THE 26th Annual
WALTHAM® Diets / OSU Symposium ♦ Small Animal Cardiology 2002

Canine Heartworm Disease: Current Treatment and Prevention Approaches

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

PREVENTION

The introduction of the macrolide agents ivermectin (Heartgard®), milbemycin oxime (Interceptor®), moxidectin (ProHeart® and ProHeart® 6) and selamectin (Revolution™) has provided the veterinary profession with effective heartworm (HW) preventatives in a variety of formulations. Such agents, because they interrupt larval development during the first 2 months after infection, have a large window of efficacy and are administered monthly or less frequently. These agents are superior to diethylcarbamazine (DEC) in: convenience; producing less severe reactions when inadvertently given to microfilaremic dogs; allowing a grace period for inadvertent lapses in administration; efficacy with treatment lapses of up to 2–3 months when used continuously for the next 12 months[1]; and lastly, having a dual role as microfilaricides.[2-4]

Ivermectin, a chemical derivative of avermectin B_1 which is obtained from *Streptomyces sp*. is effective against a range of endo- and ectoparasites and is marketed as a once monthly heartworm preventative. It is marketed in a form with pyrantel pamoate to improve efficacy against intestinal parasites (Table 1). Macrolides offer a wide window of efficacy and provide some protection when treatment lapses (of up to two months) occur. This is extended with continuous 12-month administration post-exposure to 3 months with 98% efficacy and to 4 months with 95% efficacy.[1] As stated above, ivermectin is microfilaricidal at preventative doses (6–12 µg/kg/month), resulting in a gradual decline in microfilarial numbers. Despite this gradual microfilarial destruction, generally mild, adverse reactions (transient diarrhea) can occur if administered to microfilaremic dogs.[5,6] Collies have been identified as a breed in which certain individuals are at increased risk of central nervous system signs and even death due to increased concentrations of ivermectin in the central nervous system. It is important to note that such adverse reactions have not been identified at preventative or even microfilaricidal doses of ivermectin. When used appropriately, ivermectin is virtually 100% effective in preventing HWI. Additionally, recent studies have shown ivermectin to have partial adulticidal properties when used continuously for 16 months.[7]

Milbemycin oxime is a member of a family of milbemycin macrolide antibiotics derived from a species of *Streptomyces*. At 500–999 µg/kg, it has efficacy against developing filarial larvae, arresting development in the first 6 weeks. It can therefore be given at monthly intervals with a "reachback effect" of 2 months when doses are inadvertently delayed. With 12 months' continuous treatment post-exposure, this "safety net" can be extended to 3 months with 97% efficacy, falling to 41% with lapses of 4 months.[1] At the preventative dosage, milbemycin is a broad-spectrum parasiticide, also demonstrating effectiveness against certain hookworms, roundworms, and whipworms.[2] Milbemycin is also safe for use in collies when prescribed at the preventative dose. With appropriate use, milbemycin is virtually 100% efficacious as a HW prophylactic. In microfilaremic dogs, milbemycin has greater potential for adverse reactions than do other macrolides, as it is a potent microfilaricide at preventative doses.[2] Adverse reactions, similar to those observed with ivermectin at microfilaricidal doses (50 µg/kg) may be observed in microfilaremic dogs receiving preventative doses of milbemycin.[8] Milbemycin has been used in an extra-label manner to eliminate microfilaria. As for microfilaricidal dosages of ivermectin, pretreatment with Benadryl® (2 mg/kg IM) and dexamethasone (0.25 mg/kg IV), prior to milbemycin treatment, may prevent adverse reactions, particularly in dogs with high microfilarial counts.

