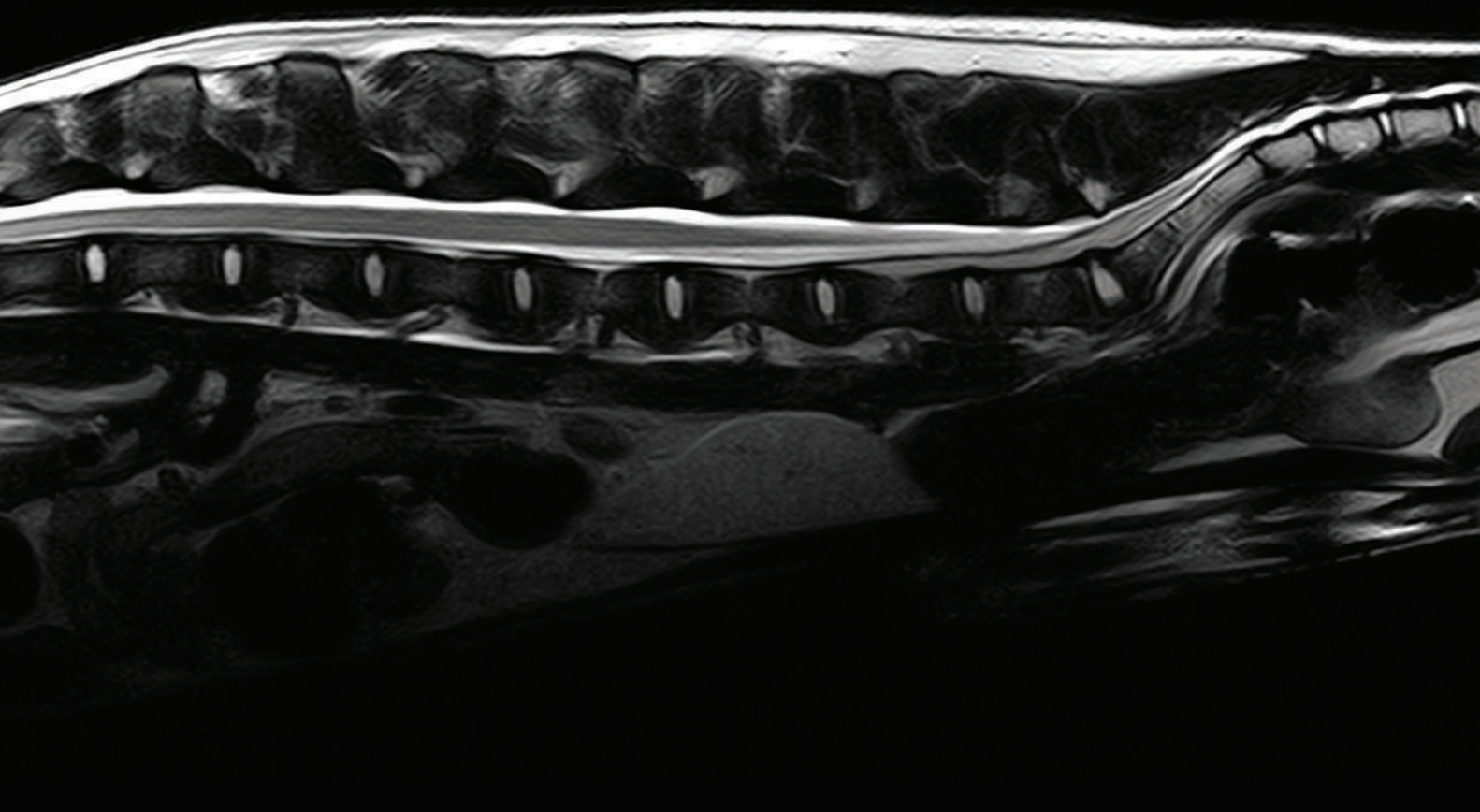


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# ACVIM consensus statement: Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats

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An update to the 2007 American College of Veterinary Internal Medicine (ACVIM) consensus statement on the identification, evaluation, and management of systemic hypertension in dogs and cats was presented at the 2017 ACVIM Forum in National Harbor, MD. The updated consensus statement is presented here. The consensus statement aims to provide guidance on appropriate diagnosis and treatment of hypertension in dogs and cats.

**KEYWORDS**

blood pressure, cardiology, cardiovascular, chronic renal failure, hemodynamics, hypertension, kidney, proteinuria, renal/urinary tract

**Abbreviations:** ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers; BP, blood pressure; CCB, calcium channel blockers; CKD, chronic kidney disease; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SDMA, symmetric dimethylarginine; TOD, target organ damage; UPC, urine protein to creatinine ratio; MRI, magnetic resonance imaging; IRIS, International Renal Interest Society; CNS, central nervous system; CRI, constant rate infusion

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**1 | INTRODUCTION**

In 2000, a group of experts was convened to develop comprehensive guidelines for the identification and treatment of systemic hypertension in cats and dogs. In 2007, the recommendations of this expert panel were published as the American College of Veterinary Internal Medicine (ACVIM) consensus statement on hypertension. Over the past 10 years, our understanding of normal systemic arterial blood pressure (BP) and systemic hypertension has expanded, but much remains to be discovered. It is our hope that these revised guidelines,

based on the latest available research, will assist practitioners in the development of a rational approach to the diagnosis and treatment of hypertension in companion animals.

## 2 | BP MEASUREMENT

Diagnosing and treating hypertension in the clinical patient necessitate accurate measurement of the patient's BP. Direct BP determination entails catheterization of a suitable artery and assessing arterial pressure using an electronic transducer.<sup>1-3</sup> Although this is the gold standard, it is not practical for hypertension screening and treatment. Clinically, noninvasive indirect estimations of BP such as Doppler and oscillometric devices are commonly used.<sup>4-6</sup>

Ideally, BP should be measured using devices that have been validated in the species of interest and under the circumstances in which the patient is being tested. Standards for the validation of indirect BP measuring devices in people are well established,<sup>7</sup> but no device has met these criteria in conscious dogs or cats. For this reason, a set of standards for validating indirect BP devices in awake dogs and cats has been proposed and accepted.<sup>8</sup> Although many studies have attempted to validate indirect BP devices in anesthetized patients, only a few have been performed in conscious animals.<sup>9-12</sup> In the devices studied to date in awake animals, either a different validation standard was used<sup>9,11,12</sup> or the device failed to meet the previously established criteria.<sup>10</sup>

Until devices that can meet the guidelines for measuring BP in conscious animals have been validated, it is our recommendation that currently available devices be used with a degree of caution. Because estimates of BP obtained using an indirect device can only be interpreted in light of results of appropriate validation testing in conscious animals, devices that have not been subjected to appropriate testing in conscious animals should not be used. Nonetheless, studies that have relied upon indirect estimation of BP using available devices have identified adverse effects of increased BP and benefits of intervention, indicating that some of these devices can provide clinically useful information.<sup>13,14</sup> Therefore, we recommend that, once commercially available, only devices that meet the established validation standards in conscious cats and dogs be used.

To obtain reliable results in the measurement of BP, it is important to follow a standard protocol (Table 1). The individual taking the measurements should be skilled and experienced in the handling of animals and the equipment. Studies have shown that operator experience can have a significant impact on BP measurements.<sup>1,15</sup> Often the most skilled individual is a well-trained technician and not a veterinarian. Anxiety- or excitement-induced situational hypertension can be marked,<sup>16,17</sup> but can be minimized by measuring BP in a quiet area, away from other animals, before other procedures and only after the patients have been acclimated to their surroundings for 5-10 minutes. Whenever possible, the owner should be present and restraint should be kept to a minimum. The selection of a correctly sized cuff is critical in obtaining accurate measurements.<sup>1</sup> Some veterinary-specific oscillometric devices have specially designed cuffs and these should always be used. When using Doppler and many oscillometric units, the width of the cuff should be 30%-40% of the circumference of the extremity at the site of cuff placement. The first measurement should be discarded and the average of 5-7 consecutive consistent indirect measurements should be obtained. If there is substantial variation, the readings should be discarded and the process repeated. In some patients, BP trends downward as the measurement process continues. In these animals, measurements should continue until a plateau is reached and then 5-7 consecutive consistent values should be recorded. Conversely in some patients, measurement of systolic blood pressure (SBP) may result in a progressive increase in readings. When this occurs, results must be interpreted in the clinical context of the individual patient. The animal's position and attitude, cuff size and site, cuff site circumference (cm), and name of the individual making the measurements should be carefully recorded and used for future pressure measurements. Individual patients may be noise-sensitive, but, in general, use of headphones by the measurer does not result in lower BP measurements.<sup>18</sup>

## 3 | NORMAL VALUES FOR CANINE AND FELINE BP

Various studies have reported values for BP in normal dogs and cats (Table 2). These values vary, reflecting differences in subject

**TABLE 1** Protocol for accurate blood pressure (BP) measurement

- Calibration of the BP device should be tested semiannually either by the user, when self-test modes are included in the device, or by the manufacturer.
- The procedure must be standardized.
- The environment should be isolated, quiet, and away from other animals. Generally, the owner should be present. The patient should not be sedated and should be allowed to acclimate to the measurement room for 5-10 minutes before BP measurement is attempted.
- The animal should be gently restrained in a comfortable position, ideally in ventral or lateral recumbency to limit the vertical distance from the heart base to the cuff (if more than 10 cm, a correction factor of +0.8 mm Hg/cm below or above the heart base can be applied).
- The cuff width should be approximately 30%-40% of circumference of the cuff site.
- The cuff may be placed on a limb or the tail, taking into account animal conformation and tolerance, and user preference.
- The same individual should perform all BP measurements following a standard protocol. Training of this individual is essential.
- The measurements should be taken only when the patient is calm and motionless.
- The first measurement should be discarded. A total of 5-7 consecutive consistent values should be recorded. In some patients, measured BP trends downward as the process continues. In these animals, measurements should continue until the decrease plateaus and then 5-7 consecutive consistent values should be recorded.
- Repeat as necessary, changing cuff placement as needed to obtain consistent values.
- Average all remaining values to obtain the BP measurement.
- If in doubt, repeat the measurement subsequently.
- Written records should be kept on a standardized form and include person making measurements, cuff size and site, values obtained, rationale for excluding any values, the final (mean) result, and interpretation of the results by a veterinarian.

