Received: 7 December 2018 | Revised: 10 December 2018 | Accepted: 8 December 2018

DOI: 10.1111/vec.12795

SPECIAL ARTICLE

WILEY Journal of Veterinary Emergency and Critical Care

Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care (CURATIVE): Domain 3—Defining antithrombotic protocols

Marie-Claude Blais DMV, DACVIM[1] | Domenico Bianco DVM, PhD, DACVIM[2]* | Robert Goggs BVSc, DACVECC, DECVECC, PhD, MRCVS[3]* | Alex M. Lynch BVSc(Hons), DACVECC, MRCVS[4]* | Lee Palmer DVM, MS, DACVECC, NRP, EMT-T, WEMT, CCRP, TP-C[5]* | Alan Ralph DVM, DACVECC[6]* | Claire R. Sharp BSc, BVMS, MS, DACVECC[7]*

[1]Department of Clinical Sciences, Faculty of Veterinary Medicine, Université de Montréal, St-Hyacinthe, Quebec, Canada

[2]Internal Medicine Department, Metropolitan Animal Specialty Hospital, Los Angeles, CA

[3]Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY

[4]Department of Clinical Sciences, North Carolina State University, Raleigh, NC

[5]Lieutenant Colonel, US Army Reserve, Veterinary Corps, Chair K9 Tactical Emergency Casualty Care Working Group, New Orleans, LA

[6]MedVet New Orleans, New Orleans, LA

[7]School of Veterinary and Life Sciences, Murdoch University, Murdoch, Australia

Correspondence
Dr. Marie-Claude Blais, Department of Clinical Sciences, Faculty of Veterinary Medicine, Université de Montréal, 3200 Sicotte, Saint-Hyacinthe, Quebec J2S 2M2, Canada.
Email: mc.blais@umontreal.ca

*These authors contributed equally to this manuscript.

Offprints: Will not be available from the authors.

Prior presentation: This work was presented at in part at the European Veterinary Emergency and Critical Care symposium in Venice, Italy, November 2018, and at the American College of Veterinary Emergency and Critical Care congress in New Orleans, LA, USA, September 2018.

Abstract

Objectives: To systematically examine the evidence for use of a specific protocol (dose, frequency, route) of selected antithrombotic drugs, in comparisons to no therapy or to other antithrombotic therapies, to reduce the risk of complications or improve outcomes in dogs and cats at risk for thrombosis.

Design: Standardized, systematic evaluation of the literature, categorization of relevant articles according to level of evidence (LOE) and quality (Good, Fair, or Poor), and development of consensus on conclusions via a Delphi-style survey for application of the concepts to clinical practice.

Settings: Academic and referral veterinary medical centers.

Results: Databases searched included Medline via PubMed and CAB abstracts. Eight different antithrombotic drugs were investigated using a standardized Patient, Intervention, Comparison, Outcome (PICO) question format both for dogs and cats, including aspirin, clopidogrel, warfarin, unfractionated heparin (UFH), dalteparin, enoxaparin, fondaparinux, and rivaroxaban, generating a total of 16 worksheets. Most studies identified were experimental controlled laboratory studies in companion animals (LOE 3) with only four randomized controlled clinical trials in companion animals (LOE 1).

Conclusions: Overall, evidence-based recommendations concerning specific protocols could not be formulated for most antithrombotic drugs evaluated, either because of the wide range of dosage reported (eg, aspirin in dogs) or the lack of evidence in the current literature. However, clopidogrel administration in dogs and cats at risk of arterial thrombosis, notably in cats at risk of cardiogenic thromboembolism, is supported by the literature, and specific protocols were recommended. Comparably, aspirin should not be used as a sole antithrombotic in cats with cardiomyopathy. Using the available safety profile information contained in the literature, the panel reached consensus on suggested dosage schemes for most antithrombotics. Significant knowledge gaps were highlighted, which will hopefully drive novel research.

KEYWORDS

administration and dosage, anticoagulant, antiplatelet agents, CURATIVE, veterinary

INTRODUCTION

Despite the widespread use of antithrombotic drugs for the prevention and treatment of arterial and venous thrombosis, thromboembolic diseases continue to be a major cause of death and morbidity both in human,[1,2] and veterinary medicine.[3–6] Antithrombotic drugs are

Abbreviations: aPTT, activated partial thromboplastin time; ATE, arterial thromboembolism; IMHA, immune-mediated hemolytic anemia; GI, gastrointestinal; LOE, level of evidence; PICO, acronyms stands for P-patient, problem or population. I—intervention. C—comparison, control or comparator. O—outcome; PT, prothrombin time; RCT, randomized controlled trial; UFH, unfractionated heparin; VTE, venous thromboembolism

prescribed to inhibit the process of thrombus formation both to prevent and to treat pathologic thrombosis, but the risk-benefit profiles of particular drugs in individual patients should be considered prior to antithrombotic drug selection. The optimal dosing regimens for each drug must be determined for each species, and cannot simply be extrapolated from the human literature. In addition, variation in disease process and severity, in drug metabolism and in individual patient responses to treatment must also be considered, and will likely be multifactorial (eg, breed, sex, age, genetics).[7]

Domains 1 and 2 of the CURATIVE guidelines sought to define the populations of dogs and cats at risk for thrombosis, and to establish the most appropriate drug(s) for specific clinical settings. The objective of Domain 3 was to determine whether some antithrombotic protocols are more effective than others in order to make recommendations about drug dose, and the route and frequency of administration. In addition, Domain 3 also sought to highlight potential adverse effects and to evaluate safety profiles in order to provide guidance to clinicians regarding the risks associated with specific drug choices.

To undertake this task, a standardized Patient, Intervention, Comparison, Outcome (PICO) question was formulated to enable a systematic review of the evidence for 8 antithrombotic drugs (aspirin, clopidogrel, warfarin, unfractionated heparin (UFH), dalteparin, enoxaparin, fondaparinux, and rivaroxaban) in dogs and cats at risk of thrombosis. While UFH was considered as a single entity despite the variation in polysaccharide chain lengths inherent to that product, separate individual low molecular-weight heparin (LMWH) products were considered individually because they do not have identical pharmacologic profiles.

The number of articles considered relevant varied considerably between drugs and species. Specifically, the following numbers of articles were considered relevant for each medication: aspirin (dogs 47, cats 14), clopidogrel (dogs 11, cats 8), warfarin (dogs 16, cats 5), UFH (dogs 8, cats 1), dalteparin (dogs 7, cats 6), enoxaparin (dogs 5, cats 3), fondaparinux (dogs 0, cats 1), and rivaroxaban (dogs 3, cats 1). With the exception of aspirin in dogs, where the literature was extensive, worksheet authors included studies assessing the in vitro effect on platelet function and on coagulation assays in addition to pharmacokinetic and pharmacodynamic modeling in healthy animals.

The standardized PICO question read as follows:

In dogs and cats at risk of arterial/venous thrombosis (P), does use of a specific protocol (dose, frequency, route) for use of [antithrombotic drug] (I) compared to no therapy or to other antithrombotic therapies (C) reduce the risk of complications (eg, fatal or nonfatal hemorrhage, transfusion requirements) or improve any outcomes (eg, survival, organ dysfunction, thrombosis) (O)?

PICO QUESTION: Aspirin therapy

Guidelines

3.1 Aspirin (Dogs)

a. We suggest that oral aspirin may be effective for prevention of arterial thromboembolism (ATE) in dogs.

b. No evidence-based recommendations can be made for a specific aspirin dosage in dogs.

c. We suggest that aspirin be given for 2–3 days before full therapeutic effects of aspirin are anticipated, although commencement of aspirin therapy after an arterial insult may still be effective at preventing thrombosis.

d. No recommendations can be made for, or against, use of aspirin for VTE (venous thromboembolism) in dogs.

3.2 Aspirin (Cats)

a. We recommend against aspirin as a sole antithrombotic in cats at risk for ATE.

b. No recommendations can be made concerning appropriate aspirin dosage in cats.

Evidence summary

Dogs

A total of 47 articles were considered relevant to the PICO question, including 20 studies suggesting that protocolized aspirin therapy is more effective, or safer than, no aspirin therapy,[8–29] or other thromboprophylaxis protocols. Twenty-five studies were considered neutral to the question.[12,15,16,25–27,30–52] The majority of the published literature regarding the administration of aspirin in dogs involves experimental (laboratory) studies (LOE 3) of arterial thrombosis,[10,18,22–24,26,28,31,45,53] fewer studies evaluated venous thrombosis.[41,46–48] Most were considered of fair quality given that controls were included.[13,15,16,18–20,22–27] Only a few studies used randomized controls, and thus were considered good quality evidence.[8–12] There were also several studies without controls, considered of poor methodological quality.[17,28]

The majority of studies were designed to model the treatment of human diseases including coronary artery disease and arterial grafting. Models included coronary angioplasty and endarterectomy-induced endothelial injury,[10,18,22–24,26,28,53,54] as well as evaluations of the effect of thromboprophylaxis on the rate of coronary arterial reocclusion after thrombolysis.[11,27,30,34,36,37,49,51] Most of these models are not directly applicable to veterinary clinical medicine. In addition, many studies evaluated only short-term outcome measures used IV aspirin formulations that are not commercially available. Within endarterectomy and angioplasty models in dogs, the difference in aspirin efficacy appears mostly related to the timing of dosing relative to the arterial injury. Aspirin therapy, including aspirin at 5 mg/kg/day,[18] was more likely to be efficacious when started >2 days prior to arterial injury.[18,28]

Studies investigating graft thrombosis are perhaps most relevant to veterinary patients with ongoing risk factors for thromboembolism, since they involve medium to long-term oral aspirin administration. Twelve studies in graft models supported the research question, but the aspirin dose used varied widely. Unfortunately, in some studies, interpretation of aspirin dosing is impossible because dog bodyweights were not reported, and a standard mg/day dose was administered, rather than a mg/kg/day dose.[8,17] Of most relevance were the

limited number of graft studies that directly compared low-dose (1–5 mg/kg/day) to high-dose (>13 mg/kg/day) aspirin therapy, but again, results varied.[12,20,26]

For instance, in a study of femoral arterial graft patency (LOE 3, Fair), high-dose (13 mg/kg/day) aspirin but not low-dose aspirin (1 mg/kg/day) improved 1-week graft patency when commenced 24 hours prior to prosthesis implantation and continued for the duration of the experiment.[20] In a similar study (LOE 3, Good) McDaniel et al,[12] found that high-dose oral aspirin (13.5–18 mg/kg/day) with dipyridamole (3 mg/kg/day), but not low-dose aspirin (1 mg/kg/day) improved 7-day graft patency compared to control when commenced 24 hours prior to carotid artery grafting.[12] In contrast, Escudero et al,[26] (LOE 3, Fair) found that 5 mg/kg/day of oral aspirin was the only effective treatment for reducing platelet deposition on 6 biomaterials used as ex vivo arterial shunts, when commenced 7 days before implantation.[26] Specifically, 5 mg/kg/day of aspirin was more effective than 20 mg/kg/day of aspirin, 5 mg/kg/day aspirin combined with 5 mg/kg/day dipyridamole, and negative control. The apparent difference in efficacy of aspirin between studies may be related to the duration of aspirin therapy prior to shunt placement. Nonetheless, the limitations of studies such as that by Escudero et al are that they only evaluate immediate platelet deposition or thrombosis, rather than over a clinically relevant time period.