The macrolide preventative, moxidectin, has been recently marketed and has been shown to be safe and virtually 100% effective at 3 µg/kg given monthly or bimonthly up to 2 months post-infection.[9] Moxidectin, at this dosage, is gradually microfilaricidal and did not produce adverse reactions in a small number of microfilaremic dogs treated with the prophylactic dose.[10] At 15 µg/kg, 98% reduction in microfilarial numbers

was documented 2 months post-treatment.[10] Lastly, moxidectin appears to be safe in collies.[11] A new liposomal formulation of moxidectin gives 6 months' protection with one subcutaneous injection.[12] With 12 months' (2 injections) continous treatment, injectable moxidectin is 97% effective at preventing infection after a 4 month lapse in preventative therapy.[13]

Most recently, a semi-synthetic macrolide, selamectin, has been developed and marketed. It is unique in its spectrum and in the fact that is applied topically once monthly. Its efficacy is similar to that of other macrolides (virtually 100%, when used as directed).[14] At 6–12 mg/kg topically, this preventative is effective at preventing heartworm infection and kills fleas and flea eggs, sarcoptic mange mites, ticks and ear mites.[14] Bathing and swimming, as soon as 2 hours after application, did not affect efficacy. Safety has been shown at 10-fold topical doses, with oral consumption of single doses, and, in ivermectin-sensitive collies, at recommended dosages and five-fold overdoses for 3 months.[15] Like other macrolides, selamectin has at least a 2 month "reachback effect" and with 12 months' continuous administration, is 99% protective after 3 month lapses in prophylaxis.[14,16] Selamectin has microfilaricidal activity similar to other macrolides.[17]

In summary, the macrolides offer a convenient, effective and safe method of HW prophylaxis with varying spectra and methods of administration (Table 1). Prophylaxis should be commenced at 6–8 weeks of age in endemic areas, or as soon thereafter as climatic conditions dictate.[5,6] Although safer than DEC in microfilaremic dogs, before first time administration, any dog over 6 months of age and at risk of infection, should be tested (antigen test, followed by a microfilaria test, if positive). Although protective for at least 8 weeks post-exposure, macrolides should be administered precisely as indicated by the manufacturer. If accidental lapses occur, the preventative should be reinstituted at recommended doses and maintained continuously for 12 months. Macrolides can also be used to "rescue" dogs that have lapsed in their DEC daily therapy for up to 60–90 days.[5,6] If a lapse in preventative is prolonged (>2 months) and the risk for HWI deemed moderate or high, macrolides should be continued for a year without interruption. In addition, an antigen test should be performed approximately 6 months after the last chance for exposure to detect infection.

THERAPY

Adulticidal therapy. An important breakthrough in the management of heartworm infection (HWI) is the adulticide melarsomine, an organoarsenical superior in safety and efficacy to thiacetarsemide.[18] This product, which is administered twice, at 2.5 mg/kg q24h, has a mean retention time 5 times longer than thiacetarsemide and its metabolites are free in the plasma, on which HW feed.[19] In a study of 382 dogs with HWI receiving melarsomine, none required cessation of therapy due to hepatorenal toxicity, as compared to 15–30% with thiacetarsemide.[19] With 2 doses, the efficacy is over 96% with the useful flexibility of a 50% worm kill with 1 dose. A "split-dose" protocol can be utilized in severely afflicted individuals or in those in which pulmonary thromboembolism (PTE) is a concern. This method allows destruction of only one-half the worms initially (1 IM injection of 2.5 mg/kg), thereby lessening the chance for embolic complications. This single dosage is followed by a 2-dose regimen in 1–3 months, if clinical conditions permit. While the manufacturer recommends this protocol for severely affected dogs, the author employs it all cases (Figure 1) unless there is financial constraint or underlying concern for potential arsenical toxicity (for example, preexistent severe renal or hepatic disease). One disadvantage to the "split-dose" method, in addition to the expense, is the need for 2 months' exercise restriction.

In 55 dogs with severe heartworm disease (HWD) and treated in this 3-dose manner, 96% had a good or very good outcome with >98% negative for antigenemia 90 days post-therapy.[19] Although symptomatic and even fatal PTE can result from treatment with melarsomine, no case of severe PTE was seen in the 382 dogs of this series.[20] Of the 55 severely affected dogs, 31% had "mild or moderate PTE"; no fatalities resulted. The most common sign was fever, cough, and anorexia 5–7 days post-treatment. This was associated with mild

perivascular caudal lobar pulmonary radiographic densities and subsided spontaneously or after corticosteroid therapy.

