Received: 30 November 2018 | Accepted: 30 November 2018

DOI: 10.1111/vec.12791

SPECIAL ARTICLE

WILEY Journal of Veterinary Emergency and Critical Care

Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care (CURATIVE): Domain 2—Defining rational therapeutic usage

Robert Goggs BVSc, DACVECC, DECVECC, PhD[1] | Lenore Bacek DVM, MS, DACVECC[2]* | Domenico Bianco DVM, PhD, DACVIM[3]* | Amy Koenigshof DVM, DACVECC[4]* | Ronald H. L. Li DVM, MVetMed, PhD, DACVECC[5]*

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

[2]Department of Clinical Sciences, College of Veterinary Medicine, Auburn University, Auburn, AL

[3]Metropolitan Animal Specialty Hospital, Los Angeles, CA

[4]Department of Small Animal Clinical Sciences, Michigan State University, East Lansing, MI

[5]Department of Veterinary Surgical and Radiological Sciences, School of Veterinary Medicine, University of California Davis, Davis, CA

Correspondence
Dr. Robert Goggs, Assistant Professor of Emergency and Critical Care, Cornell University College of Veterinary Medicine, C3-502D CPC, 930 Campus Road, Ithaca, NY 14853.
Email: r.goggs@cornell.edu

*These authors contributed equally to this manuscript.

Offprints: Will not be available from the authors.

Prior presentation: This work was presented in part at the European Veterinary Emergency and Critical Care Congress, June 2018, Venice, Italy and at the International Veterinary Emergency and Critical Care Symposium, September 2018, New Orleans, LA.

Abstract

Objectives: To systematically review available evidence to determine when small animals at risk of thrombosis should be treated with antiplatelet agents and anticoagulants, which antiplatelet and anticoagulant agents are most effective, and when multimodal therapy is indicated.

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. Draft recommendations were presented at 2 international veterinary conferences and made available for community assessment, review, and comment prior to final revisions and publication.

Settings: Academic and referral veterinary medical centers.

Results: Databases searched included Medline via PubMed and CAB abstracts. Twelve Population Intervention Comparison Outcome questions were devised and generated corresponding worksheets investigating indications for use of antithrombotic drugs in small animals. Seventy-eight studies were reviewed in detail. Most studies assessed were experimentally controlled laboratory studies in companion animals (56 LOE 3) with smaller numbers of LOE 2 (1), LOE 4 (5), LOE 5 (6), and LOE 6 (4) studies assessed. Only 5 randomized controlled clinical trials were identified (LOE 1, Good–Fair). The 12 worksheets generated 21 guidelines with 17 guideline statements that were refined during 3 rounds of Delphi surveys. A high degree of consensus was reached across all guideline recommendations during the Delphi process.

Conclusions: Overall, systematic evidence evaluations generated 2 strong recommendations, 19 weak recommendations (formulated as suggestions), 9 situations where the evidence was insufficient to make strong recommendations, and 8 situations where no relevant evidence was retrieved to aid guideline generation. Numerous significant knowledge gaps were highlighted by the evidence reviews undertaken, indicating the need for substantial additional research in this field.

KEYWORDS

anticoagulant, antiplatelet, cats, dogs, thromboprophylaxis

1 | INTRODUCTION

Although more than 100 years old, the concept of Virchow's triad (endothelial damage or dysfunction, blood flow abnormalities, and hypercoagulable syndromes) still provides us with our existing understanding of the factors that predispose our patients to thrombus formation. Risk factors for thrombosis can be classified based on this

Abbreviations: ATE, arterial thromboembolism; IMHA, immune-mediated hemolytic anemia; LMWH, low molecular weight heparin; LOE, level of evidence; PICO, population intervention comparison outcome; UFH, unfractionated heparin; VTE, venous thromboembolism

pathophysiology, but it is likely that the presence of more than 1 risk factor potentiates the formation of thrombosis in vivo. Pharmaceutical antithrombotic interventions aim to redress the imbalance by reducing the body's ability to generate thrombi, irrespective of the nature of the predisposition to clot formation. Evaluations of Population Intervention Comparison Outcome (PICO) question worksheets in Domain 1 established disorders in which there is an association between disease and thrombosis, and sought to determine to which patients antithrombotic medications should be administered. For those animals in which antithrombotic medications are deemed necessary and appropriate, Domain 2 sought to establish what drug or drug combination should be administered in venous and arterial thromboembolic disease settings, to define rational therapeutic usage. In diseases associated with venous thromboembolism (VTE) such as protein-losing nephropathy and immune-mediated hemolytic anemia (IMHA) in dogs, thrombi form under low-shear conditions.[1] Such thrombi are typically fibrin rich and their formation is less dependent upon platelet number or function. In contrast, in diseases associated with arterial thrombotic complications (such as feline cardiomyopathies), thrombi form under high-shear conditions. Arterial thromboemboli (ATE) are typically platelet rich and hence drugs that limit the ability of platelets to activate, aggregate, or adhere may be most effective. It is this pathophysiologic rationale that underpins the convention of administration of anticoagulant drugs in venous thrombosis[2] and antiplatelet agents in arterial thrombosis.[3] Nevertheless, the cell-based model of hemostasis posits that platelets are integral to hemostasis in vivo,[4,5] and there is thus a rationale for the use of antiplatelet drugs in venous thrombosis.[6–9] Experimental data support this proposition,[10] and antiplatelet drugs reduce the risk of venous thrombosis in people.[11–13] Accumulating data also suggests that anticoagulants may be valuable adjuncts to antiplatelet agents in people with acute coronary syndromes.[14] Since many hypercoagulable states in small animals can result in venous or arterial thrombosis in an unpredictable fashion, the judicious use of anticoagulants and antiplatelet drugs concurrently may also have merit. Informed but not constrained by this background information, we undertook a systematic evidence review (Appendix Data S1) to determine in small animals at risk of thrombosis: (i) when an antiplatelet agent versus an anticoagulant agent should be used; (ii) which antiplatelet agent is most effective in small animals; (iii) which anticoagulant agent is most effective in small animals; and (iv) when multimodal therapy is indicated. Within Domain 2, outcomes of interest were defined as thrombus progression, new or repeat thrombosis, development of organ dysfunction, and survival. For the comparison of novel with established antiplatelet agents, novel antiplatelet agents included the $P2Y_{12}$ receptor inhibitors prasugrel, cangrelor, ticagrelor, and the $\alpha_{IIb}\beta_3$ integrin inhibitors abciximab, tirofiban, and eptifibatide.

2 | PICO QUESTION: Antithrombotic agents in venous thrombosis

In dogs and cats at risk of venous thrombosis **(P)**, does use of an antiplatelet agent **(I)** compared to use of an anticoagulant **(C)** improve any outcomes? **(O)**

2.1 | Guidelines

2.1 Antiplatelet agents versus anticoagulants for VTE (dogs)

- **a.** We suggest that anticoagulants may be more effective than antiplatelet agents for VTE prevention in dogs in general and in dirofilariasis specifically.