Thirteen studies involving graft models were considered neutral to the PICO question because they lacked a nonaspirin control group that precluded assessment of the efficacy of aspirin. No clinical adverse effects of aspirin were noted in these studies.[15,38–40,42–44,46–48,50,55,56] An additional 2 studies were considered neutral because there was no significant difference in the thromboprophylactic efficacy between aspirin treated groups, with doses ranging from 1–50 mg/kg/day.[14,33]

Only 2 studies evaluated the antithrombotic effects of aspirin in a clinical population of dogs at risk of thrombosis. Mellet et al (LOE 2, Good) performed a single-center unblinded, randomized, positive-controlled clinical trial in which low dose oral aspirin (0.5 mg/kg/day) alone was compared to clopidogrel alone or a combination of clopidogrel and aspirin for thromboprophylaxis in dogs with immune-mediated hemolytic anemia (IMHA).[57] Twenty-four dogs were randomized to either treatment and no difference was found in survival to discharge or 90 days survival, rate of thrombosis, or other adverse effects. As such the effects of aspirin were considered to be neutral to the PICO question. One patient in each of the aspirin and clopidogrel groups was suspected to have died of a thrombotic complication. Unfortunately, this study was likely underpowered to detect a difference between groups since sample size was based on a survival difference of 50% between groups, which is likely an optimistic target in a complex disease such as IMHA. One study (LOE 4, Poor) supported the PICO question.[29] In this single center retrospective study of dogs with IMHA, aspirin (0.5 mg/kg/day) and azathioprine in addition to glucocorticoid therapy resulted in improved survival to hospital discharge and to 30 days compared to dogs that did not receive thromboprophylaxis, and to those that received azathioprine and UFH.[29]

Several studies demonstrated that a single IV aspirin dose of 10–15 mg/kg shortly after arterial intimal injury resulted in a lower incidence of occlusive thrombus formation when compared to control.[22,23,53] Similarly, Hernandez-Maldonado et al,[24] (LOE 3, Fair) reported that oral aspirin (10 mg/kg/day) was more effective than control in preventing thrombosis in injured femoral arteries in a model of extremity trauma, when commenced on the first day postoperatively and continued for 3 weeks.

Multiple studies (LOE 3, Fair) assessed the in vitro function of platelets when dogs are administered various doses of aspirin.[58–64] These studies were not considered relevant to this PICO question because they did not evaluate clinical outcomes. Nonetheless, they address an important consideration regarding the efficacy of aspirin in dogs, because a subset of dogs that received aspirin appeared to be insensitive to its effects.[59,61,65,66]

No studies directly assessed both the safety of aspirin and its antithrombotic effects; however, dogs were only rarely removed from the included studies due to adverse effects. A single case report (LOE 5, Poor) reported gastrointestinal hemorrhage in a greyhound receiving three 13 mg/kg doses of aspirin.[67] No experimental studies reported adverse gastrointestinal or renal effects from aspirin, and thus aspirin (even at 100 mg/kg/day for 8 weeks) is considered safe in healthy dogs. Safety in sick dogs has not been evaluated, however, and both comorbidities and concomitant medications are likely to affect its safety profile.

Overall, there is good evidence that aspirin effectively prevents experimental arterial thrombosis in dogs when initiated at least 2 days before a thrombogenic insult such as arterial injury or graft implantation. The reported dose range is very wide, which precludes specific dosing recommendations. It is likely that low and medium oral doses between 0.5 mg/kg/day and 15 mg/kg/day are effective at preventing thromboembolism while maintaining an acceptable safety profile. Although studies have evaluated IV use of aspirin, no commercially available IV formulation is available and thus this is not considered clinically relevant at this time.

Cats

In cats, 14 studies investigated the administration of aspirin. While 7 of these publications were to some degree supportive of the PICO question (LOE 2, 3, and 5, Poor),[68–74] 6 publications including one randomized clinical trial provided evidence opposing it (LOE 3, Poor, and LOE 1, Good).[75–80]

A wide range of oral aspirin dosages have been described in cats (from 5 mg/kg twice weekly to 25 mg/kg/day). With these varied dosages, there are varied responses, in outcome studies and following in vitro assessments of platelet function. The FATCAT study (LOE 1, Good) enrolled 75 cats following a cardiogenic thromboembolism and randomized them to receive either oral clopidogrel 18.75 mg once daily or oral aspirin 81 mg every 72 hours.[75] There was a recurrence of ATE in 75% (27/36) of cats receiving aspirin in the first year compared to 36% (14/39) for those receiving clopidogrel. The median time to a primary event (recurrence of ATE) was 346 days for clopidogrel treated cats compared to 128 days for those receiving aspirin.

A separate retrospective of cats suffering ATE found no significant difference in survival or recurrence rate between cats receiving

high-dose aspirin (≥40 mg/cat q72h) and cats receiving low-dose aspirin (5 mg/cat q72h), with recurrence rate of 28% and 20%, respectively (LOE 4, Poor).[80] In another retrospective study, aspirin was used in 12 of the 17 cats surviving their initial ATE. Four cats went on to suffer a recurrence during the follow up period with 2 in the aspirin group (16% for those receiving aspirin) and 2 not receiving antithrombotic (LOE 4, Poor).[79]

In experimental feline thrombosis models, aspirin at 10 mg/kg IV was able to attenuate markers of platelet activation (thromboxane B_2 (TXB_2), 6-keto prostaglandin F1α (6k-$PGF_{1\alpha}$), prostaglandin E_2 (PGE_2) when collagen was infused intraaortically (LOE 2, Poor).[68] Aspirin dose adjusted based upon aggregation (typically 12–15 mg/kg PO q24h) was found to be more effective at limiting pulmonary artery thrombi than 97.5 mg twice weekly dosing or placebo (LOE 2, Fair).[69]

While not addressing the PICO question, it is relevant to note that the effect of aspirin on the results of platelet function tests varies considerably in cats. One study (LOE 3, Poor) found 5 mg/kg aspirin PO q48h to have no impact on aggregation as assessed by whole blood impedance aggregometry (10 μM ADP or 5 μg/mL collagen), serotonin release, and buccal mucosal bleeding time, although there was a lower serum TXB_2.[76] Others have documented 81 mg PO q72h inhibits aggregation (whole blood aggregometry) when stimulated with arachidonic acid (AA, 10^{-2} M), but not collagen (1 and 3 μg/mL) or ADP (2 μM).[71] Mixed results on ADP-induced aggregation were noted when cats were given 5 mg/kg aspirin PO q24h with dietary fatty acids.[72] Reductions in platelet function were not identified when cats were treated with 5 mg PO q24h or 20.25 mg PO q72h and tested with Plateletworks (ADP, collagen, and AA), multiplate aggregometry, and PFA-100 (collagen/ADP).[81]

Adverse gastrointestinal (GI) effects of aspirin were specifically addressed in 2 studies. Only 1 of 5 cats was found to have GI erosions (considered minor) when dosed with 20 mg/kg acetylsalicylate IV and visualized with endoscopy 8 hours later (LOE 3, Poor).[77] Another study assessed 20 mg/kg of plain aspirin PO versus 100 mg of enteric-coated aspirin PO and found significant gastric, duodenal, and small intestinal lesions after 7 days (LOE 3, Poor).[78] Dosing 3 hours after an evening meal was best tolerated in this cohort, and cimetidine or misoprostol limited the extent of gastric lesions but not duodenal lesions.[78]

In conclusion, aspirin should not be used a sole antithrombotic in cats at risk of cardiogenic thromboembolism, with consideration given to clopidogrel in lieu of aspirin in this population. Indeed, aspirin treatment in cats at risk of cardiogenic thromboembolism is associated with a high risk of recurrence, ie, 75% in the first year. There are conflicting studies regarding the impact of aspirin on platelet function ex vivo. This may in part be attributable to varying dosages and dosing intervals, along with differing test methodologies and platelet agonists.

Knowledge gaps

There is inadequate evidence to assess the efficacy of aspirin in dogs in clinical situations predisposing to both ATE and VTE. Similarly, the clinical repercussions of the apparent in vitro lack of sensitivity to aspirin of a subset of dogs are unclear. As pointed out in Domain 2, there is a need for studies comparing the efficacy of aspirin with clopidogrel in dogs at risk of thrombosis (Guideline 2.5). Further studies are also needed to determine if a more effective dose of aspirin exists for cats while still avoiding adverse effects (eg, gastrointestinal ulceration and risk or hemorrhage), notably if given in addition to clopidogrel. Further studies are also needed to determine the optimal test for assessment of platelet inhibition by aspirin in cats.

PICO QUESTION: Clopidogrel therapy

Guidelines

3.3 Clopidogrel (Dogs)

a. We recommend clopidogrel at 1.1–3 mg/kg PO q24h for the prevention of ATE in dogs.

b. We suggest a single oral loading dose (eg, 4–10 mg/kg) may be useful for obtaining therapeutic plasma concentrations more rapidly

c. No recommendations can be made for, or against, use of clopidogrel as sole agent for VTE in dogs.

3.4 Clopidogrel (Cats)

a. We recommend clopidogrel at 18.75 mg PO q24h, for prevention of ATE in cats.

b. We suggest a single oral loading dose (eg 37.5 mg total) may be useful for obtaining therapeutic plasma concentrations more rapidly.

c. No recommendations can be made for, or against, use of clopidogrel for VTE in cats.

Evidence summary

Dogs

In dogs, 11 papers (LOE 3, Good),[82–92] and 6 papers (LOE 3, Fair),[93–98] suggest efficacy of clopidogrel. Of these publications, 10 papers suggest in vivo efficacy against provoked arterial thrombosis, while 7 publications suggest clopidogrel has significant platelet inhibitory effects ex vivo using tests such as platelet aggregometry. The dosages and routes of administration of clopidogrel varied considerably in these publications. The lowest effective dose (effective dose for 50% of the population) was reported to be 0.21 mg/kg PO q24h,[92] while in other model systems up to 10 mg/kg IV was not consistently efficacious for prevention of arterial thrombosis.[91] The efficacy of a specific dose appears to be dependent on the dog, the model system used and the nature of the stimulus provoking thrombosis or platelet activation.

In vitro tests suggest that 1.1 mg/kg PO q24h causes inhibition of ADP-dependent platelet inhibition in dogs,[95] while 4 mg/kg POq24h after a 10 mg/kg loading dose provides protection against arterial thrombosis provoked by bioprosthesis implantation.[94] In coronary or femoral arterial thrombosis models, doses of 0.5–2.0 mg/kg IV provide protection from thrombosis.[82,83,90]

The oral bioavailability of clopidogrel in dogs is reported to be 10%.[99] As such, the oral dosages that are reportedly effective may produce substantially lower plasma concentrations than the intravenous dosages reported elsewhere.

Overall, clopidogrel given orally at a dosage of 1.1–4 mg/kg q24h appears to be safe and may be efficacious for prevention of arterial thrombosis in dogs. An oral loading dose (such as double the maintenance dose or up to 10 mg/kg PO q24h) may be useful for obtaining therapeutic plasma concentrations more rapidly. Similarly, clopidogrel given intravenously at a dosage of 0.5-2.0 mg/kg prior to arterial injury appears to be safe and may be efficacious for prevention of arterial thrombosis in dogs.

