Occurrence of systemic hypertension in dogs with acute kidney injury and treatment with amlodipine besylate

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OBJECTIVES: To describe the occurrence of systemic hypertension in dogs with acute kidney injury and the efficacy of amlodipine besylate for its treatment.

METHODS: This retrospective study included 52 dogs with acute kidney injury (2007 to 2008) grouped based on the use of amlodipine in their treatment. Systemic blood pressure was measured with an oscillometric device at admission, before, during, and after amlodipine therapy.

RESULTS: Occurrence of systolic systemic hypertension (≥160 mmHg) and severe systolic systemic hypertension (≥180 mmHg) was 37% and 15% at admission and increased with hospitalisation to 81% and 62%, respectively. Twenty-two dogs were treated with amlodipine, at a median daily dosage of 0.38 mg/kg (interquartile range 0.28 to 0.49) divided in one to two applications per day. Amlodipine therapy was associated with a decrease in systolic systemic blood pressure of 24 mmHg (12 to 34) and a correction of severe systemic hypertension in 10 of 11 dogs within 24 hours. Overall, 73% of the dogs survived with a significantly lower proportion of survivors in treated compared to non-treated dogs (59% versus 83%, respectively, P=0.05).

CLINICAL SIGNIFICANCE: Results of this study reveal that systemic hypertension is common in canine acute kidney injury and that treatment with amlodipine is beneficial in reducing systemic hypertension. The potential effect of amlodipine on global outcome requires prospective assessment.

INTRODUCTION

Acute kidney injury (AKI) is defined as an abrupt decrease in the homeostatic and excretory functions of the kidney that may be caused by toxic, ischaemic, or infectious damage to the renal parenchyma (Cowgill and Francey 2005, Acierno and Maecelbergh 2008). Systemic hypertension (SHT) is one of the potentially serious complications of AKI but its occurrence in dogs has thus far received only limited review (Francey and Cowgill 2004, Acierno and Labato 2005). It has however been described as a predictable manifestation and a perpetrator of renal damage in dogs with chronic kidney disease (CKD) where it has been shown to accelerate disease progression, and shorten survival (Jacob and others 2003, Finco 2004, Brown and others 2007).

Clinical signs directly attributable to SHT in small animals are most frequently associated with damage to the eyes, heart, brain, and kidneys (Brown and others 2007). Hypertensive retinopathy and choroidopathy have been reported in up to 80 to 100% of cats with chronic unregulated SHT (Maggio and others 2000). Hypertensive encephalopathy may manifest as ataxia, depression, disorientation or seizures, and it is associated with a
poor prognosis (Maggio and others 2000, Jacob and others 2003, Brown and others 2007). In dogs and cats with CKD, renal damage seems more likely at systolic systemic blood pressure (SBP) ≥160 mmHg (Finco and others 1999, Jacob and others 2003, Mathur and others 2004). Recent research on small animal SHT has led to the publication of expert recommendations for its diagnosis and therapy (Brown and others 2007). These ACVIM Consensus Guidelines define cut-off values of systolic/diastolic SBP for minimal, mild, moderate and severe risk of hypertensive target organ damage as < 150/95 mmHg, 150-159/95-99 mmHg, 160-179/100-119 mmHg, and severe risk ≥180/≥210 mmHg, respectively. Treatment is recommended for animals with CKD and a moderate to severe risk of organ damage.

The extent to which these guidelines can be extrapolated to dogs with AKI is currently unknown since the detrimental effects of acute SHT have thus far not been investigated. Moreover, a short-term beneficial effect of elevated SBP on renal excretory function is possible, considering the loss of renal autoregulation in affected dogs (Brown and others 1995). However, SHT is potentially more likely to cause severe haemorrhage in critically ill dogs with AKI and associated haemostatic disorders than in dogs with stable CKD (Cowgill and Francey 2005). Recommendations for intervention and therapeutic goals are currently empirical and are not based on solid evidence (Cowgill and Francey 2005).

Amlodipine is a dihydropyridine calcium channel blocker (CCB) with direct peripheral vasodilatory effects and weaker central negative chronotropic and inotropic effects (Stopher and others 1988, Cooke and Snyder 1998, Atkins and others 2007). It is considered the treatment of choice for the management of SHT in cats with CKD (Henik and others 1997, Snyder 1998, Maggio and others 2000). Amlodipine has a high oral bioavailability with peak plasma concentrations occurring at 3, 6 and 8 hours in rats, dogs and human beings, respectively (Stopher and others 1988, Meredith and Elliott 1992, Yamada and others 1994). Plasma concentrations increase with chronic therapy because of the drug’s long half-life (Abernethy 1989). It is usually administered orally but rectal application has been suggested for dogs with constant vomiting (Francey 2004).