2.2 Antiplatelet agents versus anticoagulants for VTE (cats)

- **a.** No evidence-based recommendations can be made regarding the use of antiplatelet agents for VTE in cats.
- **b.** We suggest that anticoagulants rather than antiplatelet agents be used for the prevention of VTE in cats.

2.2 | Evidence summary

2.2.1 | Dogs

There is a paucity of evidence that addresses the above PICO question in dogs. There is a single prospective study directly comparing 2 antiplatelet agents (aspirin and prostacyclin) with an anticoagulant (heparin) in the setting of thrombus formation under venous shear conditions (level of evidence [LOE] 3, Good).[15] The study suggested that heparin was superior to aspirin for prevention of thrombus formation. The study has direct relevance to dogs undergoing cardiac procedures because the study design involved implantation of an arterial graft prosthesis under venous shear conditions, but the generalizability of these data to other prothrombotic conditions is uncertain. A retrospective study of dogs with IMHA, in which venous thrombosis predominates, suggested dogs that received ultralow-dose aspirin had a survival benefit compared with those dogs that received heparin (LOE 4, Fair).[16] This study is flawed, however, by the lack of control for illness severity and the likelihood that dogs which received heparin were more severely affected by the disease (eg, lower platelet counts, higher bilirubin, higher band neutrophils, and prolongations of coagulation times) and hence the comparison of these groups is confounded. Two additional studies evaluated thrombus formation in the low-shear setting of the pulmonary arterial system (both LOE 3, Good).[17,18] Both publications evaluated the performance of aspirin for the prevention of thrombosis in dogs with experimentally induced dirofilariasis. The 2 publications produced opposing findings. Convincingly, Boudreaux et al suggest that neither aspirin or aspirin and dipyridamole protect against pulmonary thromboembolism in dirofilariasis even at high dosages (mean 17 mg/kg),[18] while Schaub et al report that aspirin reduces endothelial damage, platelet adhesion, and myointimal proliferation in dogs with dirofilariasis. Notably, an earlier paper by the same authors (LOE 3, Good)[19] suggested that aspirin is only effective when given for 30 days.

2.2.2 | Cats

Two publications that addressed the above PICO question were identified (LOE 3, Good).[20,21] Both of these studies described use of aspirin for the prevention of thrombosis in the low-shear setting of the pulmonary vasculature secondary to dirofilariasis. Neither article provided any comparison with an anticoagulant and both studies suggested that aspirin has limited if any efficacy for prevention of

pulmonary thromboembolism due to dirofilariasis. Given the contradictory nature of the data and the lack of comparisons with anticoagulants, both were judged to be neutral to the PICO question overall. The additional evidence regarding the efficacy of anticoagulants for prevention of venous thrombosis in cats is presented within Domain 3.

2.3 | Knowledge gaps

Although anticoagulants are generally recommended for VTE and antiplatelet drugs for ATE prophylaxis,[22] there is some evidence in people that crossover efficacy exists.[9,23] Direct comparisons of anticoagulant and antiplatelet agents for the prevention of venous thrombosis in dogs and cats are therefore warranted and will be required to definitively address this question. Such trials should be appropriately powered to detect biologically plausible, clinically relevant, patient-centered outcome benefits.

3 | PICO QUESTION: Antithrombotic agents in arterial thrombosis

In dogs and cats at risk of arterial thrombosis **(P)**, does use of an antiplatelet agent **(I)** compared to use of an anticoagulant **(C)** improve any outcomes? **(O)**

3.1 | Guidelines

2.3 Antiplatelet agents versus anticoagulants for ATE (dogs)

- **a.** We suggest that antiplatelet agents may be more effective than anticoagulants for the prevention of ATE in dogs.
- **b.** We suggest that anticoagulants may also be effective for prevention of ATE in dogs.

2.4 Antiplatelet agents versus anticoagulants for ATE (cats)

- **a.** We recommend that antiplatelet agents be used for the prevention of ATE in cats.
- **b.** No evidence-based recommendations can be made regarding the use of anticoagulants for ATE in cats.

3.2 | Evidence summary

3.2.1 | Dogs

Very few articles directly addressed the above PICO question and directly compared antiplatelet agents with anticoagulants in the setting of arterial thrombosis. Three studies (all LOE 3, Good) reported data that opposed the PICO question, that is, these studies indicated anticoagulants were inferior to antiplatelet agents in the setting of arterial thrombosis.[24–26] In the studies by Frederick et al and Makkar et al, GPIIb/IIIa ($\alpha_{IIb}\beta_3$) inhibitors were more effective than unfractionated heparin (UFH) for prevention of provoked arterial thrombosis.[24,25] In the study by Makkar et al, aspirin was also ineffective for prevention of stent thrombosis, however. In a femoral arterial thrombosis model, Prosdocimi et al demonstrated that UFH was inferior to aspirin and other platelet aggregation inhibitors, albeit at a lower UFH dosage than in the other 2 studies.[26] Although direct comparisons suggest superiority of antiplatelet agents for arterial thrombosis in dogs, multiple studies (19 LOE 3, Good, 1 LOE 3, Fair) suggest efficacy of anticoagulants including UFH, low molecular weight heparin (LMWH), and direct inhibitors of Xa and thrombin for arterial thrombosis in dogs.[27–46] Of these, 1 study suggested that heparin may protect against renal arterial thrombosis following renal transplantation in dogs better than aspirin,[27] although the clinical applicability of that study is limited.

3.2.2 | Cats

Three publications that addressed the above PICO question were identified (LOE 4, Fair–Poor).[47–49] All 3 were retrospective studies of populations of cats with or at risk of ATE and reported various combinations of drugs, administered at multiple dosages and various dosing regimens. As such, all were judged to be neutral to the PICO question.

3.3 | Knowledge gaps

The pertinent unanswered question in dogs is whether provoked arterial thrombosis in model systems is comparable to spontaneous disease-associated aortic thrombus formation. Aortic thrombosis is the most predominant (albeit uncommon) manifestation of ATE in dogs, while coronary thrombosis is vanishingly rare in dogs. The shear stresses in these 2 areas of the vasculature are dissimilar and hence it is unknown if coronary ATE studies translate to the aorta. Comparison of the efficacy of antiplatelet agents and anticoagulants in dogs at risk for aortic thrombosis will be necessary to determine if anticoagulants and antiplatelet agents are equivalent for prevention of ATE in dogs. An ongoing study comparing rivaroxaban to clopidogrel in cats may help determine if a direct Xa inhibitor can be, or should be, used in place of clopidogrel for ATE prevention in cats.*

4 | PICO QUESTION: Clopidogrel versus aspirin in animals at risk of thrombosis

In dogs and cats at risk of thrombosis (**P**), does use of clopidogrel (**I**) compared to aspirin (**C**) improve any outcomes? (**O**)

4.1 | Guidelines

2.5 Clopidogrel versus aspirin (dogs)

- **a.** There is insufficient evidence to make strong recommendations regarding clopidogrel versus aspirin in dogs.
- **b.** We suggest that clopidogrel may be more effective than aspirin in dogs at risk for ATE.

