: none"> Do clinical findings of acute ATE provide prognostic information? Can survival curves be created for cats that survive the initial episode? To compare the use of low dose and high dose aspirin in cats surviving the initial episode
Main findings:	<ul style="list-style-type: none"> 44/127 (35%) survived to discharge <ul style="list-style-type: none"> 40/123 (33%) [excluding four cats treated with streptokinase] 39/121 (32%) [excluding six cats that had already survived >two days following ATE] 35/117 (30%) [excluding six cats that had survived >two days following ATE and four cats treated with streptokinase] 32/127 (25%) of cats were euthanised without therapy 35/83 (42%) of cats that received treatment in the acute period (excluding thrombolytic therapy) survived Rectal temperature, heart rate, number of limbs affected, motor function and serum phosphorus differed between survivors and nonsurvivors Aspirin dose did not influence recurrence or survival LDA was associated with fewer gastrointestinal side effects
Limitations:	<ul style="list-style-type: none"> Retrospective - diagnosis, treatment and patient cohort was not standardised The study might be underpowered for comparison of aspirin doses 10 year study. Earlier data demonstrated poorer survival which skews overall statistics There is limited discussion of supportive therapy. Fluid therapy may be detrimental in CHF cases

Reimer, S.B. et al. (2006)	
Population:	<ul style="list-style-type: none"> • Cats presenting to the University of California veterinary hospital with bilateral paralysis in pelvic limbs caused by aortic thromboembolism • Cats with palpable femoral pulses were excluded • All cats presented hypothermic • All cats had underlying myocardial disease • Mean time between onset of clinical signs and thrombectomy was 44.8 hours (+/- 72.6h) range 5–192 hours
Sample size:	Six cats
Intervention details:	<ul style="list-style-type: none"> • Heparin pretreatment (150 iu/kg) S/C to prevent additional thromboembolic events during vascular manipulation. This was continued q6h postoperative, for the next 24 hours • Standardised AngioJet™ rheolytic thrombectomy system via carotid artery • Enoxaparin sodium (1 mg/kg S/C BID) started 24 hours postoperative • Streptokinase (45,000 iu) was delivered locally in one patient due to unsuccessful thrombectomy
Study design:	Prospective clinical trial (nonrandomised, nonblinded)
Outcome studied:	To determine the safety and efficacy of the AngioJet™ rheolytic thrombectomy system in the treatment of ATE
Main findings:	<ul style="list-style-type: none"> • 5/6 (83%) of cats had clot dissolution • 1/6 (17%) died of uncontrollable hypotension and cardiac arrest • 2/6 (33%) were euthanised, one following streptokinase administration due to severe hypotension and extravasation from the aorta and the other 12 hours post-op due to progressive acidaemia and hypotension • 3/6 (50%) were discharged from hospital with varying degrees of ambulatory deficits but all had palpable femoral pulses • The time between clinical signs and thrombectomy was not a predictor of outcome
Limitations:	<ul style="list-style-type: none"> • Small cohort • No control group • Concurrent therapy of heparin and enoxapram • One cat received streptokinase due to unsuccessful thrombectomy • Some patients already survived up to 192 hours • It is likely that the study is underpowered from the small

	sample size
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Welch, K.M. et al. (2010)	
Population:	<ul style="list-style-type: none"> Cats presenting with clinical signs of ATE to Tufts University Hospital Limbs affected: <ul style="list-style-type: none"> 91% bilateral pelvic limbs 9% unilateral forelimb 8/11 (73%) of cats were hypothermic on presentation 1/11 (9%) cat was diagnosed with previous heart disease 9/11 (82%) cats had at least one or more limbs with absent pulses and motor function at admission 3/11 (27%) cats had motor function in one or more affected limbs prior to tPA administration
Sample size:	11 cats
Intervention details:	<ul style="list-style-type: none"> Group A (7 cats) Tissue plasminogen activator (tPA) continuous rate infusion (CRI) over 4 hours totalling 5 mg tPA per cat Group B (4 cats) Tissue plasminogen activator accelerated protocol: 1 mg IV bolus followed by 2.5 mg over 30 mins and then 1.5 mg over 1 hour Additional 5 mg CRI over 4 hours if unresponsive (two cats in both groups)
Study design:	Prospective randomised clinical trial (nonblinded)
Outcome studied:	<ul style="list-style-type: none"> To compare two different dosing strategies of tPA To determine side effects Assess treatment response through pulse and motor function
Main findings:	<ul style="list-style-type: none"> 7/11 (64%) of cats survived 24 hours 4/7 (57%) had motor function at 24 hours 3/11 (27%) survived to discharge 6/9 (67%) cats had return of pulses or improved limb scores 12 hours post drug administration (these nine cats had at least one or more limbs with absent pulses and motor function at admission) Adverse side effects in all patients led to early termination of the study. The reported adverse side effects were: arrhythmias; azotemia; hyperkalaemia; neurological signs with respiratory arrest in three cases; cardiac arrest and haemorrhage in one cat. There was no difference in

