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SPECIAL ARTICLE

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Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care (CURATIVE): Domain 4—Refining and monitoring antithrombotic therapies

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Abstract

Objectives: To systematically review the evidence for therapeutic monitoring of antithrombotic drugs in small animals, develop guidelines regarding antithrombotic monitoring, and identify knowledge gaps in the field.

Design: First, a standardized, systematic literature review was conducted to address predefined PICO (Population/Patient, Intervention, Control, Outcome) questions, with categorization of relevant articles according to level of evidence and quality. Preliminary guidelines were developed by PICO worksheet authors and the domain chair. Thereafter, a Delphi-style survey was used to develop consensus on guidelines regarding therapeutic monitoring of antithrombotics in dogs and cats.

Setting: Academic and referral veterinary medical centers.

Results: PICO questions regarding the utility of therapeutic monitoring were developed for 6 different antithrombotic drugs or drug classes, including aspirin, clopidogrel, warfarin, unfractionated heparin, the low molecular weight heparins, and rivaroxaban, The majority of the literature pertaining to therapeutic monitoring of antithrombotic drugs was either performed in experimental animal models of disease or involved studies of drug pharmacokinetics and pharmacodynamics in healthy laboratory animals. There was a paucity of high level of evidence studies directly addressing the PICO questions, which limited the strength of recommendations that could be provided. The final guidelines recommend that therapeutic monitoring should be performed when using warfarin or unfractionated heparin in dogs and cats at risk of thrombosis. There is insufficient evidence to make strong recommendations for therapeutic monitoring of aspirin or low molecular weight heparin in dogs and cats at this time.

Conclusions: As in other CURATIVE domains, significant knowledge gaps were highlighted, indicating the need for substantial additional research in this field. Ongoing investigation of the role of therapeutic monitoring of antithrombotic therapies will undoubtedly facilitate improved outcomes for dogs and cats at risk of thrombosis.

KEYWORDS
anticoagulant, antiplatelet agent, cats, dogs, thromboprophylaxis, therapeutic monitoring

Abbreviations: AA, arachidonic acid; ACT, activated clotting time; aPTT, activated partial thromboplastin time; CURATIVE, Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care; IMHA, immune-mediated hemolytic anemia; INR, international normalized ratio; LMWH, low molecular weight heparin; LOE, level of evidence; PD, pharmacodynamic; PICO, population or patient, intervention, control, outcome; PK, pharmacokinetic; PT, prothrombin time; PTE, pulmonary thromboembolism; PT^{INR},

INTRODUCTION

Therapeutic drug monitoring can be a valuable tool for guiding safe and effective drug therapy regimens in individual patients.[1] Therapeutic drug monitoring is most appropriately implemented for drugs in which the clinical response cannot be easily titrated, there is marked interindividual variation in pharmacokinetics (PKs) and pharmacodynamics (PDs), in the treatment of potentially life-threatening conditions, and for drugs with narrow safety margins.[1] These criteria have classically applied to patients receiving thromboprophylactic drugs, particularly older generation drugs such as warfarin and unfractionated heparin (UFH). The emergence of newer thromboprophylactic drugs with more reliable PK/PDs in human medicine has led to a reduced need for therapeutic drug monitoring, however monitoring is still indicated in certain situations. Given species differences in diseases predisposing to thrombosis and thromboprophylactic drug PK/PDs, veterinary specific guidelines are needed to direct the veterinary clinician with regard to therapeutic monitoring of these important drugs.

In these small animal consensus statements, Domain 1 defined dog and cat populations at risk of thrombosis, Domain 2 defined rational therapeutic use of antiplatelet and anticoagulant agents, and Domain 3 explored evidence-based protocols for antiplatelet and anticoagulant agents. The objectives of this domain, Domain 4, were to (a) systematically review and summarize the evidence for therapeutic monitoring of selected antithrombotic drugs to reduce the risk of complications or improve any outcomes in dogs and cats at risk for thrombosis, (b) develop clinical practice guidelines regarding antithrombotic monitoring, and (c) identify knowledge gaps in the field to guide future research.