2.6 Clopidogrel versus aspirin (cats)

- **a.** We recommend that clopidogrel be used instead of aspirin in cats at risk for ATE.

b. There is no evidence on which to base recommendations regarding the use of aspirin or clopidogrel in cats at risk for VTE.

4.2 | Evidence summary

4.2.1 | Dogs

There is good evidence for efficacy of both aspirin and clopidogrel for the prevention of arterial thrombosis in dogs (see Domain 3). In dogs, only 1 study directly comparing aspirin with clopidogrel for thromboprophylaxis was identified. In that study (LOE 1, Fair) of dogs with IMHA, no difference in survival or frequency of thrombotic events was identified between the 2 treatment groups.[50] However, there were only 8 dogs in each arm of the study, making the study underpowered to detect clinically relevant differences in efficacy. One experimental study (LOE 3, Fair) showed that clopidogrel was superior to aspirin in a model of coronary artery thrombosis,[51] but the applicability of this finding to clinical thrombotic conditions is unknown.

4.2.2 | Cats

There is good evidence for the efficacy of clopidogrel as an antiplatelet agent in cats both in vivo and in vitro, and some evidence for efficacy of aspirin (see Domain 3). One prospective study in cats (LOE 1, Good) provides evidence that clopidogrel is superior to aspirin for thromboprophylaxis in cats with previous cardiogenic arterial thromboembolic events.[52] That study demonstrated that relative to aspirin, clopidogrel significantly prolonged time to a subsequent thrombotic event and increased the median survival time.

4.3 | Knowledge gaps

There is a need for studies comparing the efficacy of aspirin with clopidogrel in dogs at risk for both ATE and VTE. The difficulty with such studies is the need for adequate sample size to detect what may be small differences in efficacy. Investigating a relatively homogenous population and controlling other management variables may be necessary to answer these questions. In cats, where clopidogrel is demonstrably superior to aspirin for ATE prevention, the question remains whether dual antiplatelet therapy (standard of care in human acute coronary syndromes)[53,54] provides better protection against ATE than clopidogrel alone and whether such combination therapy unacceptably increases the risk of hemorrhage.

5 | PICO QUESTION: Novel antithrombotic agents in animals at risk of thrombosis

In dogs and cats at risk of thrombosis (**P**), does use of a novel antiplatelet agent (**I**) compared to aspirin or clopidogrel (**C**) improve any outcomes? (**O**)

5.1 | Guidelines

2.7 New antiplatelet agents versus clopidogrel or aspirin (dogs)

a. There is insufficient evidence to make recommendations regarding the use of new antiplatelet agents versus clopidogrel or aspirin in dogs.

b. We suggest that both abciximab and ticagrelor appear safe and may be efficacious antiplatelet agents in dogs.

2.8 New antiplatelet agents versus clopidogrel or aspirin (cats)

a. There is insufficient evidence to make recommendations regarding the use of new antiplatelet agents versus clopidogrel or aspirin in cats.

b. We suggest that abciximab appears safe and may be efficacious as an antiplatelet agent in cats.

5.2 | Evidence summary

5.2.1 | Dogs

No clinical studies that evaluate novel antiplatelet agents in dogs were identified. Four experimental studies (all LOE 3, Fair) were identified that suggest efficacy for novel antiplatelet agents in dogs.[55–58] Specifically, agents that antagonize platelet receptors for fibrinogen (abciximab, lotrafiban), ADP (ticagrelor), collagen-VWF (GPG-290), and thromboxane (terutroban) have all been demonstrated to have efficacy against canine platelets. The studies evaluating GPG-290 and terutroban involved combination therapy only and hence were considered neutral to the PICO question. Of the 4 agents, only ticagrelor and abciximab are currently commercially available.

5.2.2 | Cats

No clinical studies that evaluate novel antiplatelet agents in cats were identified. A single experimental study (LOE 3, Fair) evaluating the effects of abciximab on thrombus formation in cats was identified.[59] That study used a feline model of arterial injury and compared the efficacy of aspirin alone with a combination of aspirin and abciximab. Cats that received aspirin and abciximab had significantly less thrombus formation compared to those receiving aspirin alone, but at the expense of significantly longer mucosal bleeding times.

5.3 | Knowledge gaps

The demonstrable efficacy of the human $P2Y_{12}$ antagonist, clopidogrel, and inverse agonist ticagrelor in dogs suggests that evaluation of other $P2Y_{12}$ inhibitors such as prasugrel and cangrelor in dogs may be of value. In addition, comparisons of the efficacy of prasugrel, ticagrelor, and clopidogrel in dogs may be warranted. Furthermore, there may yet be a role for reversible $P2Y_{12}$ drugs such as ticagrelor and cangrelor in veterinary medicine.[54] The potential limitations of abciximab in dogs and cats are the intravenous route of administration, cost, and increased risk in bleeding. This drug may be beneficial in hospitalized patients at risk for thrombosis and those undergoing interventional radiology procedures with a risk of ATE. Further evaluation of this drug in these patients and comparison with other antiplatelet agents is warranted.

6 | PICO QUESTION: Low molecular weight heparin versus unfractionated heparin in animals at risk of thrombosis

In dogs and cats at risk of thrombosis **(P)**, does the use of a LMWH **(I)** compared with the use of UFH **(C)** improve any outcomes? (**O**)

6.1 | Guidelines

2.9 UFH versus LMWH (dogs)

- **a.** There is insufficient evidence to make strong recommendations regarding the use of UFH versus LMWH in dogs.
- **b.** We suggest that LMWH may be used in preference to UFH because of the positive safety profile of LMWH and more reliable bioavailability of the LMWH products compared to UFH.

2.10 UFH versus LMWH (cats)

- **a.** No evidence-based recommendations can be made regarding the use of UFH versus LMWH in cats.
- **b.** We suggest that LMWH may be used in preference to UFH because of the documented efficacy of LMWH and the positive safety profile of LMWH.

