TITLE: American College of Veterinary Emergency and Critical Care (ACVECC) Consensus on the Rational use of Antithrombotics in Veterinary Critical Care (CURATIVE) Guidelines: Small Animal

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Abbreviations: ACT, activated clotting time; ACVECC, American College of Veterinary Emergency and Critical Care; aPTT, activated partial thromboplastin time; ATE, arterial thromboembolism; CURATIVE, Consensus on the Rational use of Antithrombotics in Veterinary Critical Care; EVECC; European Veterinary Emergency and Critical Care; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HAC, hyperadrenocorticism; INR, international normalized ratio; IMHA, immune-mediated hemolytic anemia; LOE, Level Of Evidence; LMWH, low molecular-weight heparin; PICO, Population Intervention Comparison Outcome; PECO, Patient Exposure Comparison Outcome;

PLN, protein-losing nephropathy; PROVETS, Partnership On Veterinary Rotational Viscoelastic Test Standardization; PT, prothrombin time; PTE, pulmonary thromboembolism; RECOVER, Reassessment Campaign on Veterinary Resuscitation; TEG, thromboelastography; TT, thrombin time; UFH, unfractionated heparin; VECCS, Veterinary Emergency and Critical Care Society; VTE, venous thromboembolism.

Abstract

Objectives – To systematically review available evidence and establish guidelines related to the risk of developing thrombosis and the management of small animals with antithrombotics.

Design – Standardized, systematic evaluation of the literature (identified by searching Medline via PubMed and CAB abstracts) was carried out in 5 domains (Defining populations at risk; Defining rational therapeutic use; Defining evidence-based protocols; Refining and monitoring antithrombotic therapies and Discontinuing antithrombotic therapies). Evidence evaluation was carried out by way of Population, Intervention, Comparison, Outcome (PICO) format. Each domain generated PICO questions to address specific aims. This was followed by categorization of relevant articles according to level of evidence (LOE) and quality (Good, Fair, or Poor). Synthesis of these data led to the development of a series of statements. Consensus on the final guidelines was achieved via Delphi-style surveys. 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 – Over 500 studies were reviewed in detail. Worksheets from all 5 domains generated 67 statements with 79 guideline recommendations that were refined during 3 rounds of Delphi surveys. A high degree of consensus was reached across all guideline recommendations.

Conclusions – Overall, systematic evidence evaluations yielded almost 80 recommendations for the treatment of small animals with or at-risk of developing thrombosis. Numerous significant knowledge gaps were highlighted by the evidence reviews undertaken, indicating the need for substantial additional research in this field.

Keywords: Antiplatelet agent, anticoagulant, thromboprophylaxis, dogs, cats

Introduction

Thrombosis is commonly encountered in critically-ill small animals,[1-6] and causes substantial morbidity and mortality.[3, 7-9] Thrombosis contributes to morbidity and mortality through promotion of inflammation,[10-13] and through direct end-organ damage.[14] Thrombosis complicates the management of multiple disease processes,[15] and is the primary cause of various veterinary emergency room visits.[16] Furthermore, thrombi can propagate and may increase the propensity for additional clot formation and embolization.[17-19]

The epidemiology of thrombosis in human medicine is well understood,[20-27] and the substantial economic costs entailed in the management of thrombosis are also well documented.[28-30] Such data are not available in veterinary medicine. Although the burden of disease may be less in small animals than in people, it is likely still substantial. In the United States in 2017, there were approximately 96 million cats,[a] and 90 million dogs,[b] and the US pet care segment of the veterinary services market was worth $13.5 billion.[c] If thrombotic disorders account for even 0.01% of this spending, then client costs for the diagnosis and management of thrombotic complications in small animals amount to millions of dollars annually.

In human medicine, multiple iterations of evidence-based guidelines for the management of venous,[31-35] and arterial thrombosis have been published.[36, 37] These guidelines are based on a wealth of high-quality evidence resulting from large-scale randomized controlled trials.[38-49] Although some of these guidelines may be applicable to small animals, it is clear that the underlying physiology,[50-53] the overall burden of disease and the most frequently associated disease processes are substantially different between humans and small animals.[1, 15] As such, there is a clear need for veterinary specific guidelines on the use of antithrombotics.[54-56]

The available evidence from veterinary medicine, from animal models of human disease and where necessary from human medicine relevant to the administration, monitoring and discontinuation of antithrombotic medications in small animals was compiled to produce a series of evidence-based guidelines

that were presented and discussed at both the European Veterinary Emergency and Critical Care (EVECC) Congress and the International Veterinary Emergency and Critical Care Symposium (IVECCS) in 2018. The draft guidelines were subsequently opened to community comment, revised as necessary, and edited for consistency prior to submission for publication.

In these guidelines and in the accompanying domain summary documents, we have used the terms antithrombotic and thromboprophylaxis as the common categorization encompassing antiplatelet agents and antiplatelet therapy and anticoagulants and anticoagulation. Owing to an overall paucity of evidence and limited clarity in the veterinary literature, we do not differentiate the use of these medications in patients with risk factors for thrombosis but without current thrombosis from those with existing thrombosis.

Materials and Methods

An effort to generate consensus guidelines on the use of antithrombotic drugs in small animals under the auspices of the American College of Veterinary Emergency and Critical Care (ACVECC) was initiated in 2015. At that time, the ACVECC appointed three committee co-chairs who convened to begin assembling a larger working group of participants that might be deemed "experts". Potential contributors were solicited via an electronic mailing list, and self-identified potential collaborators were required to demonstrate an established research and publication track record in the field of hemostasis via submission of a short resumé. From this group, the consensus committee co-chairs selected potential contributors who were then approved by the ACVECC Board of Regents. Subsequently, three additional co-chairs were appointed from within this group with one member of the ACVECC Board of Regents acting in an *ex officio* capacity. The committee co-chairs established five domains, each headed by a separate domain chair. These five domains were: (i) Defining populations at risk (A.M.dL.), (ii) Defining rational therapeutic use (R.G.), (iii) Defining evidence-based protocols (M-C.B.), (iv) Refining and monitoring antithrombotic therapies (C.R.S.) and (v) Discontinuing antithrombotic therapies (B.B.).

Each domain set out specific aims from which a series of clinical questions were generated that formed the basis for evidence evaluation. A Population, Intervention, Comparison, Outcome (PICO) format was used to express the clinical questions, as previously used for the 2012 Reassessment Campaign on Veterinary Resuscitation (RECOVER), and 2014 Partnership on Rotational Viscoelastic Test Standardization (PROVETS) endeavors.[57, 58] In brief, this method involved initially defining the patient or population of interest, specifically domesticated dogs and cats. For domains 2, 3 and 4 an assumption was made the patient populations being considered have a disease process that warrants antithrombotic drug administration. Venous and arterial thrombosis were considered separately where this was rational. The intervention represented the treatment choice of interest, such as the use of the antiplatelet agent aspirin, while the comparison represents the alternative treatment choice we wished to compare, such as use of the anticoagulant enoxaparin. Where necessary, drug classes were considered collectively, such as the low molecular-weight heparins (LMWHs) versus unfractionated heparin (UFH), while in other worksheets individual drugs were compared, such as clopidogrel versus aspirin. For outcome, patient-centered measures such as reductions in thrombosis, diminished organ dysfunction or improvements in survival were prioritized in evidence evaluations over surrogate measures such as alterations in biomarkers, or the results of monitoring tests. In domain 4 that focused on monitoring tests, the tests themselves were considered as the intervention rather than as the outcome. For domain 1, a PECO format was adopted to represent Patient, Exposure, Comparison and Outcome,[59] with questions formatted to compare the effect of exposure to the risk factor or development of the disease (Exposure) versus remaining disease free (Comparison) on development of thrombosis (Outcome). This adapted process was thereby used to generate a list of disorders for which antithrombotic therapy might be indicated by evaluating the strength of evidence for association of a disease with thrombosis.

