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SPECIAL ARTICLE

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Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care (CURATIVE): Domain 5—Discontinuation of anticoagulant therapy in small animals

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Abstract

Objectives: To systematically evaluate the evidence supporting the timing and mechanisms of permanent or temporary discontinuation of antiplatelet or anticoagulant medications in small animals

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

Settings: Academic and referral veterinary medical centers.

Results: Databases searched included Medline via PubMed and CAB abstracts. Two specific courses of inquiry were pursued, one focused on appropriate approaches to use for small animal patients receiving antiplatelet or anticoagulant drugs and requiring temporary discontinuation of this therapy for the purposes of invasive procedures (eg, surgery), and the other aimed at decision-making for the complete discontinuation of anticoagulant medications. In addition, the most appropriate methodology for discontinuation of heparins was addressed.

Conclusions: To better define specific patient groups, a risk stratification characterization was developed. It is recommended to continue anticoagulant therapy through invasive procedures in patients at high risk for thrombosis that are receiving anticoagulant therapy, while consideration for discontinuation in patients with low to moderate risk of thrombosis is reasonable. In patients with thrombosis in whom the underlying cause for thrombosis has resolved, indefinite treatment with anticoagulant medication is not recommended. If the underlying cause is unknown or untreatable, anticoagulant medication should be continued indefinitely. Unfractionated heparin therapy should be slowly tapered rather than discontinued abruptly.

KEYWORDS
aspirin, clopidogrel, CURATIVE, heparin, rivaroxaban

1 | INTRODUCTION

With the generation of specific recommendations for the institution of anticoagulant therapy in small animal patients comes the equally important question of the appropriate timing and manner for the discontinuation of this therapy. The situations that may merit discontinuation of anticoagulant therapy include temporary pauses to facilitate invasive medical or surgical procedures or the completion of a course of therapy. The pharmacokinetic qualities of the anticoagulant medications, duration of therapy, and individual patient health may all have a bearing on the timing and mechanism of the cessation of therapy.

Pharmacokinetic data are available in small animals for some but not all commonly used anticoagulants, and information is available

Abbreviations: CRI, constant rate infusion; F1.2, prothrombin fragment 1.2; LMWH, low molecular weight heparin; LOE, level of evidence; TAT, thrombin–antithrombin; UFH, unfractionated heparin

regarding rapid reversibility or lack of reversibility of drugs. Although a nadir of effect can be measured for some medications in terms of a single factor (eg, anti-Xa activity for heparin), prolonged anticoagulant effects may be observed in practice due to effects on other components of the coagulation cascade. Anticoagulants with irreversible mechanisms of action are more dependent on the body to regenerate either coagulation factors or platelets for restoration of coagulant competency. In these settings, even though residual drug effects may be present (and demonstrable with specific assays), they may not necessarily correlate with an increased bleeding tendency or adverse outcomes following invasive procedures. Many of these nuances remain unknown but the guidelines described herein combine clinical equipoise with known pharmacologic data and human experience to make informed statements about the discontinuation of anticoagulant medications in small animal patients.

Another important clarification is the concept of risk stratification. Some patients have a stronger tendency toward formation of thrombosis than other patients, and these individual factors have been discussed in Domain 1. The relative risk of thrombosis in animals with various conditions must be assessed on an individual patient basis, but for the purposes of this manuscript, we have defined patients with a high risk for thrombosis as dogs with immune-mediated hemolytic anemia and protein-losing nephropathy, and cats with cardiomyopathy and associated risk factors (see guideline 1.9). In addition, dogs or cats with more than one disease or risk factor for thrombosis are considered to be at high risk for thrombosis. Animals at low to moderate risk for thrombosis are dogs or cats with a single risk factor or disease and dogs or cats with known risk factor conditions that, with treatment, are likely to resolve in days to weeks. Risk is important to consider not only for the initiation of anticoagulant therapy, but also for the short- or long-term discontinuation of therapy, where the risk of recurrence is a concern. It remains important for a veterinarian to assess each patient and decide on the relative risk of continuing or discontinuing therapy.

Although the guidelines presented herein do not cover the full gamut of drugs or scenarios that may be encountered in small animal practice, the authors hope that the guidelines will provide information that may be used for justification or extrapolation for specific circumstances.

