BEYOND FUROSEMIDE: THE ROLE OF DIURETICS IN CONGESTIVE HEART FAILURE
Part 1: Torsemide

Marisa K. Ames, DVM, Diplomate ACVIM (Cardiology)
Colorado State University

Clarke E. Atkins, DVM, Diplomate ACVIM (Internal Medicine & Cardiology)
North Carolina State University

Diuretics are a critical component of the pharmacotherapy of congestive heart failure (CHF) (typically pulmonary edema or ascites).

In humans with heart failure, 90% receive at least one type of diuretic.[1] Of these, loop diuretics—furosemide, bumetanide, and torsemide—are the most potent and commonly used. When a single drug is administered in humans, furosemide is given 87% of the time.[1]

Furosemide has been, and remains, the diuretic of choice for acute and chronic management of CHF in both humans and animals since its release in 1966. However, interesting alternatives and adjunctive therapies are now available, including:

- Torsemide, a loop diuretic that can be used as an adjunct or alternative to furosemide
- Spironolactone, a weak, potassium-sparing diuretic and mineralocorticoid receptor (MR) blocker that is used primarily for additional blockade of the renin–angiotensin–aldosterone system (RAAS). In heart failure, it typically accompanies a more potent diuretic, such as furosemide.

This article, the first in a 2-part series, discusses torsemide, while the second article will address spironolactone.

LOOP DIURETICS

Loop diuretics, in general, exemplify the phrase "double-edged sword": They are typically necessary—often lifesaving—yet are invariably harmful in some respects, particularly with long-term use (**Table 1**, page 100).[2] Although adverse effects differ among the loop diuretics, complications are common to all diuretics.

Loop diuretics are pyridine-3-sulfonurea drugs that act on the thick portion of the nephron's ascending loop of Henle, where they inhibit the sodium–potassium–chloride (Na^+–K^+–$2Cl^-$) cotransporter, leaving sodium (and other ions) to be lost, with water, in the urine.

FUROSEMIDE

For nearly 50 years, furosemide has been a workhorse for cardiologists and internists. It has undoubtedly saved countless lives when used to manage acute/emergent heart failure and has increased the longevity of patients when used long term.

Furosemide is typically *not* used as a monotherapy but rather given concurrently with:

- *Inotropes:* Pimobendan, digoxin, or dobutamine
- *Other diuretics:* Thiazides and/or potassium-sparing diuretics

FIGURE 1. Mean urine aldosterone-to-creatinine ratio (A:Cr) in 12 normal dogs challenged with furosemide at 2 mg/kg Q 12 H. At day 5 and 10, the RAAS is activated and, with continuous treatment, stays activated for at least 10 days. The urine A:Cr ratio indicates the amount of aldosterone found in the urine over 24 hours and reflects RAAS activation.
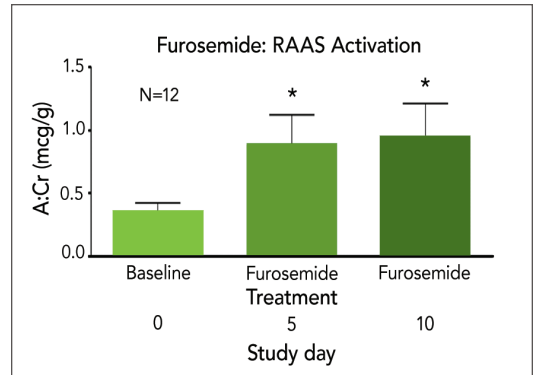
- *Vasodilators:* Angiotensin-converting enzyme (ACE) inhibitors, amlodipine, hydralazine, or nitroprusside
- *Antiarrhythmic agents:* Lidocaine, sotalol, or amiodarone.