To the authors’ knowledge, no study has described the effects of amlodipine on acute SHT in dogs with AKI. The aims of this study were to describe the occurrence of SHT in canine AKI and to evaluate the response to treatment with amlodipine besylate.

**Materials and Methods**

**Animals and diagnostics**

The study population consisted of client-owned dogs diagnosed with naturally occurring AKI at the Vetsuisse Faculty University of Berne, Switzerland, from January 2007 to December 2008. Dogs were included in the study if their SBP had been measured within 48 hours of admission and measurements were performed on at least three different occasions. Data reviewed from the medical records and from the AKI database included history, physical examination findings including fundic and rectal examination, SBP, serum chemistry, urinalysis, abdominal ultrasound, and therapy.

Diagnosis of AKI was based on a combination of anamnestic, clinical, laboratory, and ultrasonographic parameters consistent with acute renal insult in the absence of evidence suggesting CKD (Forrest and others 1998, Cowgill and Francey 2005). Dogs were included if at least two of the following criteria were fulfilled: (1) presence of renal azotaemia with a serum creatinine concentration ≥250 µmol/L, persisting at least 24 hours after correction of prerenal factors; (2) increase in serum creatinine ≥100 µmol/L or ≥100% from documented baseline in the absence of prerenal factors; (3) persistent pathological oligoanuria (<1 mL/kg/min) after volume repletion; (4) evidence of renal tubular injury on urinalysis (renal glucosuria, granular casts). Exclusion criteria were: (1) anamnestic and imaging data suggesting the presence of CKD; (2) pretreatment with antihypertensive drugs such as CCBs or angiotensin-converting enzyme inhibitors (ACEI); (3) pretreatment with prohypertensive drugs such as dopamine; and (4) treatment with antihypertensive drugs other than amlodipine or with prohypertensive drugs during the 24 hours following initiation of amlodipine therapy.

The underlying aetiology of AKI was defined on the basis of exposure history and additional testing including urinalysis, urine culture, abdominal ultrasound, serology and polymerase chain reaction for leptospirosis (LipL32 nested PCR assay). A diagnosis of leptospirosis was based on either a four-fold titre increase in paired microagglutination tests (MAT); a single MAT titre ≥1:800 for non-vaccinal serovars (Leptospira australis, L. autumnalis, L. bataviae, L. bratislava, L. grippotyphosa, L. hardjo, L. pomona, L. sejroe and L. tarassovi) or ≥1:3200 for vaccinal serovars (L. canicola, L. icterohaemorrhagiae); or a positive PCR on urine, blood or tissue.

**Blood pressure measurements and amlodipine therapy**

Systolic, diastolic and mean SBP were measured with an oscillometric blood pressure monitoring device (Surgivet V6004, Smiths Medical, Waukesha, WI, USA), using protocols recommended in the ACVIM Consensus Guidelines (Brown and others 2007). Blood pressure was measured in all dogs within 48 hours of admission, before the use of any vasoactive drugs. Dogs were divided into two groups based on treatment with amlodipine besylate: group A+ (dogs treated with amlodipine) and group A− (dogs that were not treated with amlodipine). The decision to treat with amlodipine was taken at the discretion of the primary clinician. In the amlodipine treatment group, SBP measurements were recorded for the following time points: 24, 12, 6 hours, and immediately before amlodipine administration; 1 to 3 hours and 24 hours after the first administration; as well as 24 hours after the last administration of amlodipine. Systolic SBP ≥160 mmHg was defined as SHT and systolic SBP ≥180 mmHg as severe SHT.

