



## The safety-net story about macrocyclic lactone heartworm preventives: A review, an update, and recommendations

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### Abstract

A number of safe, effective, and convenient heartworm preventatives are currently available for virtually all canine and feline pets. Yet, a 2001 survey of over 18,000 veterinary clinics in the United States identified more than 240,000 dogs and 3000 cats infected with *Dirofilaria immitis*. This high level of owner compliance failure is alarming. Prolonged administration of some of the macrocyclic lactone (ML) preventatives kills young larvae, older larvae, “immatures,” young adults, and/or old adults. Efficacy of 95% or more requires dosing for 9–30 months, with older worms being more difficult to kill. Of the various MLs, ivermectin (IVM) has the most potent safety-net and adulticidal activity, milbemycin oxime has the least, and selamectin and moxidectin injectable lie somewhere in between. The unique effects of IVM are related to the age of the heartworms at initiation of treatment. The earlier treatment is started, the more stunted and smaller the worms and the shorter their survival time. Conversely, the later treatment is started, the longer the worms live, and the more likely the dog will be antigen- and microfilariae-positive. Drug effects do not appear to be enhanced by increasing the dosage or administering at shorter intervals, and it appears that continuous monthly treatment is needed to produce the full effects of the drug. The American Heartworm Society (AHS) recognizes the safety-net (or reach-back effect) and adulticidal properties of some MLs, particularly IVM. The AHS 2003 (American Heartworm Society, 2004. 2003 Updated guidelines for the diagnosis, prevention, and management of heartworm (*Dirofilaria immitis*) infection in dogs. In: McCall, et al., (Eds.), Proceedings of the Symposium Session on Recent Advances in Heartworm Disease, The 19th International Conference of the World Association for the Advancement of Veterinary Parasitology, New Orleans, LA, 10–14 August, 2003. *Vet. Parasitol.* 125, 105–130) canine guidelines state that it is beneficial to administer prophylactic doses of IVM before treatment with melarsomine. Results of laboratory studies suggest that less active dogs are at low risk of severe thromboembolism and death. However, heartworm-positive working dogs might be more at risk. Worsened radiographic and echocardiographic images in a client-owned dog given IVM monthly for 2 years with greatly restricted exercise suggests that such treatment of dogs with clinical, radiographic, and/or echocardiographic evidence of heartworm disease as well as for asymptomatic working dogs is contraindicated. Furthermore, until further data are available, such treatment of even the less active asymptomatic dog should be administered only with much caution and with examination by a veterinarian at least once every 4–6 months. IVM clearly provides potent “safety-net” activity against older larvae, immatures, and young adults in cases of owner compliance failure, even when the owner and veterinarian are not aware that the

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animal is infected, and offers much promise as a unique “soft-kill” treatment for young, and possibly older adult heartworms, with reduced risks.

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*Keywords:* Ivermectin; Moxidectin selamectin; Milbemycin oxime; Heartworm; *Dirofilaria immitis*; Macrocytic lactones

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## 1. Introduction

Macrocytic lactones (MLs) are safe, effective, and convenient drugs for prevention of heartworm (*Dirofilaria immitis*) disease in virtually all dogs and cats when used as instructed (American Heartworm Society; AHS, 2004). These drugs are among the safest of all products prescribed for use in animals (Guerrero et al., 2002), yet a 2001 survey of more than 18,000 veterinary clinics in the United States identified more than 240,000 dogs and 3000 cats infected with *D. immitis*. Such an alarmingly high level of compliance failure confirms an earlier national survey of clinic compliance failure (Cummings et al., 1995). Fortunately, prolonged administration of some of the ML preventatives kills not only young heartworm larvae but also old larvae, immatures, young adults, and old adults. This range of activity has been reviewed previously (McCall et al., 2001a). The purpose of this article is to update and summarize the effects, or lack thereof, of the ML preventatives on heartworm larvae and adults and to provide guidance for the appropriate use of these products in the management of heartworm-positive dogs.