Adverse Effects

Furosemide's popularity is deserved, and most experienced clinicians are comfortable administering this drug. However, negative effects are associated with any potent diuretic (**Table 1**), which include:

- Production of electrolyte disturbances (notably hypokalemia and hypomagnesemia), which may contribute to muscular weakness and arrhythmias
- Activation of the RAAS due to reduced renal blood flow and sodium loss (**Figure 1**), which produces adverse effects in the heart, vessels, and kidneys.[3,4,5]

Aldosterone and angiotensin II contribute to congestion and hypertension via sodium retention and vasoconstriction, respectively. Excessive, chronic production of these 2 hormones, therefore, further increases the workload on an already failing heart. Additionally, the activated RAAS stimulates the sympathetic nervous system, which is toxic to cardiac myocytes and increases heart rate, produces vasoconstriction, and predisposes to cardiac arrhythmias.[6]

Pharmacokinetics

Furosemide's rapid onset of action makes it indispensable in the emergent treatment of cardiogenic pulmonary edema. It does, however, have a relatively short duration of action, which often necessitates repeated bolus dosing in the emergency setting and, at home, up to 3 to 4 times per day dosing in patients with advanced CHF. This characteristic—multiple peaks and valleys in serum drug concentrations—may enhance furosemide's stimulation of the sympathetic nervous system and RAAS, contributing to diuretic resistance.[7] Increasing dosages are required over time and, in many cases, other diuretics are added to maintain patient comfort.

Resistance

Diuretic resistance is multifactorial, resulting from neurohormonal activation as well as:

1. Enhanced sodium and solute reabsorption at the proximal tubule in response to diuretic-induced contraction of the extracellular fluid volume
2. Nephron hypertrophy in response to increased solute delivery to distal nephron segments
3. Decreased renal responsiveness to natriuretic peptides.[8]

Torsemide appears to be less affected by resistance, but a mechanism for this characteristic has not been identified.

TORSEMIDE

Torsemide, like furosemide, is a very potent diuretic.

In the Literature

Although not studied as thoroughly as would be desirable in animals, torsemide's profile in humans suggests that quality of life and survival are enhanced when compared with furosemide.[1,9,10]

There are no large clinical trials published to date in veterinary medicine; however:

- A study of 7 dogs with clinically stable CHF demonstrated that replacement of furosemide with torsemide was both safe and effective.[11]
- Another small case series suggested that duration and quality of life in 3 dogs with advanced refractory CHF were prolonged and improved, respectively, with torsemide.[12]
- One feline and several canine laboratory

Furosemide Versus Torsemide

Furosemide is the diuretic of choice for everyday use because it is potent, rapid in onset, relatively inexpensive, and enjoys a comfort level with clinicians based on years of clinical experience. However, its rapid onset but short duration of action and association with diuretic resistance supports consideration of alternative loop diuretics, such as torsemide.

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studies[13-15] demonstrated drug traits that could potentially make use of torsemide advantageous in treating CHF in veterinary patients (**Table 2**).

Pharmacokinetics & Pharmacodynamics

Diuretics exert their diuretic action at the nephron, and duration of diuretic action is related to urinary excretion rate.

The pharmacokinetic and pharmacodynamic characteristics of torsemide (when compared with furosemide, **Table 2**) include, slower release from the plasma to the renal tubular fluid and resultant slower urinary excretion rate. The slower transfer rate of torsemide is hypothesized to be due to inherent properties of torsemide (it is less acidic and less of it exists in an anionic form, as compared with furosemide). The result is greater, smoother, and longer-acting diuresis (**Figure 2**).[13-15]

Two veterinary studies have addressed torsemide pharmacodynamics, each showing superior diuresis when compared with furosemide (**Figures 2 and 3**, page 102), at substantially lower dosage.[13,15] In addition, furosemide begins to lose efficacy (diuretic resistance) at 14 days of oral therapy in healthy dogs (**Figure 3**, page 102), while torsemide is less affected.[7] The relevance of the latter finding in clinical cases remains to be seen.

TABLE 2.

Treatment of Congestive Heart Failure: Torsemide Compared With Furosemide[13-15]

ADVANTAGES OF TORSEMIDE
• Better diuresis (greater water loss/mg prescribed); potentially a disadvantage if administration results in excessive diuresis and electrolyte loss
• Longer-acting diuresis (longer effective half-life)
• Smoother diuresis (once daily torsemide provides constant, slowly declining thera-peutic level) (**Figures 2, 3, and 6**, page 103)