MATERIALS AND METHODS

The process of establishing the Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care (CURATIVE), the creation of domains of investigation, standardizing evidence assessment through PICO (Population or Patient, Intervention, Control or Comparison, Outcome) worksheets, and the development and refinement of guidelines with Delphi surveys are summarized in the first paper of this series.[2] As with the remainder of the CURATIVE guidelines, patient-centered safety and efficacy outcomes were used within Domain 4. Antithrombotic safety was assessed predominantly by the risk of hemorrhagic complications, including fatal and nonfatal hemorrhage. Additionally, the requirement for blood product transfusions was used as an indirect indicator of bleeding complications that are potentially attributable to antithrombotic therapies. Within Domain 4, antithrombotic efficacy was assessed with a combination of direct and indirect indicators. Direct indicators of antithrombotic efficacy were considered to be lack of thrombus progression and lack of new thrombosis in the case of existing thrombosis, or a delay in the interval to new thrombosis. Indirect indicators of antithrombotic efficacy were considered improved survival and reduction in, or avoidance of, organ dysfunctions. Evidence was sought regarding the comparison of different tests to monitor the safety and efficacy of antithrombotic therapies, and whether or not monitoring compared to no monitoring at all had an effect on safety and efficacy of antithrombotic drugs. Within Domain 4, monitoring tests were considered the intervention in the PICO format, rather than the outcome.

A spectrum of diagnostic tests discussed in the literature was considered with regard to their utility for therapeutic monitoring of antithrombotic therapy. Specifically, tests for monitoring antiplatelet therapy were considered to include measurement of closure time with a platelet function analyzer-100, platelet aggregometry, and platelet mapping. Tests for monitoring anticoagulant therapy included, but were not limited to, prothrombin time (PT), international normalized ratio (INR) calculated from the PT (PT^{INR}), activated clotting time (ACT), activated partial thromboplastin time (aPTT), anti-Factor Xa activity (anti-Xa), and viscoelastic tests, including thromboelastography (TEG; Haemonetics, Braintree, MA), rotational thromboelastometry or thromboelastometry (TEM; ROTEM Delta, Instrumentation Laboratory, A Werfen Company, Bedford, MA), and Sonoclot (Sienco Inc., Boulder, CO).

For each PICO question, level of evidence (LOE) is listed within the manuscript for literature pertaining to the PICO question. Additional literature, not directly addressing the PICO questions, is provided for the purposes of discussion but a LOE is not provided if it did not directly address the question (ie, was not in a patient population at risk for thrombosis, did not have an appropriate comparator group, or did not report patient centered outcomes). Full details of paper classification and grading are provided as supplementary data (Data S1). Studies in people (LOE 6) were not included in literature searches for Domain 4. Within each LOE, the quality of the study was subjectively assessed as Good, Fair, or Poor; it should be noted that these quality descriptors include an assessment of relevance to the PICO question, and as such a well-designed study may still be assessed as Fair or Poor if it does not directly address the PICO question.

Ten PICO questions were originally developed for Domain 4; 1 each addressing therapeutic monitoring of the antiplatelet agents aspirin and clopidogrel, 2 questions addressing warfarin, 2 questions addressing UFH, 2 addressing low molecular weight heparins (LMWH), and 2 addressing rivaroxaban. Each PICO question, the resultant guidelines, evidence summaries (described separately for dogs and cats), and remaining knowledge gaps are outlined below.

PICO QUESTION: Aspirin monitoring

In dogs and cats with a risk of arterial/venous thrombosis being treated with aspirin **(P)**, does the use of 1 tool for platelet function assessment/therapeutic monitoring **(I)** compared with no therapeutic

international normalized ratio calculated from the prothrombin time; ROTEM, rotational thromboelastometry; TEG, thromboelastography; TEM, thromboelastometry; TT, thrombin time; UFH, unfractionated heparin

monitoring or using another platelet function system **(C)** reduce the risk of complications and improve any outcomes? **(O)**

Guidelines

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 arterial thromboembolism.

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

Evidence summary

Dogs

No LOE 1 or 2 studies directly address the PICO question. Numerous LOE 3 studies support the PICO question and suggest that platelet inhibition detectable by aggregometry is associated with reduced risk of arterial thromboembolism; however, there is considerable variation in the agonists used for aggregometry in different studies.[3–6] Freeman et al reported that arachidonic acid (AA)-stimulated platelet aggregation is a better predictor of the antithrombotic effects of aspirin in a small-diameter graft model than when ADP or collagen were used as agonists (LOE 3, Fair).[3] Similarly, other authors have reported that aspirin-inhibited AA-induced platelet aggregation is a more useful monitoring tool for documenting the antithrombotic effect of aspirin than ADP-induced platelet aggregation (LOE 3, Fair),[4] and collagen-induced platelet aggregation (LOE 3, Good).[5] Yet other animal models have documented collagen to be a more useful agonist for platelet aggregometry studies of aspirin's therapeutic effect than ADP (both LOE 3, Fair).[6,7] AA and ADP have also proven to be superior agonists to serotonin when documenting aspirin-induced platelet inhibition (LOE 3, Fair).[8]