6.2 | Evidence summary

6.2.1 | Dogs

There is a paucity of information directly comparing LMWH to UFH in dogs at risk of thrombosis. One prospective study (LOE 1, Good) compared UFH at low and high doses with dalteparin.[60] Neither dalteparin or low-dose UFH dose produced meaningful anti-Xa activity. None of the dogs in the study developed thrombosis, but 4 dogs that received high-dose UFH bled. There is evidence indicating that enoxaparin may be beneficial in dogs with IMHA (LOE 5, Fair),[61] but that study did not compare LMWH with UFH. Other studies evaluating the use of UFH in IMHA offer conflicting results. The survival rate in the study by Breuhl et al. (LOE 2, Fair)[62] was lower than in the study of Panek et al,[61] while Helmond et al (LOE 1, Fair)[63] suggested that individually dose-adjusted UFH significantly improved survival compared with constant UFH dosing. Several studies evaluated UFH with LMWH in experimental models. One study (LOE 3, Good) reported a shorter time to reperfusion and a significant reduction in vessel occlusion with LMWH compared to UFH.[64] Four other studies comparing LMWH with UFH in experimental thrombosis models (all LOE 3, Good) also demonstrate that LMWH is comparable or superior to UFH and is associated with lower bleeding tendency.[30,65–67]

6.2.2 | Cats

No articles directly addressed the above PICO question, and most studies retrieved focus on the pharmacokinetics and pharmacodynamics of LMWH in cats. One study (LOE 3, Fair) demonstrated an antithrombotic effect of enoxaparin in a feline venous stasis model,[68] while another study (LOE 5, Good) retrospectively reported safe use of dalteparin in cats,[48] but neither compared LMWH with UFH. Five studies were reviewed that reported the pharmacokinetics of LMWH in cats. Of these, 2 studies (LOE 3, Fair) suggested that dalteparin had reproducible pharmacokinetics in cats[69,70] and 1 study (LOE 3, Fair) suggested that enoxaparin had reproducible pharmacokinetics in cats.[71] Two studies (LOE 3, Fair) suggest that frequent dosing of LMWHs is required to produce reliable anti-Xa activity in cats.[72,73]

6.3 | Knowledge gaps

Although there is solid evidence from experiments models that LMWH may be more effective than UFH in dogs, there are fewer data on dogs with spontaneous thrombi. This represents an area for useful study because of the evidence that UFH may improve survival in dogs with IMHA. It will be crucial in these studies that appropriate monitoring of drug activity is performed to enable valid comparisons of efficacy. In cats, there are no comparisons between UFH and the LMWHs and hence this is a clear deficit in the literature and an opportunity for future study. The advent of the direct oral anticoagulants, most notably the direct Xa inhibitors, may reduce the use of UFH in cats and hence the need for studies in this specific area. Further controlled evaluation of the efficacy of the LMWHs in cats with spontaneous venous thrombi is warranted, however, and such studies must incorporate careful therapeutic drug monitoring (see Domain 4).

7 | PICO QUESTION: Direct Xa inhibitor in animals at risk of thrombosis

In dogs and cats at risk of thrombosis **(P)**, does the use of direct Xa inhibitors **(I)** compared with the use of UFH **(C)** improve any outcomes? (**O**)

7.1 | Guidelines

2.11 Direct Xa inhibitors versus UFH (dogs)

- **a.** There is insufficient evidence to make strong recommendations regarding the use of the direct Xa inhibitors versus UFH in dogs.
- **b.** We suggest the direct Xa inhibitors may be used in preference to UFH based on evidence of equivalent efficacy, combined with reliable pharmacokinetics and the ease of oral dosing.

2.12 Direct Xa inhibitors versus UFH (cats)

- **a.** No evidence-based recommendations can be made regarding the use of the direct Xa inhibitors versus UFH in cats.
- **b.** We suggest that the direct Xa inhibitors can be considered in cats based on reliable pharmacokinetics and a favorable preliminary safety profile.

7.2 | Evidence summary

7.2.1 | Dogs

There is a paucity of information comparing direct Xa inhibitors to UFH in dogs. Several experimental studies in canine models of vessel occlusion (all LOE 3, Good) demonstrate at least equivalent efficacy for the direct Xa inhibitors compared to UFH.[36,74,75] Evidence from 1 study (LOE 1, Fair) suggests rivaroxaban may be efficacious in dogs with IMHA,[76] but that study did not compare rivaroxaban to UFH. Rivaroxaban may also aid in decreasing thrombus size in patients with venous thrombosis (LOE 5, Fair),[77] but similarly, that study did not compare rivaroxaban with UFH. In studies published to date, rivaroxaban appears to be well tolerated in dogs (1 LOE 1, Fair, 3 LOE 3, Good-Fair, 1 LOE 5, Fair).[76–80]

7.2.2 | Cats

No studies directly addressed the above PICO question. The 2 published studies that were reviewed focused on the pharmacokinetics and pharmacodynamics of direct Xa inhibitors in cats (LOE 3, Good–Fair).[81,82] Both rivaroxaban and apixaban appear to have reliable pharmacokinetic and pharmacodynamic properties in cats and were well tolerated.

7.3 | Knowledge gaps

Adequately powered, randomized controlled trials comparing the efficacy of direct Xa inhibitors with individually dose-adjusted UFH in dogs at risk for spontaneous thrombosis (eg, canine IMHA) are urgently required. An ongoing study in cats with ATE may provide some insights into the efficacy of rivaroxaban in cats with spontaneous disease, but a head to head comparison of UFH with the direct Xa inhibitors will be necessary to inform this area. Comparisons of the LMWHs with the direct Xa inhibitors may be more likely to be performed, however (see Guideline 2.13 Section 8.1).

8 | PICO QUESTION: Direct Xa inhibitors versus low molecular weight heparin on outcome

In dogs and cats at risk of thrombosis **(P),** does the use of direct Xa inhibitors **(I)** compared with the use of LMWH **(C)** improve any outcomes? **(O)**

8.1 | Guidelines

2.13 Direct Xa inhibitors versus LMWH (dogs)

- **a.** There is insufficient evidence to make strong recommendations regarding the use of the direct Xa inhibitors versus LMWH in dogs.
- **b.** We suggest that use of either the direct Xa inhibitors or LMWH in dogs is reasonable.

2.14 Direct Xa inhibitors versus LMWH (cats)

- **a.** No evidence-based recommendations can be made regarding the use of the direct Xa inhibitors versus LMWH in cats.
- **b.** We suggest that use of either the direct Xa inhibitors or LMWH in cats is reasonable.

8.2 | Evidence summary

8.2.1 | Dogs

There is a paucity of data comparing LMWH to direct Xa inhibitors in dogs. No prospective randomized clinical studies were identified that compared these 2 drug classes. One experimental study (LOE 3, Good) of electrolytic arterial and venous injury demonstrated that a direct Xa inhibitor had equivalent efficacy to enoxaparin for prevention of thrombosis.[44] Seven studies (6 LOE 3, Good–Fair; 1 LOE 5, Fair) were reviewed that described the pharmacokinetics or pharmacodynamics of direct Xa inhibitors (predominantly rivaroxaban or apixaban) in dogs.[78–80,83–86] These data suggest that the direct Xa inhibitors are safe, orally active, and have reliable and reproducible pharmacokinetics in dogs. Two studies (1 LOE 1, Fair; 1 LOE 5, Fair) reported the use of rivaroxaban in dogs with or at risk of thrombosis.[76,77] These studies had no control groups, were confounded by the concurrent use of other medications, and did not describe the pharmacodynamic effects seen. In toto, the data reviewed regarding the use of the direct Xa inhibitors in dogs suggest these drugs are safe and may be effective antithrombotics in dogs.