POTENTIAL ADVANTAGES OF TORSEMIDE
• Improvement in cardiac function[a]
• Reduced myocardial collagen content (fibrosis)[a]
• Survival benefit over furosemide[a,b]
• Fewer hospitalizations for CHF[a,b]
• Less affected by food intake[a,b]
• Less potassium loss in urine[b]
• Aldosterone receptor blocker: Inconclusive data; if this does not occur or occurs minimally, then the elevated aldosterone levels seen in some studies are undesirable[b]

a. Data from human studies
b. Unproven or contradictory results in canine or other veterinary patients
Note: Almost all the adverse effects seen with furosemide can occur with torsemide.
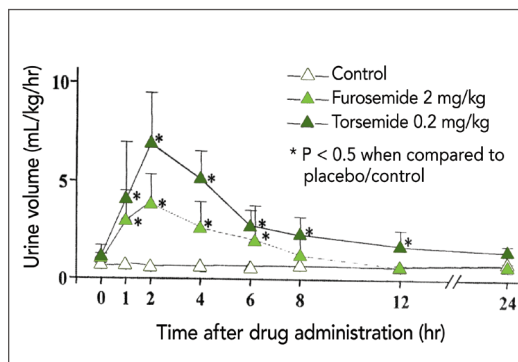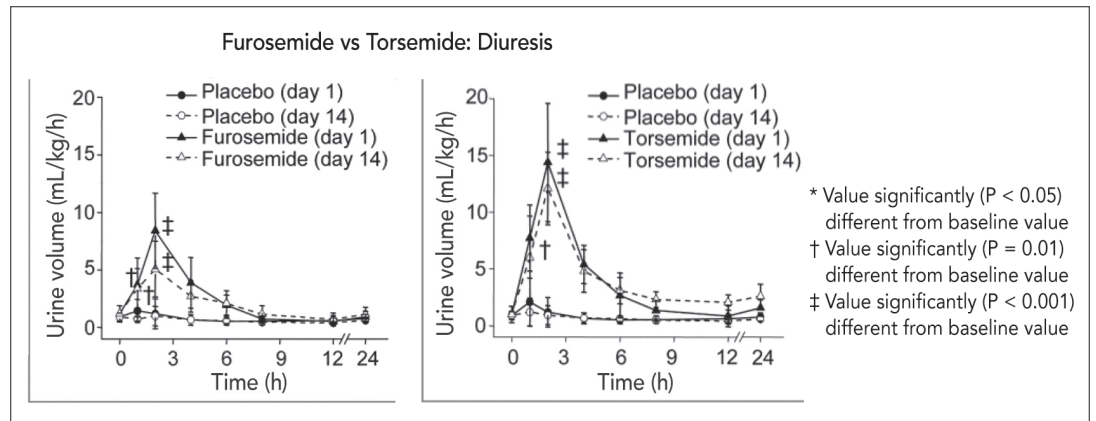

FIGURE 2. Urine production in control animals, those receiving standard-dose furosemide, and those receiving torsemide orally. Note the similar peak effect between agents and the brisk and longer-acting diuresis with torsemide. These studies were performed in normal dogs.

FIGURE 3. Crossover study performed in normal dogs that compared urine volume of dogs receiving oral furosemide (2 mg/kg Q 12 H) and torsemide (0.2 mg/kg Q 12 H) acutely and after 14 days of treatment. In the dogs receiving torsemide, note the higher peak at days 1 and 14, slightly later peak, and greater duration of enhanced urine flow compared with dogs that received furosemide. Most important, in the dogs receiving furosemide, note the decline in diuresis on day 14 compared with the lack of resistance on day 14 in dogs receiving torsemide.

TABLE 3.
Monitoring Patients on Loop Diuretics

AT HOME*
Appetite Body weight Heart rate Respiratory rate (< 30 breaths/min at home) Signs of congestion (pulmonary edema and ascites)

EACH OFFICE VISIT
Appetite Body weight Heart rate Respiratory rate Signs of congestion (pulmonary edema and ascites) Packed cell volume/total protein

TIMING FOR SPECIFIC PARAMETERS	
Serum electrolyte concentrations Renal values (blood urea nitrogen [BUN] and creatinine)	**Days 7 to 14**; then as needed (sooner if underlying kidney disease present)
Electrocardiography (routine, or if arrhythmia auscultated on physical examination)	**Q 6 to 12 months** unless a specific reason identified
Systolic blood pressure (address if < 100 mm Hg, or if dog is weak or syncopal)	**Q 6 to 12 months** or if symptomatic for hypotension
N-terminal of the prohormone brain natriuretic peptide	1. **Initially** 2. **After patient stabilizes** 3. **Q 3 to 12 months**
Urinary aldosterone-to-creatinine ratio	**Initially**, and when signs of congestion recur

Owner should report results of these parameters to veterinarian once per week

Diuretic efficacy occurs when diuretic delivery to the kidney is in the appropriate range. As shown in **Figure 4**, diuresis persists for 3 to 5 hours following once-daily administration. Using this dose of furosemide once daily, there is no risk for toxicity and the time in the therapeutic range is maximized.