	outcome between clinical signs and therapy initiation
Limitations:	<ul style="list-style-type: none"> • No control group • Small sample size • One patient received aspirin prior to study • No 'gold standard' dose • A small number of cases underwent necropsy • Arbitrary study termination at 24 hours • Arbitrary inclusion criteria of up to 12 hours following clinical signs • Some cats regained motor function in one or more limbs prior to tPA administration • 4/11 (36%) cats received the additional dose, reducing the statistical power of results when comparing the two dosing protocols • Limb scoring was subjective

Borgeat, K. et al. (2014)	
Population:	<ul style="list-style-type: none"> • Cats presenting to three practices over a 98 month period with clinical signs of arterial thromboembolism • Limbs affected: <ul style="list-style-type: none"> ○ 12% unilateral hindlimb ○ 78% bilateral hindlimbs ○ 9% unilateral forelimb ○ 1% of cats had three limbs affected; ○ one cat had all limbs affected • Of cats not euthanised at presentation and where evidence was available, 42/63 (67%) were in CHF
Sample size:	250 cats
Intervention details:	<ul style="list-style-type: none"> • 153/250 (61%) were euthanised on presentation • Analgesia was provided to all cats not euthanised • Diuretic treatment was administered to 57/97 (59%) cats • 68/97 (70%) received combinations of heparin, aspirin and clopidogrel (doses for treatments not stated)
Study design:	Retrospective case series
Outcome studied:	<ul style="list-style-type: none"> • To estimate the prevalence of arterial thromboembolism (ATE) in cats in the UK presenting to general practice (GP) • It was hypothesised that for some cats, >one year survival was possible if they were not euthanised
Main findings:	<ul style="list-style-type: none"> • 166/62856 (0.3%) prevalence of ATE (practice 1 and 3, data for total cats visiting practice 2 was not available) • 153/250 (61%) were euthanised at presentation • 68/250 (27%) survived the first 24 hours • 30/250 (12%) survived seven days • 6/250 (2%) were alive at one year • Higher mortality was associated with: <ul style="list-style-type: none"> ○ Lower rectal temperature

	<ul style="list-style-type: none"> ○ No aspirin/clopidogrel therapy ○ Management at practice 2 in the first 24 hours ● Hypothermia was associated with nonsurvivors
Limitations:	<ul style="list-style-type: none"> ● Retrospective - No control over patient population, diagnostics performed and treatment standardisation ● Small subgroups obscure overall statistics ● Variable mortality between clinics may reflect case management ● Database search terms could be more comprehensive ● Practices affiliated with specialists may have influenced clinician decision ● Insufficient numbers after seven days weaken significant predictors of mortality

Appraisal, application and reflection

Of the best available evidence, four of the studies were retrospective case series. Three of these studies were included to provide survival information for those that did not receive thrombolytic therapy and the other study explored the use of streptokinase. As retrospective case series, intervention and patient population was not standardised and therefore bias may significantly affect the results. For this reason, direct comparisons cannot be deduced between studies. Of the other two studies which evaluated the use of tPA (n = 11) and rheolytic thrombectomy (n = 6), sample sizes were small and therefore both are likely to be underpowered.

Survival to discharge in patients that did not receive thrombolytic therapy was reported: 33% (35% overall survival includes four treated with streptokinase) and 42% (survivors of the initial event treated with supportive therapy alone in the acute phase) (Smith et al., 2003); 39% (Schoeman, 1999) and 27% [first 24 hours], 12% [at seven days] (Borgeat et al., 2014). Borgeat et al., (2014) reported that 61% were euthanised at presentation and of the cats that survived the first 24 hours, 47% were euthanised in the following seven days. Many factors may influence decision making with regards to euthanasia including prognostic indicators (rectal temperature, number of limbs affected, comorbidities, electrolyte parameters etc.) client factors and welfare on an individual basis, which may explain different survival figures between studies.