## 2. Definition and clarification of terms

For practical purposes, precordial heartworms are defined as young larvae (less than 1 month post-infection (PI)) and older larvae (1–2 months PI) and heartworms in the heart and associated vessels as immatures (3–5 months PI), young adults (6–7 months PI), and older adults (8 months PI and older). “Causal prophylaxis” includes the prevention of heartworm infection by killing larvae that are up to approximately 1 month of age (e.g., using diethylcarbamazine daily or MLs monthly). “Clinical prophylaxis” generally includes killing older larvae and/or immatures and also can include killing adult heartworms before they

induce clinically detectable disease. Retroactive (reach-back) activity covers the same age of heartworms as those killed under clinical prophylaxis, but ignores the “clinically detectable disease” aspects of the latter term. “Safety-net” effect encompasses some aspects of both clinical prophylaxis and reach-back activity. In situations of owner compliance failure, particularly during the period when the heartworms are growing, monthly administration of prophylactic doses of ivermectin (IVM) or a similarly effective drug rescues the heartworm-infected animal and either prevents or greatly reduces the development of severe disease (safety-net effect) by gradually clearing the infection (soft-kill) (McCall et al., 2001a).

Owner compliance failure includes missing one or more monthly doses during the heartworm transmission season or initiating a monthly heartworm prevention program 2 months or longer after the season starts (McCall et al., 1995).

## 3. Summary of studies with monthly ivermectin

The high level of potency and safety of IVM administered monthly to dogs at a minimum oral dosage of 6 mg/kg of body weight for heartworm prevention is well established in the laboratory (Blair and Campbell, 1980; McCall et al., 1981, 1986; Ohishi et al., 1987) and in the field with continued use by veterinary practitioners for more than a decade (AHS, 2004). Moreover, it has been shown that the efficacy of IVM is maintained even if the interval is extended beyond 30 days (Blair and Campbell, 1980; McCall et al., 1981, 1986; Paul et al., 1986a,b). The broad range of activity of monthly administered IVM against older larvae, immatures, and adult parasites as well as 1-month-old larvae has practical relevance in situations of compliance failure, which is far greater than generally perceived (Cummings et al., 1995).

Several studies have been conducted to mimic monthly administration of IVM at the prophylactic

dosage of 6 mg/kg in specific cases of owner compliance failure. The formulation in some studies was the commercial product containing only IVM (Heartgard-30, Merial), and IVM (6 mg/kg) plus pyrantel pamoate (PP) (5 mg/kg) (Heartgard-30 Plus) was used in others. These studies demonstrated the potent safety-net and adulticidal activities of IVM.

### 3.1. Efficacy against older larval, immature, and adult heartworms

IVM administered monthly for approximately 1 year was 97.7 and 95.1% effective against 3- and 4-month-old heartworms, respectively (McCall et al., 1995, 1996), and administration of IVM/PP chewables for 31 consecutive months beginning 5 months PI was 98.7% effective in reducing the heartworm burden (McCall et al., 2001a). In dogs with adult heartworms, the activity of monthly administration of IVM/PP increased from 56.3% with 16 monthly doses against 8-month-old worms (McCall et al., 1998) to 94.9% with 29 monthly doses against 7-month-old worms (McCall et al., 2001a).

### 3.2. Gut epithelial changes in adult heartworms from IVM-treated dogs

Surviving adult heartworms from dogs receiving monthly prophylactic doses of IVM, beginning during the growth phase of the worm, are small (stunted) and abnormal in motility and/or appearance when compared with worms from non-treated dogs (Steffens and McCall, 1998). Using conventional transmission and scanning electron microscopy, these authors demonstrated gut epithelium changes in adult heartworms from IVM-treated dogs monthly for 1 year beginning when the worms were 5 months of age. At dissection, the intestines of treated worms were distended and contained a dark, dense amorphous material that filled the lumen. The increase in thickness of the epithelial layer resulted in a concomitant decrease in the luminal diameter. Ultrastructural differences in heartworm intestinal epithelial cells included increased intracellular lipid accumulation, a decrease in the volume of mitochondria, and a marked increase in the number and composition of cytoplasmic dense bodies, with

calcium being replaced by ferric iron in worms from treated dogs, compared with those from controls.