8.2.2 | Cats

There were no articles that directly addressed the above PICO question. The 2 published studies that were reviewed focused on the pharmacokinetics and pharmacodynamics of direct Xa inhibitors in cats (LOE 3, Good-Fair).[81,82] Both rivaroxaban and apixaban appear to have reliable pharmacokinetic and pharmacodynamic properties in cats and were well tolerated.

8.3 | Knowledge gaps

Randomized controlled trials will be necessary to compare direct Xa inhibitors with LMWHs in dogs. Trials comparing the direct Xa inhibitors with LMWHs in cats would also be very valuable, particularly because cost constraints are less problematic in cats than in dogs. In any and all such trials, it will be necessary to confirm the levels of anti-Xa activity achieved with both regimens in order to validate the comparisons of efficacy.

9 | PICO QUESTIONS: Unfractionated heparin versus warfarin on outcome in dogs

In dogs and cats at risk of thrombosis (**P**), does the use of UFH (**I**) compared with the use of warfarin (**C**) improve any outcomes? (**O**)
In dogs and cats at risk of thrombosis (**P**), does the use of LMWHs (**I**) compared with the use of warfarin (**C**) improve any outcomes? (**O**)

9.1 | Guidelines

2.15 UFH versus warfarin and LMWH versus warfarin (dogs and cats)

- **a.** There is insufficient evidence to make strong recommendations regarding the efficacy of heparin products versus warfarin in dogs or cats.
- **b.** We suggest that UFH or LMWH be used in preference to warfarin (see other recommendations regarding the choice between UFH and LMWH).

9.2 | Evidence summary

Overall, there is insufficient evidence directly comparing UFH or LMWH with warfarin in dogs or cats at risk of thrombosis, but there is some evidence suggesting that use of 1 of those drugs over the other is preferable in certain diseases of dogs or cats. However, there is no evidence to suggest that UFH or LMWH is superior to warfarin or vice versa to improve any outcomes in all dogs and cats with risk of thrombosis. For particular patient populations, a particular drug at a specific dosage may be a superior choice because its use is better described in the literature at the time of writing.

9.3 | Knowledge gaps

Although additional studies comparing UFH with warfarin and LMWH with warfarin in dogs and cats at risk for VTE would be required to help address the PICO question, the advent of the direct oral anticoagulants (Xa and IIa inhibitors) makes investigations of warfarin less important.

10 | PICO QUESTION: Combination therapy for venous thrombosis on outcome

In dogs and cats at risk of thrombosis (**P**), does the use of a direct Xa inhibitor (**I**) compared with the use of warfarin (**C**) improve any outcomes? (**O**)

Guidelines

2.16 Direct Xa inhibitors versus warfarin (dogs and cats)

- **a.** No evidence-based recommendation can be made regarding the efficacy of direct Xa inhibitors versus warfarin in dogs or cats.
- **b.** We suggest that the direct Xa inhibitors be used in preference to warfarin in both dogs and cats.

10.2 | Evidence summary

Overall, there is insufficient evidence comparing direct Xa inhibitors with warfarin in dogs or cats at risk of thrombosis. There is evidence supporting the use of the drug classes individually, which suggests their use may be preferable in certain diseases of dogs or cats at risk for thrombosis. The efficacy of the direct Xa inhibitors and warfarin is discussed elsewhere. Three large-scale studies in people (LOE 6, Good) suggest that the direct Xa inhibitors are at least as effective as warfarin and are associated with better safety profiles, specifically in terms of a reduction in the risk of life-threatening hemorrhage.[87–89]

10.3 | Knowledge gaps

Additional studies comparing the direct Xa inhibitors with warfarin in dogs and cats at risk of thrombosis would be required to help address the PICO question. However, the evidence from human medicine suggests that the direct oral anticoagulants (Xa and IIa inhibitors) are at least as efficacious and are safer than warfarin. This makes future comparisons involving warfarin in veterinary medicine less important and unlikely to be conducted. As mentioned above, comparisons of UFH or LMWH with the direct Xa inhibitors will likely be of greater value to the field.

11 | PICO QUESTION: Combination therapy for venous thrombosis on outcome

In dogs and cats at risk of venous thrombosis (**P**), does use of a combination of an anticoagulant and an antiplatelet agent (**I**), compared to the use of an anticoagulant alone (**C**) improve any outcomes? (**O**)

Guidelines

2.17 Combination anticoagulant and antiplatelet therapy for VTE (dogs)

- **a.** We suggest that administration of aspirin or clopidogrel in addition to LMWH or individually adjusted UFH therapy may be considered in dogs at high risk of VTE, where the risk of clot formation is felt to outweigh the increased risk of bleeding resulting from combination therapy.

2.18 Combination anticoagulant and antiplatelet therapy for VTE (cats)

- **a.** There is insufficient evidence to make strong recommendations regarding combination anticoagulant and antiplatelet agent therapy in cats.
- **b.** We suggest that combination therapy may be considered where there is a high risk of thrombosis and the risk of clot formation is felt to outweigh the increased risk of bleeding resulting from combination therapy.

11.2 | Evidence summary

11.2.1 | Dogs

There is little evidence from veterinary literature suggesting a benefit for combining anticoagulant and antiplatelet drugs over anticoagulant therapy alone in dogs at risk of venous thrombosis. Evidence from a single retrospective study of dogs (LOE 4, Fair) suggests combining UFH with aspirin compared to UFH alone for thromboprophylaxis

in IMHA may improve outcome.[16] However, outcome analysis in that study was confounded by inequalities in illness severity between treatment groups. Minor hemorrhagic complications have been reported with LMWH therapy in dogs,[61] although interestingly not in with combination therapy (1 LOE 3, Fair; 3 LOE 5, Fair).[16,77,90,91] In people with acute coronary syndromes, the addition of the direct oral anticoagulants to antiplatelet agents increases the risk of bleeding.[14]

11.2.2 | Cats

There are no studies that directly address the above PICO question in cats. Guideline recommendations are based on data reviewed in this and other domains and represent the current practice of the committee.

11.3 | Knowledge gaps

Future studies in this area might evaluate the efficacy of established single anticoagulant therapies against combinations of the anticoagulant with an antiplatelet agent in patients at high risk for VTE. The key aspects of such a study design would be optimization of anticoagulant dosing, careful monitoring for adverse effects (particularly bleeding), and an adequate sample size to detect clinically relevant outcome differences. There may be a limited number of patient populations in which such combination therapy might be a rational choice but dogs with IMHA or protein-losing nephropathy might provide sufficient patients for future studies.