2 | PICO Question: Discontinuation of antithrombotic therapy for invasive procedures

In dogs and cats that are being treated with antiplatelet or anticoagulant medications due to a risk for thrombosis **(P)**, does discontinuation of the agent to allow for invasive procedures **(I)** compared to not discontinuing the agent **(C)** place the animal at unacceptable risk of recurrent thrombosis? **(O)**

2.1 | Guidelines

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.

2.2 | Summary of evidence

In all cases where alteration of anticoagulant therapy is considered, the risk for bleeding must be balanced with the risk for thrombosis. In patients that require invasive procedures (eg, surgery and 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 to mitigate the risk of hemorrhage. Considering other less-invasive procedures (eg, dental extraction, truncal mass removal), or those where hemorrhage may be addressed through tamponade (eg, surgery on a peripheral limb), it is more reasonable to continue anticoagulant therapy through the procedure. In sum, the risk for alteration of therapy depends both on the intrinsic risk for thrombosis (see Domain 1) balanced with the possible outcomes of hemorrhage. In reference to the human guidelines (level of evidence [LOE] 6, Good), patients with a high risk for thrombosis should not have anticoagulation stopped abruptly for procedures, although switching to other medications with more favorable pharmacokinetics is reasonable.[1] In patients at low to moderate risk for thrombosis, cessation of anticoagulant therapy may be considered to decrease the risks for unintended hemorrhage. Consideration for the risk of rebound hypercoagulability should be given when planning complete or temporary cessation of therapy.

3 | PICO Question: Discontinuation antiplatelet agents before surgery

In dogs and cats receiving irreversible platelet antagonists (eg, aspirin and clopidogrel) and undergoing elective surgery **(P)**, does discontinuation of the agent 5–7 days prior to an elective procedure **(I)** compared to not discontinuing the agent **(C)** decrease perioperative morbidity? **(O)**

3.1 | Guidelines

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.

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

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

b. Five to 7 days is a reasonable amount of time to completely clear the effects of a drug that is an irreversible inhibitor of platelet function in small animals.

3.2 | Summary of evidence

No veterinary studies that specifically addressed this question were identified, so studies from human medicine were extrapolated to generate guidelines. Even in human medicine, there is controversy and conflicting evidence on the best practice of management of antiplatelet therapy in patients requiring invasive procedures (LOE 6, Fair). [2–10] When discontinuation is advocated, it is common to recommend discontinuation of aspirin and clopidogrel 5–7 days prior to the procedure to account for the irreversible inhibition of platelet function caused by both (LOE 6, Fair).[11–16] These drugs appear to cause irreversible inhibition of platelet function in most veterinary patients (LOE 2–3, Good),[17,18] and so the 5–7 day period is also relevant for veterinary patients.

Complications associated with the continuation of antiplatelet therapy during surgery are intra- or postprocedural hemorrhage. In human patients, treatment with aspirin and clopidogrel as single agents has been associated with increased risk of hemorrhage (LOE 6, Good–Fair).[12,13,19] In addition, dual antiplatelet therapy with aspirin and clopidogrel can result in significantly more hemorrhage compared with antiplatelet monotherapy (LOE 6, Good–Fair).[20,21] Hemorrhage can result in increased need for transfusion of blood products, and an increased rate of reoperation (LOE 6, Fair).[22] Human patient groups at higher risk for hemorrhage may include those undergoing intracranial surgery, cardiac surgery, and transurethral prostatectomy (LOE 6, Fair).[13,23,24]

Discontinuation of antiplatelet medications in human patients at high risk of thrombosis, however, has resulted in severe, often catastrophic, events associated with high morbidity and mortality (eg, vascular ischemic events; LOE 6, Good).[25] In particular, discontinuation of aspirin may result in increased thromboxane production, as well as a decrease in fibrinolysis, which can promote platelet activation and thrombosis. For this reason, in human patients receiving dual antiplatelet therapy, aspirin therapy is generally continued while the other medication is discontinued. Given the variable reaction of small animals to aspirin as an antiplatelet agent (LOE 2, Good), [26,27] it is unknown if the same risk may exist, although it is worth considering when discontinuing one drug of a dual-antiplatelet protocol. Surgical trauma may also promote a procoagulant state (LOE 2 and 6, Good–Fair).[28–30] Although vascular ischemic events are less well documented in veterinary patients, their occurrence may be equally serious (especially with less evidence for the use of thrombolytic agents), and in many cases, hemorrhage that is treatable through medication and transfusion may be preferred to an untreatable thrombotic event.