### 3.3. Unique drug effects of monthly IVM

The unique drug effects of IVM on 3- to 8-month-old heartworms are related to the age of the heartworms at initiation of the monthly treatments (Table 1). The earlier treatment is started, the more stunted are the worms. For example, worms from dogs treated with IVM starting 5 months PI were approximately 20% shorter in length and 20% lighter in weight than their counterparts from non-treated control dogs (McCall 1993, unpublished data). Worms that are fully grown when treatment is started are not shorter after prolonged monthly treatment, but worm mass is reduced by at least 20% due to the death of all uterine stages of microfilariae and the “wasting away” of the worms. The earlier treatment is started, the shorter the survival time of the worms. When continuous monthly dosing with IVM was started 4 months PI, approximately 70% of the worms were dead after 6 months of treatment (McCall 1993, unpublished data), and six additional months (total of 12 months) were required for 95.1% efficacy (McCall et al., 1995, 1996). In contrast, 16 monthly doses of IVM against 8-month-old heartworms were 56% efficacious (McCall et al., 1998), but up to 29 doses were necessary to achieve 94.7% efficacy against 7-month-old worms (McCall et al., 2001a).

### 3.4. Effect on antigen test results

The later monthly dosing with IVM is started, the longer worms will survive, the more likely antigen will be detected, the higher the antigen level, and the longer the dog will be antigen-positive. For example, when treatment was started at 3 months PI, only two of three dogs became antigen-positive, their antigen scores were low, and both of the dogs had become antigen-negative by 12 months PI (McCall et al., 1996). In a separate study (McCall et al., 2001a), all five dogs treated with IVM/PP beginning 5 months after infection were not antigen-positive until 9 months PI. The average antigen score peaked (3.0) 10 months PI and then gradually decreased to 0 at 34 months PI. Four of the five dogs were consistently antigen-negative by 20 months PI, and the remaining dog became antigen-negative 34

Table 1

Summary of safety-net (reach-back/retroactive and/or clinical prophylactic) and adulticidal activity of macrocyclic lactones on *Dirofilaria immitis*<sup>a</sup>

Drug	Age of heartworms (in months)	No. of treatments	Efficacy (%)	Appearance/motility of live heartworms	Reference
Ivermectin (6 µg/kg, per os, monthly)	2	1	100	ND	McCall et al. (1986)
	3	13	97.7	Abnormal	McCall et al. (1996)
	3.5	12	97.8	ND	Bowman et al. (2001)
	4	14	97.8	Abnormal	McCall et al. (1995)
	4	12	95.1	Abnormal	McCall et al. (1995)
	4.5	12	86.2	ND	Bowman et al. (2001)
	5	31	98.7	Abnormal	McCall et al. (2001a)
	5.5	12	52.2	ND	Bowman et al. (2001)
	7	29	94.9	Abnormal	McCall et al. (2001a,b,c,d)
	8	16	56.3	Abnormal	McCall et al. (1998)
Milbemycin (500 µg/kg per os, monthly)	NA	24	70.0 <sup>c</sup>	ND	Venco et al. (2004)
	2	1	95.1	ND	Grieve et al. (1991)
	2	2	100	ND	Grieve et al. (1991)
	3	13	96.7	Normal	McCall et al. (1996)
	3.5	12	56.5	ND	Bowman et al. (2001)
	4	14	49.3	Normal	McCall et al. (1995)
	4	12	41.4	Normal	McCall et al. (1996)
	4.5	12	12.7	ND	Bowman et al. (2001)
	5.5	12	1.1	ND	Bowman et al. (2001)
	6.5	12	15.9	ND	Bowman et al. (2001)
Selamectin (6 mg/kg, topically monthly)	8	16	0	Normal	McCall et al. (1998)
	2	1	100	ND	McTier et al. (2000)
	3	12	98.5	ND	McCall et al. (2001b)
Moxidectin (0.5 µg/kg per os) <sup>b</sup>	Adult	18	39.0	Abnormal	Dzimianski et al. (2001)
	2	1	100	ND	McTier et al. (1992)
Moxidectin (0.17 mg/kg SC, every 6 months)	4	1	85.9	Abnormal	McCall et al. (2001d)
	4/10	2	97.2	Abnormal	McCall et al. (2001d)
	6	1	25	Abnormal	McCall et al. (2001d)
	6/12/18	3	25	Abnormal	McCall et al. (2001d)

