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Does medical or surgical treatment for aortic stenosis improve outcome in dogs?

A Knowledge Summary by

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KNOWLEDGE SUMMARY

PICO question

In adult dogs with aortic stenosis does treatment with beta blockers compared with surgical intervention show a longer survival time with improved clinical parameters?

Clinical bottom line

Category of research question

Treatment

The number and type of study designs reviewed

Eight studies were reviewed. One was a randomised controlled study, three were cohort studies, one was a case series and three were case reports

Strength of evidence

Moderate to weak

Outcomes reported

Intervention appeared to improve survival times ± physiological parameters when compared to no treatment at all. The severity of clinical signs was reduced, but the risk of sudden cardiac-related death was not diminished according to a number of papers. The direct comparison of surgical treatment with the use of beta blockers showed no significant difference in survival times or physiological parameters across all papers. There is not enough evidence available comparing the different beta blockers used for treatment to draw a meaningful conclusion as to which is more effective

Conclusion

Treatment of some form should be given to a dog diagnosed with aortic stenosis. This will improve clinical signs and there is evidence to say that it will prolong survival as well as improve quality of life.
More research into this area is essential. Controlled, randomised clinical trials should be carried out in order to find a reliable and strong recommendation for treatment. Ethical implications need to be considered when going forward with this, which is why the evidence pool is likely to be so limited currently

How to apply this evidence in practice

Clinical Scenario

A dog with aortic stenosis is presented for treatment. The owner is keen for long-term survival of their pet and as a clinician you aim to find the best intervention to improve physiologic parameters and quality of life.

The evidence

A total of eight published articles were evaluated: three cohort studies, three case reports, one case series and one randomised controlled study.

Summary of the evidence

Eason et al. (2014)	
Population:	Dogs with uncomplicated, severe subaortic stenosis (SAS) diagnosed via standard transthoracic 2-dimensional and Doppler echocardiography.
Sample size:	50 dogs
Intervention details:	Treatment group 27/50 – received beta-blockers Control group 23/50 – received no treatment • Of the 27 dogs in the treatment group, 25 received atenolol. The dose of atenolol was known for 23 of these dogs. They received a median dose of 0.55 mg/kg (range 0.3–1.2 mg/kg) given orally, once every 12 hours. • 1/27 received propranolol at 0.64 mg/kg, given orally, once every 8 hours and another dog received sotalol at of 0.9 mg/kg given once orally, every 12 hours.
Study design:	Non-blinded, non-randomised, retrospective cohort study
Outcome studied:	Transvalvular pressure gradient (PG), as estimated by Doppler echocardiography. Severe stenosis was classified as >80 mmHg.
Main findings: (relevant to PICO question):	• Treatment with a beta blocker had no demonstratable effect on survival time. • Two mortality analyses were carried out; one looking at 24 dogs from the treatment group and the other at 14 dogs in the control group. A high PG (>130 mmHg) at diagnosis (20/50 dogs) in both analyses was associated with a reduced survival time of 2.8 years, compared with 8.3 years for ≤130 mmHg (30/50 dogs). • An increased age at diagnosis was associated with an increased survival time in the all-causes multivariate mortality analysis.
Limitations:	Retrospective cohort managed by multiple clinicians, so inherently biased by lack of standardisation: in decision-making; dose of medication prescribed, and recommendation for euthanasia.

Hirao et al. (2003)	
Population:	A 3 month old Golden Retriever diagnosed with subvalvular aortic stenosis
Sample size:	One dog
Intervention details:	• The dog was initially administered isosorbide dinitrate and dipyridamole but no improvement was seen. • Surgical resection of the subvalvular stenosis was therefore undertaken. • The stenosis diameter was increased from 8 mm to 12 mm.

Study design:	Case report
Outcome studied:	Left ventricular systolic pressure, and the grade of the auscultated heart murmur.
Main findings: (relevant to PICO question):	• 203 days post-surgery, the dog was re-examined. One of the tests performed was selective left cardiac catheterisation, which showed a decrease in left ventricular-aortic systolic PG from 90 (pre-operative) to 44 mmHg. • Left ventricular angiocardiography showed an increase in the diameter of the left ventricular outflow tract postoperatively. • The grade of the presenting heart murmur also decreased from grade V/VI to grade II/VI 7 months postoperatively. • The dog died suddenly 10 months postoperatively, possibly related to its heart disease. • The report postulated the benefit of administration of atenolol prior to surgical intervention, to alleviate ventricular pressure overload before the myocardium is damaged irreversibly. The report suggested further research into this area is needed.
Limitations:	• This is a case report and therefore is reporting the response to treatment of one individual. Outcome here may not be repeatable amongst other animals. • There were no defined criteria for how the dog would be treated before treatment began, it was at the clinician's discretion as the case progressed. • Short survival time post-intervention does not allow for assessment of the utility of this treatment in the long-term. • No conclusive data can be drawn from this publication.