When standard doses of diuretics become inadequate to maintain the patient's quality of life, several strategies can be used, such as increasing dosage, increasing frequency of administration, adding new drugs (ie, sequential nephron blockade with such agents as hydrochlorothiazide and spironolactone), or changing to another drug (eg, torsemide or bumetanide) to boost diuresis (**Figures 5 and 6**).

RAAS Activation
Whereas furosemide is known to activate the RAAS (**Figure 1** and **Table 1**), the reason for high plasma aldosterone concentrations associated with use of torsemide is less clear. Although torsemide may activate the RAAS, evidence suggests that serum aldosterone levels may be elevated because of
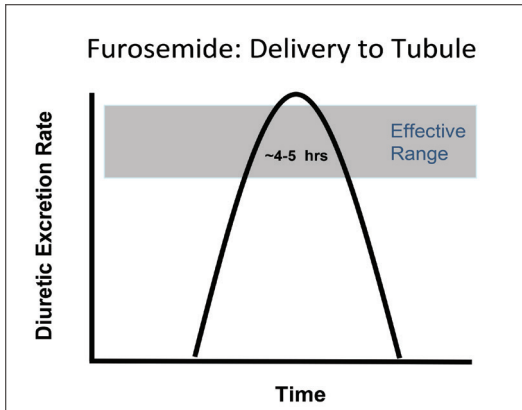
FIGURE 4. Diuresis occurs when urine levels of furosemide are within the therapeutic range. Urinary furosemide levels, of course, depend on the plasma concentration delivered to, and filtered by, the glomerulus, which, in turn, is affected by furosemide bioavailability. In this hypothetical example, diuresis begins by 1 hour and persists for 3 to 5 hours. This represents the ideal dosage for once-daily treatment, as corresponding plasma levels (reflected in urinary concentration) are high enough to maximize time in the therapeutic range but not create a risk for ototoxicity.

FIGURE 5. If resistance to furosemide results or other factors (eg, a high salt meal) dictate that more diuresis is needed, 1 of 2 strategies may be used: First is to administer a higher dosage, as shown with the red pharmacodynamic curve. The increase in dosage increases the urine level of the diuretic but provides only a small increase in time in the effective range, enhancing diuresis (**red arrow**) but increasing risk for toxicity. A better approach, although problematic in terms of owner compliance, is to administer multiple doses throughout the day. As shown in this figure, administering the same dosage 3 times triples the time in the effective range and avoids the risk for toxicity.
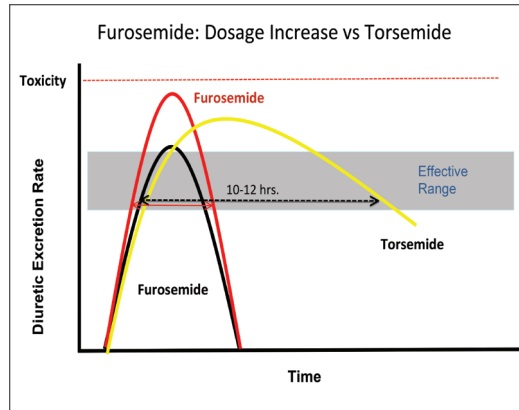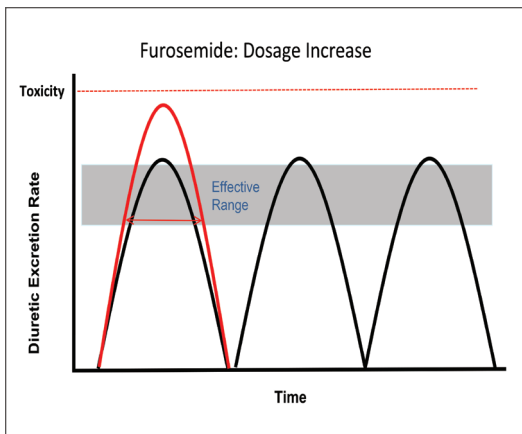