4 | PICO question: Discontinuation of heparins before surgery

In dogs and cats at high risk for thrombotic events and receiving unfractionated heparin (UFH) or low molecular weight heparin (LMWH) and undergoing routine surgery **(P)**, does discontinuation of the agent 24 hours prior to an elective procedure **(I)**, compared to not discontinuing the agent **(C)**, decrease perioperative morbidity? **(O)**

4.1 | Guidelines

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 h 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.

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

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

4.2 | Summary of evidence

Human guidelines assign both a level of risk to the procedure and to the patient, regarding the risk of both hemorrhage and thrombosis in the absence of anticoagulant medications. These guidelines are absent in animals. A study in rats (LOE 6, Fair) demonstrated increased seroma formation and reduced healing at the site of a mesh hernia repair if rats received enoxaparin therapy during surgery.[31] From a procedural standpoint, intrapleural heparin therapy was associated with increased survival in dogs with pyothorax (LOE 5, Poor).[32]

Heparin is commonly used as a bridging anticoagulant protocol for human patients that are receiving chronic warfarin or direct oral anticoagulant therapy and in whom the danger of discontinuing anticoagulant therapy carries a high risk of morbidity or mortality (LOE 6, Good).[33,34] Either UFH or LMWH may be used for this bridging therapy (LOE 6, Good).[35] For these high-risk patients, undergoing surgery while anticoagulated with heparin is safer than going without anticoagulation or having surgery while anticoagulated with warfarin or a direct oral anticoagulant (LOE 6, Good).[36] Planning surgeries around the nadir of heparin effect may result in less periprocedural hemorrhage while still maintaining an appropriate anticoagulant regimen.

5 | PICO Question: Discontinuation of antiplatelet agents before surgery

In dogs and cats at high risk for thrombosis and receiving irreversible platelet antagonists (eg, aspirin and clopidogrel) and requiring surgery

(P), does discontinuation of the agent at 5–7 days prior to the procedure **(I)**, compared to discontinuation of antiplatelet therapy 24 hours before surgery **(C)**, decrease perioperative morbidity? **(O)**

5.1 | Guidelines

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

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

5.7 Antiplatelet agent discontinuation 5–7 days prior to surgery versus 24 hours (low to moderate risk)

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

5.2 | Summary of evidence

Recommendations for irreversible antiplatelet agents in humans generally advocate discontinuation 5–7 days prior to a procedure to allow for replacement of inhibited platelets with a full new generation of functional platelets (the lifespan for a human platelet is between 7–9 days,[37] and for dogs 6.0 ± 1.1 days; LOE 6 and 3, Good).[38] This may be shorter in cats (LOE 3, Fair).[39] 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.

Few studies evaluating platelet function have reported on recovery of platelet function after antiplatelet drug withdrawal. Recovery of platelet function was identified as complete in 3, 4, or 5 days in 3 different human studies, none of which related platelet function testing to clinical bleeding (LOE 6, Fair).[40–42] In dogs treated with a single dose of aspirin, platelet aggregation response to arachidonic acid was recovered between 3–6 days (LOE 3, Fair).[43] In cats treated with aspirin, platelet aggregation to arachidonic acid recovered to baseline values between 3–5 days (LOE 3, Fair).[44] In dogs treated with clopidogrel, recovery of platelet aggregation to an adenosine diphosphate agonist occurred 5–8 days after discontinuation of drug, although significant increases in aggregation responses were seen in some dogs as early as 3 days after discontinuation of clopidogrel (LOE 3, Fair).[18] Cats in one study (LOE 3, Fair) recovered baseline platelet aggregation to adenosine diphosphate and collagen 7 days after discontinuing clopdogrel.[17]