NA = not applicable; ND = not done.

<sup>a</sup> Modified from McCall et al. (2001a).

<sup>b</sup> Efficacy in this study was based on antigen test results.

<sup>c</sup> Recommended dosage is 3.0 µg/kg per os.

months PI. When monthly dosing with IVM/PP was initiated 7 months PI, all five dogs were antigen-positive by 8 months PI. Average antigen scores increased to 4.2 by 9 months PI, remained approximately at that value through 15 months PI, and gradually decreased thereafter to a score of 0.2 by 36 months PI. One of the five dogs in this group (7-month IVM/PP) became consistently negative at 21 months PI. By 33 months PI, only two of the remaining four dogs

were antigen-positive (one very weakly positive and the other weakly positive), and at 36 months PI, only one of these two dogs was very weakly antigen-positive.

As discussed elsewhere (McCall et al., 2001c), all heartworm antigen test kits and laboratory-run antigen tests detect antigen released by adult female heartworms, and the amount of antigen in circulation is generally related to the age, number, and health of the female worms present in the animal. Antigen tests are

most useful for detecting infections with adult female worms that are at least 8-month-old. They are inconsistently positive for 5- to 7-month-old infections, do not detect infections of less than 5 months' duration, and do not detect infections consisting only of male heartworms. Although the Snap Heartworm PF test (IDEXX Laboratories) is the only test kit designed to give a low or high antigen test result, the inherent nature of all currently available ELISA and immuno-chromatographic tests provide at least limited utility for assessing the level of infection with adult female heartworms. Generally, a weak positive result and/or a slow-to-develop color reaction strongly suggests that the dog (or cat) has an infection with only one or two older ( $\geq 8$  months) adult female heartworms, a younger ( $\leq 7$  months) infection with few to many female heartworms, or an older infection with few to many moribund female heartworms, whereas a strong positive test result strongly suggests an infection with more than two older adult female heartworms (McCall et al., 1998, 2001c). The subjective scoring system used in that study was quite useful in monitoring, at least in a general sense, the "slow-kill" effect of monthly administered prophylactic doses of IVM. A weak-positive antigen test result in conjunction with the age of the dog, clinical signs, and other diagnostic procedures and testing, is generally more useful to the veterinary practitioner than a strong-positive test result in assessing the infection status and in managing the canine heartworm patient (McCall et al., 2001c).

### 3.5. Effect on microfilaremia

The earlier monthly dosing with IVM is started, the less likely a patent infection will develop, the lower the microfilariae count, and the shorter the patent period. For example, when dosing was started 3 months PI, none of the dogs developed patent infections (McCall et al., 1996). In another study (McCall et al., 2001a), only two of five dogs in the 5-month IVM/PP group had microfilariae any time during the study, and these counts were very low and transient. In the 7-month IVM/PP group, all dogs developed patent infections, reaching a relatively low peak at 9 months PI. Thereafter, the counts dropped and no microfilariae were seen in any of the dogs in this group after 13 months PI (i.e., 6 months after

treatment started). In other reported studies with monthly IVM treatment in microfilariae-positive dogs, five of six (Bowman et al., 1992), seven of eight (Courtney et al., 1998), and all five (McCall et al., 1998) dogs became microfilariae-negative within 9 months or less after treatment was started.