Cats

In cats, 8 papers (LOE 1, Good, LOE 2, Fair, and 6 LOE 3–4, Good-Poor) suggest efficacy of clopidogrel.[75,81,100–105] Of these publications, 3 papers (LOE 1, Good, LOE 3, Good, LOE 4, Poor) suggest in vivo efficacy against provoked arterial thrombosis,[75,100,101] while 5 publications (LOE 2, Fair, LOE 3, Good, LOE 4, Good) suggest clopidogrel has significant platelet inhibitory effects ex vivo using tests such as platelet aggregometry.[81,102–105] There is some variation in the tests and agonist dosages used to assess the efficacy of clopidogrel in the in vitro tests reported in these papers, which may go some way to explaining variations in the efficacy reported.

In contrast to the canine papers, there is very good consistency in the dosages used in the feline studies. The dosage used in most of the feline studies, including the LOE 1 randomized controlled trial (RCT),[75] was 18.75 mg (total) PO q24h. For a typical cat weighing 3–6 kg, this equates to a dose range of 3.13–6.25 mg/kg. A prior study by Hogan (2004) suggested that 18.75 mg total was not significantly different in efficacy than 37.5 mg or 75 mg PO q24h.[100] One publication suggested that clopidogrel 10 mg PO q24h might not be significantly different in efficacy compared to 18.75 mg PO q24h,[103] however, this conclusion was based on ex vivo platelet function test data. In addition, the authors did recommend a loading dosage. As such, given that 18.75 mg PO q24h appears to be effective and safe, there is currently no rationale to recommend using a lower dosage.

The Hogan et al RCT of clopidogrel versus aspirin in feline ATE was not placebo-controlled, likely for ethical reasons.[75] However, if one were to assume that aspirin had not beneficial impact at all (and hence behaved like placebo), then clopidogrel was still demonstrably more effective at preventing arterial thrombosis and for prolonging time to thrombosis or cardiac related death. This provides excellent evidence that clopidogrel should be used in cats with ATE, in preference to aspirin. There is virtually no evidence to determine whether aspirin should or should not be added to clopidogrel for ATE management. One retrospective study[101] suggested that receiving aspirin and/or clopidogrel was a positive prognostic indicator in cats with ATE, but the data presented was too limited to enable any further exploration of this finding.

Globally, clopidogrel given orally at a dosage of 18.75 mg q24h appears to be safe and efficacious for prevention of arterial thrombosis in cats. An oral loading dose (such as double the maintenance dose) may be useful for obtaining therapeutic plasma concentrations more rapidly.

Knowledge gaps

While clopidogrel appears safe and effective for the prevention of arterial thrombosis in dogs and cats, no evidence for or against its efficacy in venous thrombosis was identified. Strong evidence supports the use of clopidogrel in cats at risk of cardiogenic ATE, but the canine literature remains insufficient to make a similar claim in dogs at risk of thrombosis and further clinical studies are therefore warranted (eg, IMHA, PLN). As highlighted before, the question remains whether dual antiplatelet therapy would be preferable compared to clopidogrel alone, both in dogs and in cats. As novel antiplatelet agents become available (eg abciximab, ticagrelor, prasugrel), further studies will be needed to established their safety profile and clinical efficacy.

PICO QUESTION: Warfarin therapy

Guidelines

3.5 Warfarin (Dogs)

a. We suggest that warfarin should not be used in dogs because it inconsistently improves outcomes and is commonly associated with bleeding complications.

3.6 Warfarin (Cats)

a. No evidence-based recommendations can be made regarding the use of warfarin in cats at risk for thrombosis.

b. We suggest that warfarin should not be used in cats because of marked interindividual variation coupled with a narrow therapeutic index.

Evidence summary

Dogs

In dogs, 10 papers (LOE 1, 3, and 5, Poor to Good) suggest efficacy of warfarin.[106–115] Of these publications, 2 papers document that prophylactic use reduces venous thrombus formation (LOE 3, Fair),[111] and increases patency of a venous stent (LOE 3, Good)[109] compared to control. Arai et al (LOE 5, Fair)[114] and Lantz et al (LOE 3, Fair)[112] also suggest some efficacy of warfarin used prophylactically to prevent thrombosis in dogs undergoing bioprosthesis valve replacement and cranial vena cava graft, respectively. However, their conclusions are confounded by the fact that all dogs also received aspirin and a control group was not evaluated. Two papers (both LOE 5, Fair) suggested efficacy of warfarin in the treatment of acute arterial thrombosis,[115] and aortic thrombosis,[113] but again the lack of a control group and the coadministration of antiplatelet drugs weakens the conclusions that can be drawn. In an experimental canine model using filter entrapped venous thrombi (partial obstruction of blood flow), Hoffman et al documented that the treatment with warfarin accelerated lysis of mature

venous thrombi compared to no treatment (LOE 3, Good).[110] Finally, 3 papers (all LOE 3, Good),[106–108] support that warfarin at dose ranging from 0.05 to 1 mg/kg q24h is associated with fairly consistent in vitro anticoagulant efficacy described as an international normalized ratio (INR) of 2.0–4.0, depending on the study.

However, 7 papers document a lack of efficacy of warfarin in preventing thrombosis or bleeding complications (LOE 3,5; Poor-Good).[32,106,111,112,116–118] Of these publications, 4 studies suggest that warfarin lacks efficacy to prevent thrombosis of mitral valve prosthesis,[117,118] to maintain patency of venous graft compared to no treatment,[116] or patency of an intracoronary arterial stent compared to aspirin/dipyramidole.[32] Four studies also document hemorrhagic complications, often deadly, with relatively common warfarin dosage of 0.17–1.5 mg/kg q24h,[32,111,112,116] although no prothrombin time (PT) monitoring was performed in 2 of these studies.

Several studies did not address the above PICO question, but did highlight the narrow therapeutic index of warfarin. In dogs receiving long-term warfarin therapy, changes in the pharmacology of the drug over time has been documented.[119] In other words, clinical anticoagulation may require multiple dosage adjustments despite the early attainment of apparently therapeutic anticoagulation on a fixed dosage schedule. Numerous drugs, including glutethimide, amobarbital, secobarbital, meprobamate, amiodarone, halofenate, chlordane, phenobarbitone, phenylbutazone, and vitamin E, have been documented to interact with warfarin. [107,120–126] Of great clinical significance, Shen et al documented that the coadministration of aspirin increases the concentration of warfarin and associated prothrombin time, which may therefore increase the risk of bleeding.[106] Finally, warfarin is 93% protein-bound in dogs,[127] which may need to be considered when managing individual patients.

Owing to the narrow therapeutic index of warfarin, close monitoring of its anticoagulant effect using PT is emphasized throughout the literature. However, the appropriate loading dose and therapeutic targets necessary to avoid bleeding complications while producing clinically adequate anticoagulation have yet to be determined. In papers supporting the use of warfarin prophylactically or therapeutically for thrombi dissolution, and without adverse reactions (Makutani 1999 and Winter 2012, respectively),[109,113] the starting dose varied from 0.05 to 0.5 mg/kg q24h with either an antithrombotic target to prolong PT by 1.5-2-fold normal,[109] or to attain an INR of 2.0–3.0.[113] Similarly, loading doses ranging from 0.05 mg/kg to 0.3 mg/kg have been associated with in vitro anticoagulant efficacy defined as an INR 2.0–3.0, an INR 2.0–4.0, or 1.5–2 times baseline PT, without bleeding complications.[107,108,127–129] A pharmacokinetic study in healthy dogs also suggested that the dosage interval should be reduced 12 hours,[127] but this recommendation has not been applied by most subsequent studies. The most explicit dosage regime is provided by Monnet and Morgan, who evaluated the effect of 3 loading doses of warfarin on the INR in dogs in a model of postbilateral iliac artery grafting.[108] They concluded that a warfarin loading dose of 0.2 mg/kg for 2 days should induce an increase of the INR to a value between 2.0 and 3.0, during which period heparin should be administered concurrently. After 2 days, they recommended discontinuation of heparin, and a reduction in the loading dose of warfarin by half. Thereafter, the patient should be monitored daily by evaluation of the INR, aiming for a range of 2.0–3.0. In that study, no bleeding tendencies were noted, but the patency of the iliac artery grafts was not discussed. It should be noted that using a similar warfarin loading dose of 0.2–0.3 mg/kg for 3–5 days, Wheat et al, reported wide variation in the resulting INR in 9 dogs, ranging from an INR <2 in 2 dogs to >3.5 in 4 dogs, although without bleeding complications.[129]

Interestingly, in studies suggesting that warfarin is either ineffective for prevention of thrombosis or is associated with bleeding complications, the starting dose tended to be higher (1–1.5 mg/kg q24h),[111] not clearly defined,[116,117] or described without clear protocolized monitoring of PT.[32,112,118]

Overall, in dogs at risk of arterial or venous thrombosis, the use of warfarin to improve outcome is inconsistent and bleeding complications are commonly reported, especially if close monitoring is lacking. If warfarin is to be used prophylactically or therapeutically to dissolve thrombosis, a conservative loading dose is imperative (eg, 0.05–0.2 mg/kg q24h) as well as close initial and ongoing monitoring as described in Domain 4 (Guideline 4.2).

Cats

In cats, publications are scarce concerning the use of warfarin, and only 2 papers suggest some degree of efficacy.[130,131] Pouchelon et al, (LOE 5, Poor) reported the case of a cat diagnosed with pulmonary thromboemboli and treated with warfarin for a total of 20 days, which led to its clinical improvement without adverse reaction.[131] On day 5, the starting dose of 0.086 mg/kg PO was reduced to every other day administration, because PT was prolonged 7 times baseline. The lack of control and coadministration of heparin during the course of treatment limits the conclusions that can be drawn, however.[131] An experimental pharmacodynamic study in 10 healthy cats using a single IV dose of 0.5 mg/kg of racemic warfarin demonstrated that warfarin is able to block prothrombin complex synthesis as demonstrated by significant prolongation of PT.[130] A predicted median daily dose to yield therapeutic concentrations of 0.06–0.09 mg/kg per day was recommended (based on INR of 2.0-3.0). However, marked interindividual variation and a narrow therapeutic index were reported, highlighting the need for close monitoring.

Other studies available either opposed the use of warfarin in cats,[132,133] (LOE 3, Good-Fair) or do not reveal any benefit,[134] (LOE 5, Poor). The administration of warfarin at a dosage sufficient to prolonged PT by 2–4 times baseline, alone or in combination with aspirin, had no protective effect in an experimental model of arterial thrombosis in cats.[132] Similarly, warfarin administered at a dose of 0.05 mg/kg PO q12h for 9 days in a cat diagnosed with aortic thromboembolism did not appear to influence outcome.[130] Of clinical interest, it was demonstrated that the warfarin is unequally distributed within a commercial tablet that may increase the risk of over or under dosing our feline patients (or small dogs).[133]

Knowledge gaps

While in dogs there is sufficient evidence against the use of warfarin (lack of efficacy and/or high complication rates), there is a scarce body

of evidence regarding the use of warfarin compared to no therapy or other antithrombotic therapies in cats with a risk of thrombosis. In both species, narrow therapeutic indices have been documented, highlighting the need for close clinical monitoring and repeated PT assessment. Unfortunately, no data are available to predict an appropriate target range.

PICO QUESTION: Unfractionated Heparin therapy

Guidelines

3.7 Unfractionated Heparin (Dogs)

- **a.** UFH can be effectively administered by the IV or SC routes in dogs.
- **b.** Optimal UFH dose likely varies in individual dogs to maximize antithrombotic effects and minimize hemorrhagic complications.
- **c.** We suggest an initial IV dosing scheme of 100 U/kg bolus, then 480–900 U/kg/24h (20–37.5 U/kg/h) constant rate infusion in dogs.
- **d.** We suggest an initial SC dosage of UFH of 150–300 U/kg q6h in dogs.
- **e.** We recommend that UFH is not administered by inhalation or PO in dogs.