Komtebedde et al. (1993)	
Population:	Dogs with subvalvular SAS that had a systolic PG >70 mmHg and no other clinically significant cardiac defects. They had clinical signs which led to their referral for surgical correction; four dogs had systolic apical murmurs and three had syncope/exercise intolerance.
Sample size:	Seven dogs
Intervention details:	• When referred, patients were receiving a range of non-standardised medication: five dogs were receiving propranolol (beta blocker), one furosemide (loop diuretic) and another quinidine and digoxin (antiarrhythmics). • Patients underwent cardiopulmonary bypass (CPB) for a range of 130–210 minutes, as well as a transverse aortotomy to surgically correct subvalvular SAS.
Study design:	Case series
Outcome studied:	Haemodynamic parameters and cardiopulmonary data were both measured pre-operatively, perioperatively and for 3 days postoperatively.

Main findings: (relevant to PICO question):	• Six dogs were alive and stable after a mean follow-up time of 15.8 months (range from 2–27 months). • One dog died of chylothorax, 4 months postoperatively. • No dog experienced clinical signs of exercise intolerance or syncope postoperatively.
Limitations:	• The study had a small sample size, and no control group with which to compare treatment efficacy. • It is possible that the population suffered selection or referral bias due to the specific inclusion criteria in referred animals. • There was variation in medication administered prior to surgery. This makes it harder to evaluate the effectiveness of these medications, used alone or prior to surgery.

Meurs et al. (2005)	
Population:	Large breed dogs <24 months old with severe subaortic stenosis. Newfoundlands were actively recruited.
Sample size:	38 dogs
Intervention details:	BAV group – 15/28 dogs Atenolol group – 13/28 • 10/38 dogs were used to investigate the feasibility of the standard balloon valvuloplasty (BAV) surgery (not included for analysis of technique efficacy). • 28/38 dogs were enrolled in the long-term follow-up study. • The dosage of atenolol provided ranged from 0.46–1.5 mg/kg, given orally once every 12 hours. • The group of 28 dogs in the long-term follow-up study were re-assessed periodically throughout life.
Study design:	Randomised, non-blinded prospective study
Outcome studied:	The PG of all the dogs was measured pre-intervention and 6 weeks after intervention (i.e. either 6 weeks post-surgery or after 6 weeks of atenolol treatment).
Main findings: (relevant to PICO question):	• The BAV group (15/28) had a mean pre-operative PG of 147 mmHg, reduced to 86.7 mmHg post-surgery. • The atenolol group of 13 dogs had a pre-treatment PG of 122.2 mmHg, reduced to 113 mmHg after 6 weeks of atenolol. • The median survival time of the dogs treated with surgery and those treated medically were almost identical; 55 months vs. 56 months, respectively.
Limitations:	• Selection bias: Newfoundland dogs were overrepresented amongst the study population, owing to active recruitment of this breed. • There was no negative control group (due to ethical implications of not treating dogs with severe disease) and

	therefore the difference made by either intervention to the 'natural' survival time cannot be accurately determined.

Muir et al. (1989)	
Population:	4 month old St. Bernard. Presented with a grade V/VI murmur and severe aortic stenosis.
Sample size:	One dog
Intervention details:	• The dog was diagnosed with severe aortic stenosis on echocardiography. • Treatment was begun with 0.3 mg/kg propranolol, and this was gradually increased to 1.0 mg/kg. • A balloon dilation was then attempted to relieve the stenosis. • The dog then underwent surgical resection of the stenosis, 10 days after the balloon dilation. • Propranolol was maintained postoperatively.
Study design:	Case report
Outcome studied:	Systolic PG across the stenosis, derived by Doppler echocardiography
Main findings: (relevant to PICO question):	• When the aortic stenosis was diagnosed, the systolic PG across the stenosis was 100 mmHg. • Post balloon dilation, the PG across the stenosis was similar, at 90 mmHg. • As a result, surgery was performed to resect the stenotic region. • 48-hours after surgery, the heart murmur, whilst still easily audible, had reduced in intensity. • The dog died 20 days postoperatively. Post-mortem determined that death was not directly related to the surgery, but still may have been cardiac in origin. Repeat echocardiography was therefore never performed.
Limitations:	• This is a case report and therefore is reporting the response to treatment of one individual. Outcome here may not be repeatable amongst other animals. • Short survival time post-intervention does not allow for assessment of the utility of this treatment in the long-term. • The dog underwent many interventions, so the individual effectiveness of each cannot be determined. • The authors have not stated for how long the dog received medical treatment prior to undergoing surgical intervention. • No conclusive data can be drawn from this publication.