## 4. Summary of studies with other macrocyclic lactone preventatives

### 4.1. Efficacy

A summary of the published results of the efficacy of all MLs currently used in heartworm prevention is presented in Table 1.

### 4.2. Milbemycin oxime (MBO) (Interceptor, Novartis Animal Health)

In reviewing the results of several comparative studies, the safety-net and adulticidal activities of monthly administered MBO have not been as effective as those of IVM (McCall et al., 1995, 1996, 1998; Bowman et al., 2001). Ivermectin and MBO administered for 13 months were highly (97.7 and 96.8%, respectively) and equally effective against 3-month-old heartworms. However, against 4-month-old heartworms, IVM remained highly effective (95.1%) and MBO was only partially (41.4%) effective when the drugs were given monthly for 1 year (McCall et al., 1996). When the drugs were administered for 16 months against 8-month-old heartworms, MBO was ineffective, whereas IVM/PP killed 56% of the adult worms, and all of the remaining worms in the dogs treated with IVM/PP were considered moribund (McCall et al., 1998). The efficacy of MBO against 1-month-old larvae has been documented (Grieve et al., 1991), and other studies have confirmed the reduced efficacy of this drug against older worms (Bowman et al., 2001).

### 4.3. Moxidectin (MOX) (ProHeart 6, Fort Dodge Animal Health)

Safety-net activity of a single treatment with the injectable, sustained-release formulation (170  $\mu\text{g}/\text{kg}$ ) of MOX in dogs with 4-month-old infections has been reported as high (85.9% efficacy). Even higher

efficacy was reported (97.2%) when a second injection was given 6 months later (McCall et al., 2001d). This injectable formulation of MOX was only about 25% effective against 6-month-old infections, even when three injections were given at 6-month intervals, but many of the surviving worms in the treated dogs were abnormal in motility and/or appearance. The clinical prophylactic activity of orally administered MOX has been reported. Even given orally at a dosage of 0.5 µg/kg, the drug was 100% effective against 2-month-old worms, and products with this compound have a claim for efficacy of 2 months' duration (McTier et al., 1992). Dogs placed under natural conditions of exposure and treated at 2-month intervals at the recommended monthly dose of 3 µg/kg were completely free of infection (McCall et al., 1992).

#### 4.4. Selamectin (SEL) (*Revolution*, Pfizer Animal Health)

Selamectin is also 100% effective against 2-month-old heartworms (McTier et al., 2000). Moreover, monthly administration of prophylactic doses of SEL for 1 year has been shown to be 98.5% effective against 3-month-old heartworms. Selamectin had a partial effect on adult heartworms (39.4% efficacy) when administered topically at the recommended dosage for 18 consecutive months, and many of the surviving worms in treated dogs were abnormal in motility and/or appearance (Dzimianski et al., 2001).

### 5. Effects of increased dosage and shorter treatment interval

Macrocyclic lactones are now widely used in veterinary medicine for the removal of adult parasites, particularly gastrointestinal parasites of small and large animals (Guerrero et al., 2002), and the question has been raised about the possibility of increased efficacy over a shorter period by the use of a high dosage of IVM. Unpublished laboratory data by the author strongly suggest that drug (IVM) effects are not greatly enhanced by increasing the dosage (200 µg/kg) and/or administering the drug at shorter intervals (200 µg/kg daily for 1 week and

then weekly for 8 weeks, with necropsy 4 months after the last dose). Moreover, it appears that continuous monthly treatment of prophylactic doses of IVM is needed to produce the full safety-net and adulticidal effects of the drug (McCall 2001, unpublished data).