One study (LOE 3, Fair) opposes the worksheet question in an experimental model of heartworm-induced pulmonary thromboembolism, suggesting that achieving at least 50% inhibition of platelet reactivity (collagen-induced platelet aggregation) by aspirin did not reduce the severity of lung lesions induced by worm embolization and related pulmonary thromboembolism.[9] However, it is likely that this situation reflects the lack of efficacy of aspirin for thromboprophylaxis in heartworm disease specifically, rather than the lack of efficacy of achieving aspirin-induced platelet inhibition in general.

Cats

Two published manuscripts, reporting different aspects of the same LOE 3 study (Poor), directly address the PICO question.[10,11] These investigators documented a benefit of individually adjusted aspirin dosing relative to fixed dose aspirin in an experimental model of dirofilariasis. The model involved the transplantation of 4 adult heartworms into the external jugular vein of each cat, followed by 5 months of therapy or no treatment, prior to pulmonary angiography, euthanasia, and postmortem evaluation of the lungs by light microscopy and scanning electron microscopy. Cats in the fixed dose aspirin group ($n = 7$) received 97.5 mg of aspirin PO twice a week, whereas cats in the adjusted aspirin group ($n = 6$) had their oral aspirin dose adjusted every 2–3 weeks to maximize in vitro inhibition of platelet aggregation. Unfortunately, no information is provided in either manuscript regarding the aggregometry methodology used. By the end of the study, aspirin doses in the adjusted group averaged 35 mg/kg twice a week, with a range from 22 mg/kg twice a week to 15 mg/kg/day. Cats in the adjusted aspirin dose group had a lower proportion of obstructed right and left distal caudal pulmonary arteries identified with pulmonary angiography than those in the fixed dose aspirin and nontreated groups. Similarly, cats in the adjusted aspirin group had less pulmonary thrombosis at postmortem (0/6 cats) than those in the fixed aspirin dose group (6/7 cats), and untreated heartworm-infected cats (7/7 cats). Nonetheless, there was no significant difference in the mean percentage of the pulmonary arterial surface affected by villous proliferation and the overall severity of the pulmonary lesions, prompting the authors to conclude that aspirin only reduced a component of the pulmonary response to heartworm infection in these cats, and thus cannot be recommended for treatment of heartworm disease in the cat.[10,11] Although these papers suggested that individually adjusted aspirin dosing may be beneficial in cats, there was inadequate methodologic detail to facilitate replication, and these studies are limited to the very specific condition of heartworm disease, compromising their generalizability.

Numerous studies have assessed the effect of aspirin on platelet aggregation in healthy cats (ie, not in cats at risk of thrombosis and hence not directly addressing the PICO question), but their findings have been variable.[12–16] Two of these studies have observed a decreased aggregation response to AA (but not ADP[12,14] or collagen[14]), in platelets from cats treated with aspirin, suggesting that AA may be a useful agonist to demonstrate the antiplatelet effects of aspirin.[12,14] In contrast, other authors have observed aspirin to decrease collagen-induced platelet aggregation; these investigators again found no significant effect of aspirin on platelet aggregation in response to ADP.[13] A more recent study found that aspirin had no effect on whole blood (impedance) aggregometry of aspirin-treated cats with both ADP and collagen agonists.[15] Differences between studies may be due to the concentration of agonist used in the various assays, the dose of aspirin administered, and to a lesser extent the timing of blood sampling related to aspirin dosing. Alternatively, these studies may suggest that aspirin simply has limited antiplatelet potency in cats.