One human report (LOE 6, Fair)[45] that specifically evaluated discontinuation of clopidogrel at 1, 3, and 5 days prior to cardiac bypass surgery (in patients receiving both aspirin and clopidogrel) concluded that longer withdrawal times were superior, as patients with only a 24 hour withdrawal experienced more hemorrhagic complications and greater blood product usage. No differences in bleeding complications were detected between the 3 day withdrawal and 5 day withdrawal. These results are mirrored by another human report (LOE 6, Poor)[46] of higher transfusion rates in patients who discontinued antiplatelet therapy less than 7 days prior to major abdominal procedures, while another report (LOE 6, Fair) did not identify any significant hemorrhagic complications evaluating a <3 day withdrawal compared to a >3 day withdrawal of aspirin in humans undergoing elective coronary artery bypass graft surgery.[47] Differences in drugs may be relevant; one report documented that human patients receiving coronary artery grafts did not suffer major bleeding complications with a ticagrelor withdrawal >72 hours, but a clopidogrel withdrawal of >72 hours was associated with bleeding (LOE 6, Fair).[48]

6 | PICO Question: Restarting antithrombotic therapy following surgery

In dogs and cats requiring continued antithrombotic therapy following a surgical procedure **(P)**, does restarting antithrombotic therapy 24 hours following surgery **(I)**, compared to 3–5 days following surgery **(C)**, result in increased perioperative morbidity? **(O)**

6.1 | Guidelines

5.8 Restarting antithrombotic therapy 24 hours postsurgery versus 3–5 days (high-risk patient)

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 postsurgery versus 3–5 days (low to moderate 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.

6.2 | Summary of evidence

There is no evidence about the right approach in this situation in dogs and cats. In human patients with high thrombotic risk, anticoagulant or antiplatelet drugs should be started promptly when the patient is able to receive them (LOE 6, Good–Fair).[49,50] Based upon one case report in a dog developing postoperative thrombosis (LOE 5, Good),[51] if postoperative thrombosis occurs, anticoagulant therapy should be started promptly. One study of dogs following bioprosthesis valve placement (LOE 3, Fair) documented continued warfarin therapy following surgery. Recommendations in human medicine are dependent on risk stratification.

Studies in human medicine generally support the presence of increased bleeding if an antiplatelet drug is used postoperatively, but overall, the bleeding is mild (LOE 6, Good–Fair).[52–54] However,

if the patient is at high risk for thrombosis, it is unlikely that any hemorrhage associated with restarting anticoagulant therapy will result in morbidity that is worse than the formation of postoperative thrombosis.

7 | PICO Question: Discontinuing antithrombotic agents following dissolution of arterial clot

In dogs and cats with in situ arterial blood clots **(P)**, should antithrombotic therapy be discontinued **(I)** once there is no identifiable blood clot **(C)** or continued indefinitely? **(O)**

7.1 | Guidelines

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.

7.2 | Summary of evidence

There are few high-quality studies on the long-term treatment and recurrence of arterial thrombi in veterinary patients. The only LOE 1 (Good) study[55] found a significant difference in recurrence rate of cardiogenic arterial thromboembolism in cats between those receiving clopidogrel (49%) and those receiving aspirin (75%). Cats had clinically improved from the thrombus, but in general, diagnostics were not performed to track the presence of the clot itself, and the cardiac disease that caused the clot was not a predisposing factor that could be eliminated, supporting indefinite therapy with clopidogrel in this population. A broader case series of feline arterial thromboembolism (LOE 3, Poor) described a recurrence rate of 20% and 28% in cats when treated with low (5 mg/cat, PO, q72h) and high-dose (>40 mg/cat PO q24–72h) aspirin, respectively.[56] The majority of reviewed studies (LOE 4–5, Poor) support the long-term (indefinite) use of antithrombotics. The cessation of antithrombotic therapy, upon resolution of an arterial thrombus, is supported here by 2 single case reports and a case series (LOE 4–5, Poor).[51,57–59] In all but one instance, the underlying cause was a condition that could be directly addressed (vehicular trauma with humeral fracture). Patients in these studies had anticoagulant medication safely discontinued following resolution of the underlying cause(s). Studies supporting the indefinite use of antithrombotics were more likely to have an underlying noncurable condition (eg, cardiomyopathy or neoplasia),[60,61] and includes a case report (LOE 5, Poor) of a dog with hyperadrenocorticism that had anticoagulant therapy stopped following resolution of a vena caval thrombus and who subsequently developed a pulmonary thromboembolism and died.[62]

8 | PICO Question: Discontinuation of antithrombotic therapy following dissolution of venous clot

In dogs and cats with in situ venous blood clots **(P)**, should antithrombotic therapy be discontinued **(I)** once there is no identifiable blood clot **(C)** or continued indefinitely? **(O)**

8.2 | Guidelines

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.