3.8 Unfractionated Heparin (Cats)

- **a.** Only a SC route of administration of UFH has been investigated in cats.
- **b.** We suggest an initial SC dosage of UFH of 250 U/kg q6h in cats.

Evidence summary

Dogs

The apparent antithrombotic efficacy of unfractionated heparin (UFH) is substantiated by 8 publications (LOE 1–4, Fair-Good).[128,135–141] While UFH administered via several routes appears potentially effective, the optimal dosing scheme is unestablished based on the current literature base. Subcutaneous[135,140,142] (LOE 1 and 3, Good and Fair, respectively) and intravenous[141] (LOE 4, Fair) routes are both acceptable. Oral administration of UFH was shown to induced changes in coagulation diagnostics (eg, anti-Xa activity, aPTT (activated partial thromboplastin time), and antithrombin), but its biological antithrombotic effects have not been documented to date (LOE 3, Fair).[143] Inhaled unfractionated heparin does not appear effective in dogs however (LOE 3, Fair).[144]For intravenous administration, a bolus dose of unfractionated heparin (100 U/kg) followed by constant rate infusion (480–900 U/kg/day) is reasonable, with escalation or deescalation of this dose depending on the results of therapeutic monitoring.[141,145,146]

A starting subcutaneous dose in the range of 150–300 U/kg q6h, with subsequent dose adjustment based on monitoring, is recommended.[135,140,142,147] The optimal dose of unfractionated heparin likely varies in individual patients and dose adjustment based on appropriate coagulation monitoring tests appears effective in dogs (LOE 1, Good).[135] Similarly, certain patient populations (eg, IMHA) may benefit from considerably higher doses than these starting points (LOE 1, Good; LOE 5, Fair).[135,147] Therapeutic monitoring is recommended irrespective of the route of administration. In that regard, several publications gauge apparent dosing efficacy by the ability to achieve the target unfractionated heparin specific anti-Xa activity range (0.35–0.7 U/mL) (Guideline 4.3b).

Cats

There is a scarce body of evidence regarding the use of unfractionated heparin in cats, and none in cats at risk of thrombosis, with only one study (LOE 3, Fair),[148] investigating the apparent antithrombotic effect of unfractionated heparin compared to low molecular weight heparin in healthy cats. Relatively minor hemorrhage may occur with unfractionated heparin irrespective of the dosing scheme, reiterating another advantage of therapeutic monitoring in small animals. A reasonable starting subcutaneous dose for unfractionated heparin in cats is 250 U/kg q6h.[148]

Knowledge gaps

With only one study available in healthy cats, further studies are warranted to establish the most appropriate starting dose of UFH in a feline population at risk of thrombosis and to investigate alternative routes of administration. That said, a consistent fixed dose of unfractionated heparin for dogs and cats likely does not exist. Individual dose adjustment, based on therapeutic monitoring, is advised and may be associated with improved clinical outcome. In that regard, a knowledge gap exists regarding the importance of anti-Xa activity achievement with respect to clinical efficacy in small animals (Guideline 4.3bc). There are insufficient data to support a clear superiority or inferiority of either UFH over low molecular weight heparin in dogs, and even less so in cats (Guidelines 2.9 and 2.10).

PICO QUESTION: Dalteparin therapy

Guidelines

3.9 Dalteparin (Dogs)

- **a.** We suggest an initial SC dosage of 100–175 U/kg q8h in dogs.
- **b.** Minor bleeding may be noted at the doses reported above, but serious bleeding is unlikely.

3.10 Dalteparin (Cats)

- **a.** In cats, frequent SC administration is likely necessary for maintenance of the human target anti-Xa activity range.
- **b.** We suggest lower dosages compared to dogs may be acceptable at increased frequency eg, 75 U/kg SC q6h.
- **c.** Bleeding complications, usually minor and self-limiting, may occur with a variety of dosing schemes.

Evidence summary

Dogs

Despite several publications, little data exist regarding the influence of dosing scheme on clinical efficacy or complications of dalteparin in small animals.[142,146,149–153] Only 4 studies suggest some degree of efficacy of dalteparin in dogs (LOE 3, 4, and 5, Poor and Fair),[142,150,151,153] as other studies were considered neutral to the PICO question.[146,149,154] It is to be noted that several manuscripts share the common assumption that the human target therapeutic anti-Xa activity range (eg, 0.5–1.0) is an appropriate target for dogs,[141,149–151,154,155] and may correlate to clinical antithrombotic effect. Bearing in mind this concept, doses of 100–175 U/kg SC may result in achievement of the human anti-Xa activity range,[149–151,154,155] with consistent achievement more likely if administration occurs three times daily.[149] Bleeding complications in dogs appear uncommon, although clear overdosage of dalteparin may result in severe potentially life-threatening bleeding (LOE 5 poor),[151] while most bleeding events otherwise appear relatively minor (eg, hematuria, venipuncture site bleeding).[151] Dalteparin may be associated with fewer bleeding complications than high-dose unfractionated heparin (ie, bolus of 100 U/kg of UFH IV, then constant rate infusion of 900 U/kg/day), although the antithrombotic effect of dalteparin at this dose (ie, 100 U/kg SQ q12h) is uncertain (LOE 4 fair).[141]

Cats

In cats, 6 publications address the usage of dalteparin, but were considered neutral to the PICO question listed above (LOE 3 and 5, Poor and Fair).[74,148,152,156–158] Frequent dosing may be appropriate, yet this is typically derived from studies performed in a small number of cats or based on pharmacokinetic models.[148,152,156] Based on the limited literature, a dosing scheme of 75–150 U/kg administered subcutaneously q6h appears to be a reasonable dosing strategy (LOE 3, Poor, and Fair).[148,156] Minor bleeding may be noted even at the clinical doses reported above, but serious bleeding is unlikely unless severe overdosing occurs.[148,156,157]

Knowledge gaps

There is incomplete information in the current literature to confidently answer the above PICO questions concerning the use of dalteparin in both dogs and cats. Further studies, ideally RCTs, are warranted to investigate the efficacy and safety of dalteparin in canine and feline patients at risk of thrombosis. A knowledge gap also exists regarding the importance of anti-Xa activity achievement with respect to clinical efficacy in small animals.

PICO QUESTION: Enoxaparin therapy

Guidelines

3.11 Enoxaparin (Dogs)

a. We suggest enoxaparin at a dosage of 0.8 mg/kg SC q6h is safe and well tolerated in dogs.

b. This dose may not achieve anti-Xa levels considered to be therapeutic in people in all breeds of dog.

c. Only minor bleeding complications have been reported in association with enoxaparin use in dogs.

3.12 Enoxaparin (Cats)

a. We suggest enoxaparin at a dosage of 0.75–1 mg/kg SC q6-12h should be considered in cats with a risk of VTE.

b. We suggest enoxaparin be administered q6h to reduce inter-individual variation in peak anti-Xa activity.

Evidence summary

Dogs

In dogs, 5 papers suggested efficacy of enoxaparin (LOE 3, 4, and 5, Poor to Good),[142,159–162] and the most commonly used protocol is 0.8 mg/kg SC q6h.[159–161] Although there is a scarce body of evidence regarding the use of enoxaparin compared to no antithrombotic therapy or other antithrombotic therapies in dogs a risk of thrombosis, there is some evidence suggesting the preferable use of a specific enoxaparin protocol in certain diseases with a risk of thrombosis. For example, the use of enoxaparin at a dose of 0.8 mg/kg SC q6h appeared well tolerated and relatively safe in dogs with presumed primary IHMA.[160] However, this protocol may not be adequate across all breeds, as demonstrated by a lack of efficacy (eg, targeted anti-Xa activity) in healthy adult beagles.[163]

Cats

Publications are scarce concerning the use of enoxaparin in cats, and only 3 papers suggest some degree of efficacy in healthy cats (LOE 3, Fair).[148,164,165] The use of enoxaparin at 1 mg/kg SC q12h in healthy cats failed to induce sustained anti-Xa activity.[148] However, Van De Wiele et al concluded that enoxaparin, administered at the same dosage (ie, 1 mg/kg SC q12h) in a venous stasis model in healthy cats, produces an antithrombotic effect, but that anti-Xa activity is a poor predictor of that effect.[165] Finally, based on pharmacokinetic data, Mischke et al concluded that a dosage schedule of 0.75 mg/kg four times a day seems suitable for therapeutic use of enoxaparin in cats as it leads to reproducible peak anti-Xa activities within the target range for the treatment of thrombosis in humans with low interindividual variation.[164]

Knowledge gaps

There is a scarce body of evidence regarding the use of enoxaparin compared to no antithrombotic therapy or other antithrombotic therapies in dogs or cats with a risk of thrombosis. RCTs, including appropriate monitoring of drug activity, are warranted to establish clear recommendations regarding appropriate protocol and valid comparisons of efficacy in clinical patients.

PICO QUESTION: Fondaparinux therapy

Guidelines

3.13 Fondaparinux (Dogs and Cats)

- **a.** No studies of fondaparinux in dogs were identified.
- **b.** A dose of fondaparinux of 0.06 or 0.20 mg/kg SC q12h was sufficient to achieve a peak plasma anti-Xa activity in cats considered effective in people, without bleeding complications.

Evidence summary

Dogs and cats

To date, scientific evidence to answer the PICO question is lacking. There are no studies evaluating fondaparinux in dogs and only one study in cats (LOE 3, Fair).[166] The study was a dose-determination study in 6 healthy purpose bred cats targeting anti-factor Xa levels comparative to what is considered effective in humans. Briefly, based upon evaluating anti-Xa activity, the investigators' data revealed that fondaparinux dosage of 0.06 or 0.20 mg/kg SC q12h was sufficient to achieve a peak plasma anti-factor Xa activity in cats that has been deemed therapeutic in people. No bleeding complications were reported.

Knowledge gaps

Basic pharmacokinetics and pharmacodynamics studies in healthy dogs are needed to established reasonable dosing scheme for fondaparinux. Thereafter, clinical trials evaluating fondaparinux in dogs and cats are warranted.

PICO QUESTION: Rivaroxaban therapy

Guidelines

3.14 Rivaroxaban (Dogs)

- **a.** Based on preliminary data, rivaroxaban appears safe and well tolerated in dogs.
- **b.** We suggest a dosage of 1–2 mg/kg/day in dogs.

3.15 Rivaroxaban (Cats)

- **a.** Based on preliminary data, rivaroxaban appears safe and well tolerated in cats.
- **b.** We suggest a dosage of 0.5-1 mg/kg/day in cats.

Evidence summary

Dogs

A total of 3 studies suggest the efficacy of rivaroxaban in dogs (LOE 2 and 4, Fair and Poor),[167–169] with only 1 study assessing its efficacy in the prevention of thrombosis.[167] Overall, rivaroxaban appears to be safe and well tolerated based upon the available evidence for dogs.