Within each domain PICO questions were assigned to individual worksheet authors. These reviewers performed the bulk of the initial work through performance of comprehensive database searches, assessments of the quality and applicability of the resultant literature and detailed reviews of the evidence

applicable to the PICO question set. The end result of each worksheet was a summary of the evidence and a guideline recommendation. Worksheets were then reviewed by domain chairs with further iterations of literature searching, manuscript review and guideline revision performed as necessary in consultation with worksheet authors. Several worksheet authors worked within more than one domain and several of the domain chairs also contributed worksheets to other domains. Instructions for worksheet authors (Data S1), blank worksheets (Data S2) for completion and an example completed worksheet from the PROVETS effort were distributed to worksheet authors for guidance on the process.

Comprehensive searches of the Medline and CAB (Commonwealth Agricultural Bureau) databases were performed for each worksheet using PubMed, OVID, and Web of Knowledge and supplemented by additional searches through Google Scholar and by hand where necessary. Search strategies, inclusion and exclusion criteria,

and search results were recorded in the relevant worksheets. Identified relevant studies were then reviewed and the following assessed: (i) level of evidence (LOE), (ii) methodological quality, (iii) magnitude of any observed

effect, (iv) direction of support or otherwise for the question asked, (v) outcome(s) assessed, and (vi) relevance to the question asked. LOEs were allocated as for the RECOVER process,[57] such that LOE 1 represented randomized controlled trials in dogs or cats; LOE 2 represented prospective clinical studies in dogs or cats with concurrent controls, but without randomization; LOE 3 represented experimental laboratory studies in dogs or cats; LOE 4 represented clinical retrospective studies in dogs or cats with both study and control groups from a previous period in time; LOE 5 represented case series and case reports in dogs or cat without a control group; and LOE 6 represented studies in humans. Within each LOE, the quality of the study was then subjectively assessed as Good, Fair, or Poor based on descriptors from The Centre for Evidence-Based Medicine.[d]

It should be noted that because some aspects of these assessments were subjective variation in the scores assigned to individual studies across domains is possible. In addition, while an LOE and quality score could be assigned to every study assessed, not every study was equivalently applicable to the PICO question at hand. Worksheet authors and domain chairs therefore made determinations as to the relevance of the study to the PICO question and hence some studies were classified as neutral to the PICO question, irrespective of their evidence level or quality. Some studies that did not directly address the PICO question regarding efficacy were included nonetheless, because they provided evidence for safety or adverse effects that was considered pertinent to prescribing practices.

Following evidence assessment, worksheet authors were asked to digest and weigh the evidence, to discuss the results of their review, to summarize the body of evidence, and to draft guideline recommendations. The generic format for these statements was: *Evidence from # [study design and quality] studies in dogs and # [study design and quality] studies in cats, in addition to # additional studies in humans [insert range of LOE] document improvement in [outcome measure] when [intervention] is compared to [control] for management of [disease process]. Therefore, [intervention] for management of [disease process] in [patient type] is [recommended/should be considered/not-recommended]*.

Domain chairs then reviewed all worksheets and suggested revisions, edits, and additional searches as required. Draft guidelines were reviewed and revised as deemed necessary by the domain chairs. These draft guidelines were summarized and presented to the community at the 2018 EVECC Congress. Feedback provided by delegates at the EVECC Congress enabled and prompted some revision of the guidelines. These revised guidelines were then subjected to three rounds of a Delphi survey process,[60-63] to reach consensus on the content and formulation of the final draft of the guidelines. This Delphi process was conducted anonymously over a 3-week period via an online survey instrument,[e] and involved the committee chairs and all worksheet authors. Participants were given comprehensive instructions on the conduct of the Delphi survey prior to beginning. Following each iteration, collated collective feedback from the prior

round and copies of both the previous and the revised versions of the guidelines were distributed to participants (Data S3). Below each guideline, the degree of consensus achieved is presented in addition to a short narrative statement describing the rationale and listing the supporting evidence assessments. Accompanying manuscripts in this edition of the *Journal* present the PICO questions, corresponding guidelines, discuss the relevant evidence in more detail and highlight key knowledge gaps. In addition, we have provided a series of case vignettes to illustrate the practical implementation of the guidelines using common clinical scenarios.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process provides guidance on quality of evidence rating and on the expression of strength of recommendations in systematic reviews, health technology assessments, and clinical practice guidelines.[64] Under the GRADE scheme, recommendations are characterized as strong or weak (conditional or discretionary) according to the supporting evidence quality and the balance between desirable and undesirable consequences of the alternative options.[65] The CURATIVE guidelines adopt this 2-tier recommendation system and are formatted per the 2016 Surviving Sepsis Campaign.[66] Thus, strong recommendations in CURATIVE are written as "We recommend..." while weak recommendations are in the format "We suggest...".

Guidelines

Domain 1: Defining populations at risk

1.1. Immune-mediated hemolytic anemia (Dogs only)

a. Immune-mediated hemolytic anemia (IMHA) is strongly associated with the development of thrombosis in dogs.

b. We recommend antithrombotic therapy for dogs with IMHA.

Delphi process: 13/13 panel members responding agreed (round 2).

Three retrospective studies (LOE 5, xxxx) and one uncontrolled prospective study (all LOE 5, xxxx) suggest an association between IMHA in dogs and thrombosis, particularly pulmonary thromboembolism.[9, 67-69] In

addition, multiple studies (LOE 2-5, xxxx) suggest that IMHA in dogs is associated with a hypercoagulable state,[70-73] characterized by increased tissue factor expression,[74] platelet activation,[75, 76] procoagulant microparticle release,[77] and neutrophil extracellular trap generation.[13, 78]

1.2. Protein Losing Nephropathy (Dogs only)

a. Protein losing nephropathy (PLN) is associated with the development of thrombosis in dogs.

b. We recommend antithrombotic therapy for dogs with PLN.

Delphi process: 13/13 panel members responding agreed (round 2).

Seventeen studies (LOE 2-5, xxxx) support an association between PLN and thrombosis.[14, 79-94] Most of these studies lack a control group, precluding establishment of a clear cause and effect relationship. When evaluated as a whole, however, the total number of dogs with PLN described across all studies with various thrombotic conditions strongly suggests an association between PLN and pathologic thrombosis. Studies investigating hemostatic changes in dogs with PLN describe thromboembolic complications in 6% to 42% of dogs.[83-87, 89, 93-96]

1.3. Pancreatitis (Dogs only)

a. Severe pancreatitis, in particular acute necrotizing pancreatitis, may be associated with the development of thrombosis in dogs.

b. We suggest that antithrombotic therapy be considered for dogs with acute pancreatic necrosis, particularly when concurrent prothrombotic conditions are present.

Delphi process: 13/13 panel members responding agreed (round 2).

Three studies (LOE 2-5, xxxx) suggest that canine pancreatitis is associated with a hypercoagulable state,[11, 97, 98] although none of these studies included dogs with clinical evidence of thrombosis. One study (LOE 4, xxxx) suggested an over-representation of thrombosis in dogs with pancreatitis compared to other presenting complaints.[99] Multiple studies (LOE 3-5, xxxx) document concomitant pancreatitis in dogs with known thrombosis,[79-81, 88, 96, 100-104] and acute pancreatic necrosis was the histopathologic diagnosis in four

of these studies. It should be acknowledged that thrombosis is not reported as a complication in all pancreatitis populations.[105] The frequent presence of comorbidities in published reports also complicates the assessment of the association between pancreatitis and thrombosis in dogs.[80]

1.4. Glucocorticoid Administration (Dogs only)

a. Corticosteroid administration favors a hypercoagulable state.

b. Treatment with corticosteroids may be associated with the development of thrombosis in dogs, in particular those with other risk factors for thrombosis.

c. We suggest that antithrombotic therapy be considered for dogs receiving corticosteroids where other risk factors for thrombosis exist.