**TABLE 2** Arterial blood pressure (mm Hg) values obtained from normal, conscious, dogs and cats

Measurement method	n	Systolic	Mean	Diastolic	Nonparametric
<b>DOGS:</b>					
<b>Intra-arterial:</b>					
Anderson et al (1968) <sup>191</sup>	28	144 ± 156	104 ± 13	81 ± 9	
Cowgill et al (1983) <sup>192</sup>	21	148 ± 16	102 ± 9	87 ± 8	
Chalifoux et al (1985) <sup>193</sup>	12	154 ± 31	115 ± 16	96 ± 12	
Stepien et al (1999) <sup>194</sup>	27	154 ± 20	107 ± 11	84 ± 9	
<b>Oscillometry:</b>					
Bodey and Michell <sup>20</sup>	1267	131 ± 20	97 ± 16	74 ± 15	
Coulter et al (1984) <sup>6</sup>	51	144 ± 27	110 ± 21	91 ± 20	
Kallet et al, 1997 <sup>51</sup>	14	137 ± 15	102 ± 12	82 ± 14	
Stepien et al (1999) <sup>194</sup>	28	150 ± 20	108 ± 15	71 ± 18	
Meurs et al (2000) <sup>23</sup>	22	136 ± 16	101 ± 11	81 ± 9	
Hoglund et al (2012) <sup>36</sup>	89	139 ± 16		71 ± 13	
<b>Doppler ultrasonography:</b>					
Chalifoux et al (1997) <sup>193</sup>	12	145 ± 23			
Stepien et al (1999) <sup>194</sup>	28	151 ± 27			
Rondeau et al (2013) <sup>46</sup>	51	147 ± 25			
<b>CATS:</b>					
<b>Intra-arterial:</b>					
Brown et al (1997) <sup>195</sup>	6	125 ± 11	105 ± 10	89 ± 9	
Belew et al (1999) <sup>16</sup>	6	126 ± 9	106 ± 10	91 ± 11	
Slingerland et al (2007) <sup>196</sup>	20	132 ± 9	115 ± 8	96 ± 8	
Zwijnenberg et al (2011) <sup>197</sup>	6	160 ± 12	138 ± 11	116 ± 8	
Jenkins et al (2014) <sup>198</sup>	6	111 ± 4		75 ± 2	
<b>Oscillometry:</b>					
Bodey et al (1998) <sup>24</sup>	104	139 ± 27	99 ± 27	77 ± 25	
Mishina et al (1998) <sup>26</sup>	60	115 ± 10	96 ± 12	74 ± 11	
<b>Doppler ultrasonography:</b>					
Kobayashi et al (1990) <sup>4</sup>	33	118 ± 11			
Sparkes et al (1999) <sup>25</sup>	50	162 ± 19			
Lin et al (2006) <sup>199</sup>	53	134 ± 16			
Dos Reis et al (2014) <sup>200</sup>	30	125 ± 16			
Taffin et al (2016) <sup>201</sup>	113 <sup>a</sup>	133 ± 20			
Quimby et al (2011) <sup>202</sup>	30	137 ± 16 <sup>b</sup>			Median 138 (range 106-164)
Paige et al (2009) <sup>203</sup>	87	131 ± 18			
Chetboul et al (2014) <sup>133</sup>	20	151 ± 5		78 ± 3	
Payne et al (2017) <sup>28</sup>	780	122 ± 16 <sup>b</sup>			Median 121 (IQR 110-132)

<sup>a</sup> Includes 3 cats with renal azotemia.

<sup>b</sup> Data not included in original publication but obtained after a direct approach to the authors interquartile range (IQR).

populations, measurement techniques, and animal handling. This variability emphasizes the importance of standardization of technique in veterinary practice. Additional factors affect what is considered “normal” BP. In people, age-related increases in SBP and pulse pressure have been well characterized.<sup>19</sup> The effect of age is less clear in dogs and cats. A small increase in BP of 1-3 mm Hg/year has been noted with aging in dogs,<sup>20,21</sup> but such an age effect has not been observed in all studies.<sup>22,23</sup> In 1 study, BP increased with age in a heterogeneous population of cats,<sup>24</sup> but no age effect was observed in 2 other studies of normal cats.<sup>4,25</sup> In an additional study of apparently healthy cats, a comparatively small increase of 1.5 mm Hg/year was noted for mean BP.<sup>26</sup> More recently, a larger study identified an increase in BP

over time in cats aged >9 years of age with repeated BP measurements, but the risk of developing hypertension was lower in apparently healthy cats than in those with azotemic chronic kidney disease (CKD).<sup>27</sup> A large cross-sectional study also has identified an increase in BP with age in apparently healthy cats,<sup>28</sup> but the cats were not screened for concurrent disease.

An effect of sex on BP was identified in 1 study of dogs<sup>20</sup> in which intact males had higher BP and intact females had lower BP as compared to neutered dogs; in all cases, differences among groups were <10 mm Hg. In other studies, no association between sex and higher or lower BP was found.<sup>29,30</sup> Most cats evaluated by veterinarians are neutered and in most studies an effect of sex has not been

evident in this species.<sup>24,26</sup> In a recent large study, males had higher BP than females and neutered cats had higher BP than intact animals, but the differences were very small.<sup>28</sup>

There are substantial interbreed differences in canine BP, most notably for hounds (eg, Greyhounds, Deerhounds) in which BP is higher than in mongrels<sup>31</sup> by approximately 10-20 mm Hg.<sup>20,29,31,32</sup> The BP among other breeds varies by 7-10 mm Hg<sup>20,33</sup> perhaps based on temperament.<sup>34-36</sup> The panel recognizes the need for breed-specific BP ranges to be developed. In cats, no effect of breed has been observed on BP.<sup>24,28</sup>

Obesity is associated with increases in BP in several species.<sup>37-42</sup> This effect has been studied experimentally in dogs.<sup>37,43</sup> A small (<5 mm Hg) increase in BP was noted in obese dogs by oscillometry<sup>20</sup> but not by Doppler sphygmomanometry.<sup>22</sup> The relationship between obesity and higher BP in dogs may be related to the prevalence of underlying disease.<sup>30</sup> In cats, no effect of obesity on BP was observed by oscillometry,<sup>24</sup> but cats that were underweight had slightly lower BP when measured with Doppler than those that were of ideal body weight or obese.<sup>28</sup> Recent studies suggested no association among body condition score, body weight, and SBP measurements in dogs or cats, but muscle condition score and sarcopenia have been reported to affect radial but not coccygeal BP measurements in the cat.<sup>44,45</sup>

Blood pressure measurement results in normal animals are highly variable based on breed, temperament, patient position, measurement method, operator experience, and inpatient variability,<sup>15,17,29,46,47</sup> and it is difficult to determine a single value and range that might be applicable to all dogs or cats. Ranges of expected values in many studies of normal dogs and cats using various measurement techniques are presented in Table 2. In disease-free patient populations, in which the BP values typically are expected to be distributed normally, expected normal values are presented as mean  $\pm$  SD, but in hypertensive patients, the frequency distribution of BP measurements tends to be skewed with fewer patients having very high measurements.<sup>48</sup> For this reason, the panel recommends that data from future studies of abnormal populations be presented as median and interquartile range.

## 4 | HYPERTENSION DEFINITIONS

The term systemic hypertension is applied to sustained increases in SBP, and generally can be categorized into 1 of 3 types. It may be caused by environmental or situational stressors, it may occur in association with other disease processes that increase BP (ie, secondary hypertension), or it may occur in the absence of other potentially causative disease processes (ie, idiopathic hypertension). Accordingly, we suggest the definitions and criteria described below.