The most common complication to melarsomine therapy is the local inflammatory reaction at the injection site. This can be minimized by following the manufacturer's directions explicitly (change needles before injecting, choose deep IM site with care, put pressure on site after injection, and alternate sites). In addition, corticosteroids (e.g., dexamethasone) can be given at the time melarsomine is administered to lessen the reaction.

It is now known that certain macrolides have adulticidal properties.[17,21,22] Ivermectin, when administered for 31 months continuously has nearly 100% efficacy in young heartworm infections.[22] It has been shown, however, that lung and pulmonary vascular manifestations of HWD still result when ivermectin "prophylaxis" is begun 5.5 and 6.5 months post-infection and continued for 1 year.[22] Selamectin, when administered continuously for 18 months killed approximately 40% of transplanted worms.[17] Milbemycin and sustained release moxidectin appear to have only modest adulticidal efficacy.[13] While there may be a role for this therapeutic strategy in cases in which financial constraints or concurrent medical problems prohibit melarsomine therapy, the current recommendations are that marcolides not be adapted as the primary adulticidal approach.

Surgical removal of HW can minimize PTE, as compared to pharmacologic adulticides, such as melarsomine.[23,25] This procedure, however, requires specialized training and instrumentation, including fluoroscopic imaging capabilities. Nevertheless, it remains a useful alternative for the management of high risk patients.

Ancillary therapy. Corticosteroids are indicated in HWD **only** in the face of pulmonary parenchymal complications (including PTE), to treat or prevent adverse reactions to microfilaricides, and possibly to minimize tissue reaction to melarsomine. Early studies demonstrated that corticosteroid therapy reduced pulmonary blood flow and worsened intimal disease in a model of HWI after adulticide.[26] For allergic pneumonitis, prednisolone (1 mg/kg/day) is administered for 3–5 days and discontinued or tapered, as indicated.[27] The response is generally favorable. Prednisolone has also been advocated for the management of PTE. Because of the potential for fluid retention, steroids should be used cautiously in the face of heart failure.

Antithrombotic agents have received a good deal of attention in the management of HWD.[26,28-31] Potential benefits include reduction in severity of vascular lesions of HWD, reduction in pulmonary arterial vasoconstriction and pulmonary hypertension, as well as minimization of post-adulticidal PTE. Aspirin has shown success in diminishing the vascular damage caused by segments of dead worms[28], reduced the extent and severity of myointimal proliferation caused by implanted living worms[29], and improved pulmonary parenchymal disease and intimal proliferation in dogs receiving thiacetarsemide after previous living HW implantation.[26] More recent studies, however, have produced controversial results. Aspirin administered to dogs with implanted HW, receiving adulticide, showed no improvement in pulmonary angiographic lesions and had more severe vascular tortuousity than did controls and dogs receiving heparin.[30] These authors emphasized that the ideal aspirin dosage would inhibit platelet function, but not PGI_2 production. Dillon and associates demonstrated that the aspirin dosage required to decrease platelet reactivity by at least 50% was increased by nearly 70% with HWI (implantation model) and by nearly 200% with a model (dead worm implantation) of PTE.[31] There were not significant differences in severity of pulmonary vascular lesions in aspirin-treated vs control dogs. For these reasons, the American Heartworm Society does not endorse antithrombotic therapy for routine treatment of HWD.[5,6]

Cage rest is an important aspect of the management of HWD after adulticidal therapy, after PTE, or during therapy of heart failure. This can often be best, or only, accomplished in the veterinary clinic. If financial constraints preclude this, crating at home and/or tranquilization are useful alternatives.