12 | PICO QUESTION: Combination therapy on arterial thrombosis on outcome

In dogs and cats at risk of arterial thrombosis (**P**), does use of a combination of an anticoagulant and an antiplatelet agent (**I**), compared to the use of an anticoagulant alone (**C**) improve any outcomes? (**O**)

12.1 | Guidelines

2.19 Combination antiplatelet and anticoagulant therapy for ATE (dogs)

- **a.** There is insufficient evidence to make strong recommendations for or against the use of combination antiplatelet and anticoagulant therapy in dogs at risk for ATE.
- **b.** We suggest that administration of clopidogrel or aspirin with LMWH may be considered in dogs at risk for ATE.

2.20 Combination antiplatelet and anticoagulant therapy for ATE (cats)

- **a.** No evidence-based recommendations can be made regarding the addition of anticoagulants to antiplatelet agents for ATE in cats.
- **b.** We suggest that administration of clopidogrel in combination with LMWH may be considered in cats at risk for ATE.

12.2 | Evidence summary

12.2.1 | Dogs

There is little evidence from the veterinary literature evaluating the combined use of anticoagulant and antiplatelet therapy over antiplatelet therapy alone in dogs and cats at risk of thrombosis. Evidence from 2 studies in people (LOE 6, Good)[14,92] and 3 studies (LOE 5, Fair) in dogs, documented improved outcomes (recurrence of thrombosis/return of ambulatory function) when the use of anticoagulant and antiplatelet agents was compared with the use of an anticoagulant agent alone for managing patients at risk of recurring arterial thrombosis.[77,90,93] In a meta-analysis of 6 trials comprising 29,667 people with acute coronary syndromes, the use of direct oral anticoagulants in addition to antiplatelet therapy reduced ischemic events.[14] Two studies (LOE 5, Fair)[93,94] described the use of antiplatelet therapy, whereas 3 studies (LOE 5, Fair)[77,90,93] documented the use of combination therapies in dogs after their first incident of aortic thrombosis [N.B. Lake-Bakaar et al[93] included dogs that received single agent and dogs that received combination therapy]. Based on these studies, dogs treated with antiplatelet therapy alone had a higher recurrence rate compared to dogs treated with a combination of anticoagulant and antiplatelet drugs.

12.2.2 | Cats

Evidence from 2 studies (LOE 4, Fair) in cats suggests that multimodal therapy compared to antiplatelet therapy may decrease recurrence of feline ATE.[47,48] In these 2 studies, aspirin was combined with either UFH[47] or dalteparin.[48] Compared to cats receiving combination therapy, cats receiving aspirin alone in a separate study (LOE 4, Fair) had a higher recurrence rate.[95] A recent clinical trial reported that clopidogrel was superior to aspirin for prevention of recurrence and prolongation of survival in cats with a history of cardiogenic ATE.[52] As such, combining clopidogrel with an anticoagulant such as LMWH or an anti-Xa inhibitor may yield better outcomes in cats with ATE than previously reported.

12.3 | Knowledge gaps

As with Guidelines 2.17 and 2.18 in Section 11.1, future studies in this area might evaluate the efficacy of established antiplatelet therapies against combinations of antiplatelet agent with an anticoagulant in patients at high risk for ATE. Again, there may be a limited number of patient populations in which such combination therapy is likely to be a viable proposition, but feline ATE is one such area. Once the results of the rivaroxaban versus clopidogrel study mentioned above are known, it may be viable to consider comparing the combination of these 2 agents against either alone.

Footnotes

* https://www.morrisanimalfoundation.org/study/investigating-new-anti-clotting-drug-cats-heart-disease

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

Funding information

Funding for this work was provided by the American College of Veterinary Emergency and Critical Care (ACVECC) and the Veterinary Emergency and Critical Care Society (VECCS).

ORCID

Robert Goggs BVSc, DACVECC, DECVECC, PhD
https://orcid.org/0000-0001-7446-6987
Lenore Bacek DVM, MS, DACVECC
https://orcid.org/0000-0002-1046-9297
Ronald H. L. Li DVM, MVetMed, PhD, DACVECC
https://orcid.org/0000-0002-3325-2744