Hospital protocol for antihypertensive treatment included oral administration of amlodipine besylate (Norvasc; Pfizer) at a dosage of 0.25 mg/kg for severe SHT. Amlodipine was repeated in increments of 0.25 mg/kg q1 to 3 hours until a goal systolic SBP of 140 to 160 mmHg was reached or up to a maximal cumulative dose of 1 mg/kg/day. Dose increments were postponed for 2 hours in dogs responding to amlodipine therapy with a decrease...
in systolic SBP ≥20 mmHg, but not reaching the target, except if potentially life-threatening hypertensive complications were observed. In dogs with refractory vomiting, amlodipine was dissolved in water and administered rectally, using the same dose and schedule. Therapy protocol prescribed a substitution dose administered rectally for dogs vomiting within 15 minutes of oral administration, but this was never necessary. Subsequent doses of amlodipine were based on the cumulative 24-hour dose necessitated for initial control and on individual clinical response to maintain the target SBP. Dogs reaching this target were considered responders, independent of the absolute change in SBP. Dogs with decrease in systolic SBP ≥20 mmHg but failing to reach the goal SBP were considered partial responders and dogs with a decrease of SBP less than 20 mmHg not reaching the target despite maximal daily dose of amlodipine were considered non-responders and treated with additional antihypertensive drugs at the discretion of the primary clinician.

Clinical manifestations of SHT and side effects potentially attributable to amlodipine therapy were reviewed from the medical records.

### Statistical Analysis

Statistical analyses were performed using statistical software (NCSS 2007, NCSS Kaysville, Utah, USA). Since multiple sets of data were not normally distributed based on a Shapiro-Wilk W test, all data are presented as median and interquartile range and analysed using non-parametric methods. Descriptive statistics were used to describe population characteristics. A Wilcoxon rank-sum test was used for comparison of numerical clinical, laboratory and blood pressure data; a Fisher’s exact test was used for comparison of categorical data. The change in SBP with amlodipine therapy over time was evaluated using a Kruskal-Wallis test and post hoc comparison was performed using the Kruskal-Wallis multiple-comparison Z-value test. Blood pressure data at time points before treatment were compared to data at the next time point and after treatment, SBP data were compared to the SBP data at treatment time. The level of statistical significance was set at P<0.05, except for multiple comparisons before and after amlodipine therapy, where the P cut-off was adjusted to less than 0.01.

### Results

Fifty-two dogs fulfilled the inclusion criteria and were grouped as follows: 22 dogs in the amlodipine treatment group (A+) and 30 dogs in the group not receiving amlodipine (A−). There were 20 intact males (38-5%), 11 neutered males (21-2%), 4 intact females (7-7%) and 17 spayed females (32-7%), with an age of 6-8 years (3-0 to 9-5) and a bodyweight of 23-7 kg (10-3 to 30-0). Forty dogs were diagnosed with leptospirosis (19 dogs in group A+ and 21 in group A−) based on seroconversion with paired MAT titres in 16 dogs, single serology in 23 dogs and positive PCR in 4 dogs. The 12 dogs diagnosed with AKI from other aetiologies (3 dogs in group A+ and 9 dogs in group A−) included 4 dogs with a suspicion of toxicosis, 3 with ischaemic nephrosis and 5 with AKI of unknown origin.

At initial presentation, serum creatinine concentration was 609 µmol/L (371 to 923) (reference interval: 53 to 120), serum urea concentration was 46-9 mmol/L (36-6 to 67-4) (reference interval: 3-5 to 11-1), serum phosphorus concentration was 3-51 mmol/L (2.81 to 5-20) (reference interval: 0.9 to 1-9) and serum potassium concentration was 4-88 mmol/L (4.05 to 6-37) (reference interval: 4-1 to 5-3). Serum phosphorus and potassium concentrations were significantly higher in the A+ group than in the A− group (Table 1). Peak serum concentrations of creatinine, phosphorus and potassium during the course of the disease were also significantly higher in the A+ group than in the A− group (Table 1).

Systolic, diastolic and mean SBPs of all dogs at the time of admission were 150 (134 to 173), 94 (78 to 112), and 114 (99 to 131) mmHg, respectively. No significant difference was found for initial SBP between males and females, but neutered dogs showed significantly lower initial systolic and mean SBPs than intact dogs (Fig 1).

Nineteen dogs (37%) were hypertensive at initial evaluation, and eight of these (15%) were severely hypertensive. Cumulative proportions of SHT and severe SHT increased during hospitalisation to 81% (42 of 52) and 62% (32 of 52), respectively. Maximal recorded SBP was 187 (168 to 203), 132 (114 to 146) and 147 (132 to 162) mmHg for all dogs, with a significantly higher SBP for dogs treated with amlodipine (Table 1). In the A− group, SBP and occurrence of SHT did not vary significantly over time from day 0 to day 8 (P>0.05).