Delphi process: 13/13 panel members responding agreed (round 2).

No studies directly investigating the relationship between glucocorticoids and the increased risk of thrombosis in dogs were identified. The guideline is based on retrospective studies (LOE 5, xxxx) of thrombotic states where concurrent or recent therapy with glucocorticoids featured prominently,[14, 79-81, 88, 102, 106-108] and experimental studies (LOE 3, xxxx) of healthy dogs administered oral prednisone that document generation of a hypercoagulable state.[109-112] Two prospective studies provide additional indirect evidence of an association between glucocorticoid administration and thrombosis in dogs.[113, 114] Studies investigating hemostatic changes secondary to glucocorticoids are lacking in cats.

1.5. Hyperadrenocorticism (Dogs only)

a. Hyperadrenocorticism (HAC) is associated with the development of thrombosis in a small subset of dogs only.

b. Hyperadrenocorticism alone does not warrant antithrombotic therapy in the majority of dogs, unless other risk factors for thrombosis exist.

Delphi process: 13/13 panel members responding agreed (round 2).

Ten studies (2 LOE 4, 8 LOE 5) suggest that HAC is associated with the development of thrombosis in dogs.[79, 80, 88, 106, 107, 115-119] However, all were retrospective, most did not have a control group and comorbidities were frequent. Assessing the sum of the literature, HAC is reported in 4-17% of dogs with a known thrombotic event.[79-81, 88, 106, 107, 115] Studies investigating the hemostatic profiles of dogs with HAC have reached opposing conclusions about whether a hypercoagulable state is present, suggesting the phenomenon is not universal to dogs with HAC.[120-124]

1.6. Cancer (Dogs only)

a. Cancer in dogs, in particular (adeno)carcinoma, is associated with the development of thrombosis in a small subset of dogs only.

b. There is insufficient evidence to support routine anticoagulation of dogs with cancer.

c. We suggest that antithrombotic therapy be considered for dogs with cancer where hypercoagulability is demonstrated, or where other risk factors for thrombosis exist.

Delphi process: 12/12 panel members responding agreed (round 3).

Neoplasia is frequently identified as an underlying disease in retrospective studies of canine thrombosis (LOE 5, xxxx),[79-81, 96, 106, 125] but thrombosis does not affect the majority of dogs with neoplasia. In addition, comorbidities and recent or concurrent glucocorticoid administration complicates the direct assessment of the risk of thrombosis in dogs with cancer. Multiple studies (LOE 2-5, xxxx) have documented hypercoagulability in dogs with neoplasia, particularly in carcinoma, sarcoma and lymphoma,[126-129] and the presence of thrombi in tumors.[130-132] Hypercoagulability in dogs with neoplasia appears to be multifactorial.[98, 127, 129, 133-135]

1.7. Sepsis (Dogs only)

a. Sepsis is associated with the development of thrombosis in a small subset of dogs only.

b. There is insufficient evidence to support routine anticoagulation of dogs with sepsis.

c. We suggest that antithrombotic therapy be considered for dogs with sepsis where hypercoagulability is demonstrated, or where other risk factors for thrombosis exist.

Delphi process: 12/12 panel members responding agreed (round 3).

Sepsis is a common disease process in retrospective studies of dogs with thrombosis,[14, 79, 81, 88, 96, 106, 116] but most studies lack controls (LOE 5, xxxx), and the direct association between sepsis and thrombosis is confounded by concurrent disease processes.[136] Hemostatic alterations consistent with hypercoagulability have been identified in dogs with sepsis.[11, 12, 135, 137-140]

1.8. Cerebrovascular Disease

a. Cerebrovascular disease is more likely to result from a thrombotic event rather than be the cause of one.

b. We suggest that antithrombotic therapy be considered when an ischemic stroke is identified and a concurrent medical condition associated with a risk for thrombosis is present.

Delphi process: 12/13 panel members responding agreed (round 2). One panel member felt that the guideline might be less applicable to patients with concurrent ischemic and hemorrhagic strokes.

Information provided by three studies (LOE 5, xxxx) suggest that ischemic strokes are more likely the result of a hypercoagulable conditions than a risk factor for thrombosis themselves.[141-143] None of the dogs included in retrospective studies of PTE, ATE, portal vein or splenic vein thrombosis, had cerebrovascular disease.[79-81, 88, 102, 106, 107, 115, 116, 118]

1.9 Heart Disease (Cats)

a. Feline cardiomyopathy is strongly associated with a risk of ATE.

b. Cats with: a history of ATE, left atrial (LA) dilation, spontaneous echocontrast, or reduced LA appendage flow velocity may be at particular risk.

c. We recommend antithrombotic therapy for cats with cardiomyopathy, particularly in those with the above risk factors.

Delphi process: 12/13 panel members responding agreed (round 2). One panel member felt this guideline should state “we strongly recommend”.

Three studies (LOE 2-4, xxxx) strongly support the association of feline cardiomyopathy with ATE.[144-146] The cumulative risk of ATE at 1yr, 5yr, and 10yr was 3.5%, 9.5%, and 11.3% in cats with hypertrophic cardiomyopathy (HCM) or hypertrophic obstructive cardiomyopathy (HOCM) compared to 0.0%, 0.4%, and 0.7% in apparently healthy cats (LOE 2, xxxx).[144] Five other studies (LOE 2-4, xxxx) suggest that feline cardiac disease accompanied by spontaneous echocontrast, LA dilation, reduced LA function and low flow velocities may portend ATE or death.[82, 147-150]

1.10 Heart Disease (Dogs)

a. Canine cardiac diseases are not associated with a high risk for the development of thrombosis.

b. We suggest that antithrombotic therapy be considered in individual dogs where other risk factors for thrombosis exist.

Delphi process: 12/13 panel members responding agreed (round 2). One panel member felt that if canine structural heart disease was not associated with thrombosis that the presence of another minor risk factor should not prompt antithrombotic therapy.

Only one study was identified linking cardiac disease in dogs to the development of thrombosis (LOE 4, Fair).[108] Most retrieved studies (LOE 2-5, Good-Fair) were considered neutral to the relevant PICO question,[14, 101, 106, 116, 151-153] and a similar quantity of evidence (LOE 4-5, Fair-Poor) refuted a link as suggested one.[4, 88, 115]

1.11 We define high risk for thrombosis as:

a. Dogs with IMHA or PLN.

b. Cats with cardiomyopathy and associated risk factors (see guideline 1.9).

c. Dogs or cats with more than one disease/risk factor for thrombosis (e.g. pancreatitis with sepsis).

Delphi process: 13/13 panel members responding agreed (round 2).

As discussed above, strong associations exist between thrombosis and IMHA and PLN in dogs and with cardiomyopathy in cats. Where the association is weaker, reference to human scoring systems and guidelines provides a rational approach to risk stratification.[154-156] It is likely that risk factors for thrombosis are cumulative.[154] The risk of bleeding, versus the risk of thrombosis should be considered for each individual patient before deciding upon initiation or discontinuation of antithrombotics. Individual risk should account for the underlying condition(s), the inflammatory state of the animal, planned procedures, the likelihood the underlying condition can be resolved in a timely fashion and the impact of medications such as glucocorticoids on thrombotic risk.