Briefly, Conversy et al assessed the short-term safety and anticoagulant effect of rivaroxaban in healthy dogs (LOE 2, Fair). Twice daily (q 8 hour) dosing of ~2 mg/kg resulted in an anticoagulant effect lasting almost 24 hours (returned to baseline after 17.5–26.8 hours versus 7.9–18.7 hours for once daily administration) as assessed by anti-Xa activity and thrombin generation.[168] The peak anticoagulant effect was seen at 1.5–2 hours, and there was no further increase in peak anticoagulation effect with twice daily administration versus once daily. No adverse effects were noted. Morassi et al (LOE 2, Fair) assessed the safety and tolerability of rivaroxaban in a prospective, positive-controlled, unblinded clinical trial including 24 dogs with primary immune-mediated hemolytic anemia.[167] Patients were scheduled to receive either 0.5–1 mg/kg rivaroxaban PO q24h or dual antiplatelet therapy (2–3 mg/kg clopidogrel PO q24h and 1 mg/kg aspirin PO q 24 h). There was no identified adverse drug reaction, evidence of hemorrhage, significant prolongation in PT/aPTT, increase in transfusion requirement, or difference in rate of thrombotic events, or survival to discharge at 1 month and 3 months. Three out of 5 dogs that did not survive the study period had thrombotic complications, including one dog receiving rivaroxaban (mesenteric thrombosis).

Lastly, therapeutic efficacy of rivaroxaban (0.6–1.25 mg/kg PO q24h) is supported by a single case series of 4 dogs suffering from various thromboses (arterial and venous), which showed an apparent benefit (for thrombus resolution) when switched from other antithrombotics.[169]

Cats

Only a pharmacokinetic and pharmacodynamics study is available in healthy cats to base recommendation in that species (LOE 2, Fair).[170] Healthy cats administered single doses of 2.5 and 5 mg of rivaroxaban PO achieved anti-Xa activities of 2.8 ± 1.3 and 3.5 ± 0.6 IU/mL, respectively, with a quick onset (3 hours) and a dose-dependent anticoagulation effect. Anti-Xa activities were maintained near the therapeutic target for thromboprophylaxis in humans at 24 hours (0.3 ± 0.2 and 0.47 ± 0.2 IU/mL, respectively; target of 0.5–1 IU/mL). However, cats achieved target plasma rivaroxaban concentration for thromboprophylaxis in people (140–240 ng/mL) when the anti-Xa activity was 2.6–4.1 IU/mL. There were no adverse effects noted with rivaroxaban administration in the healthy cats.[170]

Knowledge gaps

Rivaroxaban appears safe and well tolerated in both dogs and cats, however studies designed to assess the efficacy of rivaroxaban are lacking in animal at risk of thrombosis. In addition, the optimal dose and dosing interval for thromboprophylaxis and the treatment of thrombotic issues requires further study.

CONCLUSION

There is an obvious need for further studies relating to dosing of antithrombotic medications in veterinary medicine. Most notably

randomized controlled clinical trials will be essential to enable formulation of robust evidence-based recommendations concerning specific antithrombotic protocols in companion animals and in specific disease states. Additional studies are particularly warranted for drugs where dosage schemes are currently suggested based on limited literature and the clinical expertise of the panel.

In continuation of aspirin, clopidogrel is now used widely in companion animals, with solid support from the veterinary literature particularly in cats. Novel antiplatelet agents, including novel $P2Y_{12}$ inhibitors (prasugrel, ticagrelor, and cangrelor)[171] and the GPIIb/IIIa inhibitors (abciximab, tirofiban, and eptifibatide),[172] may eventually be included in future iterations of these guidelines as these medications become more affordable. Progress is occurring in the use of anticoagulant therapies also. As a result of the narrow therapeutic index, potential for side effects and drug interactions, the field is moving away from warfarin toward the direct oral anticoagulants. Rivaroxaban is an exciting new drug that appears safe and effective in dogs and cats, and will likely be the subject of further studies in the near future. More work is urgently required in this area to establish the most appropriate protocols for our patients and to confirm the efficacy and safety of the direct oral anticoagulants in clinical practice. Likewise, apixaban,[173] another novel direct oral Xa-inhibitor, and dabigatran a direct oral thrombin inhibitor,[174] warrant further investigation in small animals.

The phenomenon of individual drug response variability is well-recognized in human medicine,[175] but needs to be better defined in small animals. Individual variability in response to antithrombotics is likely due to various factors including disease state, age, breed, sex and neuter status, nutrition, concomitant medications, and genetics. It is likely the underlying causes of individual drug response variability will not be straightforward to confirm, but this area of veterinary pharmacology demands further attention. Moving forward, new antithrombotic drugs will continue to be investigated in human medicine to optimize their pharmacological properties and improve their benefit–risk profiles. Veterinarians need to do the same before incorporating these drugs into our clinical practice. Overall, significant knowledge gaps were highlighted by this work, which will hopefully drive novel research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Marie-Claude Blais DMV, DACVIM
https://orcid.org/0000-0003-0877-4425
Robert Goggs BVSc, DACVECC, DECVECC, PhD, MRCVS
https://orcid.org/0000-0001-7446-6987
Lee Palmer DVM, MS, DACVECC, NRP, EMT-T, WEMT, CCRP, TP-C
https://orcid.org/0000-0002-3849-1736
Claire R. Sharp BSc, BVMS, MS, DACVECC
https://orcid.org/0000-0002-1797-9783

References

1. Winter M, Schernthaner GH, Lang IM. Chronic complications of venous thromboembolism. *J Thromb Haemost*. 2017; *15*(8):1531–1540.
2. Tsai J, Grant AM, Beckman MG, et al. Determinants of venous thromboembolism among hospitalizations of US adults: a multilevel analysis. *PLoS One*. 2015; *10*(4):e0123842.
3. Johnson LR, Lappin MR, Baker DC. Pulmonary thromboembolism in 29 dogs: 1985–1995. *J Vet Intern Med*. 1999; *13*(4):338–345.
4. Winkle TJ, Liu SM, Hackner SG. Clinical and pathological features of aortic thromboembolism in 36 dogs. *J Vet Emerg Crit Care*. 1993; *3*(1):13–21.
5. Goggs R, Dennis SG, Di Bella A, et al. Predicting outcome in dogs with primary immune-mediated hemolytic anemia: results of a multicenter case registry. *J Vet Intern Med*. 2015; *29*(6):1603–1610.
6. Payne JR, Borgeat K, Brodbelt DC, et al. Risk factors associated with sudden death vs. congestive heart failure or arterial thromboembolism in cats with hypertrophic cardiomyopathy. *J Vet Cardiol*. 2015; (17 Suppl *1*):S318–S328.
7. Fuster V, Bhatt DL, Califf RM, et al. Guided antithrombotic therapy: current status and future research direction: report on a National Heart, Lung and Blood Institute working group. *Circulation*. 2012; *126*(13):1645–1662.
8. Kempczinski RF, Ramalanjaona GR, Douville C, Silberstein EB. Thrombogenicity of a fibronectin-coated, experimental polytetrafluoroethylene graft. *Surgery*. 1987; *101*(4):439–444.
9. Bearn PE, Moffat C, Seddon AM, et al. The effect of platelet inhibitory therapy on prosthetic graft maturation. *Int J Exp Pathol*. 1993; *74*(1):1–8.
10. Mickelson JK, Hoff PT, Homeister JW, et al. High dose intravenous aspirin, not low dose intravenous or oral aspirin, inhibits thrombus formation and stabilizes blood flow in experimental coronary vascular injury. *J Am Coll Cardiol*. 1993; *21*(2):502–510.
11. Prager NA, Torr-Brown SR, Sobel BE, Abendschein DR. Maintenance of patency after thrombolysis in stenotic coronary arteries requires combined inhibition of thrombin and platelets. *J Am Coll Cardiol*. 1993; *22*(1):296–301.
12. McDaniel MD, Huntsman WT, Miett TO, Cronenwett JL. Effect of a selective thromboxane synthase inhibitor on arterial graft patency and platelet deposition in dogs. *Arch Surg*. 1987; *122*(8):887–892.
13. Freeman MB, Sicard GA, Valentin LI, et al. The association of in vitro arachidonic acid responsiveness and plasma thromboxane levels with early platelet deposition on the luminal surface of small-diameter grafts. *J Vasc Surg*. 1988; *7*(4):554–561.
14. Hess F, Steeghs S, Braun B, et al. Patency rate of small caliber fibrous polyurethane vascular prostheses implanted in the dog carotid and femoral artery improved by use of acetylsalicylic acid and dipyridamol. *Thorac Cardiovasc Surg*. 1988; *36*(4):221–226.
15. Hess F, Steeghs S, Jerusalem C, et al. Implantation of 20 cm long polyurethane vascular prostheses in the femoral artery of dogs. Preliminary results. *Thorac Cardiovasc Surg*. 1988; *36*(6):348–350.
16. Valentin LI, Sicard GA, Freeman MB, et al. Combined arachidonic acid and ADP platelet inhibition maximizes patency of small-diameter vascular grafts. *Surgery*. 1988; *104*(2):178–184.
17. Brothers TE, Vincent CK, Darvishian D, et al. Effects of duration of acetylsalicylic acid administration on patency and anastomotic hyperplasia of ePTFE grafts. *ASAIO Trans*. 1989; *35*(3):558–560.
18. Escudero-Vela MC, Alvarez L, Rodriguez V, et al. Prevention of the formation of arterial thrombi using different antiplatelet drugs: experimental study in dogs. *Thromb Res*. 1989; *54*(3):187–195.