Twenty-two dogs (42%) received amlodipine. Eleven dogs of the A+ group showed only minimal elevation of SBP above the treatment threshold (<185 mmHg; n=8) or transient severe SHT (n=3) and were thus not treated (Fig 2). Amlodipine therapy was initiated 1.3 days (0-5 to 2-5) after admission. The total daily dose was 0.38 mg/kg (0-28 to 0-49), administered in 1 dose per day (1 to 2), for 2-0 days (1-0 to 4-8). Amlodipine was administered orally in 19 dogs and the first dose rectally in 3 dogs.

In dogs treated with amlodipine, mean and diastolic SBPs increased significantly between 12 and 6 hours before amlodipine administration (Fig 3). Systolic SBP was 179 mmHg (168 to 196) immediately before amlodipine administration, 167 mmHg (151 to 194) 1 to 3 hours after administration, and 157 mmHg (143 to 170) 24 hours after administration. Change in systolic SBP was −15.5 mmHg (−27.4 to +12.5) at 1 to 3 hours and −24.0 mmHg (−33.6 to −11.9) at 24 hours.

The proportion of dogs with SHT (and severe SHT) in the group A+ decreased from 86% (50%) immediately before therapy, to 59% (27%) 1 to 3 hours after, and to 45% (14%) 24 hours after initial amlodipine administration. Response to therapy is summarised in Fig 4. The three dogs administered amlodipine rectally were classified as full responders (2) and partial responders (1).

Dogs with AKI from acute leptospirosis did not differ significantly in baseline physical examination, laboratory and blood pressure data compared to dogs with AKI from other aetiologies,
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### Table 1. Clinical and laboratory characteristics of dogs with AKI grouped by treatment with amlodipine

<table>
<thead>
<tr>
<th></th>
<th>A+ group n = 22</th>
<th>A− group n = 30</th>
<th>P (Reference interval)</th>
</tr>
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<tbody>
<tr>
<td><strong>Clinic and aetiology</strong></td>
<td></td>
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<tr>
<td>Anuria n (%)</td>
<td>9 (41)</td>
<td>8 (27)</td>
<td>0-37</td>
</tr>
<tr>
<td>Hemodialysis n (%)</td>
<td>20 (91)</td>
<td>15 (50)</td>
<td>0-002*</td>
</tr>
<tr>
<td>Leptospirosis n (%)</td>
<td>19 (86)</td>
<td>21 (70)</td>
<td>0-17</td>
</tr>
<tr>
<td><strong>Blood pressure at presentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic SBP mmHg</td>
<td>155 (141 to 181)</td>
<td>148 (124 to 167)</td>
<td>0-02*</td>
</tr>
<tr>
<td>Diastolic SBP mmHg</td>
<td>100 (87 to 119)</td>
<td>87 (71 to 108)</td>
<td>0-02*</td>
</tr>
<tr>
<td>Mean SBP mmHg</td>
<td>120 (107 to 135)</td>
<td>110 (90 to 124)</td>
<td>0-02*</td>
</tr>
<tr>
<td>SHT n (%)</td>
<td>10 (45)</td>
<td>9 (30)</td>
<td>0-25</td>
</tr>
<tr>
<td>Severe SHT n (%)</td>
<td>7 (32)</td>
<td>1 (3)</td>
<td>0-005*</td>
</tr>
<tr>
<td><strong>Blood pressure: maximal values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic SBP mmHg</td>
<td>203 (186 to 210)</td>
<td>174 (152 to 183)</td>
<td>&lt;0-001*</td>
</tr>
<tr>
<td>Diastolic SBP mmHg</td>
<td>147 (139 to 166)</td>
<td>119 (107 to 130)</td>
<td>&lt;0-001*</td>
</tr>
<tr>
<td>Mean SBP mmHg</td>
<td>163 (156 to 177)</td>
<td>137 (122 to 144)</td>
<td>&lt;0-001*</td>
</tr>
<tr>
<td>SHT n (%)</td>
<td>22 (100)</td>
<td>20 (67)</td>
<td>0-002*</td>
</tr>
<tr>
<td>Severe SHT n (%)</td>
<td>21 (95)</td>
<td>11 (37)</td>
<td>&lt;0-001*</td>
</tr>
<tr>
<td><strong>Chemistry at presentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine µmol/L</td>
<td>732 (508 to 1042)</td>
<td>559 (303 to 821)</td>
<td>0-07</td>
</tr>
<tr>
<td>Urea mmol/L</td>
<td>59-5 (41-0 to 72-1)</td>
<td>45-7 (33-9 to 61-5)</td>
<td>0-12</td>
</tr>
<tr>
<td>Phosphorus mmol/L</td>
<td>4-14 (3-30 to 5-60)</td>
<td>3-29 (2-34 to 4-55)</td>
<td>0-049*</td>
</tr>
<tr>
<td>Potassium mmol/L</td>
<td>4-35 (3-78 to 5-45)</td>
<td>3-65 (3-08 to 4-58)</td>
<td>0-02*</td>
</tr>
<tr>
<td><strong>Chemistry: maximal values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine µmol/L</td>
<td>794 (585 to 1090)</td>
<td>588 (355 to 899)</td>
<td>0-04*</td>
</tr>
<tr>
<td>Urea mmol/L</td>
<td>59-5 (44-6 to 74-6)</td>
<td>48-5 (36-0 to 61-5)</td>
<td>0-05</td>
</tr>
<tr>
<td>Phosphorus mmol/L</td>
<td>5-05 (4-08 to 6-05)</td>
<td>3-73 (2-34 to 4-87)</td>
<td>0-01*</td>
</tr>
<tr>
<td>Potassium mmol/L</td>
<td>5-00 (4-50 to 5-75)</td>
<td>4-35 (4-08 to 5-18)</td>
<td>0-01*</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival n (%)</td>
<td>13 (59)</td>
<td>25 (83)</td>
<td>0-05</td>
</tr>
</tbody>
</table>