### 4.1 | Situational hypertension

Increases in BP that occur as a consequence of the in-clinic measurement process in an otherwise normotensive animal are termed situational hypertension. Situational hypertension is caused by autonomic nervous system alterations that arise from the effects of excitement or anxiety on higher centers of the central nervous system. This type of hypertension resolves under conditions that decrease or eliminate

the physiologic stimulus (eg, altering measurement conditions to decrease the animal's anxiety and measuring BP in the animal's home environment). In people, there is question as to whether the so-called "white coat hypertension" actually represents a risk factor for subsequent hypertensive damage, with some evidence suggesting increased long-term cardiovascular risk in these, as compared to normotensive patients.<sup>49,50</sup> There presently is no justification to treat situational hypertension in dogs or cats. More importantly, anxiety- or excitement-induced increases in BP can lead to an erroneous diagnosis of true pathologic systemic hypertension.<sup>22,51</sup>

Unfortunately, the effects of anxiety on BP are not predictable, and some animals exhibit a marked increase in BP whereas others do not. Some animals even may exhibit a decrease in BP as a result of the measurement process.<sup>16</sup> In human patients, awareness of the phenomena of "white coat" hypertension and of "masked hypertension" (the latter term applied to cases in which in-clinic BP measurements are normal for a patient who is hypertensive in the nonmedical environment) has encouraged the evaluation of ambulatory or at-home BP as a complement to conventional in-clinic BP measurements.<sup>52,53</sup> Whether masked hypertension is important in veterinary species is unclear, and the use of ambulatory BP monitoring has not been systematically evaluated in veterinary medicine.

### 4.2 | Secondary hypertension

Secondary hypertension represents persistent, pathologically increased BP concurrent with a disease or condition known to cause hypertension (Table 3), or hypertension associated with the administration of a therapeutic agent or ingestion of a toxic substance known to cause an increase in BP (Table 4). Hypertension may persist despite effective treatment of the primary condition<sup>54-56</sup> and BP may increase after treatment is initiated.<sup>57</sup> The presence of a condition known to cause secondary hypertension, even if effectively resolved by therapeutic intervention, should prompt serial follow-up evaluations.

### 4.3 | Idiopathic hypertension

The term "primary" or "essential" hypertension often is used in people to describe persistent pathological hypertension in the absence of any identifiable underlying cause and represents a complex multifactorial disorder involving genetic, lifestyle, and environmental factors. Essential hypertension has been reported in dogs.<sup>58-62</sup> Because subclinical kidney disease is present frequently in people and animals with hypertension, a valid diagnosis of primary or essential hypertension can be difficult to establish. Furthermore, the presence of chronically increased BP suggests that one or more of the neurohumoral and renal systems responsible for regulating BP is abnormal. Thus, the panel recommends the use of the term "idiopathic" in place of "essential" for animals in which high BP occurs in the absence of an overt clinically apparent disease that is known to cause secondary hypertension.

A diagnosis of idiopathic hypertension is suspected when reliable BP measurements demonstrate a sustained increase in BP concurrent with normal CBC, serum biochemistry, and urinalysis results. Unfortunately, increased BP may induce polyuria (the so-called pressure diuresis), and thus the presence of low urine-specific gravity (<1.030) in a

**TABLE 3** Diseases associated with secondary hypertension in dogs and cats

Disease or condition	Prevalence of hypertension (%)	Reference(s)
<b>DOGS:</b>		
Chronic kidney disease	93	191
	60	192
	80	192
	79	204
	9	20
	62	81
	19	205
	28.8	79
	14	206
	47	Jacob et al (1999) (ACVIM abstract)
Acute kidney disease	87	207
	15%-37% (at admission) 62%-81% (during hospitalization)	208
Hyperadrenocorticism (naturally occurring or iatrogenic)	73	55
	80	204
	35	209
	36.8	210
	20-46.7	211
Diabetes mellitus	46	212
	24	204
	67	213
	55	214
Obesity	Small effect	20,22,30,37,43 215,216
Primary hyperaldosteronism	Rare disease	217
		218
Pheochromocytoma	43%	219
	86%	220
	54.5-65%	221
Hypothyroidism	Uncommon	222
Brachycephalic	No prevalence data	223
<b>CATS:</b>		
Chronic kidney disease	46	4
	65	85
	19	48
	39.6% at diagnosis of CKD	27
	If normotensive at diagnosis of CKD 17% develop	
	Hypertension >3 months after diagnosis	
	29% (stable CKD over 12 months)	74
	40% (progressive CKD over 12 months)	

(Continues)

**TABLE 3** (Continued)

Disease or condition	Prevalence of hypertension (%)	Reference(s)
Diabetes mellitus	0	111
	No increase of BP	224
	15%	225
Hyperthyroidism	87	4
	23	85
	5 pretreatment and 25 posttreatment	56
	10% pretreatment	
	12.8% (pre) and 22% (post)	226
	22% (pre) and 24% (post)	227 228
Obesity	Hypertension uncommon	24
Primary hyperaldosteronism	50%-100% Uncommon disease	63,229-235
Pheochromocytoma	Unusual disease	236
		237
		181
Hyperadrenocorticism	19%	238,239

Variability in inclusion criteria, measurement techniques, and definition of hypertension makes direct comparison of prevalence data difficult.

patient with high BP does not establish that kidney disease is present. On the other hand, the presence of concentrated urine (>1.030) makes kidney disease less likely. Because subclinical kidney disease or other conditions known to cause secondary hypertension may be present in animals with idiopathic hypertension, the panel recommends that diagnostic tests in addition to CBC, serum biochemistry, and urinalysis be considered in affected animals. Depending on the clinical findings, these tests may include renal ultrasound examination (dog, cat), evaluation of serum symmetric dimethylarginine (SDMA) concentrations (dog, cat), measurement of glomerular filtration rate (GFR) (dog, cat), quantitative assessment of proteinuria (dog, cat), serum thyroxine hormone concentration (cat), and serum cortisol concentrations (dog). Additional tests to consider in individual patients include serum and urine aldosterone and catecholamine concentrations as well as adrenal ultrasound examination.

Although secondary hypertension is most common in dogs and cats, idiopathic hypertension is more common than previously recognized, accounting for approximately 13%-20% of cases in cats.<sup>13,63,64</sup> Approximately 12% of nonazotemic nonhyperthyroid cats were hypertensive at baseline in one report,<sup>65</sup> and in a more recent study of 133 apparently healthy initially normotensive cats aged ≥9 years, 7% developed idiopathic hypertension over the study's follow-up period.<sup>27</sup>

## 5 | TARGET ORGAN DAMAGE (TOD)

Systemic hypertension is problematic only because chronically sustained increases in BP cause injury to tissues; the rationale for treatment of hypertension is prevention of this injury. Damage that results

**TABLE 4** Therapeutic agents and intoxicants associated with secondary hypertension in dogs and cats

Agent	Species	Notes
Glucocorticoids	Dog	<ul style="list-style-type: none"> <li>Statistically significant, mild to moderate, dose-dependent increases in BP noted at dosages sufficient to induce signs of iatrogenic hyperadrenocorticism.<sup>240-242</sup></li> <li>Systemic hypertension (ie, SBP <math>\geq</math>160) is uncommon in dogs administered agents with pure glucocorticoid activity at clinically relevant dosages.<sup>240,242-244</sup></li> </ul>
Mineralocorticoids	Dog	<ul style="list-style-type: none"> <li>At high dosages and in normal dogs, administration of desoxycorticosterone (DOC) is associated with statistically significant increases in BP,<sup>245,246</sup> most especially when combined with unilateral nephrectomy or high dietary sodium intake.<sup>247,248</sup></li> <li>Desoxycorticosterone pivalate (DOCP), administered at clinically relevant dosage rate (2.2 mg/kg IM q 30 days) to dogs with naturally occurring hypoadrenocorticism was not associated with significant increase in BP.<sup>249</sup></li> </ul>
Erythropoiesis-stimulating agents	Dog, cat	<ul style="list-style-type: none"> <li>Worsening or onset of systemic HT is common in animals with CKD related anemia when treated with recombinant human erythropoietin,<sup>250</sup> recombinant canine or feline erythropoietin,<sup>251,252</sup> or darbepoetin alfa.<sup>253,254</sup> <ul style="list-style-type: none"> <li>96% of dogs administered darbepoetin alfa experienced an increase in BP<sup>253</sup></li> <li>37% of previously normotensive cats developed HT during darbepoetin alfa treatment<sup>254</sup></li> <li>HT noted in 40% and 50% of dogs and cats, respectively, treated with rhEPO<sup>250</sup></li> </ul> </li> <li>It is difficult to know to what degree disease progression alone contributes to observed BP increases.</li> </ul>
Phenylpropanolamine (PPA)	Dog	<ul style="list-style-type: none"> <li>Normal dogs administered PPA (1.5-12.5 mg/kg PO), experience transient, significant increases in BP peak 30-120 minutes post-dose and last approximately 3-5 hours.<sup>255</sup></li> <li>Persistent HT is uncommon when administered long-term at recommended dosage (1.5 mg/kg PO q8h) in incontinent dogs.<sup>256,257</sup></li> <li>At high doses, acute intoxication may cause severe systemic HT.<sup>258,259</sup></li> </ul>
Phenylephrine hydrochloride	Dog	Systemic HT reported in normal dogs, <sup>260</sup> and those scheduled for cataract surgery, <sup>261</sup> administered topical ocular phenylephrine hydrochloride.
Ephedrine	Dog	Significant increases in direct BP were noted in normal dogs administered ephedrine (1.5 mg/kg PO q12h). <sup>262</sup>
Pseudoephedrine	Dog	<ul style="list-style-type: none"> <li>At high doses, acute intoxication may cause systemic HT.<sup>263</sup></li> <li>When administered for long term to dogs with urinary incontinence, significant increases in indirect BP were not noted.<sup>257</sup></li> </ul>
Toceranib phosphate	Dog	Systemic HT documented in 28% of previously normotensive dogs treated for various neoplastic diseases for 14 days. <sup>264</sup>
Chronic, high-dose sodium chloride		<ul style="list-style-type: none"> <li>BP in normal cats and dogs appears to be relatively salt-insensitive.<sup>134,265-267</sup></li> <li>High-sodium diets do not appear to promote HT in cats with reduced renal function,<sup>131,266</sup> and salt-induced HT in the dog seems to be limited to experimental models that also involve nephrectomy<sup>268,269</sup> or mineralocorticoid administration.<sup>248</sup></li> <li>BP effects of high-sodium intake in cats and dogs with pre-existing naturally occurring systemic HT, have not been systematically evaluated.</li> </ul>
<b>Intoxicants with which systemic hypertension has been reported/associated:</b>		
Cocaine <sup>270,271</sup>	Dog	
Methamphetamine/amphetamine <sup>272-274</sup>	Dog	
5-hydroxytryptophan <sup>275</sup>	Dog	
<b>Agents associated with systemic hypertension in people, but whose BP effects have not been well characterized in dogs and cats: guarana (caffeine), ma huang (ephedrine), tacrolimus, licorice, and bitter orange.<sup>276,277</sup></b>		