19. Matsumoto M, Ban T, Okamoto Y. Behavior of platelets and leukocytes on the luminal surface of small caliber polyurethane grafts. *J Cardiovasc Surg (Torino)*. 1989; *30*(4):609–613.
20. Bech FR, Cronenwett JL, McDaniel MD, et al. The effect of thromboxane receptor blockade versus thromboxane synthase inhibition on canine arterial graft patency. *J Vasc Surg*. 1990; *12*(2):119–125.
21. Bates ER, McGillem MJ, Mickelson JK, et al. A monoclonal antibody against the platelet glycoprotein IIb/IIIa receptor complex prevents platelet aggregation and thrombosis in a canine model of coronary angioplasty. *Circulation*. 1991; *84*(6):2463–2469.
22. Roux SP, Sakariassen KS, Turitto VT, Baumgartner HR. Effect of aspirin and epinephrine on experimentally induced thrombogenesis in dogs. A parallelism between in vivo and ex vivo thrombosis models. *Arterioscler Thromb*. 1991; *11*(5):1182–1191.
23. Yao SK, Benedict CR, Rosolowsky M, et al. Effect of aspirin on local prostaglandin production and serotonin accumulation in a canine model with coronary cyclic flow variations or thrombosis. *J Mol Cell Cardiol*. 1991; *23*(4):473–482.
24. Hernandez-Maldonado JJ, Padberg FT Jr., Teehan E, et al. Arterial intimal flaps: a comparison of primary repair, aspirin, and endovascular excision in an experimental model. *J Trauma*. 1993; *34*(4):565–569; discussion 569–570.
25. Escudero C, Alvarez L, de Haro J, et al. Prevention of arterial thrombosis by a monoclonal antibody against the 100 to 109 amino acid sequence stretch of the beta-subunit of the human platelet fibrinogen receptor: a comparative study with low dose aspirin. *J Am Coll Cardiol*. 1994; *23*(2):483–486.
26. Escudero MC, Alvarez L, de Haro J, et al. Prevention of thrombus formation on biomaterials exposed to blood using different antiplatelet drugs: experimental study in dogs. *J Biomed Mater Res*. 1994; *28*(1):1–6.
27. Roux SP, Tschopp TB, Kuhn H, et al. Effects of heparin, aspirin and a synthetic platelet glycoprotein IIb-IIIa receptor antagonist (Ro 43–5054) on coronary artery reperfusion and reocclusion after thrombolysis with tissue-type plasminogen activator in the dog. *J Pharmacol Exp Ther*. 1993; *264*(1):501–508.
28. Bush HL Jr., Jakubowski JA, Sentissi JM, et al. Neointimal hyperplasia occurring after carotid endarterectomy in a canine model: effect of endothelial cell seeding vs. perioperative aspirin. *J Vasc Surg*. 1987; *5*(1):118–125.
29. Weinkle TK, Center SA, Randolph JF, et al. Evaluation of prognostic factors, survival rates, and treatment protocols for immune-mediated hemolytic anemia in dogs: 151 cases (1993–2002). *J Am Vet Med Assoc*. 2005; *226*(11):1869–1880.
30. Mellott MJ, Holahan MA, Lynch JJ, et al. Acceleration of recombinant tissue-type plasminogen activator-induced reperfusion and prevention of reocclusion by recombinant antistasin, a selective factor Xa inhibitor, in a canine model of femoral arterial thrombosis. *Circ Res*. 1992; *70*(6):1152–1160.
31. Bates ER, McGillem MJ, Beals TF, et al. Effect of angioplasty-induced endothelial denudation compared with medial injury on regional coronary blood flow. *Circulation*. 1987; *76*(3):710–716.
32. Roubin GS, Robinson KA, King SB 3rd, et al. Early and late results of intracoronary arterial stenting after coronary angioplasty in dogs. *Circulation*. 1987; *76*(4):891–897.
33. DeCampli WM, Kosek JC, Mitchell RS, et al. Effects of aspirin, dipyridamole, and cod liver oil on accelerated myointimal proliferation in canine veno-arterial allografts. *Ann Surg*. 1988; *208*(6):746–754.
34. Yasuda T, Gold HK, Fallon JT, et al. Monoclonal antibody against the platelet glycoprotein (GP) IIb/IIIa receptor prevents coronary artery reocclusion after reperfusion with recombinant tissue-type plasminogen activator in dogs. *J Clin Invest*. 1988; *81*(4):1284–1291.
35. Boudreaux MK, Dillon AR, Ravis WR, et al. Effects of treatment with aspirin or aspirin/dipyridamole combination in heartworm-negative, heartworm-infected, and embolized heartworm-infected dogs. *Am J Vet Res*. 1991; *52*(12):1992–1999.
36. Olson RW, Dotson R, Mathis J, et al. Beneficial effects of combined thromboxane synthase inhibition/receptor blockade with CGS 22652 in a canine model of coronary thrombosis. *Eur J Pharmacol*. 1993; *236*(1):75–87.
37. McAuliffe SJ, Moors JA, Jones HB. Comparative effects of antiplatelet agents as adjuncts to tissue plasminogen activator in a dog model of occlusive coronary thrombosis. *Br J Pharmacol*. 1994; *112*(1):272–276.
38. Campbell JB, Glover JL, Herring B. The influence of endothelial seeding and platelet inhibition on the patency of ePTFE grafts used to replace small arteries—an experimental study. *Eur J Vasc Surg*. 1988; *2*(6):365–370.
39. Kaya M, Grogan JB, Lentz D, et al. Glutaraldehyde-preserved venous valve transplantation in the dog. *J Surg Res*. 1988; *45*(3):294–297.
40. Ortenwall P, Bylock A, Kjellstrom BT, Risberg B. Seeding of ePTFE carotid interposition grafts in sheep and dogs: species-dependent results. *Surgery*. 1988; *103*(2):199–205.
41. Vo NM, Arbogast LY, Friedlander E, et al. Aspirin improves the patency rate of seeded vena cava grafts. *J Cardiovasc Surg (Torino)*. 1989; *30*(6):936–941.
42. Greisler HP, McGurrin JF, Klosak JJ, et al. The validity of canine platelet aggregometry in predicting vascular graft patency. *J Cardiovasc Surg (Torino)*. 1990; *31*(6):712–718.
43. Lantz GC, Badylak SF, Coffey AC, et al. Small intestinal submucosa as a small-diameter arterial graft in the dog. *J Invest Surg*. 1990; *3*(3):217–227.
44. Bonan R, Bhat K, Lefevre T, et al. Coronary artery stenting after angioplasty with self-expanding parallel wire metallic stents. *Am Heart J*. 1991; *121*(5):1522–1530.
45. Hansen DD, Auth DC, Hall M, Ritchie JL. Rotational endarterectomy in normal canine coronary arteries: preliminary report. *J Am Coll Cardiol*. 1988; *11*(5):1073–1077.
46. Koveker GB, Burkel WE, Graham LM, et al. Endothelial cell seeding of expanded polytetrafluoroethylene vena cava conduits: effects on luminal production of prostacyclin, platelet adherence, and fibrinogen accumulation. *J Vasc Surg*. 1988; *7*(4):600–605.
47. Wang ZG, Du W, Li GD, et al. Rapid cellular luminal coverage of Dacron inferior vena cava prostheses in dogs by immediate seeding of autogenous endothelial cells derived from omental tissue: results of a preliminary trial. *J Vasc Surg*. 1990; *12*(2):168–179.
48. Deaton DW, Stephens JK, Karp RB, et al. Evaluation of cryopreserved allograft venous conduits in dogs. *J Thorac Cardiovasc Surg*. 1992; *103*(1):153–162.
49. Stassen JM, Rapold HJ, Vanlinthout I, Collen D. Comparative effects of enoxaparin and heparin on arterial and venous clot lysis with alteplase in dogs. *Thromb Haemost*. 1993; *69*(5):454–459.
50. Wilson GJ, MacGregor DC, Klement P, et al. A compliant Corethane/Dacron composite vascular prosthesis. Comparison with 4-mm ePTFE grafts in a canine model. *Asaio J*. 1993; *39*(3):M526–M531.
51. Collen D, Stassen JM, Yasuda T, et al. Comparative thrombolytic properties of tissue-type plasminogen activator and of a plasminogen activator inhibitor-1-resistant glycosylation variant, in a combined

arterial and venous thrombosis model in the dog. *Thromb Haemost*. 1994; *72*(1):98–104.

52. Degen MA, Feldman BF, Turrel JM, et al. Thrombocytosis associated with a myeloproliferative disorder in a dog. *J Am Vet Med Assoc*. 1989; *194*(10):1457–1459.
53. Atkins CE, Snyder PS, Keene BW. Effect of aspirin, furosemide, and commercial low-salt diet on digoxin pharmacokinetic properties in clinically normal cats. *J Am Vet Med Assoc*. 1988; *193*(10):1264–1268.
54. Roux SP_Arterioscl Thromb_1991.pdf.
55. Vo NM, Arbogast L, Arbogast B, Stanton PE. Effect of preclotting and precoating agents on seeded venous grafts. *J Cardiovasc Surg (Torino)*. 1989; *30*(4):604–608.
56. Greisler HP, Tattersall CW, Henderson SC, et al. Polypropylene small-diameter vascular grafts. *J Biomed Mater Res*. 1992; *26*(10):1383–1394.
57. Mellett AM, Nakamura RK, Bianco D. A prospective study of clopidogrel therapy in dogs with primary immune-mediated hemolytic anemia. *J Vet Intern Med*. 2011; *25*(1):71–75.
58. Nielsen LA, Zois NE, Pedersen HD, et al. Platelet function in dogs: breed differences and effect of acetylsalicylic acid administration. *Vet Clin Pathol*. 2007; *36*(3):267–273.
59. Sharpe KS, Center SA, Randolph JF, et al. Influence of treatment with ultralow-dose aspirin on platelet aggregation as measured by whole blood impedance aggregometry and platelet P-selectin expression in clinically normal dogs. *Am J Vet Res*. 2010; *71*(11):1294–1304.
60. Blois SL, Allen DG, Wood RD, Conlon PD. Effects of aspirin, carprofen, deracoxib, and meloxicam on platelet function and systemic prostaglandin concentrations in healthy dogs. *Am J Vet Res*. 2010; *71*(3):349–358.
61. Haines JM, Thomason JM, Seage EC, et al. In vitro and in vivo assessment of platelet function in healthy dogs during administration of a low-dose aspirin regimen. *Am J Vet Res*. 2016; *77*(2):174–185.
62. Thomason J, Archer T, Wills R, et al. The Effects of Cyclosporine and Aspirin on Platelet Function in Normal Dogs. *J Vet Intern Med*. 2016; *30*(4):1022–1030.
63. Haines JM, Lee PM, Hegedus RM, et al. Establishment of reference ranges and evaluation of in vitro concentration-dependent platelet inhibition by acetylsalicylic acid for multiple electrode impedance aggregometry in healthy dogs. *J Vet Pharmacol Ther*. 2017; *40*(6):618–628.
64. McLewee N, Archer T, Wills R, et al. Effects of aspirin dose escalation on platelet function and urinary thromboxane and prostacyclin levels in normal dogs. *J Vet Pharmacol Ther*. 2018; *41*(1):60–67.
65. Dudley A, Thomason J, Fritz S, et al. Cyclooxygenase expression and platelet function in healthy dogs receiving low-dose aspirin. *J Vet Intern Med*. 2013; *27*(1):141–149.
66. Thomason J, Lunsford K, Mullins K, et al. Platelet cyclooxygenase expression in normal dogs. *J Vet Intern Med*. 2011; *25*(5):1106–1112.
67. Shaw N, Burrows CF, King RR. Massive gastric hemorrhage induced by buffered aspirin in a greyhound. *J Am Anim Hosp Assoc*. 1997; *33*(3):215–219.
68. De Clerck F, Loots W, Somers Y, et al. 5-Hydroxytryptamine and arachidonic acid metabolites modulate extensive platelet activation induced by collagen in cats in vivo. *Br J Pharmacol*. 1990; *99*(4):631–636.
69. Rawlings CA. Pulmonary arteriography and hemodynamics during feline heartworm disease. Effect of aspirin. *J Vet Intern Med*. 1990; *4*(6):285–291.
70. Rawlings CA, Farrell RL, Mahood RM. Morphologic changes in the lungs of cats experimentally infected with *Dirofilaria immitis*. Response to aspirin. *J Vet Intern Med*. 1990; *4*(6):292–300.
71. Behrend EN, Grauer GF, Greco DS, et al. Comparison of the effects of diltiazem and aspirin on platelet aggregation in cats. *J Am Anim Hosp Assoc*. 1996; *32*(1):11–18.
72. Davidson BC, Haggan J., Dietary polyenoic fatty acids change the response of cat blood platelets to inductions of aggregation by ADP. *Prostaglandins Leukot Essent Fatty Acids*. 1990; *39*(1):31–37.
73. Borenstein N, Gouni V, Behr L, et al. Surgical treatment of Cor triatriatum sinister in a cat under cardiopulmonary bypass. *Vet Surg*. 2015; *44*(8):964–969.
74. Davidson BL, Rozanski EA, Tidwell AS, Hoffman AM. Pulmonary thromboembolism in a heartworm-positive cat. *J Vet Intern Med*. 2006; *20*(4):1037–1041.
75. Hogan DF, Fox PR, Jacob K, et al. Secondary prevention of cardiogenic arterial thromboembolism in the cat: the double-blind, randomized, positive-controlled feline arterial thromboembolism; clopidogrel vs. aspirin trial (FAT CAT). *J Vet Cardiol*. 2015; (17 Suppl *1*):S306–S317.
76. Cathcart CJ, Brainard BM, Reynolds LR, et al. Lack of inhibitory effect of acetylsalicylic acid and meloxicam on whole blood platelet aggregation in cats. *J Vet Emerg Crit Care*. 2012; *22*(1):99–106.
77. Parton K, Balmer TV, Boyle J, et al. The pharmacokinetics and effects of intravenously administered carprofen and salicylate on gastrointestinal mucosa and selected biochemical measurements in healthy cats. *J Vet Pharmacol Ther*. 2000; *23*(2):73–79.
78. Satoh H, Amagase K, Takeuchi K. The role of food for the formation and prevention of gastrointestinal lesions induced by aspirin in cats. *Dig Dis Sci*. 2013; *58*(10):2840–2849.
79. Schoeman JP. Feline distal aortic thromboembolism: a review of 44 cases (1990–1998). *J Feline Med Surg*. 1999; *1*(4):221–231.
80. Smith SA, Tobias AH, Jacob KA, et al. Arterial thromboembolism in cats: acute crisis in 127 cases (1992–2001) and long-term management with low-dose aspirin in 24 cases. *J Vet Intern Med*. 2003; *17*(1):73–83.
81. Ho KK, Abrams-Ogg AC, Wood RD, et al. Assessment of platelet function in healthy cats in response to commonly prescribed antiplatelet drugs using three point-of-care platelet function tests. *J Feline Med Surg*. 2017; *19*(6):638–647.
82. Bjorkman JA, Zachrisson H, Forsberg GB, et al. High-dose aspirin in dogs increases vascular resistance with limited additional antiplatelet effect when combined with potent P2Y12 inhibition. *Thromb Res*. 2013; *131*(4):313–319.
83. Hasa AA, Schmaier AH, Warnock M, et al. Thrombostatin inhibits cyclic flow variations in stenosed canine coronary arteries. *Thromb Haemost*. 2001; *86*(5):1296–1304.
84. Hennan JK, Swillo RE, Morgan GA, et al. Pharmacologic inhibition of platelet vWF-GPIb alpha interaction prevents coronary artery thrombosis. *Thromb Haemost*. 2006; *95*(3):469–475.
85. Hong TT, Huang J, Driscoll E, Lucchesi BR. The antithrombotic effect of melagatran in combination with clopidogrel and/or aspirin (carotid artery primary thrombosis study). *J Cardiovasc Pharmacol*. 2005; *46*(4):526–533.
86. Hong TT, Huang J, Driscoll E, Lucchesi BR. Preclinical evaluation of S18886 in an experimental model of coronary arterial thrombosis. *J Cardiovasc Pharmacol*. 2006; *48*(5):239–248.
87. Nylander S, Wagberg F, Andersson M, et al. Exploration of efficacy and bleeding with combined phosphoinositide 3-kinase beta inhibition and aspirin in man. *J Thromb Haemost*. 2015; *13*(8):1494–1502.