FIGURE 6. If resistance to furosemide results or other factors (eg, a high salt meal) dictate that more diuresis is needed, another approach (versus the 2 strategies demonstrated in **Figure 5**) would be to change to a longer-acting diuretic, such as torsemide (**yellow curve**). Note the higher peak urine level compared with furosemide at the original dosage, slight delay in peak diuresis, and prolonged period of time in the therapeutic range (**dashed arrow**; 10–12 H in this model).

antialdosterone effects via MR blockade, whereby high dosages of torsemide led to *in vivo* binding of the MR in rat kidney cells.[16]

A subsequent study,[17] however, demonstrated that torsemide does not bind the MR in rat cardiomyocytes. This suggests that the increase in serum aldosterone seen in the study by Hori and colleagues[15] is not entirely the result of MR blockade and likely represents RAAS activation from sodium depletion and diuresis.

Other antialdosterone and antifibrotic effects of torsemide are postulated, however, and warrant further study.[18-20] Regardless of whether there is an MR-blocking effect, it seems prudent to administer an ACE inhibitor or spironolactone with torsemide due to the very high plasma aldosterone concentrations associated with its use (**Figure 7**, page 104).

Electrolyte Effects
One study indicated that in experimental mitral insufficiency, there was less potassium loss with torsemide than with furosemide.[12] Another study that compared normal dogs receiving an ACE inhibitor alone or an ACE inhibitor with torsemide (0.2 mg/kg for 28 days) showed no significant decrease in serum magnesium (Mg^{++}) and only a slight decrease in serum potassium (K^+), despite an increase in urine fractional excretion of both electrolytes.[21]

These small studies could not prove whether

torsemide is actually less "wasteful" of potassium and magnesium than furosemide.

Monitoring of serum electrolytes is still advisable (**Table 3**, page 102).

Indications & Dosage

Torsemide is available for both intravenous and oral use, with tablet sizes of 5, 10, 20, and 100 mg. The accepted oral torsemide dosage is one tenth that of the expected, or current, furosemide dosage, which works out to 0.2 mg/kg Q 12 H if a patient is started on torsemide initially (ie, 10% of the 2 mg/kg furosemide dosage).

To our knowledge, intravenous administration of torsemide has not been studied in veterinary medicine. We are reluctant to speculate from the human dosage because of the apparent differences between species with regard to administration of oral torsemide.

Currently, torsemide is used most often as a rescue agent when furosemide (usually with standard CHF drugs, including hydrochlorothiazide and spironolactone) no longer adequately controls signs of congestion (**Table 4**, page 106).

One author considers using torsemide when the furosemide response is inadequate at a furosemide dosage of 4 mg/kg Q 24 H or greater.[12] In our practices, the set point for change is somewhat higher, at a furosemide dosage greater than 6 to 8 mg/kg Q 24 H. Torsemide can be initiated in this circumstance as one dose per day, replacing one
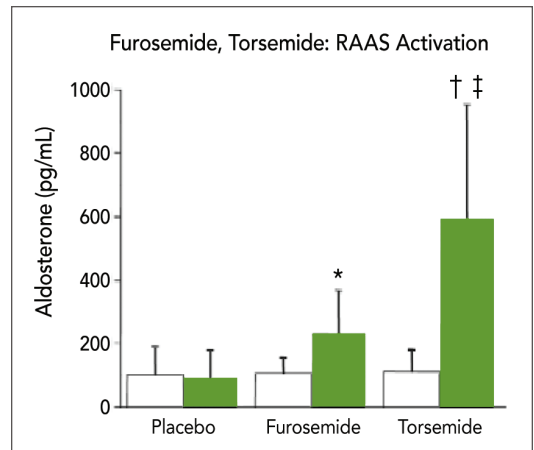
FIGURE 7. Serum aldosterone concentrations in normal dogs receiving placebo, furosemide, or torsemide on days 1 (**white bar**) and 14 (**green bar**). Note the 6-fold increase with torsemide. This finding is potentially related to RAAS activation or blockade of MR. If the former, this effect would be a disadvantage of using torsemide as opposed to furosemide.
= value significantly ($P < 0.05$) different from short-term administration value; † = value significantly ($P = 0.01$) different from placebo treatment value; ‡ = value significantly ($P = 0.01$) different from value of the corresponding furosemide administration

dose of furosemide (at one tenth the mg dosage) and leaving other treatments (including later daily doses of furosemide) intact.