from the presence of sustained high BP is commonly referred to as end organ or TOD (Table 5) and the presence of TOD generally is a strong indication for antihypertensive treatment.

Hypertension has been associated with proteinuria and histological renal injury in both experimental studies and in naturally occurring disease, an effect that has been identified in several species including humans,<sup>66,67</sup> dogs,<sup>14,68,69</sup> and cats.<sup>70,71</sup> Proteinuria, in turn, has been associated with more rapid progression of renal disease and increased all-cause mortality in numerous clinical settings, including CKD and hypertension.<sup>70,72</sup> Antihypertensive treatment generally decreases the severity of proteinuria, at least if the hypertension is severe.<sup>13,72-74</sup> What remains unproven, at least in dogs and cats, is whether or not this decrease in proteinuria with antihypertensive drug treatment mitigates

renal injury, or is simply a surrogate for improved renal outcomes, such as rate of decrease in GFR (usually assessed by measurement of serum creatinine concentration) or renal-related mortality.<sup>13,72</sup> Although the benefit is unproven, hypertension-induced or hypertension-exacerbated proteinuria currently remains an attractive target for treatment in veterinary patients.

Several epidemiological studies have associated hypertension with proteinuria (and in some studies specifically albuminuria) in cats with naturally occurring diseases.<sup>70,72,74</sup> In addition, albuminuria has been related to an increase in BP in experimental studies of induced renal disease in cats.<sup>75</sup> A recent study of cats found that even with anti-hypertensive treatment, higher time-averaged SBP was associated with glomerulosclerosis and hyperplastic arteriosclerosis

**TABLE 5** Evidence of target organ damage (TOD)

Tissue	Hypertensive injury (TOD)	Clinical findings indicative of TOD	Diagnostic test(s)
Kidney	Progression of chronic kidney disease	Serial increases in SCr, SDMA, or decrease in GFR Persistent proteinuria, microalbuminuria	Serum creatinine, SDMA and BUN Urinalysis with quantitative assessment of proteinuria and/or albuminuria GFR measurement
Eye	Retinopathy/choroidopathy	Acute onset blindness Exudative retinal detachment Retinal hemorrhage/edema Retinal vessel tortuosity or perivascular edema Papilledema Vitreous hemorrhage Hyphema Secondary glaucoma Retinal degeneration	Ophthalmic evaluation including a fundoscopic examination
Brain	Encephalopathy Stroke	Centrally localizing neurological signs (brain or spinal cord)	Neurological exam Magnetic resonance or other imaging
Heart and blood vessels	Left ventricular hypertrophy Left-sided congestive heart failure (uncommon) Aortic aneurysm/dissection (rare)	Left ventricular concentric hypertrophy Gallop sound Arrhythmias Systolic heart murmur Evidence of left-sided congestive failure Hemorrhage (eg, epistaxis, stroke, and aortic rupture)	Auscultation Thoracic radiography Echocardiography Electrocardiogram

BUN, blood urea nitrogen concentration; GFR, glomerular filtration rate; SCr, serum creatinine concentration; SDMA, symmetric dimethylarginine.

lesions after the patient's death.<sup>71</sup> However, this effect was not replicated in a second, smaller, study.<sup>76</sup>

In dogs with azotemic CKD, magnitude of BP has been associated with proteinuria, and this has been associated with shortened survival times.<sup>14,77</sup> Hypertension also was associated with shorter renal survival, but only if proteinuria was excluded from the analysis.<sup>14</sup> Proteinuria was directly related to the extent of increase in BP and to the rate of decrease in GFR in an experimental study in dogs.<sup>78</sup> Dogs with leishmaniasis frequently have proteinuria and systemic hypertension, even when nonazotemic, although in this setting the proteinuria is thought to relate mainly to immune-mediated glomerular lesions, rather than occurring as a consequence of the hypertension.<sup>68,79</sup> Hypertensive greyhounds have an increased prevalence of microalbuminuria, although most dogs do not have histological evidence of renal injury.<sup>29</sup> Hypertension may be present in any stage of CKD, and serum creatinine concentration is not directly related to BP.<sup>4,80</sup> Hypertensive cats and dogs often have minimal or no azotemia.<sup>81</sup>

Ocular lesions are observed in many cats with hypertension and although prevalence rates for ocular injury vary, the frequency of ocular lesions has been reported to be as high as 100%.<sup>60,63,64,82-89</sup> Ocular lesions also are common in hypertensive dogs.<sup>14,59,60,90,91</sup> The syndrome<sup>91</sup> is commonly termed hypertensive retinopathy and choroidopathy and has been frequently reported in dogs<sup>14,59,60,92</sup> and cats.<sup>63,64,84,85,93-96</sup> Exudative retinal detachment is the most commonly observed finding. Other lesions include retinal hemorrhage, multifocal retinal edema, retinal vessel tortuosity, retinal perivascular edema, papilledema, vitreal hemorrhage, hyphema, secondary glaucoma, and retinal degeneration.<sup>92</sup> Acute onset of blindness from complete bilateral exudative retinal detachment may be a presenting complaint in both species.<sup>60,93,94</sup> Effective antihypertensive treatment can lead to retinal reattachment, but restoration of vision<sup>87</sup> generally occurs in only a minority<sup>63</sup> of patients, and successful treatment of hypertension may not resolve ocular abnormalities.<sup>92</sup> Hypertensive

ocular injury has been reported in patients with SBP as low as 168 mm Hg,<sup>86</sup> and there is a substantially increased risk of occurrence when SBP exceeds 180 mm Hg.<sup>60,82,93,95</sup>

Hypertensive encephalopathy<sup>97</sup> has been reported in dogs<sup>14</sup> and cats,<sup>63,94,98</sup> and it occurs in people as a well-described entity characterized by white matter edema and vascular lesions.<sup>99,100</sup> Neurologic signs were reported in 29%<sup>63</sup> and 46%<sup>94</sup> of hypertensive cats. Hypertensive encephalopathy also occurs after renal transplantation in people<sup>101</sup> and is a cause of otherwise unexplained death in this setting in cats.<sup>98,102,103</sup> This syndrome, in its early phases, is responsive to anti-hypertensive treatment.<sup>75,98</sup> Hypertensive encephalopathy is more likely to occur in cats with a sudden increase in BP, a SBP that exceeds 180 mm Hg, or both.<sup>75</sup> Observed clinical signs are typical of intracranial disease and include lethargy, seizures, acute onset of altered mentation, altered behavior, disorientation, balance disturbances (eg, vestibular signs, head tilt, and nystagmus), and focal neurologic defects because of stroke-associated ischemia. Other central nervous system abnormalities, including hemorrhage and infarction, which occur with chronic hypertension in people,<sup>104</sup> also are observed in dogs and cats.<sup>105</sup> A recent study described lesions on magnetic resonance imaging consistent with vasogenic edema in the occipital and parietal lobes of the brain in affected cats and dogs with neurologic signs.<sup>106</sup> Hypertension appears to be a risk factor for ischemic myelopathy of the cranial cervical spinal cord, resulting in ambulatory tetraparesis or tetraplegia with intact nociception in old cats.<sup>107</sup>