88. Ravnefjord A, Weilitz J, Emanuelsson BM, van Giezen JJ. Evaluation of ticagrelor pharmacodynamic interactions with reversibly binding or non-reversibly binding P2Y(12) antagonists in an ex-vivo canine model. *Thromb Res*. 2012; *130*(4):622–628.
89. Toomey JR, Samanen J, Valocik RE, et al. The antithrombotic efficacy of lotrafiban (SB 214857) in canine models of acute coronary thrombosis. *Curr Drug Targets Cardiovasc Haematol Disord*. 2002; *2*(1):13–25.
90. van Giezen JJ, Berntsson P, Zachrisson H, Bjorkman JA. Comparison of ticagrelor and thienopyridine P2Y(12) binding characteristics and antithrombotic and bleeding effects in rat and dog models of thrombosis/hemostasis. *Thromb Res*. 2009; *124*(5):565–571.
91. Wang K, Zhou X, Huang Y, et al. Adjunctive treatment with ticagrelor, but not clopidogrel, added to tPA enables sustained coronary artery recanalisation with recovery of myocardium perfusion in a canine coronary thrombosis model. *Thromb Haemost*. 2010; *104*(3):609–617.
92. Wang YX, Vincelette J, da Cunha V, et al. A novel P2Y(12) adenosine diphosphate receptor antagonist that inhibits platelet aggregation and thrombus formation in rat and dog models. *Thromb Haemost*. 2007; *97*(5):847–855.
93. Abid M, Kalbantner K, Mischke R. Influence of test time on results of the impedance aggregometer multiplate analyser in dogs. *Comp Clin Pathology*. 2014; *23*(5):1387–1393.
94. Borgarelli M, Lanz O, Pavlisko N, et al. Mitral valve repair in dogs using an ePTFE chordal implantation device: a pilot study. *J Vet Cardiol*. 2017; 19(3):256–267.
95. Brainard BM, Kleine SA, Papich MG, Budsberg SC. Pharmacodynamic and pharmacokinetic evaluation of clopidogrel and the carboxylic acid metabolite SR 26334 in healthy dogs. *Am J Vet Res*. 2010; *71*(7):822–830.
96. Thames BE, Lovvorn J, Papich MG, et al. The effects of clopidogrel and omeprazole on platelet function in normal dogs. *J Vet Pharmacol Ther*. 2017; *40*(2):130–139.
97. Yao SK, Ober JC, Ferguson JJ, et al. Combination of inhibition of thrombin and blockade of thromboxane A2 synthetase and receptors enhances thrombolysis and delays reocclusion in canine coronary arteries. *Circulation*. 1992; *86*(6):1993–1999.
98. Yao SK, Ober JC, Ferguson JJ, et al. Clopidogrel is more effective than aspirin as adjuvant treatment to prevent reocclusion after thrombolysis. *Am J Physiol*. 1994; *267*(2 Pt 2):H488–H493.
99. Hagihara K, Kazui M, Ikenaga H, et al. Comparison of formation of thiolactones and active metabolites of prasugrel and clopidogrel in rats and dogs. *Xenobiotica*. 2009; *39*(3):218–226.
100. Hogan DF, Andrews DA, Green HW, et al. Antiplatelet effects and pharmacodynamics of clopidogrel in cats. *J Am Vet Med Assoc*. 2004; *225*(9):1406–1411.
101. Borgeat K, Wright J, Garrod O, et al. Arterial thromboembolism in 250 cats in general practice: 2004–2012. *J Vet Intern Med*. 2014; *28*(1):102–108.
102. den Toom ML, van Leeuwen MW, Szatmari V, Teske E. Effects of clopidogrel therapy on whole blood platelet aggregation, the Plateletworks(R) assay and coagulation parameters in cats with asymptomatic hypertrophic cardiomyopathy: a pilot study. *Vet Q*. 2017; *37*(1):8–15.
103. Teuber M, Mischke R. Influence of a low dosage of clopidogrel on platelet function in cats as measured by the platelet function analyser PFA-100 and the multiplate analyser. *Res Vet Sci*. 2016; *109*:149–156.
104. Hamel-Jolette A, Dunn M, Bedard C. Plateletworks: a screening assay for clopidogrel therapy monitoring in healthy cats. *Can J Vet Res*. 2009; *73*(1):73–76.
105. Li RH, Stern JA, Ho V, et al. Platelet activation and clopidogrel effects on ADP-induced platelet activation in cats with or without the A31P mutation in MYBPC3. *J Vet Intern Med*. 2016; *30*(5):1619–1629.
106. Shen C, Huang X, Li J, et al. Pharmacokinetic and pharmacodynamic interactions of aspirin with warfarin in beagle dogs. *Xenobiotica*. 2016; *46*(6):530–541.
107. Choppin A, Irwin I, Lach L, et al. Effect of tecarfarin, a novel vitamin K epoxide reductase inhibitor, on coagulation in beagle dogs. *Br J Pharmacol*. 2009; *158*(6):1536–1547.
108. Monnet E, Morgan MR. Effect of three loading doses of warfarin on the international normalized ratio for dogs. *Am J Vet Res*. 2000; *61*(1):48–50.
109. Makutani S, Kichikawa K, Uchida H, et al. Effect of antithrombotic agents on the patency of PTFE-covered stents in the inferior vena cava: an experimental study. *Cardiovasc Intervent Radiol*. 1999; *22*(3):232–238.
110. Hoffman MJ, Stewart JR, Greenfield LJ. Effects of coumadin on the resolution of canine venous thrombi. *J Surg Res*. 1986; *40*(1):1–5.
111. Hoak JC, Connor WE, Warner ED. The antithrombotic effects of sodium heparin and sodium warfarin. *Arch Intern Med*. 1966; *117*(1):25–31.
112. Lantz GC, Badylak SF, Coffey AC, et al. Small intestinal submucosa as a superior vena cava graft in the dog. *J Surg Res*. 1992; *53*(2):175–181.
113. Winter RL, Sedacca CD, Adams A, Orton EC. Aortic thrombosis in dogs: presentation, therapy, and outcome in 26 cases. *J Vet Cardiol*. 2012; *14*(2):333–342.
114. Arai S, Griffiths LG, Mama K, et al. Bioprosthesis valve replacement in dogs with congenital tricuspid valve dysplasia: technique and outcome. *J Vet Cardiol*. 2011; *13*(2):91–99.
115. Arai S, Callan MB. Warfarin therapy in a dog with acute arterial thrombosis and pyometra. *Can Vet J*. 2014; *55*(11):1066–1068.
116. Todd RS, Sive EB, Dejode LR, et al. Replacement of segments of the venous system. *Arch Surg*. 1963; *87*:998–1002.
117. Dale J, Aasen AO, Resch F, et al. Mitral disc valve implantation in the dog: early and late valve thrombosis and its prevention. *Eur Surg Res*. 1983; *15*(5):249–255.
118. Orton EC, Hackett TB, Mama K, Boon JA. Technique and outcome of mitral valve replacement in dogs. *J Am Vet Med Assoc*. 2005; *226*(9):1508–1511, 1500.
119. Covell DG, Abbrecht PH, Powers WF. Changes in the pharmacology of warfarin during long-term administration in dogs. *J Lab Clin Med*. 1984; *103*(2):272–283.
120. Hunninghake DB, Azarnoff DL. Drug interactions with warfarin. *Arch Intern Med*. 1968; *121*(4):349–352.
121. Weintraub M, Griner PF. Alterations in the effects of warfarin in dogs by halofenate: an influence upon the kinetics of prothrombin. *Thromb Diath Haemorrh*. 1975; *34*(2):445–454.
122. Bachmann KA, Burkman AM. Phenylbutazone-warfarin interaction in the dog. *J Pharm Pharmacol*. 1975; *27*(11):832–836.
123. Esquivel M, Blaschke TF, Snidow GH, Meffin PJ. Effect of phenobarbitone on the disposition of lignocaine and warfarin in the dog. *J Pharm Pharmacol*. 1978; *30*(12):804-805.
124. Bachmann KA, Burkman AM. Topical application of a chlordane-containing ectoparasiticide: effect on the plasma half-life of warfarin in dogs. *Lab Anim*. 1975; *9*(2):135–137.
125. Corrigan JJ Jr., Coagulation problems relating to vitamin E. *Am J Pediatr Hematol Oncol*. 1979; *1*(2):169–173.
126. Corrigan JJ Jr., The effect of vitamin E on warfarin-induced vitamin K deficiency. *Ann NY Acad Sci*. 1982; *393*:361–368.