Nelson et al. (2004)	
Population:	10 month old Golden Retriever presenting with grade V/VI heart murmur, systolic PG of 159 mmHg, diagnosed with severe subaortic stenosis.
Sample size:	One dog
Intervention details:	• The dog was diagnosed with severe aortic stenosis, using echocardiography, and initially treated with 0.8 mg/kg atenolol, given orally once every 12 hours. • 11 months after presentation, the systolic PG had increased to 240 mmHg, but the atenolol dosage was deemed adequate and not altered. • 1 year later the dog presented with clinical signs of exercise intolerance and syncope; PG remained the same. • Surgery was performed; a modified Konno procedure, involving the complete removal of the affected area of septal outflow tract via right ventriculotomy. • A permanent intra-abdominal pacemaker was inserted because of potential damage to the atrioventricular node. • Postoperative ventricular arrhythmias were present and treated with amiodarone. This resolved after 8 days.
Study design:	Case report
Outcome studied:	Systolic PG across the stenosis.
Main findings: (relevant to PICO question):	• 8 days postoperatively, the systolic PG had reduced to 78 mmHg. • This decreased further after 24 months to 40 mmHg.
Limitations:	• This is a case report and therefore is reporting the response to treatment of one individual. Outcome here may not be repeatable amongst other animals. • A 2 year follow-up post-intervention does not allow for assessment of the utility of this treatment in the long-term. • No conclusive data can be drawn from this publication.

Orton et al. (2000)	
Population:	Dogs diagnosed with subvalvular aortic stenosis with instantaneous systolic PG >50 mmHg and known survival outcomes.
Sample size:	44 dogs
Intervention details:	The 44 dogs were divided into two groups; Surgical group 22/44 Non-surgical group 22/44 • All dogs in the surgery group were administered long-term atenolol, as were all but three dogs in the non-surgical group. The dosage range of atenolol was 0.7–1.2 mg/kg, given orally, once every 24 hours. • The surgery group had undergone open surgical correction of the subaortic stenosis with the aid of cardiopulmonary

	bypass. All 22 dogs underwent a membranectomy; of these, 14 underwent a concurrent quadratic septal myectomy in addition (dependent on degree of myocardial hypertrophy).
Study design:	Non-blinded, non-randomised retrospective cohort study
Outcome studied:	Systolic PG.
Main findings: (relevant to PICO question):	• There was no significant difference in the early reduction of PG between the two groups. In the surgery group, the PG range was 54–232 mmHg, and in the non-surgical group the PG range was 51–272 mmHg. • At 2–4 months postoperatively, for the surgery group the systolic PG was significantly lower, at 22–100 mmHg. This equates to a 41–75% reduction. There is no comparative data reported for the non-surgical group. • The addition of a septal myectomy performed alongside the membranectomy documented no further systolic PG reduction, nor an altered survival time compared to those who had not undergone this additional surgery. • In the surgery group, 5/22 dogs had recorded deaths related to surgical complications, and a further 6/22 recorded because of the disease itself (total 11/22 cardiac related deaths). • In the non-surgical group, 11/22 cardiac related deaths were also recorded. • No benefit to survival was documented between surgical and medical intervention. • The paper suggests a benefit in the use of atenolol to treat when compared with no treatment, due to overall longer survival times in dogs in this study, when compared to those of another study (Kienle et al. 1994) who did not receive atenolol. However, there was no negative control group in this comparison.
Limitations:	• There was no negative control group with which to compare the effects of these two treatment options, and the authors suggest a controlled clinical study to investigate this hypothesis may be warranted. • The reliability of the results was affected by the fact that this was a retrospective study and therefore nothing was performed under controlled conditions. • No follow-up echocardiographic data was available from the atenolol treatment group; therefore we cannot say that surgery was any better than medical management based on this data.

Shen et al. (2017)	
Population:	Dogs with severe SAS with a mean transvalvular PG of 143 mmHg (ranging 80–332 mmHg) that had undergone combined cutting and high-pressure balloon valvuloplasty (CB/HPBV).