Cardiac abnormalities are common in hypertensive cats<sup>63,64,82</sup> and dogs.<sup>108</sup> When affected, the heart is a target organ and increased cardiac output is rarely the cause of hypertension in animals.<sup>63</sup> In both dogs<sup>59,108</sup> and cats,<sup>63,64,82</sup> physical examination abnormalities may include systolic murmurs and/or gallop sounds. The most common cardiac change associated with hypertensive cardiomyopathy in dogs and cats is cardiomegaly associated with left ventricular concentric hypertrophy (LVH),<sup>109,110</sup> although echocardiographic findings are variable



and may be indistinguishable from those associated with feline idiopathic hypertrophic cardiomyopathy.<sup>63,93,94,110-113</sup> Although LVH may not be a risk factor for decreased survival time,<sup>82</sup> effective antihypertensive treatment may decrease the prevalence of LVH in affected cats.<sup>114</sup> Cardiac failure and other serious complications are infrequent, but may occur.<sup>63,94,115</sup>

Cats with previously undiagnosed hypertension may unexpectedly develop signs of congestive heart failure after fluid therapy. Furthermore, cats with secondary hypertension because of other causes (eg, CKD) may die of cardiovascular complications,<sup>64</sup> as frequently is the case in hypertensive people.<sup>116</sup> Epistaxis, because of hypertension-induced vascular abnormalities, has been associated with systemic hypertension but hypertension rarely is the primary cause of epistaxis in either species.<sup>117-119</sup> Aortic aneurysm and aortic dissection are rare and serious complications of hypertension reported in both dogs and cats, and typically require a high index of suspicion and advanced imaging to diagnose.<sup>115,120,121</sup>

## 6 | PREVALENCE AND SELECTION OF PATIENTS FOR HYPERTENSION SCREENING

There are 2 clear indications for evaluating BP in a patient for which systemic hypertension may be a concern. First, BP should be measured in patients with clinical abnormalities consistent with hypertensive TOD (Table 5), specifically, the presence of otherwise unexplained clinical findings associated with systemic hypertension should prompt BP measurement at the time of diagnosis. These include signs of hypertensive choroidopathy or retinopathy, hyphema, intracranial neurologic signs (eg, seizures, altered mentation, and focal neurological deficits), renal abnormalities (eg, proteinuria, microalbuminuria, and azotemia), and cardiovascular abnormalities (eg, LVH, gallop sound, arrhythmia, systolic murmur, and epistaxis). In the absence of these clinical findings, a high index of suspicion must be maintained to diagnose systemic hypertension and to avoid misclassification as situational hypertension. Clinical signs relating to systemic hypertension, evident to the owner or the veterinarian, may be subtle and attributable to aging or underlying clinical conditions that may as yet be undiagnosed. In people, early signs of hypertension are subjective and include morning headaches, facial flushing and feelings of anxiety. Such clinical signs would be difficult to recognize in dogs and cats. In cats, some nonspecific clinical signs have been associated with hypertension in the laboratory setting, including inactivity, lethargy, photophobia, and altered (increased or decreased) appetite (S.A. Brown, unpublished observations, 2004).

The presence of diseases or conditions causally associated with secondary hypertension (Table 3), treatment with pharmacological agents with a known effect on BP, or known or suspected exposure to intoxicants that may increase BP (Table 4) comprise the second group of indication for BP measurement. A thorough physical examination, including funduscopic evaluation, cardiac auscultation, assessment of renal function including proteinuria, and neurologic examination, should also be performed in at-risk populations to assess for TOD. The correlation between advancing age and prevalence of systemic hypertension is not as clear in cats and dogs as in people,

although recent data in healthy normotensive geriatric cats suggest an expected increase in BP of  $0.4 \pm 0.1$  mm Hg per 100 days.<sup>122</sup> Conditions resulting in secondary hypertension more frequently are observed in mature to geriatric cats (eg, those with CKD or hyperthyroidism) and dogs (eg, those with hyperadrenocorticism) and, therefore, it may be prudent to screen older animals for these conditions.

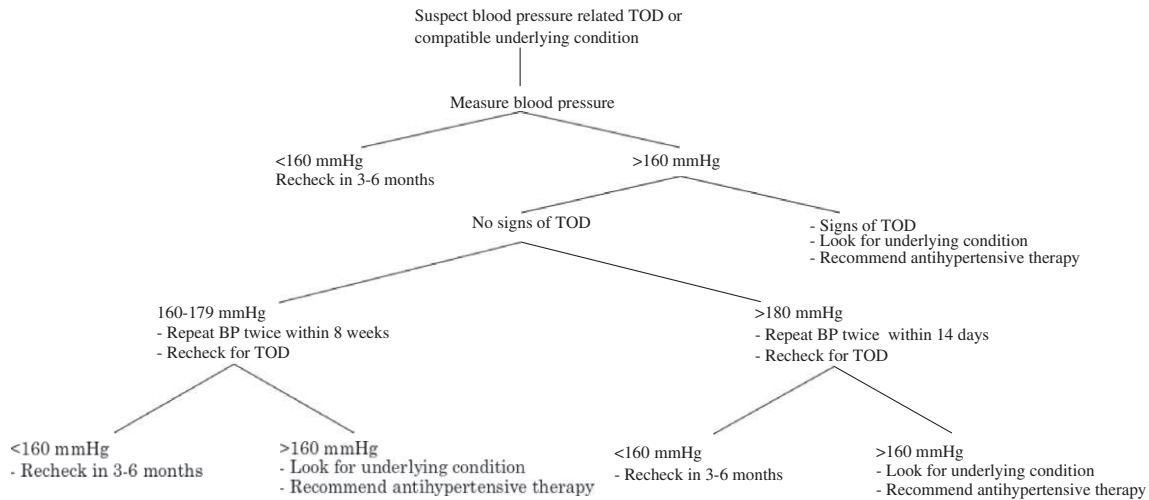
The prevalence of hypertension in dogs and cats is not known. Surveys of apparently healthy dogs have identified hypertension in 0.5% of 400 dogs,<sup>123</sup> 0.9% of 1000 young dogs,<sup>124</sup> 2% of 215 dogs,<sup>125</sup> 10% of 102 dogs,<sup>22</sup> and 13% of healthy Shetland Sheepdogs.<sup>126</sup> Others have provided evidence that suggests dogs are resistant to the development of hypertension.<sup>20,80,127</sup> The prevalence of hypertension may be comparable in cats. In a study of 104 apparently healthy cats, 2% had SBP > 170 mm Hg.<sup>24</sup> However, as noted elsewhere in these guidelines, the lack of uniform measurement techniques, variable inclusion criteria, and inconsistent thresholds for establishing a diagnosis of hypertension in veterinary medicine make prevalence data difficult to interpret. Nonetheless, hypertension seems to be rare in young otherwise healthy dogs and cats. Based on available data, it is still unclear whether or not routine screening of apparently healthy dogs and cats is a reliable method for detecting true hypertension in the population, because the risk of false diagnosis is likely to be high with widespread screening. Therefore, the panel does not recommend routine screening of all dogs and cats for the presence of systemic hypertension. Some conditions (eg, hyperthyroidism, hyperadrenocorticism, and CKD) that result in secondary hypertension are more prevalent in older animals, yet may be occult. Thus, it is reasonable to institute annual screening of cats and dogs  $\geq 9$  years of age. Still, high BP in otherwise healthy, particularly young, animals should be assumed to represent situational hypertension until proven otherwise with confirmatory measurements on multiple occasions.

## 7 | DIAGNOSIS OF HYPERTENSION

The diagnosis of hypertension always should be based on reliable BP measurements, and therapeutic decisions in cats and dogs typically are based on SBP results (Figure 1). The presence of TOD (eg, retinopathy and CKD) justifies initiating treatment after a single measurement session, but in most cases, results should be confirmed by measurements repeated on multiple (>2) occasions. In cases of prehypertension (140-159 mm Hg) or hypertension at moderate risk of TOD (160-179 mm Hg), these measurement sessions can occur over 4-8 weeks. With more severe hypertension ( $\geq 180$  mm Hg), however, the risk of TOD dictates that the measurement sessions be completed in 1-2 weeks. Once increases in BP are determined to be persistent, and not associated with measurement error or situational hypertension, the search for conditions associated with secondary hypertension (Table 3) should begin.

Hypertension in both dogs and cats is classified based on the risk of TOD:

- Normotensive (minimal TOD risk) SBP <140 mm Hg
- Prehypertensive (low TOD risk) SBP 140-159 mm Hg
- Hypertensive (moderate TOD risk) SBP 160-179 mm Hg
- Severely hypertensive (high TOD risk) SBP  $\geq 180$  mm Hg



**FIGURE 1** The recommended approach to the evaluation of a possibly hypertensive patient involves reliable measurements of blood pressure as well as the identification of possible target organ damage. Once a diagnosis of hypertension is established, a search for a compatible underlying condition and appropriate treatment should commence

At this time, information regarding breed-specific reference ranges is limited, but sight hounds are known to have higher in-hospital BP than other breeds.<sup>32,128</sup> This difference appears to be because of situational hypertension and not a true difference in SBP.<sup>17</sup> Nevertheless, a risk of TOD has been proposed for these dogs when in-hospital SBP is >180 mm Hg.<sup>129</sup> These guidelines likely will be refined as additional breed-specific information becomes available.