Microfilaricidal therapy. Despite the fact that no available agent is FDA-approved for the elimination of microfilaria, microfilaricidal therapy is traditionally instituted 4–6 weeks after adulticide administration. The

macrolides offer a new and effective alternative to levamisole and dithiazanine.[5,6] Microfilaria are efficiently and rapidly cleared with ivermectin at 50 µg/kg (approximately 8 times the preventative dose) or with milbemycin at 500 µg/kg (the preventative dose), although each of these treatments represent extra-label uses of the drugs.[5,6] Ivermectin can be diluted 1:9 in propylene glycol (Ivomec^{R}, MSD Agvet, Rahway, NJ) or in water (Eqvalan^{R}, MSD Agvet, Rahway, NJ) and administered orally at 1 ml/20 kg[27], although is practice is now discouraged.[6]

Adverse reactions, the severity of which is likely related to microfilarial numbers, were observed in 10% (6% severe and 4% mild) of 126 dogs receiving ivermectin at the microfilaricidal dose.[32] Signs included shock, depression, hypothermia, and vomiting. With fluid and corticosteroid (dexamethasone at 2–4 mg/kg IV) therapy, all dogs recovered within 12 hours. One fatality was observed 4 days after microfilaricidal therapy. Similar findings and frequency have been reported with milbemycin at the preventative dosage.[33] Dogs so treated should be hospitalized and carefully observed for the day. Dogs <16 kg, harboring >10,000 microfilaria per ml blood are more apt to suffer adverse reactions.[34] Benadryl (2 mg/kg IM) and dexamethasone (0.25 mg/kg IV) can be administered prophylactically to prevent adverse reactions to microfilaricidal doses of macrolides.

A 90% microfilaricidal success rate can be expected with ivermectin.[27] Milbemycin, at 500 µg/kg, cleared 6/8 (75%) dogs which had received adulticide therapy and did not harbor male and female adults; microfilarial numbers were reduced by 99% on the day after treatment.[33] A slower microfilarial kill rate can also be achieved with ivermectin, moxidectin, and selamectin at preventative doses.[1-4]

The American Heartworm Society recommends that macrolide therapy (50 µg/kg for ivermectin or 500 µg/kg milbemycin) for microfilaria be instituted 3–6 weeks after adulticide.[5,6] In 2–3 weeks, a second microfilaria concentration test should be performed and, if negative, preventative started. If still positive, the treatment is repeated or alternatively, chemoprophylaxis begun (assuming that no adverse reaction occurred on the initial treatment).[5,6] Persistent antigenemia indicates continued patent infection.

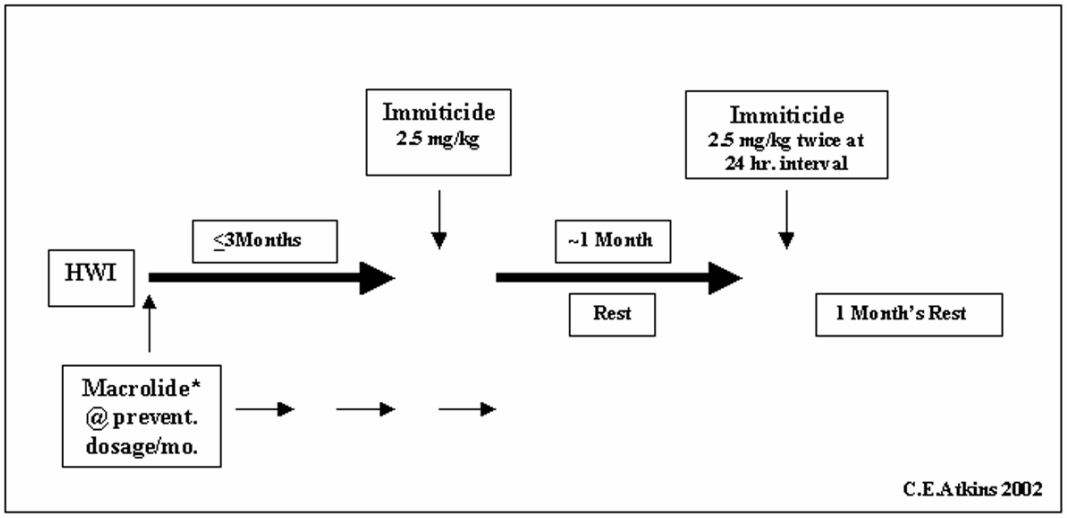
This author chooses an alternative approach (Figure 1), beginning the administration of a macrolide preventative at the time of diagnosis, often days to weeks prior to adulticidal therapy. The advantage to this approach is that preventative is administered earlier. This allows immediate closure of the open window of HW exposure, while awaiting and 6 weeks beyond adulticide administration. With the "slow microfilaricides" (ivermectin, moxidectin, or selamectin), there is little chance of an adverse reaction, but the owner is warned and advised to administer the medication on a day when he/she will be at home. If milbemycin is used, it is administered in the hospital and/or preceded by administration of dexamethasone and benadryl, as described above.