8.3 | Summary of evidence

There are few quality studies assessing the long-term treatment of venous thrombi in veterinary patients. The available evidence is comprised of single case reports (LOE 5, Poor) and small case series (LOE 4, Poor). In general, there is more evidence supporting the indefinite use of antithrombotics for the treatment of venous thrombi. The majority of the cases (LOE 4 and 5, Poor) supporting the discontinuation of antithrombotics upon resolution of the thrombus had an underlying causative condition/trigger that could be directly eliminated (eg, vascular access port causing cranial vena caval thrombosis).[57] This was supported in 4 of the 7 manuscripts that were reviewed, with the underlying cause not able to be determined for the other 3.[63–66] In people, studies (LOE 6, Good–Fair) support discontinuation of anticoagulation in patients with risk factors for thrombosis (eg, oral contraceptive use, surgery, and immobility) that can be resolved or removed.[67,68] The veterinary case reports (LOE 5, Poor) supporting the indefinite use of antithrombotics were more likely to have a chronic (noncurable) underlying cause (eg, hyperadrenocorticism).[62,66,69–74] There are no studies that have been designed to assess the efficacy or compare specific antithrombotics in this subset of the population.

In human medicine, risk stratification for recurrence of venous thromboembolism is based on DASH[75] (D-dimer, age, sex, hormonal therapy [predictive score for recurrence of thromboembolism in humans]) or HERDOO2 (hyperpigmentation, edema or redness of either leg; D-dimer ≥250 μg/L while taking warfarin; body mass index ≥30 kg/m^2; or age ≥65 years [predictive score for recurrence of thromboembolism in humans]) criteria,[76] and the presence of residual vein obstruction as well as elevations of D-dimer concentrations after 3 months of anticoagulation have been used as criteria for

continued anticoagulant therapy (LOE 6, Good–Fair). [77,78] Taken as a group, however, results of studies that have specifically evaluated ultrasonographic resolution of venous thromboembolism to dictate the duration of anticoagulant therapy have been inconsistent with regards to their recommendations (LOE 6, Good–Fair). [79–81]

9 | PICO Question: Abrupt versus tapered discontinuation of unfractionated heparin

In dogs and cats receiving UFH therapy **(P)**, does abrupt discontinuation of heparin therapy **(I)** versus tapered discontinuation of therapy **(C)** result in rebound hypercoagulability? **(O)**

9.1 | Guideline

5.13 Weaning of UFH therapy

- **a.** We recommend that if UFH is administered as an IV constant rate infusion (CRI) it should be tapered (weaned) rather than abruptly discontinued.
- **b.** Clinicians should consider weaning UFH therapy administered by the subcutaneous route.

10 | PICO Question: Abrupt versus tapered discontinuation of low molecular weight heparin therapy

In dogs and cats receiving LMWH therapy **(P)**, does abrupt discontinuation of heparin therapy **(I)** versus tapered discontinuation of therapy **(C)** result in rebound hypercoagulability? **(O)**

10.1 | Guidelines

5.14 Weaning of LMWH therapy

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

11 | PICO Question: Abrupt versus tapered discontinuation of oral Xa inhibitors

In dogs and cats receiving direct oral Xa inhibitor therapy **(P)**, does abrupt discontinuation of this therapy **(I)** versus tapered discontinuation of therapy **(C)** result in rebound hypercoagulability? **(O)**

11.1 | Guideline

5.15 Weaning of direct oral Xa inhibitor therapy

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

11.2 | Summary of evidence

Theroux et al first described a "rebound" hypercoagulation phenomenon following discontinuation of heparin therapy (LOE 6, Good).[82] In this study, 403 patients were randomized to receive IV CRIs of UFH, aspirin, both drugs, or neither drug during the acute phase of unstable angina. Thirteen percent (14/107) of the patients receiving UFH alone had repeat ischemic events a median of 9.5 hours after discontinuation of the CRI. In addition, these events were more likely to be characterized as severe. Only 4.9% of patients in the other 3 groups (4/101, 5/108, and 4/87) experienced a "reactivation" of unstable angina. The patients in this report that received both heparin and aspirin had the fewest repeat ischemic events, suggesting that platelet inhibition might be protective in this population.