Sample size:	22 dogs
Intervention details:	• Angiographic and echocardiographic video loops were collected within the 24 hours prior to intervention. • Screenshots were taken during diastole (in right-sided parasternal long-axis view) and measured for aortoseptal angle (AoSA) – an assessment of how steep the angle of left ventricular outflow is, previously associated with severity of subaortic stenosis. • A PG measurement was taken by direct cardiac catheterisation in anaesthetised animals before and immediately after CB/HPBV, and measured by Doppler echocardiography at diagnosis, then again 24 hours, 6 months and 12 months post-procedure. • All dogs were treated with atenolol when images were acquired (Atenolol dose regimen was adapted to suit the individual needs of each dog and was not standardised. The authors have not provided the individual dosages).
Study design:	Blinded, non-randomised retrospective cohort study
Outcome studied:	PG change over time, survival data
Main findings: (relevant to PICO question):	• Dogs with an obtuse AoSA >160° (4/22) had a greater decrease in PG following CB/HPBV compared to those with a more acute AoSA (<160° – 18/22 dogs). • At 24 hours post-procedure, PG reduction was 54 mmHg in dogs with obtuse AoSA. Reduction was lower, at 40 mmHg in the acute AoSA group. • At 6 months, in dogs with obtuse AoSA PG remained at a reduction of 58 mmHg, compared to 28 mmHg in acute AoSA dogs. • By 12 months, PG was reduced by 76 mmHg in dogs with obtuse AoSA vs. 28 mmHg acute AoSA. • This suggests that dogs with an obtuse AoSA may benefit more and for longer by undergoing a CB/HPBV procedure than those with an acute (<160°) AoSA.
Limitations:	• All dogs were treated with atenolol when images were acquired. As the study was retrospective, there was no control over dosage and compliance. • No control group of atenolol only or negative control group was used as a comparator.

Appraisal, application and reflection

The weakest level of evidence was provided by three case reports (Hirao et al., 2003; Muir et al., 1989; and Nelson et al., 2004), as each of these involved only one animal. Papers with a larger sample size (Eason et al., 2014; and Orton et al., 2000) were more valuable, but often limited by a retrospective design (Shen et al., 2017; and Orton et al., 2000). This leads to inherent bias because of no standardisation in decision-making, testing or treatment with historic clinical cases, and the involvement of random factors, such as owner opinion and financial influences. However, publications spanning the period 1989–2017 all used comparable surgical procedures and medical treatment, despite the lengthy time frame. All found similar results – that some sort

of treatment likely benefits dogs with aortic stenosis – and suggested further research is indicated and required to determine which treatment option is the most effective to improve quality of life and prolong survival.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts (Ovid SP): 1973–2021, week 13 Medline (Ovid SP): 1946–present
Search terms:	CAB Abstracts: (canine OR canines OR dog*).mp AND (aortic stenosis OR aortic valve stenosis).mp AND (Atenolol OR "beta blockers" OR "beta-blockers" OR propranolol OR "surgical correction" OR surgical OR surg* OR "balloon valvuloplasty").mp AND (Outcome OR survival OR "survival time" OR management OR result).mp Medline: (Canine OR Canines OR Dog*).mp AND (aortic stenosis OR "aortic valve stenosis").mp AND (Atenolol OR "beta blockers" OR "beta-blockers "OR propranolol OR "surgical correction" OR surgical OR surg* OR "balloon valvuloplasty").mp AND (Outcome OR survival OR "survival time" OR result).mp
Dates searches performed:	11 Apr 2021

Exclusion / Inclusion Criteria	
Exclusion:	• Discussion of surgical method without focus on individual patients • Discussion of the progression of aortic stenosis as a disease without focus on treatment methods • Presence of concurrent or secondary disease at the time of treatment that could influence outcome • Iatrogenically created aortic stenosis • Irrelevance to PICO question • Full text inaccessible
Inclusion:	• Available in English • Aortic stenosis treated with any surgical intervention or atenolol or propranolol

Search Outcome									
Database	**Number of results**	**Excluded – Concurrent or secondary disease**	**Excluded – Not available in English**	**Excluded – Describes surgical method, not outcomes**	**Excluded – Focused on aortic stenosis as a disease, not on treatment methods**	**Excluded – Iatrogenic aortic stenosis**	**Excluded – Not animals**	**Excluded – Irrelevant to PICO question**	**Total relevant papers**
CAB Abstracts	10	2	1	3	0	0	0	0	4
Medline	24	2	1	5	1	1	1	7	6
Total relevant papers when duplicates removed									**4**

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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