In people, decreasing BP in hypertensive people lowers the risk of TOD. The precise BP at which TOD occurs in dogs and cats is not known. Nevertheless, treatment should be instituted in any patient that has a BP persistently in the hypertensive or severely hypertensive category. The goal should be to decrease BP into the prehypertensive or normotensive range.

## 8 | THE HYPERTENSIVE PATIENT: EVALUATION AND DECISION TO TREAT

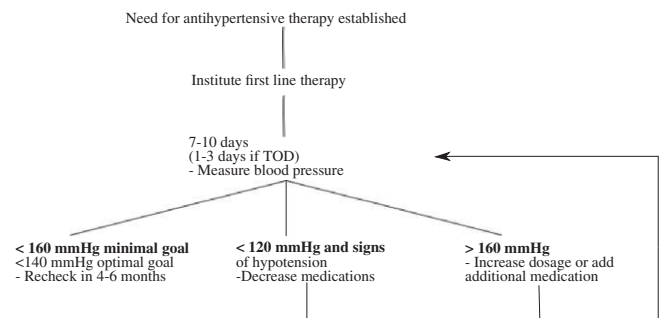
Patients with BP in the prehypertensive category typically are not treated with antihypertensive medications, but may benefit from increased frequency of monitoring of overall condition as well as BP. Patients in known renal risk categories (International Renal Interest Society CKD stage 2 or higher) or patients with systemic diseases associated with development of systemic hypertension (eg, hyperthyroidism and hyperadrenocorticism) may benefit from systemic wellness and BP evaluations every 6 months in order to manage systemic disease optimally and detect systemic hypertension when and if it develops.

Once a diagnosis of hypertension has been made and the possibility of situational hypertension has been eliminated, the search for a possible underlying disease or pharmacologic agent associated with secondary hypertension should be commenced. For cases in which secondary hypertension is identified, treatment of the underlying condition should be implemented immediately. Although doing so may decrease systemic BP and make the patient's hypertension more amenable to treatment, most pets fail to become normotensive and will

continue to be at risk for TOD. For this reason, treatment of a patient's hypertension should not be postponed until the underlying condition is controlled.

Client education is paramount. In most cases, hypertension is silent and damage to target organs occurs over long periods of time, and it is easy for owners to underestimate the importance of appropriate treatment and follow-up. Owners must realize that control of hypertension is likely to improve the quality of their pet's life over the long term, but potentially with little immediate observable benefit. The client should be provided with BP results, a working knowledge of the complications of both hypertension and the drugs used to manage it, and a clear understanding for the goals of treatment. The owner should never leave the office without a clear plan for reevaluation, including a future appointment.

For most patients, the onset of hypertension has been gradual and it can be treated and controlled as outlined below, but a few patients may experience acute increases in BP resulting in hypertensive choroidopathy, encephalopathy, or rapidly progressive acute kidney injury. In these patients, the increase in BP should be considered a hypertensive emergency. For recommendations regarding the management of these patients, the reader is referred to the section on hypertensive emergencies.



**FIGURE 2** Management of hypertension involves a stepwise approach, including repeat blood pressure measurement and medication adjustments

**TABLE 6** Hypertension in both dogs and cats classified based on the risk of target-organ damage (TOD)

Normotensive (minimal TOD risk)	SBP <140 mm Hg
Prehypertensive (low TOD risk)	SBP 140-159 mm Hg
Hypertensive (moderate TOD risk)	SBP 160-179 mm Hg
Severely hypertensive (high TOD risk)	SBP ≥180 mm Hg

## 8.1 | General treatment guidelines

Because hypertension in dogs and cats often is secondary (≥80% of cases), antihypertensive drug treatment should be initiated along with treatment for any underlying or associated condition. Initial considerations (Figure 2) always should include identification and management of conditions likely to be causing secondary hypertension and identification and treatment of TOD. If possible, these considerations should be addressed with specific targeted diagnostic and therapeutic regimens. Effective management of a condition causing secondary hypertension may lead to complete or partial resolution of the high BP in some, but not all, cases.<sup>4,14,55</sup> Decisions to use antihypertensive drugs should be based on the integration of all clinically available information, and a decision to treat (which may effectively mandate lifelong drug treatment) warrants periodic re-evaluation.

Treatment for hypertension must be individualized to the patient and take into account concurrent conditions. Once daily treatment is ideal; fewer treatments always are preferred. A gradual persistent decrease in BP is the therapeutic goal. Acute marked decrease in BP should be avoided. If the chosen antihypertensive agent is only partially effective, the usual approach is to consider increasing the dosage or adding an additional drug. Management of highly resistant hypertension in people often requires multiagent (≥2) protocols; a similar situation often occurs in dogs, although this appears to be relatively rare in cats. It is often helpful to discuss with the owner the interindividual variability of response to antihypertensive medications when the first medication is prescribed, and the need for frequent monitoring until a therapeutic goal is reached.

The goal of antihypertensive treatment is to decrease the likelihood and severity of TOD. Hypertension generally is not an emergency, and rapid decreases in BP usually should not be sought aggressively. Studies in people indicate that reduction of risk for TOD by antihypertensive treatment is a continuum and that the lower the BP, the lower the risk for TOD. Results of a recent laboratory study in dogs<sup>78</sup> suggest that BP is a continuous risk marker for progression of kidney disease and may justify a similar treatment approach in veterinary patients. The panel feels that regardless of the initial magnitude of BP, the goal of treatment should be to maximally decrease the risk of TOD (SBP < 140 mm Hg) and that antihypertensive treatment should be adjusted on re-evaluation if SBP is ≥160 mm Hg, with a minimal goal of treatment being to achieve a decrease in SBP to ≤160 mm Hg (Table 6). Blood pressure <120 mm Hg, combined with clinical findings of weakness, syncope, or tachycardia, indicates systemic hypotension and treatment should be adjusted accordingly (Figure 2).

Although frequently recommended as an initial step in the pharmacological management of high BP (Figure 2), dietary salt restriction is controversial,<sup>84,130,131</sup> and available evidence suggests that

substantial sodium restriction alone generally does not decrease BP.<sup>130-132</sup> Although sodium restriction activates the renin-angiotensin-aldosterone system (RAAS) axis<sup>59,131</sup> and has variable effects on BP,<sup>130,132</sup> it may enhance the efficacy of antihypertensive agents that interfere with this hormonal system (eg, angiotensin-converting enzyme inhibitors [ACEi], angiotensin receptor blockers [ARB], and aldosterone receptor blockers). Although normal cats<sup>133,134</sup> and dogs<sup>135</sup> generally are not salt-sensitive, high salt intake may produce adverse consequences in some settings,<sup>136,137</sup> including animals with CKD.<sup>84</sup> The panel therefore recommends avoiding high dietary sodium chloride intake. However, the selection of appropriate diet should include other patient-specific factors, such as underlying or concurrent diseases and palatability.

## 8.2 | Management of hypertension in dogs

Once a decision is made to treat a dog with hypertension, antihypertensive treatment should be individualized to the patient, based in large part on the animal's concurrent conditions, with a therapeutic goal of decreasing the likelihood of future TOD (ie, decreasing SBP by at least 1 SBP substage). In most dogs, hypertension is not an emergency and SBP should be decreased gradually over several weeks. Certain disease conditions may be best addressed using specific classes of agents, such as alpha- and beta-adrenergic blockers for hypertension associated with pheochromocytoma or aldosterone receptor blockers for hypertension because of adrenal tumors associated with hyperaldosteronism.<sup>75,138-141</sup> Otherwise, RAAS inhibitors and calcium channel blockers (CCB) are the most widely recommended antihypertensive agents for use in dogs.<sup>142</sup> Because of their antiproteinuric effect and the high prevalence of CKD in hypertensive dogs, RAAS inhibitors are often chosen as first-line antihypertensive agents in dogs. In dogs with concurrent CKD, a clinically relevant decrease in proteinuria (ie, urinary protein-to-creatinine [UPC] ratio decreased by ≥50%, preferably to <0.5) is a secondary goal of antihypertensive treatment. Available RAAS inhibitors include ACEi, ARB, and aldosterone antagonists, but most clinical experience in veterinary medicine has been with ACEi. An ACEi (eg, 0.5-2.0 mg enalapril or benazepril/kg PO q12h) usually is recommended as the initial drug of choice in a hypertensive dog. An ARB (eg, 1.0 mg telmisartan/kg PO q24h) is an alternative method for RAAS inhibition. The exception to the use of a RAAS inhibitor as initial, sole agent, treatment is severely hypertensive dogs (SBP > 200 mm Hg) for which the initial coadministration of a RAAS inhibitor and a CCB (eg, 0.1-0.5 mg/kg amlodipine PO q24h) is appropriate. The use of CCB as monotherapy in dogs should be avoided because CCB preferentially dilate the renal afferent arteriole potentially exposing the glomerulus to damaging increases in glomerular capillary hydrostatic pressure. Because ACEi and ARBs preferentially dilate the renal efferent arteriole, the coadministration of a RAAS inhibitor and a CCB may have a limited effect on glomerular capillary hydrostatic pressures.