1.12 We define low/moderate risk for thrombosis as:

a. Dogs or cats with a single risk factor/disease.

b. Dogs or cats with known risk factor conditions that, with treatment, are likely to resolve in days to weeks.

Delphi process: 13/13 panel members responding agreed (round 2).

See 1.11 for key supporting evidence.

Domain 2: Defining rational therapeutic use

2.1. Antiplatelet Agents vs 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.

Delphi process: 14/14 panel members responding agreed (round 1).

Evidence from one study in dogs (LOE 3, Good) suggested that heparin was superior to aspirin for prevention of thrombus formation under venous shear.[157] An additional study (LOE 3, Good) evaluated thrombus formation in the low-shear setting of the pulmonary arterial system in dogs with experimentally induced dirofilariasis and demonstrated that neither aspirin or aspirin and dipyridamole protect against PTE in dirofilariasis.[158]

2.2. Antiplatelet Agents vs 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.

Delphi process: 14/14 panel members responding agreed (round 1).

Two publications were identified (LOE 3, Good) suggesting that aspirin has limited if any efficacy for prevention of pulmonary thromboembolism due to dirofilariasis in cats.[159, 160] Evidence for efficacy of anticoagulants in VTE in cats is presented elsewhere (guidelines 2.10, 2.12, 2.14, 3.8, 3.10, 3.12).

2.3. Antiplatelet Agents vs 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.

Delphi process: 12/14 panel members responding agreed (round 1). One panel member felt the rarity of ATE in dogs limited the evidence base and hence increased the risk associated with this guideline. One panel member felt that thrombosis in canine coronary vessels might be distinct from thrombosis in the aorta.

Three studies (all LOE 3, Good) suggested that anticoagulants were inferior to antiplatelet agents in the setting of provoked arterial thrombosis.[161-163] Multiple studies, (19 LOE 3, Good, 1 LOE 3, Fair) also suggest efficacy of anticoagulants for arterial thrombosis in dogs, however.[164-183]

2.4. Antiplatelet Agents vs 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.

Delphi process: 14/14 panel members responding agreed (round 1).

Evidence supporting the use of antiplatelet agents for ATE in cats is presented elsewhere (guidelines 2.6, 2.8, 3.4). Three publications reported use of anticoagulants in cats with ATE (LOE 4, Fair), but all were judged to be neutral to the PICO question.[82, 184, 185]

2.5. Clopidogrel vs 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.

Delphi process: 12/13 panel members responding agreed (round 2). One panel member agreed with 2.5.a. but felt the evidence in favor of clopidogrel was insufficient to support 2.5.b.

Evidence for efficacy of aspirin and clopidogrel for ATE in dogs is presented elsewhere (guidelines 3.1, 3.3). One study (LOE 1, Fair) directly compared aspirin with clopidogrel for thromboprophylaxis in dogs, but was underpowered to detect clinically relevant differences in efficacy.[186] One experimental study (LOE 3, Fair) suggests clopidogrel is superior to aspirin in a model of coronary artery thrombosis.[187]

2.6. Clopidogrel vs 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.

Delphi process: 13/13 panel members responding agreed (round 2).

One prospective study in cats (LOE 1, Good) provides evidence that clopidogrel is superior to aspirin for thromboprophylaxis in cats with previous aortic thromboembolic events.[188]

2.7. New antiplatelet agents vs 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.

Delphi process: 13/13 panel members responding agreed (round 2).

No clinical studies evaluating novel antiplatelet agents in dogs were identified. Four experimental studies (all LOE 3, Fair) suggest efficacy for novel antiplatelet agents in dogs,[189-192] but of these only ticagrelor and abciximab are commercially available.

2.8. New antiplatelet agents vs 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.

Delphi process: 13/13 panel members responding agreed (round 2).

No clinical studies evaluating novel antiplatelet agents in cats were identified. In one experimental study (LOE 3, Fair) abciximab demonstrated efficacy in a feline model of arterial injury.[193]

2.9. UFH vs 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.

Delphi process: 12/13 panel members responding agreed (round 2). One panel member felt that 2.9.b. was not justifiable because of the cost and greater difficulty monitoring LMWH. Another panel member agreed with the statement, but commented that 2.9.b. was most reasonable in a hospital setting.

There is a paucity of information directly comparing LMWH to UFH in dogs at risk of spontaneous thrombosis. Five studies comparing LMWH with UFH in experimental thrombosis models (all LOE 3, Good) demonstrate that LMWH is comparable or superior to UFH and is associated with lower bleeding tendency.[167, 194-197]

2.10. UFH vs 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.

Delphi process: 13/13 panel members responding agreed (round 2).

No articles directly addressed the relevant PICO question. One study (LOE 3, Fair) demonstrated an antithrombotic effect of enoxaparin in a feline venous stasis model.[198] Multiple studies (5 LOE 3, Fair, 1 LOE 4, Fair) suggest that LMWHs are safe and have reproducible pharmacokinetics in cats.[184, 199-203]

2.11. Direct Xa inhibitors vs 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.

Delphi process: 12/12 panel members responding agreed (round 3).

Three 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.[173, 204, 205] Various studies (1 LOE 1 Fair, 3 LOE 3, Good-Fair, 1 LOE 5, Fair) suggest rivaroxaban is safe and may be efficacious in dogs,[206-210] but evidence comparing the direct Xa inhibitors with UFH in dogs with spontaneous disease is lacking.

2.12. Direct Xa inhibitors vs 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.

Delphi process: 12/12 panel members responding agreed (round 3).

No studies directly addressed the relevant PICO question. Two pharmacokinetic-pharmacodynamic (PK-PD) studies (LOE 3, Good),[211, 212] suggest that rivaroxaban and apixaban are well tolerated in cats and have reproducible PK-PD parameters.

2.13. Direct Xa inhibitors vs 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.

Delphi process: 13/13 panel members responding agreed (round 2).

No prospective randomized clinical studies were identified comparing these two drug classes in dogs. One experimental study (LOE 3, Good) demonstrated that a direct Xa inhibitor had equivalent efficacy to enoxaparin for prevention of arterial and venous thrombosis.[181] Seven studies (all LOE 3, Good-Fair) of direct Xa inhibitors suggest these drugs are safe, orally active and have reliable and reproducible PK-PD parameters in dogs.[208-210, 213-216]

2.14. Direct Xa inhibitors vs 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.

Delphi process: 13/13 panel members responding agreed (round 2).

No studies directly addressed the relevant PICO question. Two pharmacokinetic-pharmacodynamic (PK-PD) studies (both LOE 3, Good),[211, 212] suggest that rivaroxaban and apixaban are well tolerated in cats and have reproducible PK-PD parameters.

2.15. UFH vs Warfarin and LMWH vs 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).

Delphi process: 12/12 panel members responding agreed (round 3).

There is insufficient evidence comparing UFH or LMWH 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 UFH, LMWHs and warfarin are discussed elsewhere.

2.16. Direct Xa inhibitors vs 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.

Delphi process: 12/12 panel members responding agreed (round 3).

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. Large scale studies in people 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.[41, 44, 217]

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.

Delphi process: 14/14 panel members responding agreed (round 1).

Very little evidence was identified the addressed the relevant PICO question. A single study of dogs (LOE 4, Fair) suggested an outcome advantage for UFH combined with aspirin compared to UFH in dogs with IMHA,[218] but the comparison is confounded by differences in illness severity between groups. The guideline recommendation is primarily based on data reviewed in this and other domains and represent the current practice of the committee.

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.

Delphi process: 13/13 panel members responding agreed (round 2).