*Indicates statistical significance

except for a significantly higher systolic SBP at presentation (Fig 2).

Acepromazine (Prequillan; Fatro) was the sole additional anti-hypertensive drug prescribed at a dose of 5 µg/kg in 10 dogs for its antiemetic properties. It was administered at least 24 hours after initial amlodipine treatment and thus did not influence the initial treatment response.

Haemodialysis was required for the treatment of 91% of the dogs from the A+ group and 50% of the dogs from the A− group. Dialytic fluid removal by ultrafiltration was performed in 9 of 20 A+ dogs on the initial day of amlodipine therapy. Fluid removal was 0 mL/kg (0 to 12-3) on that treatment for the dogs of the A+ group. Haemodialysis-associated change in systolic, diastolic and mean SBP was +5 (~7 to +16), +4 (~8 to +20) and +14 (~8 to +26) mmHg. No significant difference in the control of SHT was noted between dogs treated with and without haemodialysis.

Although 62% of the dogs had severe SHT with systolic SBP ≥180 mmHg at some point during hospitalisation, no obvious sequelae attributable to SHT were noted in any of the dogs. Systemic hypotension or other potential side effects of amlodipine therapy were not observed. Overall mortality was 14 of 52 dogs (27%). Group A+ had the highest mortality with 9 of 22 dogs (41%), compared to 5 of 30 (17%) in group A− (P=0-05).

**DISCUSSION**

This retrospective study shows that dogs with AKI are highly prone to SHT with a cumulative proportion of 81% SHT and 62% severe SHT. Contrary to the observations reported by Brown and others (2007), no gender difference in SBP was found in this study. However, spayed and neutered dogs with AKI had significantly lower SBP compared to the intact population. This corroborates findings in previous studies in which a 20 to 30 mmHg lower SBP was observed in prepubertal, spontaneously hypertensive neutered male rats compared to intact rats or a decrease in SBP was observed in rats after castration (Masubuchi and others 1982, Jerkins and others 1994, Martin and others 2005). Gonadectomy is thought to influence SBP through its effects on the kallikrein-kinin system (Sharma and Sharma 2002, Azurmendi and others 2009). Dogs with acute leptospirosis as the underlying cause of AKI differed from dogs with AKI from other aetiologies only with regard to systolic SBP at presentation. Although significant, this difference is unlikely to be clinically relevant but cannot be excluded by this study because only 23% of dogs suffered AKI from other causes.