References

1. Aird WC. Vascular bed-specific thrombosis. *J Thromb Haemost*. 2007;*5*:283-291.
2. Wolberg AS, Rosendaal FR, Weitz JI, et al. Venous thrombosis. *Nat Rev Dis Primers*. 2015;*1*:15006.
3. Smith JN, Negrelli JM, Manek MB, et al. Diagnosis and management of acute coronary syndrome: an evidence-based update. *J Am Board Fam Med*. 2015;*28*:283-293.
4. Hoffman M, Monroe DM. A cell-based model of hemostasis. *Thromb Haemost*. 2001;*85*:958-965.
5. Smith SA. The cell-based model of coagulation. *J VEt Emerg Crit Care*. 2009;*19*:3-10.
6. Mackman N. New insights into the mechanisms of venous thrombosis. *J Clin Invest*. 2012;*122*:2331-2336.
7. Lowe GD. Common risk factors for both arterial and venous thrombosis. *Br J Haematol*. 2008;*140*:488-495.
8. Agnelli G, Becattini C. Venous thromboembolism and atherosclerosis: common denominators or different diseases? *J Thromb Haemost*. 2006;*4*:1886-1890.
9. Lowe GD. Arterial disease and venous thrombosis: are they related, and if so, what should we do about it? *J Thromb Haemost*. 2006;*4*:1882-1885.
10. Cooley BC, Herrera AJ. Cross-modulatory effects of clopidogrel and heparin on platelet and fibrin incorporation in thrombosis. *Blood Coagul Fibrinolysis*. 2013;*24*:593-598.
11. Brighton TA, Eikelboom JW, Mann K, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med*. 2012;*367*:1979-1987.
12. Castellucci LA, Cameron C, Le Gal G, et al. Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis. *BMJ*. 2013;*347*:f5133.
13. Simes J, Becattini C, Agnelli G, et al. Aspirin for the prevention of recurrent venous thromboembolism: the INSPIRE collaboration. *Circulation*. 2014;*130*:1062-1071.
14. Chiarito M, Cao D, Cannata F, et al. Direct oral anticoagulants in addition to antiplatelet therapy for secondary prevention after acute coronary syndromes: a systematic review and meta-analysis. *JAMA Cardiol*. 2018;*3*:234-241.
15. Merhi Y, Bernier J, Marois Y, Guidoin R. Acute thrombogenicity of arterial prostheses exposed to reduced blood flow in dogs: effects of heparin, aspirin, and prostacyclin. *J Cardiovasc Pharmacol*. 1995;*26*:1-5.
16. 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*:1869-1880.
17. Schaub RG, Keith JC, Jr, Rawlings CA. Effect of acetylsalicylic acid on vascular damage and myointimal proliferation in canine pulmonary arteries subjected to chronic injury by Dirofilaria immitis. *Am J Vet Res*. 1983;*44*:449-454.
18. 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*:1992-1999.
19. Schaub RG, Rawlings CA, Keith JC, Jr. Effect of long-term aspirin treatment on platelet adhesion to chronically damaged canine pulmonary arteries. *Thromb Haemost*. 1981;*46*:680-683.
20. Rawlings CA. Pulmonary arteriography and hemodynamics during feline heartworm disease. Effect of aspirin. *J Vet Intern Med*. 1990;*4*:285-291.
21. 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*:292-300.
22. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease antithrombotic therapy and prevention of thrombosis, 9th ed: american college of chest physicians evidence- based clinical practice guidelines. *Chest*. 2012;*141*(2 Suppl):E419S-E496S.
23. Watson HG, Chee YL. Aspirin and other antiplatelet drugs in the prevention of venous thromboembolism. *Blood Rev*. 2008;*22*:107-116.
24. Frederick LG, Suleymanov OD, King LW, et al. The protective dose of the potent GPIIb/IIIa antagonist SC-54701A is reduced when used in combination with aspirin and heparin in a canine model of coronary artery thrombosis. *Circulation*. 1996;*93*:129-134.
25. Makkar RR, Litvack F, Eigler NL, et al. Effects of GP IIb/IIIa receptor monoclonal antibody (7E3), heparin, and aspirin in an ex vivo canine arteriovenous shunt model of stent thrombosis. *Circulation*. 1997;*95*:1015-1021.
26. Prosdocimi M, Zatta A, Finesso M. Stenosis and vascular damage as a cause of thrombosis in the dog femoral artery. *Naunyn Schmiedebergs Arch Pharmacol*. 1988; *338*:430-437.
27. Macdonald A, Busch GJ, Alexander JL, et al. Heparin and aspirin in the treatment of hyperacute rejection of renal allografts in presensitized dogs. *Transplantation*. 1970;*9*:1-7.
28. Chandler WF, Ercius MS, Ford JW, et al. The effect of heparin reversal after carotid endarterectomy in the dog. A scanning electron microscopy study. *J Neurosurg*. 1982;*56*:97-102.
29. Ercius MS, Chandler WF, Ford JW, Burkel WE. Early versus delayed heparin reversal after carotid endarterectomy in the dog. A scanning electron microscopy study. *J Neurosurg*. 1983;*58*:708-713.
30. Mestre M, Clairefond P, Mardiguian J, et al. Comparative effects of heparin and PK 10169, a low molecular weight fraction, in a canine model of arterial thrombosis. *Thromb Res*. 1985;*38*:389-399.
31. Ljungberg B, Johnsson H. In vivo effects of a low molecular weight heparin fragment on platelet aggregation and platelet dependent hemostasis in dogs. *Thromb Haemost*. 1988;*60*:232-235.
32. Fujii T, Matsuzaki M, Oda T, et al. Effect of the combination of anticoagulant and thromboxane synthetase inhibitor (Y-20811) or recep-

tor blockade (S-1452) on preventing thrombotic cyclic coronary flow reduction in dogs with coronary stenosis. *Jpn Circ J*. 1992;*56*:1191-1197.

33. Jackson CV, Crowe VG, Frank JD, et al. Pharmacological assessment of the antithrombotic activity of the peptide thrombin inhibitor, D-methyl-phenylalanyl-prolyl-arginal (GYKI-14766), in a canine model of coronary artery thrombosis. *J Pharmacol Exp Ther*. 1992;*261*:546-552.
34. Benedict CR, Ryan J, Todd J, et al. Active site-blocked factor Xa prevents thrombus formation in the coronary vasculature in parallel with inhibition of extravascular coagulation in a canine thrombosis model. *Blood*. 1993;*81*:2059-2066.
35. White BP, Sullivan AT, Lumley P. Prevention of intra-coronary thrombosis in the anaesthetised dog: the importance of thromboxane A2 and thrombin. *Thromb Haemost*. 1994;*71*:366-374.
36. Lynch JJ Jr, Sitko GR, Lehman ED, Vlasuk GP. Primary prevention of coronary arterial thrombosis with the factor Xa inhibitor rTAP in a canine electrolytic injury model. *Thromb Haemost*. 1995;*74*:640-645.
37. Cousins GR, Friedrichs GS, Sudo Y, et al. Orally effective CVS-1123 prevents coronary artery thrombosis in the conscious dog. *Circulation*. 1996;*94*:1705-1712.
38. Duval N, Lunven C, O'Brien DP, et al. Antithrombotic actions of the thrombin inhibitor, argatroban, in a canine model of coronary cyclic flow: comparison with heparin. *Br J Pharmacol*. 1996;*118*:727-733.
39. Roux S, Tschopp T, Baumgartner HR. Effects of napsagatran (Ro 46–6240), a new synthetic thrombin inhibitor and of heparin in a canine model of coronary artery thrombosis: comparison with an ex vivo annular perfusion chamber model. *J Pharmacol Exp Ther*. 1996;*277*:71-78.
40. Sudo Y, Lucchesi BR. Antithrombotic effect of GYKI-14766 in a canine model of arterial and venous rethrombosis: a comparison with heparin. *J Cardiovasc Pharmacol*. 1996;*27*:545-555.
41. Rebello SS, Miller BV, Basler GC, Lucchesi BR. CVS-1123, a direct thrombin inhibitor, prevents occlusive arterial and venous thrombosis in a canine model of vascular injury. *J Cardiovasc Pharmacol*. 1997;*29*:240-249.
42. 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*:908-914.
43. Ohyama T, Hori T, Moriike M, et al. Anti-thrombotic effects of CX-397, a recombinant hirudin analog, in a canine model of coronary artery thrombosis. *Thromb Haemost*. 1998;*79*:423-430.
44. McClanahan TB, Hicks GW, Morrison AL, et al. The antithrombotic effects of CI-1031 (ZK-807834) and enoxaparin in a canine electrolytic injury model of arterial and venous thrombosis. *Eur J Pharmacol*. 2001;*432*:187-194.
45. Rebello SS, Kasiewski CJ, Wang W, et al. Role of short-term inhibition of factor Xa by FXV673 in arterial passivation: a study in a chronic model of thrombosis in conscious dogs. *J Cardiovasc Pharmacol*. 2001;*38*:288-297.
46. Viigimaa M, Ohnogi H, Hattori R, et al. Antithrombotic effect and reperfusion by low molecular weight heparin in a canine model of coronary artery thrombosis. *Jpn Circ J*. 1993;*57*:553-557.
47. 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*:73-83.
48. 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*:1237-1241.
49. Borgeat K, Wright J, Garrod O, et al. Arterial thromboembolism in 250 cats in general practice: 2004–2012. *J Vet Intern Med*. 2014;*28*:102-108.
50. 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*:71-75.
51. 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.
52. 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.
53. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation*. 2016;*134*:e123-155.
54. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;*37*:267-315.
55. Hennan JK, Swillo RE, Morgan GA, et al. Pharmacologic inhibition of platelet vWF-GPIb alpha interaction prevents coronary artery thrombosis. *Thromb Haemost*. 2006;*95*:469-475.
56. 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*:239-248.
57. 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*:609-617.
58. 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*:13-25.
59. Bright JM, Dowers K, Powers BE. Effects of the glycoprotein IIb/IIIa antagonist abciximab on thrombus formation and platelet function in cats with arterial injury. *Vet Ther*. 2003;*4*:35-46.
60. 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*:74-80.
61. 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*:273-277.
62. 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*:125-133.