No studies directly address the relevant PICO question in cats. The guideline recommendation is primarily based on data reviewed in this and other domains and represent the current practice of the committee.

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.

Delphi process: 13/13 panel members responding agreed (round 2).

No studies directly compare combined anticoagulant and antiplatelet therapy over antiplatelet therapy alone in dogs. Comparison of outcomes in two separate case series (LOE 5, Good-Fair),[108, 116] where dogs received antiplatelet therapy alone with outcomes of dogs in three separate case series (LOE 5, Good-Fair),[4, 108, 207] where dogs received combination therapies suggest lower recurrence rates in dogs receiving combination therapy. It should be recognized that comparison of patient outcomes in these studies in this manner is strictly hypothesis generating, however. A meta-analysis of 6 trials comprising 29,667 people with acute coronary syndromes, suggests use of direct oral anticoagulants in addition to antiplatelet therapy reduced ischemic events.[219]

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.

Delphi process: 12/12 panel members responding agreed (round 3).

No studies directly addressed the relevant PICO question. Comparisons of recurrence rates from three separate retrospective studies in cats (LOE 4, Fair) suggest that multimodal therapy compared to antiplatelet therapy alone may decrease recurrence of feline arterial thromboembolism.[82, 184, 220] It should be recognized that comparison of patient outcomes in these studies in this manner is strictly hypothesis generating. On the basis of separate evidence of efficacy for clopidogrel and for LMWH in cats,[184, 188, 198] this combination of drugs represents the first choice of the panel if combination therapy is selected for an individual patient.

Domain 3: Defining evidence-based protocols

3.1. Aspirin (Dogs)

a. We suggest that oral aspirin may be effective for prevention of 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 in dogs.

Delphi process: 12/13 panel members responding agreed (round 2). One panel member felt that a dosage recommendation should be made to provide clinicians with guidance.

Multiple studies in various thrombosis model systems demonstrate that aspirin effective prevents induced ATE in dogs when commenced at least 2 days prior to the thrombogenic insult. Seven studies (all LOE 3, Good-Poor) suggest that protocolized aspirin therapy is more effective than no aspirin therapy in endarterectomy and angioplasty models.[221-228] Two studies (both LOE 3, Good-Fair) using re-occlusion models suggested aspirin is efficacious following therapeutic fibrinolysis in dogs.[229, 230] Multiple studies (all LOE 3, Good-Poor) in graft models suggest aspirin is efficacious in dogs but the aspirin dose used varied widely amongst studies, with only a limited number directly comparing dosages.[223, 231-239] The reported dose range is very wide, however between 0.5 mg/kg/day and 15 mg/kg/day are reportedly effective. There is inadequate evidence to assess the efficacy of aspirin in dogs in clinical situations predisposing to thromboembolism.

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.

Delphi process: 13/13 panel members responding agreed (round 2).

Clinically, aspirin as the sole treatment in cats at risk of ATE is associated with a 75% incidence of recurrence within 12 months of an event (LOE 1, Good), and is inferior to clopidogrel for feline ATE thromboprophylaxis.[188] Two retrospective studies (LOE 4, Poor) also identified ATE recurrence in 20-28% cases.[82, 220] Multiple experimental studies offer conflicting assessments of the inhibitory effect of aspirin on

feline platelet function. Seven studies (LOE 2-5, Poor) suggest efficacy for aspirin in cats,[159, 160, 240-244] while 6 studies (LOE 1,3, Good-Poor) suggest aspirin is poorly effective against ATE in cats.[82, 188, 220, 245-247] This may be attributable to varying dosages and differing outcome measures and test methodologies.

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 (e.g. 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 a sole agent for VTE in dogs.

Delphi process: 12/13 panel members responding agreed (round 2). One panel member felt that the risks of clot formation should be weighed against the risk of gastrointestinal bleeding resulting from administration of a loading dose.

In dogs, 17 papers (LOE 3, Good-Fair) suggest efficacy of clopidogrel.[187, 189-192, 248-259] Of these publications, 10 (all LOE 3, Good-Fair) suggest *in vivo* efficacy against provoked arterial thrombosis. Reported dosages vary considerably, with efficacy varying between dogs, model systems and thrombotic stimulus. *Ex vivo* tests suggest 1.1 mg/kg PO SID inhibits ADP-induced platelet aggregation.[257] A dose of 4 mg/kg PO SID after a 10 mg/kg loading dose provides protection against provoked arterial thrombosis.[256] No evidence for or against the efficacy of clopidogrel in venous thrombosis in dogs was identified.

3.4. Clopidogrel (Cats)

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

b. We suggest a single oral loading dose (e.g. 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.

Delphi process: 13/13 panel members responding agreed (round 2).

In cats, 8 studies (LOE 1-4, Good-Poor) suggest clopidogrel is effective in cats.[185, 188, 260-265] Three studies (LOE 1-4, Good-Poor) suggest *in vivo* efficacy against provoked arterial thrombosis.[185, 188, 260] In contrast to dogs, there is very good consistency in the dosages used in the feline studies (18.75 mg PO q24h, equivalent to 3-6 mg/kg for a typical cat). One RCT (LOE 1, Good) comparing clopidogrel with aspirin in feline ATE suggests clopidogrel should be used in cats with ATE, in preference to aspirin.[188] No evidence for or against the efficacy of clopidogrel in venous thrombosis in cats was identified.

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.

Delphi process: 11/14 panel members responding agreed (round 1). One panel member felt the guideline should specify "for thromboprophylaxis". One panel member felt warfarin could still be considered with some patients and compliant clients. One panel member dissented but an alternative suggestion was not made.

In dogs, 10 studies (LOE 1-5, Good-Poor) suggest efficacy of warfarin *in vivo* in dogs or using *in vitro* tests.[4, 266-274] Seven studies (LOE 3-5, Good-Poor) document a lack of efficacy of warfarin in preventing thrombosis and/or demonstrate bleeding complications.[236, 271, 272, 275-277] Three additional studies (LOE 3, Good-Poor) highlight the narrow therapeutic index of warfarin, the alterations in warfarin pharmacokinetics over time,[278] high levels of protein binding,[279] and the effects of co-administration of aspirin.[266]

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 inter-individual variation coupled with a narrow therapeutic index.

Delphi process: 13/14 panel members responding agreed (round 1). One panel member dissented but an alternative suggestion was not made.

Two studies (both LOE 3, Fair-Poor) suggest warfarin has some efficacy in cats.[280, 281] Three studies (LOE 3-5, Good-Poor) suggest a lack of efficacy for warfarin in the cat.[282-284]

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.

Delphi process: 13/13 panel members responding agreed (round 2).

Eight studies (LOE 1-4, Good-Fair) suggest UFH is efficacious in dogs.[8, 285-289] The optimal dosing scheme is unestablished however and a consistent, effective and safe fixed UFH dose likely does not exist. Individual dose adjustment based on anti-Xa monitoring appears effective in dogs (LOE 1, Good).[286] Inhaled UFH does not appear effective in dogs (LOE 3, Fair).[290]

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.

Delphi process: 13/13 panel members responding agreed (round 2).

Only one study (LOE 3, Fair) was identified investigating the effect of UFH 250 units/kg q6h in cats.[202] There is insufficient data to suggest superiority or inferiority of UFH compared to other regimens in cats.

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.

Delphi process: 13/13 panel members responding agreed (round 2).