127. Neff-Davis CA, Davis LE, Gillette EL. Warfarin in the dog: pharmacokinetics as related to clinical response. *J Vet Pharmacol Ther*. 1981; *4*(2):135–140.
128. Dixon-Jimenez AC, Brainard BM, Cathcart CJ, Koenig A. Evaluation of a point-of-care coagulation analyzer (Abaxis VSPro) for identification of coagulopathies in dogs. *J Vet Emerg Crit Care*. 2013; *23*(4):402–407.
129. Wheat JC, Hall TL, Hempel CR, et al. Prostate histotripsy in an anticoagulated model. *Urology*. 2010; *75*(1):207–211.
130. Smith SA, Kraft SL, Lewis DC, et al. Pharmacodynamics of warfarin in cats. *J Vet Pharmacol Ther*. 2000; *23*(6):339–344.
131. Pouchelon JL, Chetboul V, Devauchelle P, et al. Diagnosis of pulmonary thromboembolism in a cat using echocardiography and pulmonary scintigraphy. *J Small Anim Practice*. 1997; *38*(7):306–310.
132. Piegras DG, Sundt TM Jr., Didisheim P. Effect of anticoagulants and inhibitors of platelet aggregation on thrombotic occlusion of endarterectomized cat carotid arteries. *Stroke*. 1976; *7*(3):248–254.
133. Smith SA, Kraft SL, Lewis DC, Freeman LC. Plasma pharmacokinetics of warfarin enantiomers in cats. *J Vet Pharmacol Ther*. 2000; *23*(6):329–337.
134. Koyama H, Matsumoto H, Fukushima RU, Hirose H. Local intra-arterial administration of urokinase in the treatment of a feline distal aortic thromboembolism. *J Vet Med Sci*. 2010; *72*(9):1209–1211.
135. Helmond SE, Polzin DJ, Armstrong PJ, et al. Treatment of immune-mediated hemolytic anemia with individually adjusted heparin dosing in dogs. *J Vet Intern Med*. 2010; *24*(3):597–605.
136. Rebello SS, Kasiewski CJ, Bentley RG, et al. Superiority of enoxaparin over heparin in combination with a GPIIb/IIIa receptor antagonist during coronary thrombolysis in dogs. *Thromb Res*. 2001; *102*(3):261–271.
137. Leadley RJ Jr., Kasiewski CJ, Bostwick JS, et al. Inhibition of repetitive thrombus formation in the stenosed canine coronary artery by enoxaparin, but not by unfractionated heparin. *Arterioscler Thromb Vasc Biol*. 1998; *18*(6):908–914.
138. Thompson MF, Scott-Moncrieff JC, Brooks MB. Effect of a single plasma transfusion on thromboembolism in 13 dogs with primary immune-mediated hemolytic anemia. *J Am Anim Hosp Assoc*. 2004; *40*(6):446–454.
139. Babski DM, Brainard BM, Ralph AG, et al. Sonoclot(R) evaluation of single- and multiple-dose subcutaneous unfractionated heparin therapy in healthy adult dogs. *J Vet Intern Med*. 2012; *26*(3):631–638.
140. Diquelou A, Barbaste C, Gabaig AM, et al. Pharmacokinetics and pharmacodynamics of a therapeutic dose of unfractionated heparin (200 U/kg) administered subcutaneously or intravenously to healthy dogs. *Vet Clin Pathol*. 2005; *34*(3):237–242.
141. Scott KC, Hansen BD, DeFrancesco TC. Coagulation effects of low molecular weight heparin compared with heparin in dogs considered to be at risk for clinically significant venous thrombosis. *J Vet Emerg Crit Care*. 2009; *19*(1):74–80.
142. Morris TA, Marsh JJ, Konopka R, et al. Anti-thrombotic efficacies of enoxaparin, dalteparin, and unfractionated heparin in venous thrombo-embolism. *Thromb Res*. 2000; *100*(3):185–194.
143. Erickson M, Hiebert LM, Carr AP, Stickney JD. Effect of oral administration of unfractionated heparin (UFH) on coagulation parameters in plasma and levels of urine and fecal heparin in dogs. *Can J Vet Res*. 2014; *78*(3):193–201.
144. Manion JS, Thomason JM, Langston VC, et al. Anticoagulant effects of inhaled unfractionated heparin in the dog as determined by partial thromboplastin time and factor Xa activity. *J Vet Emerg Crit Care* 2016; *26*(1):132–136.
145. Cunningham SM, Ames MK, Rush JE, Rozanski EA. Successful treatment of pacemaker-induced stricture and thrombosis of the cranial vena cava in two dogs by use of anticoagulants and balloon venoplasty. *J Am Vet Med Assoc*. 2009; *235*(12):1467–1473.
146. DePaula KM, deLaorcade AM, King RG, et al. Arterial thrombosis after vehicular trauma and humeral fracture in a dog. *J Am Vet Med Assoc*. 2013; *243*(3):394–398.
147. Breuhl EL, Moore G, Brooks MB, Scott-Moncrieff JC. A prospective study of unfractionated heparin therapy in dogs with primary immune-mediated hemolytic anemia. *J Am Anim Hosp Assoc*. 2009; *45*(3):125–133.
148. Alwood AJ, Downend AB, Brooks MB, et al. Anticoagulant effects of low-molecular-weight heparins in healthy cats. *J Vet Intern Med*. 2007; *21*(3):378–387.
149. Brainard BM, Koenig A, Babski DM, et al. Viscoelastic pharmacodynamics after dalteparin administration to healthy dogs. *Am J Vet Res*. 2012; *73*(10):1577–1582.
150. Gara-Boivin C, Del Castillo JRE, Dunn ME, Bedard C. Effect of dalteparin administration on thrombin generation kinetics in healthy dogs. *Vet Clin Pathol*. 2017; 46(2):269–277.
151. Lynch AM, deLaforcade AM, Sharp CR. Clinical experience of anti-Xa monitoring in critically ill dogs receiving dalteparin. *J Vet Emerg Crit Care*. 2014; *24*(4):421–428.
152. Mischke R, Schmitt J, Wolken S, et al. Pharmacokinetics of the low molecular weight heparin dalteparin in cats. *Vet J*. 2012; *192*(3):299–303.
153. Scott KC, Hansen BD, DeFrancesco TC. Coagulation effects of low molecular weight heparin compared with heparin in dogs considered to be at risk for clinically significant venous thrombosis. *J Vet Emerg Crit Care*. 2009; *19*(1):74–80.
154. Mischke R, Grebe S, Jacobs C, Kietzmann M. Amidolytic heparin activity and values for several hemostatic variables after repeated subcutaneous administration of high doses of a low molecular weight heparin in healthy dogs. *Am J Vet Res*. 2001; *62*(4):595–598.
155. Gara-Boivin C, Del Castillo JRE, Dunn ME, Bedard C. In vitro effects of dalteparin on thrombin generation in canine plasma. *Vet Clin Pathol*. 2017; 46(3):442–450.
156. Schonig JC, Mischke RH. Assessment of the effects of dalteparin on coagulation variables and determination of a treatment schedule for use in cats. *Am J Vet Res*. 2016; *77*(7):700–707.
157. Smith CE, Rozanski EA, Freeman LM, et al. Use of low molecular weight heparin in cats: 57 cases (1999–2003). *J Am Vet Med Assoc*. 2004; *225*(8):1237–1241.
158. Vargo CL, Taylor SM, Carr A, Jackson ML. The effect of a low molecular weight heparin on coagulation parameters in healthy cats. *Can J Vet Res*. 2009; *73*(2):132–136.
159. Lunsford KV, Mackin AJ, Langston VC, Brooks M. Pharmacokinetics of subcutaneous low molecular weight heparin (enoxaparin) in dogs. *J Am Anim Hosp Assoc*. 2009; *45*(6):261–267.
160. Panek CM, Nakamura RK, Bianco D. Use of enoxaparin in dogs with primary immune-mediated hemolytic anemia: 21 cases. *J Vet Emerg Crit Care*. 2015; *25*(2):273–277.
161. Rhue KE, Taylor AR, Cole RC, Winter RL. Bilateral vertebral venous sinus thrombosis causing cervical spinal cord compression in a dog. *Front Vet Sci*. 2017; *4*:8.
162. Gregory CR, Kyles AE, Bernsteen L, Mehl M. Results of clinical renal transplantation in 15 dogs using triple drug immunosuppressive therapy. *Vet Surg*. 2006; *35*(2):105–112.

163. Pouzot-Nevoret C, Barthelemy A, Cluzel M, et al. Enoxaparin has no significant anticoagulation activity in healthy Beagles at a dose of 0.8 mg/kg four times daily. *Vet J*. 2016; *210*:98–100.

164. Mischke R, Schonig J, Doderlein E, et al. Enoxaparin: pharmacokinetics and treatment schedule for cats. *Vet J*. 2014; *200*(3):375–381.

165. Van De Wiele CM, Hogan DF, Green HW, 3rd, Sederquist KD. Antithrombotic effect of enoxaparin in clinically healthy cats: a venous stasis model. *J Vet Intern Med*. 2010; *24*(1):185–191.

166. Fiakpui NN, Hogan DF, Whittem T, et al. Dose determination of fondaparinux in healthy cats. *Am J Vet Res*. 2012; *73*(4):556–561.

167. Morassi A, Bianco D, Park E, et al. Evaluation of the safety and tolerability of rivaroxaban in dogs with presumed primary immune-mediated hemolytic anemia. *J Vet Emerg Crit Care*. 2016; *26*(4):488–494.

168. Conversy B, Blais MC, Dunn M, et al. Anticoagulant activity of oral rivaroxaban in healthy dogs. *Vet J*. 2017; *223*:5–11.

169. Yang VK, Cunningham SM, Rush JE, de Laforcade A. The use of rivaroxaban for the treatment of thrombotic complications in four dogs. *J Vet Emerg Crit Care*. 2016; *26*(5):729–736.

170. Dixon-Jimenez AC, Brainard BM, Brooks MB, et al. Pharmacokinetic and pharmacodynamic evaluation of oral rivaroxaban in healthy adult cats. *J Vet Emerg Crit Care*. 2016; *26*(5):619–629.

171. Westman PC, Lipinski MJ, Torguson R, Waksman R. A comparison of cangrelor, prasugrel, ticagrelor, and clopidogrel in patients undergoing percutaneous coronary intervention: a network meta-analysis. *Cardiovasc Revasc Med*. 2017; *18*(2):79–85.

172. Brown DL, Fann CS, Chang CJ. Meta-analysis of effectiveness and safety of abciximab versus eptifibatide or tirofiban in percutaneous coronary intervention. *Am J Cardiol*. 2001; *87*(5):537–541.

173. Wong PC, Crain EJ, Xin B, et al. Apixaban, an oral, direct and highly selective factor Xa inhibitor: in vitro, antithrombotic and antihemostatic studies. *J Thromb Haemost*. 2008; *6*(5):820–829.

174. Gomez-Outes A, Suarez-Gea ML, Calvo-Rojas G, et al. Discovery of anticoagulant drugs: a historical perspective. *Curr Drug Discov Technol*. 2012; *9*(2):83–104.

175. Storelli F, Daali Y, Desmeules J, et al. Pharmacogenomics of oral antithrombotic drugs. *Curr Pharm Des*. 2016; *22*(13):1933–1949.

How to cite this article: Blais M-C, Bianco D, Goggs R, et al. Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care (CURATIVE): Domain 3—Defining antithrombotic protocols. *Journal of Veterinary Emergency and Critical Care*. 2019;29:60–74. https://doi.org/10.1111/vec.12795