Table 1. Comparison clinical spectrum of commercially available macrolides

Drug	HW	Mf	Adulticidal	Hook	Whip	Round	Tape	Flea/eggs	Tick	Sarcoptes	Ear Mites	
Ivermectin	+	+	+	+*		+*						Ch
Milbemycin	+	++		+	+	+		-/+**				Tab
Moxidectin	+	+		+***								T/I
Selamectin	+	+	(+)					+/+	+	+	+	Top

. () = partially effective or incompletely studied. Ch = chewable, Tab = flavored tablet, T/I = tablet or injectable, Top = topical. *ivermectin/pyrantel pamoate, **milbemycin/lufenuron, ***injectable formulation

Figure 1.
The author's preferred approach to adulticidal therapy in virtually **all** (severely affected or not) dogs infected with heartworms includes 3 doses of melarsomine. Macrolide prophylaxis is begun at the time of diagnosis, if not already in use. *If microfilaremic, care should be taken to prevent or observe and treat adverse reactions, based on microfilarial numbers and macrolide used. See text for complete description.



REFERENCES

1. McCall, JW, et al. Evaluation of ivermectin and milbemycin oxime efficacy against Dirofilaria immitis infections of three and fours months' duration. *Amer J Vet Res* 1996; 57:1189-1192.
2. Bowman, D.D., Johnson, R.C., Ulrich, M.E., et al.: Effects of Long-Term Administration of Ivermectin and Milbemycin Oxime on Circulating Microfilariae and Parasite Antigenemia in Dogs with Patent Heartworm Infections. In Soll, M.D, ed. *Proc Amer Heartworm Sym '92.* Austin, TX: American Heartworm Society 1992; 151.
3. Hendrix CM, Blagburn BL, Bowles JV, et al. The safety of moxidectin in dogs with microfilariae and adults of Dirofilaria immitis. In Soll, M.D, ed. *Proc Amer Heartworm Sym '92.* Austin, TX: American Heartworm Society 1992; 183-187.
4. Dzimianski MT, McCall JW, Steffens, WL, et al. The safety of selamectin in heartworm infected dogs and its effect on adult worms and microfilariae. In Seward, L., ed. *Proc Amer Heartworm Sym '01.* Batavia, IL: American Heartworm Society, 2001; in press.
5. American Heartworm Society: Recommended Procedures for the Diagnosis and Management of Heartworm (Dirofilaria immitis) Infection. In Soll, M.D, ed. *Proc Amer Heartworm Symp '92,* Austin, TX: American Heartworm Society 1992; 289-294.
6. American Heartworm Society: 1999 Guidelines for the Diagnosis, Prevention, and Management of Heartworm (Dirofilaria immitis) Infection in Dogs. In Seward, L., ed. *Proc Amer Heartworm Sym '98.* Batavia, IL: American Heartworm Society 1998; 257-264.
7. McCall, J.W., Ryan, W.G, Roberts, R.E., Dzimianski, M.T. Heartworm adulticidal activity of prophylactic doses of ivermectin (6 µg/kg) plus pyrantel pamoate administered monthly to dogs. In Soll, M.D., ed. *Proc Amer Heartworm Sym '98.* Batavia, IL: American Heartworm Society 1998, 209-215.
8. Blagburn, B.L., Hendrix, C.M., Lindsay, D.S., et al. Post-adulticide milbemycin oxime microfilaricidal activity in dogs naturally infected with Dirofilaria immitis. In Soll, M.D., ed. *Proc Amer Heartworm Sym '92.* Batavia, IL: American Heartworm Society 1992; 159-164.
9. McCall, J.W., McTier, T.L., Homes, R.A., et al.: Prevention of Naturally Acquired Heartworm Infection in Heartworm-Naive Beagles by Oral Administration of Moxidectin at an Interval of One or Two Months. In Soll, M.D., ed. *Proc Amer Heartworm Sym '92.* Batavia, IL: American Heartworm Society 1992; 169.