End organ damage has been described in dogs with systolic SBP ≥160 mmHg (Finco and others 1999, Jacob and others 2002).
The amlodipine treatment protocol used in the present study was chosen empirically, based on the previous experience with its use in dogs. The hospital canine protocol with an initial dose of 0·25 mg/kg and titration to effect up to a maximal dose of 1 mg/kg/day differs from the protocol suggested for cats with a starting dose of 0·625 mg/cat (Henik and others 1997). Even though peak plasma concentration is expected only 6 hours after administration, additional doses were given every 1 to 2 hours in order to attain rapid control of SHT. This protocol was not associated with hypotension and resulted in control of SBP with complete response in 41% of dogs with SHT and 27% of dogs with severe SHT within 1 to 3 hours. In the absence of an evidence-based target, the present study used the same treatment goal as recommended for CKD-associated SHT (systolic SBP 140 to 160 mmHg). This target was reached in 64% of the dogs within 24 hours and in 91% of dogs within 48 hours. Amlodipine was administered rectally in only three dogs. Although a similar response to treatment was observed in these dogs compared to dogs in which amlodipine was administered orally, such a small number of cases precludes further evaluation of the efficacy of rectal amlodipine administration.

The increase in SBP observed in the pretreatment period may be due to worsening of the disease and subsequent progressive failure to regulate SBP, to aggressive fluid therapy and solute overload, or to increasing stress, pain and adrenergic stimulation during hospitalisation or during the course of the disease. Only 19% of the study dogs never became hypertensive and 38% never developed severe SHT. Further prospective evaluation of factors potentially associated with this initial increase in SBP may offer insight in therapeutic strategies to minimise progression or secondary kidney damage in dogs with AKI.

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Potential confounding effects of other treatments, including fluid removal with haemodialysis and fluid administration, could
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not be evaluated because of the retrospective nature of the study. However, ultrafiltration was minimal in the study dogs and no difference was observed between dogs treated with and without haemodialysis, although individual benefits in blood pressure control cannot be excluded.

The most common adverse effects reported in human beings treated with amlodipine are oedema, dizziness, fatigue, and heart palpitations (Osterloh 1991, Webster and others 1993, Burges and Moisey 1994, Weir 2003). Systemic hypotension is a rare but reported complication in cats, and gingival hyperplasia has been described in dogs treated with amlodipine over several months (Henik and others 1997, Thomason and others 2009). In our study, no adverse reactions were recorded, possibly because of careful titration of amlodipine, frequent post-treatment monitoring, and the short overall duration of treatment. The dose of amlodipine required for controlling SHT in these dogs with AKI seems to be well tolerated. It is however possible that some of the adverse effects recognised in human patients, such as headache, tiredness, nausea, or abdominal pain, are not recognised in dogs or are attributed to uraemia.

Both ACEI and CCB have been shown to decrease the glomerular filtration rate in human beings, eliciting concerns about potential secondary renal damage (Onuigbo and Onuigbo 2008, Onuigbo 2009). Current recommendations for the antihypertensive treatment of dogs with AKI clearly oppose the use of ACEI because of their preferential dilatation of the efferent glomerular arteriole, decreasing glomerular capillary pressure and glomerular filtration rate (Langston 2010). As a result, no dog was treated with ACEI in the present study. The safety concerns related to preservation of renal function during treatment of hypertensive dogs with AKI remain to be studied prospectively or experimentally.

The difference in survival rates between dogs treated with and without amlodipine is likely related to a greater severity of disease.
in the treatment group, suggested by their higher peak serum concentrations of creatinine, urea and phosphorus, a higher proportion of severe SHT, and more frequent requirement for haemodialysis. However, this could only be confirmed by a prospective placebo-controlled trial.

The main limitations of this study are due to its retrospective and descriptive design. Although adhering closely to pre-established hospital protocols for fluid and medical therapy, treatment choices for individual dogs were largely at the discretion of the primary clinician, especially for dogs with borderline high SBP. The non-treatment group included in the present study suffers from an inherent selection bias as it is based on a decision to treat and therefore on the SBP. However, the ethics of including a placebo group in client-owned dogs with naturally occurring AKI and potentially life-threatening severe SHT limits the feasibility of such a study.

In conclusion, results of this study suggest that SHT is common in dogs with AKI and that a marked increase in SBP is associated with initial in-hospital therapy. Treatment with amlo-dipine besylate results in a significant and rapid reduction of SBP and control of SHT. Further prospective controlled studies are necessary to confirm efficacy, to evaluate potential negative effects of treatment on renal function and global outcome, and to refine treatment recommendations, including trigger SBP for medical intervention, dosing schedule and treatment targets.

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Conflict of interest
None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

References
Sharma, J. N. & Sharnau, J. (2002) Cardiovascular properties of the kalikrein-kinin system. Current Medical Research and Opinion 18, 10-17