Four studies (LOE 3-5, Fair-Poor) suggest some of efficacy for dalteparin in dogs.[287, 291-293] Most assume that human target therapeutic anti-Xa range (0.5-1.0) is an appropriate target in dogs, but the relationship between anti-Xa activity and clinical efficacy in dogs has not been firmly established. Bleeding complications in dogs are uncommon and typically minor, but overdosage can result in potentially life-threatening bleeding.[293]

3.10 Dalteparin (Cats)

a. In cats, frequent SC administration is likely necessary for maintenance of the human target anti-Xa range.

b. Lower dosages compared to dogs may be acceptable at increased frequency e.g. 75 U/kg SC q6h.

c. Bleeding complications, usually minor and self-limiting, may occur with a variety of dosing schemes.

Delphi process: 14/14 panel members responding agreed (round 1).

Six studies (LOE 3-5, Fair-Poor) report usage of dalteparin in cats but were considered neutral to the relevant PICO question.[184, 199, 200, 202, 203, 244] A dosing scheme of 75-150 units/kg administered subcutaneously q6 h may be reasonable,[199, 202] but the relationship between anti-Xa activity and clinical efficacy in cats has not been firmly established. Bleeding complications, usually self-limiting and minor in nature, may occur with a variety of dosing schemes in cats.[184, 199, 202]

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.

Delphi process: 13/13 panel members responding agreed (round 2).

Five studies (LOE 3-5, Good-Poor) suggest enoxaparin is effective in dogs,[287, 294-297] with 0.8 mg/kg SC q6h the most commonly reported protocol.[294-296] There is no evidence suggesting that enoxaparin is superior to other drugs or protocols and doubt has been raised about the uniformity of enoxaparin's activity at 0.8 mg/kg SC q6h across all dog breeds.[298]

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.

Delphi process: 12/13 panel members responding agreed (round 2). One panel member felt that q6h and q12h dosing were not equivalent, indicating comparisons of q6 with q12h dosing using clinically relevant endpoints are lacking.

Three studies (all LOE 3 fair) suggest efficacy for enoxaparin in healthy cats,[198, 201, 202] The most commonly used protocol is 0.75-1 mg/kg SC q6-12h. A dose of 0.75 mg/kg q6h is documented to generate reproducible peak anti-Xa activity within the human target range.[201] Enoxaparin at 1 mg/kg SC q12hrs in cats at risk of thrombosis may be effective,[198] but inadequate to increase anti-Xa activity.[202]

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.

Delphi process: 14/14 panel members responding agreed (round 1).

There are no studies evaluating fondaparinux in dogs. A single dose determination study (LOE 3, Fair) in 6 cats suggests anti-Xa levels comparative to those considered effective in humans can be achieved safely.[299]

3.14 Rivaroxaban (Dogs)

a. We suggest that 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.

Delphi process: 13/13 panel members responding agreed (round 2).

Two studies (LOE 2-4, Fair) reported on the use of rivaroxaban in clinical patients, but data are insufficient to determine if rivaroxaban is efficacious in dogs at risk for thrombosis.[206, 207] Two studies (LOE 2-3, Fair) suggest efficacy for rivaroxaban in vitro and in healthy dogs administered the drug using ex vivo tests.[208, 209]

3.15 Rivaroxaban (Cats)

a. We suggest that based on preliminary data, rivaroxaban appears safe and well tolerated in cats.

b. We suggest a dosage of 0.5-1mg/kg/day in cats

Delphi process: 12/12 panel members responding agreed (round 3).

A single PK-PD study (LOE 2, Fair) in cats was identified.[211] No reports of feline clinical patients receiving rivaroxaban were retrieved.

Domain 4: Refining and monitoring antithrombotic therapies

4.1 Aspirin

a. Adjusting therapy to achieve platelet inhibition via platelet aggregometry in dogs receiving aspirin therapy can be considered.

b. Some evidence suggests that in dogs receiving aspirin, platelet inhibition detectable via aggregometry (various agonists), is associated with reduced risk of ATE.

c. Monitoring techniques are currently too varied to provide uniform recommendations at this time.

Delphi process: 14/14 panel members responding agreed (round 1).

Several LOE 3 studies suggest that platelet inhibition detectable by aggregometry is associated with reduced risk of ATE, however there is considerable variation in the agonists used for aggregometry in different studies.[226-229, 233, 234] Two publications (LOE 3, Poor), reporting different aspects of the same study, directly addressed the PICO question.[159, 160] These investigations suggest aspirin dosing individually adjusted based on aggregometry provided superior thromboprophylaxis relative to fixed dose aspirin in an experimental model of dirofilariasis. Although dose-adjusted aspirin was superior, the overall efficacy was limited, prompting the authors to conclude that aspirin cannot be recommended for treatment of heartworm disease in cats. The general applicability of these data is uncertain. Numerous studies have assessed the effect of aspirin on platelet function in healthy cats, using a variety of *in vitro* methods.[241, 245, 264, 300, 301] Results are variable, which may reflect methodologic differences, but overall, they suggest aspirin has limited antiplatelet efficacy in cats, particularly against potent platelet agonists.

4.2 Warfarin

a. We suggest that warfarin should not be used in dogs or in cats.

b. If warfarin is used we recommend monitoring warfarin therapy ideally with PT^{INR} to achieve a target of 2-3, or 1.5-2.0 times the baseline prothrombin time (PT).

c. Close therapeutic monitoring, particularly early in the course of therapy, is indicated to maximize efficacy and reduce the risk of complications.

Delphi process: 11/12 panel members responding agreed (round 3). One panel member felt that the guideline should indicate that continuous (ideally weekly) monitoring is advisable given the reported variability in warfarin PK and the potential for interactions with concomitant medications.

No studies in dogs specifically addressed the relevant PICO question. Two LOE 2 (Fair) studies evaluated warfarin therapy in dogs undergoing cardiac valve replacement and monitored dogs with PT. These studies suggested some therapeutic efficacy of warfarin when adjusted to achieve target INR. Of the 20 dogs

reported across the two studies, 9 dogs died of confirmed or suspected thrombosis despite INR monitoring of warfarin therapy.[273, 276] Two other studies (both LOE 3, Fair) reported the use of warfarin in dogs undergoing vascular grafting (n=27 total), adjusted based on the PT. Overall graft patency rates were good, but one dog died of hemorrhage.[272, 302] One study (LOE 3, Poor) involved the administration of warfarin to cats at risk of thrombosis that underwent therapeutic monitoring.[282] That study did not specifically address the relevant PICO question, but did demonstrate a lack of association between PT prolongation and the therapeutic efficacy of warfarin. A PK-PD study of warfarin in healthy cats documented wide variations in PK-PD parameters that would likely necessitate individual dose algorithms to ensure optimal warfarin dosing in cats.[280]

4.3 Unfractionated heparin (UFH)

a. We recommend anti-Xa activity for UFH monitoring in dogs since evidence supporting the use of other monitoring tests (e.g. activated clotting time (ACT), activated partial thromboplastin time (aPTT), thromboelastography (TEG), Sonoclot) is limited at this time.

b. An anti-Xa target of 0.35-0.7U/mL is recommended in dogs to minimize thrombosis risk and improve outcome, although minor hemorrhage may still occur.

c. There is insufficient evidence to make a strong recommendation for a specific anti-Xa target in cats.

d. An anti-Xa target of 0.35-0.7U/mL is reasonable in cats until more evidence is available.

Delphi process: 13/13 panel members responding agreed (round 2).