If an antihypertensive regimen is ineffective, the usual decision is to increase the dosage of currently used agents or to add an alternative agent. A variety of other agents have BP-lowering efficacy (Table 7) and these may be used as appropriate in patients for which risk reduction is not adequate with ACEi or CCB or a combination of

**TABLE 7** Oral antihypertensive agents

Class	Drug	Usual oral dosage
Angiotensin converting enzyme inhibitor	Benazepril	D: 0.5 mg/kg q12-24h C: 0.5 mg/kg q12h
	Enalapril	D: 0.5 mg/kg q12-24h C: 0.5 mg/kg q24h
Angiotensin receptor blocker	Telmisartan	C: 1 mg/kg q24h D: 1 mg/kg q24h
Calcium channel blocker	Amlodipine	D/C: 0.1-0.25 mg/kg q24h (up to 0.5 mg/kg in cats and dogs) C: 0.625-1.25 mg per cat q24h
$\alpha_1$ blocker	Prazosin	D: 0.5-2 mg/kg q8-12h C: 0.25-0.5 mg/cat q24h
	Phenoxybenzamine	D: 0.25 mg/kg q8-12h or 0.5 mg/kg q24h C: 2.5 mg per cat q8-12h or 0.5 mg/cat q24h
	Acepromazine	D/C: 0.5-2 mg/kg q8h
Direct vasodilator	Hydralazine	D: 0.5-2 mg/kg q12h (start at low end of range) C: 2.5 mg/cat q12-24h
Aldosterone antagonist	Spirolactone	D/C: 1.0-2.0 mg/kg q12h
$\beta$ blocker	Propranolol	D: 0.2-1.0 mg/kg q8h (titrate to effect) C: 2.5-5 mg/cat q8h
	Atenolol	D: 0.25-1.0 mg/kg q12h C: 6.25-12.5 mg/cat q12h
Thiazide diuretic	Hydrochlorothiazide	D/C: 2-4 mg/kg q12-24h
Loop diuretic	Furosemide	D/C: 1-4 mg/kg q8-24h

C, cat; D, dog.

these drugs (Figure 2). Although diuretics are frequently administered to hypertensive people, these agents are not first-choice drugs for veterinary patients, particularly given the prevalence of CKD in hypertensive dogs and the adverse consequences of diuretic-induced dehydration and volume depletion in this setting. However, diuretics can be considered in the small subset of hypertensive animals in which volume expansion is clinically apparent (eg, those with edema).

Antihypertensive agents in general, and RAAS inhibitors in particular, should be used with caution in dehydrated dogs in which GFR may decrease precipitously with their use. Unless severe hypertension with rapidly progressive TOD is present, these patients should be carefully rehydrated and then re-evaluated before instituting antihypertensive treatment.

### 8.3 | Management of hypertension in cats

Despite the potential role of either the systemic or intrarenal RAAS axis in the pathogenesis or maintenance of hypertension,<sup>26,143-148</sup> CCB, specifically amlodipine besylate, have been the first choice for antihypertensive treatment because of established efficacy<sup>64,75,114,149-152</sup> in cats with idiopathic hypertension or in those with CKD. A mean decrease in SBP of 28-55 mm Hg typically is observed in cats in hypertensive to severely hypertensive cats.<sup>64,149,150,152</sup> Recent data indicate that an initial starting dose of 0.625 mg per cat per day amlodipine besylate is effective in cats in

which initial SBP is <200 mm Hg, but that those cats with SBP >200 mm Hg may benefit from a higher starting dosage of 1.25 mg per cat per day.<sup>151</sup> Rarely, dosages of up to 2.5 mg per cat per day however may be required. Given the efficacy of amlodipine as an antihypertensive agent, careful investigation of owner compliance should occur before increasing to the dose of amlodipine. Research evaluating plasma amlodipine concentration indicates that the need for dose escalation to adequately control BP appears to relate to severity of the hypertension rather than to body weight or amlodipine pharmacokinetics.<sup>151</sup> Although transdermal application has been explored, efficacy of this route of administration has not been established and PO administration is therefore the preferred route of administration.<sup>153,154</sup> Adverse effects of amlodipine, including peripheral edema and gingival hyperplasia, are rarely reported in the dog and are also uncommon in cats. Although gingival hyperplasia has been reported in licensing studies during administration to young healthy cats, this seems to be relatively rare in clinical practice.<sup>155,156</sup>

Despite dramatic antihypertensive efficacy, longitudinal control of SBP with amlodipine besylate has not been shown to increase survival time in hypertensive cats,<sup>64,157</sup> and its use may activate the systemic or intrarenal RAAS.<sup>148</sup>

A key predictive factor in the survival of hypertensive cats is proteinuria. A significant decrease in proteinuria has been identified in cats that are initially either borderline proteinuric or proteinuric when treated with CCB.<sup>157</sup> However, although the combined use of

amlodipine and an ACEi or amlodipine and an ARB is reportedly well tolerated,<sup>158,159</sup> studies exploring any additional survival benefit of add-on antiproteinuric agents in hypertensive cats that remain proteinuric after BP control with amlodipine besylate are lacking. Nevertheless, based on the potential for proteinuria to contribute to the development and progression of renal disease in cats and its association with survival of cats with CKD,<sup>65,160,161</sup> antiproteinuric treatment should be considered in this situation.<sup>162,163</sup>

Telmisartan is an ARB currently licensed in Europe for the treatment of feline proteinuria due to CKD.<sup>158</sup> Initial studies in healthy anesthetized cats undergoing radiotelemetric BP monitoring, telmisartan, but not losartan, significantly attenuated the pressor response to angiotensin I.<sup>164</sup> Attenuation of the SBP rise was significantly higher than for benazepril when telmisartan was administered at a higher than currently licensed dosage (3 mg/kg PO q24h).<sup>164</sup> More recently, a double-blinded, randomized, placebo-controlled clinical trial has explored the use of telmisartan administered at a dosage of 2 mg/kg/day for the treatment of naturally occurring hypertension in cats.<sup>165</sup> In this study, after 14 days of treatment, a significantly larger decrease in mean SBP from baseline was identified for the telmisartan-treated ( $-19 \pm 22$  mm Hg) compared to the placebo-treated ( $-9 \pm 17$  mm Hg;  $P < 0.0001$ ) group. After 28 days of treatment, 54.6% of cats receiving telmisartan had reached a target end point of a decrease in SBP  $> 20$  mm Hg, compared to 27.6% in the placebo group. However, excluded from this study were cats with SBP  $> 200$  mm Hg, cats with evidence of ocular or central nervous system (CNS) TOD and those already being treated with vasoactive agents. Efficacy of telmisartan in severely hypertensive cats and in those with overt ocular and CNS hypertensive TOD has not been demonstrated. In addition, predefined inclusion removal criteria included cats that developed TOD or SBP  $> 200$  mm Hg, thus narrowing the population in the longitudinal study. The combination of amlodipine besylate and telmisartan was shown to be well tolerated in a small number ( $n = 8$ ) of cats in which the antiproteinuric efficacy of telmisartan was evaluated, but the antihypertensive effect of telmisartan was not a primary outcome in this study.<sup>158</sup>

Use of ACEi in cats as a first-line antihypertensive agent is not recommended. Although statistically significant decreases in SBP have been identified when direct arterial BP monitoring is possible, the decrease in SBP is small ( $\pm 10$  mm Hg) and unlikely to be sufficient in most cats.<sup>166</sup> However, benazepril has been used in cats that require a second antihypertensive agent and, clinically, the combination of ACEi and amlodipine besylate is well tolerated.<sup>159</sup>

Angiotensin converting enzyme inhibitors and ARB preferentially dilate the renal efferent arteriole thereby decreasing intraglomerular pressure and the magnitude of proteinuria.<sup>158,167,168</sup> However, a secondary consequence of efferent arteriolar dilatation is a theoretical tendency for GFR to decrease. Single nephron studies indicate that such is not necessarily the case in cats,<sup>169</sup> and indeed administration of ACEi commonly produces only very modest increases in serum creatinine concentration ( $< 0.5$  mg/dL;  $< 50$   $\mu$ mol/L), which is generally well tolerated. However, in a recent study, approximately 30% of cats with confirmed or suspected CKD experienced an increase in serum creatinine concentration within 30 days of starting benazepril with a  $> 30\%$  increase in serum creatinine concentration seen in 23.8% of

cats with confirmed CKD.<sup>170</sup> Deterioration in renal function tests and uremic crisis also was reported as an adverse event in 2/112 cats and 1/112 cats receiving telmisartan, respectively, although the initial stage of CKD in these cats is uncertain from data provided.<sup>73</sup> In contrast, no alteration in serum creatinine concentration would be anticipated with introduction of a CCB such as amlodipine besylate.<sup>171</sup> Clinicians should be aware of the potential for acute exacerbation of azotemia with concurrent ACEi and ARB, and careful monitoring is recommended.<sup>167,169,172,173</sup> Angiotensin converting enzyme inhibitors and ARB should not be started in dehydrated cats in which GFR may decrease precipitously. These patients should be carefully rehydrated and then re-evaluated before instituting ACEi or ARB treatment.