63. 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*:597-605.
64. 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*:261-271.
65. Leadley RJ Jr, Kasiewski CJ, Bostwick JS, et al. Comparison of enoxaparin, hirulog, and heparin as adjunctive antithrombotic therapy during thrombolysis with rtPA in the stenosed canine coronary artery. *Thromb Haemost*. 1997;*78*:1278-1285.
66. Libersan D, Khalil A, Dagenais P, et al. The low molecular weight heparin, enoxaparin, limits infarct size at reperfusion in the dog. *Cardiovasc Res*. 1998;*37*:656-666.
67. Jun L, Arnout J, Vanhove P, et al. Comparison of a low-molecular-weight heparin (nadroparin calcium) and unfractionated heparin as adjunct to coronary thrombolysis with alteplase and aspirin in dogs. *Coron Artery Dis*. 1995;*6*:257-263.
68. Van De Wiele CM, Hogan DF, Green HW 3rd, Sederquist, K. D.. Antithrombotic effect of enoxaparin in clinically healthy cats: a venous stasis model. *J Vet Intern Med*. 2010;*24*:185-191.
69. 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*:700-707.
70. Mischke R, Schmitt J, Wolken S, et al. Pharmacokinetics of the low molecular weight heparin dalteparin in cats. *Vet J*. 2012;*192*:299-303.
71. Mischke R, Schonig J, Doderlein E, et al. Enoxaparin: pharmacokinetics and treatment schedule for cats. *Vet J*. 2014;*200*:375-381.
72. Alwood AJ, Downend AB, Brooks MB, et al. Anticoagulant effects of low-molecular-weight heparins in healthy cats. *J Vet Intern Med*. 2007;*21*:378-387.
73. 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*:132-136.
74. Rebello SS, Bentley RG, Morgan SR, et al. Antithrombotic efficacy of a novel factor Xa inhibitor, FXV673, in a canine model of coronary artery thrombolysis. *Br J Pharmacol*. 2001;*133*:1190-1198.
75. Abendschein DR, Baum PK, Verhallen P, et al. A novel synthetic inhibitor of factor Xa decreases early reocclusion and improves 24-h patency after coronary fibrinolysis in dogs. *J Pharmacol Exp Ther*. 2001;*296*:567-572.
76. 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*:488-494.
77. 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*:729-736.
78. Conversy B, Blais MC, Dunn M, et al. Rivaroxaban demonstrates in vitro anticoagulant effects in canine plasma. *Vet J*. 2013;*198*:437-443.
79. Conversy B, Blais MC, Dunn M, et al. Anticoagulant activity of oral rivaroxaban in healthy dogs. *Vet J*. 2017;*223*:5-11.
80. Weinz C, Schwarz T, Kubitza D, et al. Metabolism and excretion of rivaroxaban, an oral, direct factor Xa inhibitor, in rats, dogs, and humans. *Drug Metab Dispos*. 2009;*37*:1056-1064.
81. 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*:619-629.
82. Myers JA, Wittenburg LA, Olver CS, et al. Pharmacokinetics and pharmacodynamics of the factor Xa inhibitor apixaban after oral and intravenous administration to cats. *Am J Vet Res*. 2015;*76*:732-738.
83. Lang D, Freudenberger C, Weinz C. In vitro metabolism of rivaroxaban, an oral, direct factor Xa inhibitor, in liver microsomes and hepatocytes of rats, dogs, and humans. *Drug Metab Dispos*. 2009;*37*:1046-1055.
84. Zhang D, He K, Raghavan N, et al. Comparative metabolism of 14C-labeled apixaban in mice, rats, rabbits, dogs, and humans. *Drug Metab Dispos*. 2009;*37*:1738-1748.
85. He K, Luettgen JM, Zhang D, et al. Preclinical pharmacokinetics and pharmacodynamics of apixaban, a potent and selective factor Xa inhibitor. *Eur J Drug Metab Pharmacokinet*. 2011;*36*:129-139.
86. Zhang D, Frost CE, He K, et al. Investigating the enteroenteric recirculation of apixaban, a factor Xa inhibitor: administration of activated charcoal to bile duct-cannulated rats and dogs receiving an intravenous dose and use of drug transporter knockout rats. *Drug Metab Dispos*. 2013;*41*:906-915.
87. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;*363*:2499-2510.
88. Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J*. 2013;*11*:21-21.
89. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;*369*:799-808.
90. Winter RL, Sedacca CD, Adams A, Orton EC. Aortic thrombosis in dogs: presentation, therapy, and outcome in 26 cases. *J Vet Cardiol*. 2012;*14*:333-342.
91. Kruttavecho C, Wongpanich V, Rungsipipat A, et al. Acute aortic thromboembolism in dogs: case reports. *Thai J Vet Med*. 2017;*47*(Suppl):149-151.
92. Massel DR, Little SH. Antiplatelet and anticoagulation for patients with prosthetic heart valves. *Cochrane Database Syst Rev*. 2013;(7):CD003464.
93. Lake-Bakaar GA, Johnson EG, Griffiths LG. Aortic thrombosis in dogs: 31 cases (2000-2010). *J Am Vet Med Assoc*. 2012;*241*:910-915.
94. Boswood A, Lamb CR, White RN. Aortic and iliac thrombosis in six dogs. *J Small Anim Pract*. 2000;*41*:109-114.
95. Schoeman JP. Feline distal aortic thromboembolism: a review of 44 cases (1990-1998). *J Feline Med Surg*. 1999;*1*:221-231.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Goggs R, Bacek L, Bianco D, Koenigshof A, Li RHL. Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care (CURATIVE): Domain 2—Defining rational therapeutic usage. *Journal of Veterinary Emergency and Critical Care*. 2019;29:49–59. https://doi.org/10.1111/vec.12791