Data from a single randomized controlled trial (LOE 1, Fair) suggests that there is an outcome benefit from adjusting UFH doses based upon therapeutic monitoring.[286] That study and an experimental study (LOE 3, Fair) support the use of an anti-Xa activity range of 0.35-0.7 IU/mL.[287] The Helmond et al. study,[286] and a second prospective study (LOE 2, Fair) indicate that anti-Xa activity is the criterion (gold) standard for UFH monitoring.[8] Additional studies (LOE 3, Fair-Poor) suggest that other hemostatic tests may have a role in monitoring UFH in dogs but clinical utility remains to be demonstrated.[285, 289, 303-307] No studies in cats directly addressed the PICO question. One study suggests that the anti-Xa assay is the standard method

for UFH monitoring in cats, and that achievement of anti-Xa activity of 0.3-0.7 U/L causes anticoagulation in cats.[202]

4.4 Low molecular weight heparin (LMWH)

a. There is insufficient evidence to make strong recommendations for therapeutic monitoring of LMWH in dogs or cats.

b. We suggest adjusting therapy in dogs, targeting anti-Xa levels of 0.5-1.0U/mL 2-4 hours post dose can be considered.

Delphi process: 12/12 panel members responding agreed (round 3).

Four experimental studies in dogs (LOE 3, Good-Fair) addressed the PICO question, but provide limited evidence relevant to clinical practice.[181, 194, 196, 308] Various monitoring tests for LMWH in dogs including anti-Xa activity, PT, aPTT, thrombin time (TT), activated clotting time, TEG and the Sonoclot assay have been evaluated.[181, 194, 196, 288, 292, 308, 309] The anti-Xa assay appears to be the most sensitive test of the anticoagulant effect of LMWHs in dogs.[292, 294, 303, 309-311] Two studies (LOE 3, Fair-Poor) demonstrated a protective effect of achieving an anti-Xa activity of 0.55-0.9 U/mL in dogs using LMWH.[312, 313] Studies in healthy dogs (LOE 3, Poor) targeting anti-Xa activities of 0.5-1.0 IU/mL, have demonstrated safety at this dose.[294, 303] No studies in cats specifically addressed either of the relevant PICO questions and there is considerable variation in the anti-Xa activity achieved in cats after SC administration of LMWH, however peak anti-Xa activity appears to occur at around 2 hours after SC dosing in this species.[199, 200, 202, 203]

Domain 5: Discontinuing antithrombotic therapies

5.1 Discontinuation of antithrombotic agents

a) *In patients at high risk for thrombosis, anticoagulation should not be discontinued for invasive procedures*
b) *In patients at low to moderate risk for thrombosis, consideration may be given for discontinuation of anticoagulation prior to invasive procedures.*

The risk for bleeding must be balanced with the risk for thrombosis. In patients that require invasive procedures (eg., surgery, biopsy), this balance is particularly acute and will depend on the underlying risk factors for thrombosis and hemorrhage as well as the type of procedure. In procedures where hemorrhage may be catastrophic (eg., neurosurgery) or unable to be easily controlled (eg., percutaneous renal biopsy), discontinuation or alteration of therapy is prudent. For less-invasive procedures (eg., dental extraction, truncal mass removal), or those where hemorrhage may be addressed through tamponade (eg., surgery on a peripheral limb), anticoagulant therapy may through the procedure if there is a high risk of thrombosis without anticoagulation. These patients may also be switched to other medications with favorable pharmacokinetics for the periprocedural period. Consideration for the risk of rebound hypercoagulability should be given when planning complete or temporary cessation of therapy.

5.2 Antiplatelet agent discontinuation 5-7 days prior to an elective procedure versus no discontinuation (high risk)

a. We recommend that antiplatelet therapy with a single antiplatelet agent should be continued.

b. We recommend discontinuing one agent if animals are receiving dual antiplatelet therapy.

c. We suggest that these patients are at increased risk of bleeding and that close attention be paid to surgical hemostasis.

Delphi process: 13/13 panel members responding agreed (round 2).

No veterinary studies specifically addressed the relevant PICO question and hence multiple studies from human medicine (LOE 6, Fair) were extrapolated to generate this guideline.[314-328] The guideline represents a balance of the increased risk of thrombosis associated with drug discontinuation in patients with high-risk conditions,[329] or where multiple risk factors exist compared to the perceived lower risk of surgical hemorrhage that may result from ongoing platelet inhibition. of hemorrhage.[324, 325, 330] In addition, dual antiplatelet therapy with aspirin and clopidogrel can result in significantly more hemorrhage compared with antiplatelet monotherapy.[331, 332]

5.3 *Antiplatelet agent discontinuation 5-7 days prior to an elective procedure versus no discontinuation (low/moderate risk)*

a. We recommend that antiplatelet agents should be discontinued prior to the planned procedure.

Delphi process: 13/13 panel members responding agreed (round 2).

No veterinary studies specifically addressed the relevant PICO question and hence multiple studies from human medicine (LOE 6, Fair) were extrapolated to generate this guideline.[314-328] The guideline represents a balance of the perceived low risk of thrombosis associated with drug discontinuation in this patient population compared to the risk of perioperative bleeding.

5.4 UFH / LMWH discontinuation 24 hours prior to an elective procedure versus no discontinuation (high risk)

a. We recommend that heparin therapy should not be discontinued.

b. We recommend that surgery be planned to occur at nadir of anticoagulant effect (approximately 6-8 hours after prior dose if given by subcutaneous injection).

c. We suggest that these patients are at increased risk of bleeding and that close attention be paid to surgical hemostasis.

Delphi process: 12/12 panel members responding agreed (round 3).

No veterinary studies specifically addressed the relevant PICO question and hence multiple studies from human medicine (LOE 6, Good) were extrapolated to generate this guideline.[314-328] Patients at high risk of thrombosis are considered more likely to suffer consequences from thrombosis following discontinuation of heparin therapy than they are to suffer morbidity or mortality from procedure related hemorrhage.[333] Timing surgery to occur around the nadir of anticoagulant effect,[334] coupled with scrupulous surgical hemostasis may mitigate the bleeding risk.

5.5 UFH / LMWH discontinuation 24 hours prior to an elective procedure vs no discontinuation (low/moderate risk)

a. We recommend that consideration may be given to taper (UFH) or stop (LMWH) therapy prior to a procedure.

Delphi process: 13/13 panel members responding agreed (round 2).

No veterinary studies specifically addressed the relevant PICO question. Evidence summary is as for guideline 5.5 above. In patients at low to moderate risk of thromboembolic disease tapering or discontinuing heparin therapy may limit hemorrhage during procedures without significantly increasing the risk of thrombosis.

5.6 Antiplatelet agent discontinuation 5-7 days prior to surgery vs 24 hours (high risk)

a. We recommend against withdrawing antiplatelet agents within 5 days of a procedure.

Delphi process: 13/13 panel members responding agreed (round 2).

Four veterinary studies (LOE 3, Fair),[257, 260, 300, 335] and three from human medicine (LOE 6, Good),[336-338] provided evidence for this guideline. In patients receiving irreversible antiplatelet agents, a 24-hour withdrawal time is unlikely to be different than not discontinuing the agent at all in patients at high risk for thrombosis,[339, 340] and hence this guideline reflects 5.2 above.

5.7 Antiplatelet agent discontinuation 5-7 days prior to surgery vs 24 hours (low/moderate risk)

a. We recommend that antiplatelet agents be discontinued within 5 days of a procedure.

Delphi process: 12/12 panel members responding agreed (round 3).

Four veterinary studies (LOE3, Fair),[257, 260, 300, 335] and three from human medicine (LOE 6, Good),[336-338] provided evidence for this guideline. Platelet lifespans are 7-9 days in people,[341] 6.0 ±1.1 days in dogs,[342] and possibly shorter in cats.[343] However, platelet function may be acceptable to provide adequate surgical hemostasis prior to 5-7 days following cessation of medications, as functional platelets are introduced into the bloodstream on a continuous basis. In patients receiving irreversible antiplatelet agents, but with a low risk of thrombosis, progress towards a return of normal platelet function may be achieved prior to surgery by drug discontinuation and hence this guideline reflects 5.3 above.