### 6. Anthelmintic resistance

The gradual decrease and eventual elimination of circulating microfilariae within a period of several months in most dogs receiving monthly prophylactic doses of either IVM, MBO, or SEL (Bowman et al., 1992, 2001; Lok et al., 1992; McCall et al., 1995, 1996, 1998; Dzimianski et al., 2001) or the injectable, sustained-release formulation of MOX (McCall et al., 2001d) is well documented in other reports. Bowman et al. (2001) have proposed that the administration of heartworm preventatives to microfilaremic dogs without first eliminating the adult worms by treatment with melarsomine dihydrochloride will lead to the selection of populations of heartworms that are resistant to these products. Although resistance of heartworms or any other filarial parasite to these MLs has not been reported, the concern that widespread use, and particularly misuse, of these drugs will lead to the development of resistant populations of heartworms is a valid one. Monthly preventatives, such as MBO, that are highly, but not completely, effective as a microfilaricide are leaving microfilariae that are potentially resistant to the drug. Repeated use of such a drug would increase the chance for development of resistance by the parasite, particularly considering the high level of owner compliance failure and the resulting potentially large numbers of microfilaremic dogs that are on incomplete monthly preventive programs. For drug resistance to develop under these conditions, it must be assumed that the microfilariae acquired by the vector mosquitoes are capable of developing to the third stage. In contrast, the low dose of IVM (minimum of 6 µg/kg) used as a monthly preventative is not considered to be microfilaricidal. In only one of four studies (144 dogs) in which IVM was administered at 10 µg/kg for three monthly doses was there any suggestion of microfilaricidal activity of low doses of IVM (Schlotthauer et al., 1986). Moreover, Lok et al., 1989 saw no evidence of microfilaricidal

activity of three monthly doses of Heartgard (6–12 µg IVM/kg) and suggested that the prophylactic dosage of IVM seems to fall on the “margin of microfilaricidal efficacy.” If monthly prophylactic dosing with IVM is not killing microfilariae, the gradual decrease in microfilariae count is due to natural death of microfilariae (attrition), and there is no opportunity for the development of drug resistance. Within a few months after continuous monthly dosing is started, microfilariae production ceases, and few, if any, additional microfilariae are released as long as the dog is being treated (Bowman et al., 1992; Courtney et al., 1998). When monthly dosing is started, the age of the existing microfilariae generally ranges from very young to very old. Thus, the oldest microfilariae die right away, those of intermediate age live for a few months, and the youngest live for several months, as the life span of microfilariae has been estimated to be about 6–12 months. The possible contribution of an immune response in eliminating these microfilariae should not be ignored. Thus, the cessation in production of microfilariae, death and removal of microfilariae by attrition, and/or enhanced immune clearance of microfilariae could explain the gradual reduction in microfilarial count over a period of approximately 6–9 months in dogs on continuous monthly dosing with IVM.

Regarding other MLs, SEL appears to have moderate microfilaricidal activity. Selamectin administered at the prophylactic dosage of 6 mg/kg (minimum) gradually reduced the microfilariae count during the month after the first of three doses and the reduction compared with the controls on day 30 was 87.5% (Dzimianski et al., 2001). The rate of reduction remained near this value through the last examination on day 74. Prolonged monthly dosing with SEL in microfilariae-positive dogs showing high initial counts has not been reported, but most dogs with low pretreatment counts had become microfilariae-negative by the sixth treatment (Dzimianski et al., 2001). The monthly prophylactic dose (3 µg/kg) of MOX is not microfilaricidal (Hendrix et al., 1992). The results of prolonged monthly administration of this low dosage of MOX to microfilaria-positive dogs has not been reported. A 3× dose (0.51 mg MOX by body weight) of the sustained-release injectable canine formulation of MOX reduced microfilarial count by 97.6%, compared with controls, on day 7, and the

count remained suppressed through the remainder of the month (Blagburn et al., 2001), but the microfilaricidal effects of the recommended dose (0.17 mg/kg) of this formulation has not yet been reported.