10. Hendrix, C.M., Blagburn, B.L, Bowles, J.V., et al.: The Safety of Moxidectin in Dogs Infected with Microfilariae and Adults of Dirofilaria Immitis.In Soll, M.D., ed. *Proc Amer Heartworm Sym '92.* Batavia, IL: American Heartworm Society 1992; 183.
11. Paul, A.J., Tranquilli, W.J., Todd, K.S., Aguilar, R.: Evaluation of Moxidectin in Collies. In Soll, M.D., ed. *Proc Amer Heartworm Sym '92.* Batavia, IL: American Heartworm Society 1992; 189.
12. Lok JB, Knight DH, Wang GT, et al. Activity of an injectable, sustained-release formulation of moxidectin administered prophylactically to mixed-breed dogs to prevent infection with Dirofilaria immitis. *Am Jour Vet Res 2001* 62:1721-1726.
13. McCall JW, Suprakorndej P, Dzimianski MT, et al. Evaluation of retroactive and adulticidal activity of moxidectin canine SR (sustained release) injectable formulation against dirofilaria immitis infections in beagles. In Seward, L., ed. *Proc Amer Heartworm Sym '01.* Batavia, IL: American Heartworm Society, 2001; in press.
14. Thomas, C.A. Revolution™: A unique endectocide providing comprehensive, convenient protection. *Compend Contin Educ Pract Vet (Suppl)* 1999; 21:2-25.
15. Thomas, C.A. Revolution™ safety profile. *Compend Contin Educ Pract Vet (Suppl)* 1999; 21:26-31.
16. McCall JW, Suprakorndej P, Dzimianski MT, et al. Evaluation of retroactive and adulticidal activity of moxidectin canine SR (sustained release) injectable formulation against dirofilaria immitis infections in beagles. In Seward, L., ed. *Proc Amer Heartworm Sym '01.* Batavia, IL: American Heartworm Society, 2001; in press.
17. McCall JW, Hack R, McCall SD, et al. Evaluation of repeated monthly dosing of selamectin against Dirofilaria immitis beginning at three months after experimental inoculation of heartworm larvae in dogs. In Seward, L., ed. *Proc Amer Heartworm Sym '01.* Batavia, IL: American Heartworm Society, 2001, in press.
18. Knight, D.H.: How Current Knowledge Has Affected the Diagnosis, Prevention, and Treatment of Heartworm Infection. In Soll, M.D, ed. *Proc Amer Heartworm Sym '92.* Austin, TX: American Heartworm Society 1992; 253.
19. Vezzoni, A., Genchi, C., Raynaud, J-P.: Adulticide Efficacy of RM 340 in Dogs with Mild and Severe Natural Infections. In Soll, M.D, ed. *Proc Amer Heartworm Sym '92.* Austin, TX: American Heartworm Society 1992; 231.
20. Keister, D.M., Dzimianski, M.T., McTier, T.L., et al.: Dose Selection and C onfirmation of RM 340, a New Filaricide for the Treatment of Dogs with Immature and Mature Dirofilaria Immitis. In Soll, M.D, ed. *Proc Amer Heartworm Sym '92.* Austin, TX: American Heartworm Society 1992; 225.
21. McCall JW, Ryan WG, Roberts RE, Dzimianski MT. Heartworm adulticidal activity of prophylactic doses of ivermectin (6 µg/kg) plus pyrantel administered monthly to dogs. In Seward, L., ed. *Proc Amer Heartworm Sym '98.* Batavia, IL: American Heartworm Society, 1998; 209-215.
22. McCall JW, Roberts RE, Suprakorndej N, et al. Further evidence of clinical prophylactic (reach-back) and adulticidal activity of monthly administration of ivermectin and pyrantel pamoate in dogs experimentally infected with heartworms. In Seward, L., ed. *Proc Amer Heartworm Sym '01.* Batavia, IL: American Heartworm Society, 2001; in press.
23. Rawlings CA, Bowman DD, Howerth EW, et al. Response of dogs treated with ivermectin or milbemycin starting at various intervals after Dirofilaria immitis infection. *Vet Ther* 2001; 2:193-207.
24. Sasaki, Y., Kitagawa, H, Ishihara, K.: Clinical and Pathological Effects of Heartworm Removal from the Pulmonary Arteries Using Flexible Alligator Forceps. In Otto GF, ed. *Proc Amer Heartworm Sym '89.*Washington, DC: 1989; 45-51.
25. Morini S, Venco L, Fagioli P, Genchi C. Surgical removal of heartworms versus melarsomine treatment of naturally-infected dogs with risk of thromboembolism. In Seward, L., ed. *Proc Amer Heartworm Sym '98.* Batavia, IL: American Heartworm Society, 1998; 235-240.
26. Rawlings, C.A., Keith, J.C., Schaub, R.G., et al. Post Adulticide Treatment Pulmonary Disease and its Modification with Prednisolone and Aspirin. In Otto GF, ed. *Proc Amer Heartworm Sym '83,* Edwardsville, KS: Veterinary Medical Publishing Co, 1983; 122.
27. Calvert C.A., Rawlings C.A.: Treatment of Heartworm Disease in Dogs. Canine Pract 1994;18:13.
28. Atwell, R.B., Sutton, R.H., Carlisle, C.H.: The Reduction of Pulmonary Thromboembolic Disease (D. Immitis) in the Dog Associated with Aspirin Therapy. In Otto GF, ed. *Proc Amer Heartworm Sym '83,* Edwardsville, KS: Veterinary Medical Publishing Co, 1983; 115.
29. Keith, J.C., Rawlings, C.A., Schaub, R.G.: Effect of Aspirin on Canine Pulmonary Artery Disease Caused by Dirofilaria Immitis. In Otto GF, ed. *Proc Amer Heartworm Sym '83,* Edwardsville, KS: Veterinary Medical Publishing Co, 1983; 119.