5.8 Restarting antithrombotic therapy 24 hours post-surgery vs 3-5 days

a. We recommend that in patients at high risk, antithrombotic therapy should be restarted as soon as possible after surgery provided there is no evidence of ongoing bleeding.

5.9 Restarting antithrombotic therapy 24 hours post-surgery vs 3-5 days (high risk patient)

a. No evidence-based recommendation can be made for patients at low/moderate risk.

b. We suggest that in patients at low/moderate risk, antithrombotic therapy be restarted once there is no evidence of ongoing bleeding.

5.10 Restarting antithrombotic therapy 24 hours post-surgery vs 3-5 days (patients that develop thrombosis)

a. We recommend that antithrombotic therapy should be initiated immediately in patients that develop thrombosis in the postoperative period.

Delphi process: 13/13 panel members responding agreed (round 2).

Five studies in human medicine (LOE 6, Good-Fair) provided evidence for guideline a, which is based on an assessment of the likelihood of thrombosis compared to bleeding.[273, 344] High-risk patients are more likely to be harmed by delays in administration of thromboprophylaxis than by mild post-operative bleeding.[345-347] There was insufficient evidence to make a recommendation regarding low-risk patients, but the panel has provided a consensus recommendation for guidance. One veterinary study (LOE 5, Good) supports prompt initiation of thromboprophylaxis in patients that develop thrombosis post-operatively.[274]

5.11 Discontinuation of antithrombotic therapy in patients where an in-situ blood clot is no longer identifiable

a. We recommend that if the underlying causative conditions have resolved, that antithrombotic therapy should be discontinued following thrombus resolution.

b. In patients with unknown underlying conditions or where these conditions cannot be cured or resolved, we recommend antithrombotic therapy should be continued indefinitely.

Delphi process: 13/13 panel members responding agreed (round 2).

Evidence from 2 veterinary studies (LOE 1-5, Good) suggest that patients at high risk of thrombosis may have recurrent thrombi despite antithrombotic medications.[82, 188] Several studies (LOE 1-3, Good-Poor) suggest that patients with a non-curable predisposing condition should not have therapy discontinued,[119, 207, 348] and discontinuation is not recommended in such patients. Cessation of antithrombotic therapy, upon resolution of thrombosis when the underlying cause was resolved is supported by three case reports and a case series (LOE 4-5, Poor).[117, 274, 349, 350]

5.11 Discontinuation of antithrombotic therapy in patients where an in-situ arterial blood clot is no longer identifiable

a. We recommend that if the underlying causative conditions have resolved, that antithrombotic therapy should be discontinued following thrombus resolution.

b. In patients with unknown underlying conditions or where these conditions cannot be cured or resolved, we recommend antithrombotic therapy should be continued indefinitely.

5.12 Discontinuation of antithrombotic therapy in patients where an in-situ venous blood clot is no longer identifiable

a. We recommend that if the underlying causative conditions have resolved, that antithrombotic therapy should be discontinued following thrombus resolution.

b. In patients with unknown underlying conditions or where these conditions cannot be cured or resolved, we recommend antithrombotic therapy should be continued indefinitely.

c. In patients with a low or moderate risk of thrombosis, we suggest that the risk of hemorrhage and the ability of the animal to tolerate antithrombotic therapy should be weighed against the risk of recurrence of the prothrombotic condition.

Delphi process: 12/13 panel members responding agreed (round 2). One panel member felt it was not clear that dogs receiving immunosuppressive corticosteroids for a condition such as IMHA that was resolving would require indefinite antithrombotics.

There are few quality studies assessing the long-term treatment of venous thrombi in veterinary patients. The available evidence is comprised of case series (LOE 4, Good-Fair) and single case reports (LOE 5, Fair) and supports discontinuation of antithrombotics, upon resolution of the thrombus, when the underlying cause could be eliminated or had resolved.[14, 117, 244, 351, 352] In humans, studies (LOE 6, Good-Fair) support discontinuation of anticoagulation in patients with risk factors for thrombosis that can be resolved or removed.[353, 354] Multiple veterinary case reports (LOE 5, Poor) support indefinite use of antithrombotics in patients with chronic (non-curable) underlying causes particularly for the treatment of venous thrombi.[5, 14, 119, 355-359]

5.13 Weaning of UFH therapy

a. We recommend that if UFH is administered as an IV constant rate infusion it should be tapered (weaned) rather than abruptly discontinued.

b. Clinicians should consider weaning UFH therapy administered by the subcutaneous route.

Delphi process: 14/14 panel members responding agreed (round 1).

A single veterinary study (LOE 3, Good),[360] and five from human medicine (LOE 6, Good-Fair) provided evidence for this guideline.[361-365] A rebound hypercoagulable syndrome is described following abrupt discontinuation of UFH therapy in people and may increase the incidence of thrombotic events. A recent pilot study (LOE 3, Fair) also suggested increased thrombin production following discontinuation of subcutaneous UFH in dogs.[360]

5.14 Weaning of LMWH therapy

a. Clinicians do not need to wean low molecular weight heparin therapy prior to discontinuation.

Delphi process: 14/14 panel members responding agreed (round 1).

No veterinary studies specifically addressed the relevant PICO question. Data from 4 studies from human medicine (LOE 6, Good-Fair) were extrapolated to generate this guideline. The rebound hypercoagulability described for UFH has not been consistently observed following enoxaparin discontinuation,[366-368] although a single report was identified suggesting this might occur with dalteparin, but to a lesser extent than with UFH.[365]

5.14 Weaning of direct oral Xa inhibitor therapy

a. Clinicians should consider weaning direct oral Xa inhibitor therapies.

Delphi process: 14/14 panel members responding agreed (round 1).

No relevant veterinary studies were identified and hence 3 studies from human medicine (LOE 6, Poor) were extrapolated to generate this guideline.[369-371] Overall, there is insufficient evidence to confirm or refute a rebound effect following discontinuation of the direct Xa inhibitors. Several human case reports describe thrombotic events following discontinuation of rivaroxaban.[369-371] There are no data in dogs or cats on rivaroxaban withdrawal to provide guidance. Until more data are available, the panel suggests weaning of these therapies is reasonable.

Conclusions

These guidelines on the indications for, and prescribing, monitoring and discontinuation of antithrombotics in small animals represent the current consensus of a panel of veterinary experts. These guidance statements are based on assessments of the evidence available at the time of writing including clinical and epidemiological evidence, experimental studies, and human guidelines where appropriate. Consensus statements aim to provide guidance on potentially contentious topics, particularly where data informing clinical decisions are limited or conflicting. As will be apparent from the supporting evidence statements above, there are very few level one or two studies (randomized controlled clinical trials and prospective controlled clinical studies) in this field and the overall evidence quality was not optimal in many cases. This necessarily limits the strength of the recommendations that can be made and it is likely that some of our

recommendations will be controversial. The panel also recognizes that the evidence assessments and hence the resulting guidelines have likely been biased by our collective clinical experience.

The panel's hope for these guidelines, the domain summary manuscripts and the accompanying case illustrations is that they provide a basis for antithrombotic prescribing in small animals. We recognize and strongly believe that such guidance does not, and should not, replace the careful consideration by qualified and committed veterinarians assessing and making management decisions for individual patients. This field also continues to evolve and novel research findings potentially relevant to this topic were being presented at international meetings even as these guidelines were being prepared. As a result, the panel recognizes that these guidelines will not remain current for long and that new information will necessitate revision in the foreseeable future. The panel is therefore committed to re-appraising the literature in 5 years' time (2024) and to generating revised guidelines at that time.

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Footnotes

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