Although several other antihypertensive agents (Table 7) were explored in early studies, their use rarely is required for treatment of hypertension in cats. Diuretics are not routinely used as antihypertensive agents in cats.<sup>63,94</sup> Beta-blockers (eg, atenolol) may be useful to control heart rate in some tachycardic hypertensive cats (eg, those with hyperthyroidism), but have negligible antihypertensive effect in such patients and therefore should not be used as a sole agent for the management of hypertension.<sup>63,94,174</sup> For cats diagnosed with concurrent systemic hypertension and hyperthyroidism, amlodipine besylate remains the first-line antihypertensive agent, combined with management of hyperthyroidism. Vasodilator drugs such as hydralazine rarely are required for management of hypertension in cats, but they have historically been useful in emergency situations (see emergency management).<sup>175</sup>

In cats with primary hyperaldosteronism, management with aldosterone antagonists (eg, spironolactone), potassium supplementation, and adrenalectomy (if feasible) is necessary.<sup>176</sup> However, antihypertensive treatment with amlodipine besylate often is required for adequate BP control and should be started concurrently, particularly in those patients presented with ocular TOD.<sup>177</sup> Medical combination treatment can be utilized in long term for management of patients with primary hyperaldosteronism and hypertension when surgery is not an option.<sup>177</sup> Facial dermatitis and excoriation have been reported as a rare adverse effect associated with the use of spironolactone in cats.<sup>178</sup> Limited information is available about the effect of adrenalectomy on the ongoing requirements for antihypertensive treatment in cats with primary hyperaldosteronism. Some individual affected cats have not required treatment with amlodipine besylate postoperatively, but the frequency of BP monitoring in these patients is not clear.<sup>177</sup> If another, nonadrenal, concurrent disease (such as CKD) was present and contributing to the pathogenesis of hypertension in an individual cat, adrenalectomy alone would not be expected to resolve systemic hypertension. In such case, ongoing antihypertensive management with amlodipine besylate would be required. Careful monitoring of BP therefore is recommended in the peri- and postoperative period in cats with primary aldosteronism treated with adrenalectomy.

Phenochromocytoma has been reported rarely in the cat.<sup>179–182</sup> Combination treatment with phenoxybenzamine, an  $\alpha_1$ - and  $\alpha_2$ -adrenergic blocker, and amlodipine besylate, may be required to adequately control BP in affected cats.<sup>181</sup> For cats in which tachyarrhythmias are of concern, beta-adrenergic blocker (eg, atenolol) treatment may be considered, but it should only be added after  $\alpha$ -adrenergic blockade. For cats undergoing adrenalectomy, careful BP monitoring

is required in the postoperative period, as persistent hypertension or hypotension may occur.

## 8.4 | Hypertensive emergencies

When marked increases in BP are accompanied by signs of ongoing acute TOD, immediate and aggressive treatment is warranted. Clinical trials of therapies and therapeutic strategies for acute hypertensive crises in dogs and cats have not been published, and recommendations are anecdotal and extrapolated from recommendations made for human patients. In dogs and cats, overt evidence of acute TOD is most likely to be ocular (eg, retinal hemorrhage or detachment, hyphema) or neurologic (eg, coma, decreased mentation, generalized, or focal facial seizures). Regardless of knowledge of predisposing disease conditions, diagnosis of SBP  $\geq$  180 mm Hg (high TOD risk category) in a patient with signs of intracranial TOD (eg, focal facial seizures) necessitates immediate emergency treatment. The need for aggressive treatment in such cases typically requires 24-hour care capability, and referral to such a facility is warranted when 24-hour care is not available.

The therapeutic target in patients with acute hypertensive emergencies is an incremental decrease in SBP rather than acute normalization of BP. In cases of chronic hypertension, autoregulatory vascular beds in the brain and kidneys may have adapted to higher perfusion pressure, and acute marked BP reduction may result in hypoperfusion. Initial SBP should be decreased by approximately 10% over the first hour and another approximately 15% over the next few hours,<sup>183</sup> followed by gradual return to normal BP.

Because of the requirement for incremental SBP decreases, optimal acute management of hypertensive emergencies requires parenteral treatment that can be titrated to effect, with rapid onset and conclusion of action. Several medications have been discussed in this setting in hypertensive human patients, and although several of these medications have been used anecdotally in dogs and cats, no comparative studies of these drugs in severely hypertensive dogs or cats are available. Current recommendations are based on mechanism of action, recommendations in human medicine and reports and anecdotal experience in veterinary patients.

One of the most feasible parenteral medications in veterinary clinical use (where available) may be fenoldopam,<sup>184</sup> a selective dopamine-1-receptor agonist currently approved for use in hypertensive human emergency patients.<sup>185,186</sup> Although no veterinary studies of this medication are available in acute hypertension in dogs or cats, fenoldopam appears to be safe for treatment of acute kidney injury in veterinary patients.<sup>184</sup> Through its dopamine-1 agonist action, fenoldopam causes renal arterial vasodilation, natriuresis, and increased GFR in normal dogs,<sup>187</sup> and it is associated with diuresis in healthy cats,<sup>188</sup> all of which may be beneficial in veterinary patients with hypertensive emergencies. Fenoldopam is delivered as a constant rate infusion (CRI), initially at a dosage of 0.1  $\mu$ g/kg/min with careful (ie, at intervals of at least 10 minutes) monitoring of BP. The dosage can be titrated up by 0.1  $\mu$ g/kg/min increments every 15 minutes to the desired SBP, to a maximal dosage of 1.6  $\mu$ g/kg/min. The plasma half-life of fenoldopam in dogs and cats is short,<sup>106,189</sup> and effects can be expected to subside within several minutes of discontinuing the infusion. Other parenteral medications that may be effective in

hypertensive dogs include labetalol (0.25 mg/kg IV over 2 minutes, repeated to a total dosage of 3.75 mg/kg, followed by a CRI of 25  $\mu$ g/kg/min), hydralazine (loading dosage of 0.1 mg/kg IV over 2 minutes, followed by a CRI of 1.5-5.0  $\mu$ g/kg/min) or nitroprusside (0.5-3.5  $\mu$ g/kg/min IV CRI), although none of these medications has the advantage of renal vasodilatation. Phentolamine, a short-acting competitive  $\alpha$ -adrenergic blocking drug anecdotally has been used successfully to manage intraoperative hypertension that may occur during removal of pheochromocytomas (loading dose, 0.1 mg/kg IV; CRI, 1 to 2  $\mu$ g/kg/min).<sup>190</sup> In cats, even anecdotal information regarding the use of parenterally administered vasodilators is sparse. Subcutaneous administration of hydralazine (1.0-2.5 mg per cat SC) has been used to treat acute hypertension in postoperative feline renal transplant patients.<sup>98</sup> In all cases of parenteral vasodilator administration, continuous or frequent monitoring of BP is required to ensure that adequate BP reductions are achieved, and to avoid hypotension. Orally administered medications can be started when BP has been controlled for 12-24 hours, and parenteral medication can be titrated down as PO medication takes effect. In cases in which recommended parenteral medications are not available, and the patient can take PO medication, PO amlodipine or hydralazine may be administered as outlined below.

Patients with markedly increased SBP ( $\geq$ 180 mm Hg) but without evidence of acute TOD may be treated with PO medication. Preferred medications have a rapid onset of action when administered PO and decrease BP regardless of primary disease. Hydralazine (0.5-2 mg/kg PO q12h) has a rapid onset of action and can be used for rapid reduction of BP in both cats and dogs. Amlodipine besylate can be administered at a dosage of 0.2-0.4 mg/kg PO q24h; dosages up to 0.6 mg/kg PO q24h may be employed cautiously. Many clinicians prefer PO CCB such as amlodipine, particularly in cats, because these agents have limited risk of causing hypotension.

## 9 | CONCLUSION

Despite more than a decade since the original ACVIM consensus statement on the management of hypertension, our understanding of the pathophysiology, measurement, and treatment of systemic hypertension in companion animals continues to evolve. Substantial gaps in our knowledge remain.

To bridge these gaps, we recommend large multicenter clinical studies aimed at refining our understanding of normal BP and how it is best assessed. In addition, long-term studies are necessary to determine the best approach to hypertension treatment, and how these treatments will affect patient quality of life and life expectancy of our patients. We hope this document will be updated periodically to reflect advances in the field of veterinary medicine.

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Authors declare no off-label use of antimicrobials.

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Authors declare no IACUC or other approval was needed.

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