30. Leuthy, M.W., Sisson, D.D., Kneller, S.K., et al.: Angiographic Assessment of Aspirin for the Prevention of Pulmonary Thromboembolism Following Adulticide Therapy. In Otto GF, ed. *Proc Amer Heartworm Sym '89.*Washington, DC: 1989; 53.
31. Boudreaux, M.K., Dillon, A.R., Ravis, W.R., et al.: Effects of Treatment with Aspirin or Aspirin/dipyridamole Combination in Heartworm-negative, Heartworm-infected, and Embolized Heartworm-infected Dogs. *Amer J Vet Res* 1992; 52:1991.
32. Neer, T.M., Hoskins, J.D.: Clinical Experience with Ivermectin Used as a Microfilaricide and for Prophylaxis in the Dog. In Otto GF, ed. *Proc Amer Heartworm Sym '89.*Washington, DC: 1989; 95.
33. Blagburn, B.L, Hendrix, C.M., Lindsay, D.S., et al.: Post-adulticide Milbemycin Oxime Microfilaricidal Activity in Dogs Naturally Infected with Dirofilaria Immitis. In Soll, M.D, ed. *Proc Amer Heartworm Sym '92.* Austin, TX: American Heartworm Society, '92, 1992; 159.
34. Atwell, RB, et al: Studies on the adverse reactions to dethylcarbamazine to microfilaria-positive (*D. immitis*) dogs. In Otto GF, ed. *Proc Amer Heartworm Sym '83,* Edwardsville, KS: Veterinary Medical Publishing Co, 1983;105-109.