Alternatively, with twice daily furosemide therapy, torsemide could be added as the third diuretic dose of the day. Lastly, it might be used to replace all diuretic therapy, given orally Q 12 H at one tenth the furosemide dosage, and titrated upward as needed.

Renal function should be carefully monitored during the addition of, or transition to, torsemide, and use of additional diuretics, such as hydrochlorothiazide, should be limited. **Table 3** suggests monitoring practices for patients receiving potent loop diuretics.

IN SUMMARY

Unfortunately, the data available on diuretics in veterinary patients are still limited. More studies are needed to establish comparative aspects of the undesirable adverse effects and the efficacy of various loop diuretics.

Read Part 2 of this article series—a discussion on spironolactone—in an upcoming issue of *Today's Veterinary Practice*.

Furosemide & Torsemide: Effects on Renal Function

All diuretics can have a negative effect on renal perfusion if they produce excessive diuresis, resulting in prerenal azotemia and contributing to renal failure in:
• Older dogs
• Dogs with underlying kidney disease
• Dogs with multipronged off-loading therapy (amlodipine, sildenafil, nitroglycerin, and ACE inhibitors) in the treatment of CHF.

Serum creatinine, phosphorus, and blood urea nitrogen (BUN) concentrations all rise with the use of furosemide or torsemide, in both normal dogs and those with heart disease, and in those with and without CHF.[11-13,15]

In a study by Peddle and colleagues, BUN, serum creatinine, and phosphorus were increased to a significantly greater degree with torsemide than with furosemide in dogs with heart failure, although the values remained within the normal reference range.[11]

For these reasons, the lowest effective dosage of furosemide and/or torsemide should be sought and use of these drugs should be coupled with careful monitoring of renal function. However, we believe that changes in drugs or dosages based simply on serum creatinine concentration should not be made unless levels increase at least 35%.

Most often, the loop diuretic will be temporarily discontinued or have its dosage reduced first, with the ACE inhibitor being manipulated last.

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TABLE 4.
Indications for Torsemide

- Failure of high-dosage diuretic to keep patient free of signs (ie, pulmonary edema, ascites)
- When furosemide dosage exceeds 6 to 8 mg/kg Q 24 H
- If a need to increase furosemide dosing frequency (eg, from Q 12 H to Q 8 H) cannot be met due to owners' schedule

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ACE = angiotensin-converting enzyme; BUN = blood urea nitrogen; CHF = congestive heart failure; MR = mineralocorticoid receptor; RAAS = renin–angiotensin–aldosterone system

FIGURE CREDITS

Figure 1 reprinted with permission from Lantis AC, Atkins CE, DeFrancesco TC, Keene BW. The effect of furosemide and pimobendan on the circulating renin angiotensin aldosterone system (RAAS) in dogs. *Am J Vet Res* 2011; 72:1646-1651.

Figure 2 reprinted with permission from Uechi M, Matsuoka M, Kuwajima E, et al. The effects of the loop diuretics furosemide and torasemide on diuresis in dogs and cats. *J Vet Med Sci* 2003; 65(10):1057-1061.

Figures 3 and 7 reprinted with permission from Hori Y, Takusagawa F, Ikadai H, et al. Effects of oral administration of furosemide and torsemide in healthy dogs. *Am J Vet Res* 2007; 68(10):1058-1063.

Figures 4 to 6 adapted from Vargo DL, Kramer WG, Black PK, et al. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. *Clin Pharm Therap* 1995; 57(60):601-609.

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MARISA K. AMES

Marisa K. Ames, DVM, Diplomate ACVIM (Cardiology), is an assistant professor at Colorado State University College of Veterinary Medicine. Dr. Ames received her DVM from Ohio State University. She completed a cardiology residency and the Jane Lewis Seaks postdoctoral fellowship at North Carolina State University. Her research interests include neurohormonal activation in heart failure, specifically the pharmacologic blockade of the renin–angiotensin–aldosterone system (RAAS).

CLARKE E. ATKINS

Clarke E. Atkins, DVM, Diplomate ACVIM (Internal Medicine & Cardiology), is the Jane Lewis Seaks Distinguished Professor Emeritus of Companion Animal Medicine at North Carolina State University. He is also a member of the *Today's Veterinary Practice* Editorial Peer Review Board and American Heartworm Society's Executive Board. Dr. Atkins' research involves canine and feline heartworm disease and pharmacologic therapies for cardiac disease. He received the 2004 Norden Award for excellence in teaching.