## 7. Benefits of monthly ivermectin for heartworm-positive dogs

In virtually all cases of owner compliance failure where dogs are harboring infections 4 months or older, monthly administration of prophylactic doses of IVM offers substantial benefits over MBO, and the efficacies of MOX and SEL lies between that of IVM and MBO. In many cases, dogs are given a monthly preventive for at least 2–3 years before they are examined for heartworm microfilariae or Ag. If IVM is used, most of the dogs will become heartworm-free and microfilariae- and Ag-negative, but some will harbor only a few adult worms (stunted and/or reduced worm mass) and become microfilariae-negative and Ag-positive during this period. The trickle effect of worm death over a period of several months (generally 4–24 months, depending on the age of the worms when treatment is started) should virtually eliminate the occurrence of severe thromboembolism, the most serious consequence of adulticidal therapy with arsenicals. For dogs with a few live adult worms remaining after prolonged monthly dosing, it is reasonable to assume that the smaller worms induce less cardiopulmonary disease while alive and are less likely to cause thromboembolism when they die later (either by arsenical therapy or natural causes) than larger worms. In contrast, if MBO is used during this period, very few, if any, of the worms will be killed or adversely affected by the drug; some pathology due to the live worms will be induced and the potentially large worm burden remaining at the end of this period must be eliminated by arsenical therapy, with the potentially high risk of thromboembolism, and possibly death, of the dogs.

## 8. Concerns about monthly ivermectin for heartworm-positive dogs

Although dead adult heartworms induce more acute clinical signs (which sometimes include death of

the dog) than do live adult heartworms, the presence of live worms during this protracted monthly treatment with IVM might eventually lead to irreversible pathologic sequelae (Rawlings et al., 2001). It seems likely that such changes are minimal and acceptable, compared with the serious consequences frequently resulting from arsenical therapy; however, this is yet to be determined.

## 9. Conclusions and recommendations

The AHS recognizes the safety-net and adulticidal properties of some of the MLs, particularly IVM. For example, the AHS 2003 canine guidelines (AHS, 2004) state “it is also beneficial to administer a prophylactic dose(s) of IVM for one to 6 months prior to administration of melarsomine, when the presentation does not demand immediate intervention. The reasoning for this approach is to allow older larvae and immatures time to develop to an age at which they can be killed by melarsomine” (Atkins and Miller, 2003), since the effect of melarsomine on heartworms younger than 4 months of age has not been reported (Keister et al., 1992). It also is “. . . to greatly reduce or eliminate circulating microfilariae and migrating larvae, stunt immature *D. immitis* and reduce female worm mass by destroying the reproductive system. This results in reduced antigenic mass, which in turn reduces the risk of thromboembolism.” The guidelines further add that “the long-term continuous administration of IVM generally is not a substitute for conventional adulticide treatment. If arsenical therapy is declined, a lengthy course of prophylactic doses of IVM will gradually reduce the number of adult heartworms, but in chronic mature infections this may not be as clinically beneficial.” In a recent study, client-owned dogs were given IVM monthly for 2 years with greatly restricted exercise. The worsened radiographic and echocardiographic images in one of three dogs was especially alarming (Venco et al., 2004). It has been demonstrated that forced rest is the most important measure in the prevention of thromboembolism and pulmonary damage (Dillon et al., 1995; Fukami et al., 1998). Thus monthly administration of IVM to dogs with clinical, radiographic and/or echocardiographic evidence of heartworm disease (Venco et al., 2004) or asymptomatic working dogs (McCall et al., 2001a) is

ill-advised. And, even considering that no heartworm-positive dogs on monthly IVM in laboratory studies have died, in contrast with the death of two non-treated control dogs, there is a strong suggestion that less active dogs are at low risk of severe thromboembolism and death (McCall et al., 2001a; McCall, 2003). Such treatment of even the less active asymptomatic dog should be done only with much caution and with examination by a veterinarian at least once every 4–6 months until further data are available (McCall et al., 2001a; Venco et al., 2004).

Monthly IVM clearly provides potent safety-net activity against older larvae, immatures, and young adults in cases of owner compliance failure, even when the owner and veterinarian are not aware that the animal is infected, and offers much promise as a unique “soft-kill” treatment for young, and possibly older adult, heartworms, with reduced risks.

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