Subsequent studies (LOE 6, Good–Fair) have suggested that elevated thrombin production (indicated by elevated concentrations of prothrombin fragment 1.2 [F 1.2]) following discontinuation of UFH may contribute to postinfusion thrombophilia, and a prospective human study[83] noted that patients subjected to an abrupt cessation of UFH therapy had a significant increase (164%) in F 1.2, contrasted to a 57% increase in patients given a tapering dose IV, and a 44.5% increase in patients transitioned to a subcutaneous weaning protocol. Decreased activity of tissue factor pathway inhibitor (TFPI) may also have contributed to thrombophilia in this study. These studies taken together suggested that abrupt cessation of UFH CRIs may increase the risk of thrombosis and is not recommended. Subsequent studies in people (LOE 6, Good–Fair)[84,85] verified this effect with UFH therapy but did not note it with LMWH therapy (enoxaparin).[86–88]

Another human report (LOE 6, Good) demonstrated a rebound phenomenon with both UFH and LMWH (dalteparin) in patients with unstable angina.[89] In this study, F1.2 levels increased more rapidly following drug discontinuation in the UFH group, with a more gradual increase in the LMWH group. Circulating thrombin–antithrombin (TAT) complexes were increased in both groups but increased more rapidly in the UFH-treated patients.

A recent pilot study in dogs (LOE 3, Fair)[90] suggested increased thrombin production following discontinuation of primarily subcutaneous UFH in the dog (an IV UFH bolus was given for the final dose). In this study, increased concentrations of TAT complexes were apparent 12 hours following discontinuation of UFH.

Although there is not enough strong evidence to support a rebound effect following discontinuation of the newer Xa inhibitor medications (eg, rivaroxaban and apixaban), there is also not strong evidence to refute this possibility. The concern is relevant both for termination of a course of anticoagulant therapy as well as for short-term discontinuation to allow invasive procedures (where use of a bridging anticoagulant such as UFH or LMWH may be prudent). The widespread use of these drugs in humans is relatively recent, and while some human case reports (LOE 6, Poor) have suggested temporal thrombotic events following discontinuation of rivaroxaban,[91–93] it may be a number of years before the full physiologic effects of discontinuation of or switching from Xa inhibitor medications are known.

Confirmatory studies of the initial presented evidence in the dog, and information about discontinuation of heparin therapy in the cat

are needed to give strength to the guideline recommendations. Given the relatively high frequency of use of heparin in the critical care setting, this information could have significant impacts on patient management and the cost of treatment. Available assays such as TAT complex concentration or more advanced testing such as thrombin generation or thromboelastography may help to document ex vivo thrombophilia. Studies in both experimental animals and those with naturally occurring disease associated with thrombophilia are important in this context.

12 | CONCLUSION

As is expected in any comprehensive review of a topic, knowledge gaps for specific clinical questions are as likely to be identified as concrete guidelines. Although there are reasonable guidelines that exist in human medicine for management of thrombotic conditions, the immediate relevance to veterinary conditions associated with thrombosis or thromboembolism is not always clear, and this data must be generated in species-specific corhorts to provide high-quality evidence on which to base recommendations.

In particular, the indications for single and dual antiplatelet therapy in animals are not defined, and consequently, the relative risk reduction from discontinuation of one or both is unknown. Likewise, quantitative measures of the benefits of anticoagulant or antiplatelet therapy are absent from the veterinary literature, partly due to low number of animals reported, and partially due to an inability to definitively display effective protection from thrombosis for a given anticoagulant regimen. Future steps, such as a registry of patients receiving anticoagulant medications for specific diagnoses, may help to generate enough data to draw meaningful conclusions of the benefits of anticoagulant therapy and additionally the indications (or not) for discontinuing therapy. Quantifications of hemorrhage or complications in animals that have had specific procedures while being treated with platelet antagonist drugs are also lacking in the veterinary literature, and while some papers have described increased bleeding associated with preoperative nonsteroidal anti-inflammatory drug use (ketoprofen), others have not (ketoprofen, carprofen, deracoxib, meloxicam).[94–97] Although it is difficult to quantify, the collection of information with a specific focus on complications associated with concurrent anticoagulation and invasive procedures will be beneficial.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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