Reimer, et al. (2006) evaluated the use of rheolytic thrombectomy with a survival of 50% (three cats). The entire population presented with hindlimb paralysis, absent femoral pulses and hypothermia which has been reported to carry a poor prognosis (Smith et al., 2003; Borgeat et al., 2014). All cats had underlying structural heart disease. Of the 50% of cats that did not survive to discharge, hypotension was a common clinical finding. Cats also received heparin therapy which has been proposed to influence survival (Moore et al., 2000). Some cats had already survived 192 hours following initial ATE episode so its arguable that these had already survived the acute phase without thrombolytic intervention. The small sample size of this study weakens the statistical power of results.

Moore et al. (2000) reported a survival of 33% in patients that received streptokinase therapy. 89% presented with hindlimb paresis/paralysis to which 54% regained pulses 2–24 hours following infusion. The incidence of congestive heart failure was 21/32 (66%) and of the 36 cats that underwent echocardiography, all cats had evidence of structural heart disease. Infusion time of streptokinase was largely variable (1–28 hours) and other treatment was not standardised with some patients receiving heparin. 35% of patients were hyperkalaemic post streptokinase therapy which was associated with longer infusion times. Hyperkalaemia is likely a result of reperfusion injury and was negatively associated with survival. Only one cat with documented hyperkalaemia survived to discharge, however six cats did not have serum potassium measured following streptokinase infusion. 39% of the population developed clinical signs of bleeding or coagulation

abnormalities and three cats required blood transfusion.

Welch et al. (2010) evaluated the use of two dosing strategies with tissue plasminogen activator (tPA). 64% of cats survived the initial 24 hours post therapy and 27% survived to discharge. The study was terminated early due to adverse side effects in all patients. Adverse side effects included: arrhythmias, azotemia, hyperkalemia, neurological signs with respiratory arrest in three cases; cardiac arrest in one cat and haemorrhage. After the first 24 hours, ongoing treatment was at the clinician's discretion and therefore treatment was no longer standardised. A limb scoring system was used to assess pulse and motor quality. Twelve hours post tPA administration, 6/7 (67%) cats regained pulses or had improvements in limb scores. Smith et al. (2003) has reported a correlation between improving motor function and survival, however many factors could influence this finding including severity of the initial ATE event and the subjectivity of these scoring systems. Similar to the rheolytic thrombectomy study, the sample size was small and therefore statistics are likely to be underpowered.

Decision making with regards to treatment of feline ATE is a multifactorial process that requires careful consideration on a patient by patient basis. This makes it difficult to compare different studies especially those carried out retrospectively. Of the evidence available exploring the use of thrombolytic therapies, sample sizes are small and lack comparative control groups. As discussed, the decision for euthanasia is based on many factors. This should be considered when comparing the survival figures between studies as those investigating the use of thrombolytic therapy represent a population of cats that have been selected for treatment and not euthanised. Although Reimer, et al. (2006) reported a 50% survival to discharge rate, the significance of this result is questionable by the small sample size and other factors discussed above. The other studies did not demonstrate superior survival compared to conventional supportive therapy. Frequently reported adverse side effects further questions the use of thrombolytic therapy as adjunct treatment.

Ultimately, randomised, large scale controlled clinical trials would be required to see whether there is any merit in the use of thrombolytic therapy in the acute phase of aortic thrombosis.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts on OVID platform 1973 to 2017 week 49 MEDLINE on OVID platform 1946 to present
Search terms:	(cats or cat diseases) OR (cats OR cat OR feline* OR felis) AND (thromboembolism or embolism or thrombosis) OR (arterialthromboembolism or arterial-thromboembolism or thromboembolism or embolism or thrombus)
Dates searches performed:	CAB Abstracts (20/12/17); Ovid MEDLINE (19/12/17)

Exclusion / Inclusion Criteria	
Exclusion:	Papers inappropriate to the PICO (non-related title and abstract; other species; papers unable to demonstrate post therapy outcome) conference proceedings; case reports; non-English language; opinion articles; papers not accessible; experimental ATE; book chapters
Inclusion:	Papers identifying acute outcome following use of thrombolytic therapy for ATE; papers with survival statistics for acute period in patients that did not receive thrombolytics (due to lack of comparative studies); naturally occurring ATE; ATE causing limb dysfunction

Search Outcome									
Database	Number of results	Excluded – not in English language	Excluded – Non-relevant to PICO	Excluded – Conference proceedings	Excluded- book chapter etc.	Excluded – Case reports	Excluded- Opinion article	Excluded- unable to access	Total relevant papers
CAB abstracts	479	105	299	6	49	9	4	1	6
Medline	600	101	487	0	0	6	0	1	5
Total papers when duplicates removed:									6

CONFLICT OF INTEREST

The author declares no conflicts of interest.

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