Although most of the aforementioned studies focus on platelet aggregometry, 1 study has compared different test types, with a focus on point-of-care tests, to assess platelet function in response to antiplatelet therapy in cats.[16] These authors compared the Multiplate (impedance aggregometry; Diapharma Group Inc., West Chester, OH), with the platelet function analyzer-100 (mechanical aperture closure; Siemens Healthcare Diagnostics Inc., Tarrytown, NY), and Plateletworks (platelet counting; Helena Laboratories, Beaumont, TX) in cats treated with aspirin, clopidogrel, or a combination of aspirin and clopidogrel. The only antiplatelet effect of aspirin alone was detected using

the Plateletworks with collagen, whereas clopidogrel induced platelet inhibition with all of the test types. The authors suggest that their findings either demonstrate that aspirin is a less effective antiplatelet drug in cats or the tests used were not ideal to assess aspirin's antiplatelet effects.[16]

The majority of the literature describing the administration of aspirin to cats at risk of thrombosis, in a clinical setting, does not involve therapeutic monitoring and hence cannot be used to inform the PICO question.[17–20]

Knowledge gaps

Further studies are needed to inform the PICO question and determine whether or not therapeutic monitoring of aspirin could be beneficial in improving its antithrombotic efficacy in dogs and cats. With the increased use of fixed dose clopidogrel as a first line antiplatelet agent, and its documented efficacy in reducing thrombosis in at risk cats,[18] it is possible that knowledge gaps regarding aspirin may go unfilled. Nonetheless, further investigation of the utility of dual antiplatelet therapy is warranted, and therapeutic monitoring may have a role to optimize safety and efficacy in this setting.

PICO QUESTION: Clopidogrel monitoring

In dogs and cats with a risk of arterial/venous thrombosis being treated with clopidogrel **(P)**, does the use of 1 tool for platelet function assessment/therapeutic monitoring **(I)** compared with no therapeutic monitoring or using another platelet function system **(C)** reduce the risk of complications and improve any outcomes? **(O)**

Guidelines

Guidelines for clopidogrel monitoring were not formulated at this time due to time constraints of the CURATIVE initiative, given the lack of literature directly addressing the PICO question, and the apparently safe, routine use of standard doses of clopidogrel as an antiplatelet drug in clinical practice.

PICO QUESTION: Warfarin monitoring

Originally, 2 PICO questions regarding the therapeutic monitoring of warfarin were developed. First, in dogs and cats with a risk of arterial/venous thrombosis being treated with warfarin **(P)**, does the use of the 1 coagulation test for therapeutic monitoring (eg, PT, ACT, aPTT, anti-Xa, or viscoelastic tests [TEG/TEM/Sonoclot]) **(I)** compared with no therapeutic monitoring or using another coagulation test type **(C)** reduce the risk of complications and improve any outcomes? **(O)** And second, in dogs and cats with a risk of arterial/venous thrombosis being treated with warfarin **(P)**, does the use of the PT^{INR} for therapeutic monitoring **(I)** compared with PT **(C)** reduce the risk of complications and improve any outcomes? **(O)** Since there was surprisingly little literature identified during the literature search that directly addressed these PICO questions, they were combined into 1 PICO question, and a single worksheet was completed. The final worksheet question stated: In dogs and cats with a risk of arterial/venous thrombosis being treated with warfarin **(P)**, does the use of the 1 coagulation test for therapeutic monitoring **(I)** compared with no therapeutic monitoring or using another coagulation test type **(C)** reduce the risk of complications and improve any outcomes? **(O)**

Guidelines

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 PT.

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

Evidence summary

Dogs

No studies in dogs specifically addressed the PICO question. Additional rationale for the suggestion that warfarin should not be used in dogs and cats is provided in Domain 2 (See Guideline 2.15). A thorough review of the literature pertaining to therapeutic monitoring of warfarin in dogs and cats is provided below as a definitive reference given that it is unlikely that warfarin will be included in future CURATIVE iterations.

Two case series evaluated warfarin therapy in dogs undergoing valve replacement (ie, at risk of thrombosis); although dogs in both studies were monitored with PT^{INR}, neither study assessed the utility of therapeutic monitoring, rather both studies performed therapeutic monitoring in all dogs.[21,22] Although this lack of a comparator group meant that these studies did not directly address the PICO question, they nonetheless suggested some therapeutic efficacy of warfarin when adjusted to achieve target INR. The first study included 8 dogs undergoing mitral valve replacement; the 7 dogs that survived the perioperative period were treated with warfarin, starting within 2–4 days of surgery with the goal to continue life-long.[21] Warfarin was adjusted (0.05–0.2 mg/kg PO q 24 h) to achieve a target INR of 2.5–3.5.[21] Ultimately, 3 dogs died of confirmed thrombosis of the valve prosthesis, and 3 of suspected thrombosis resulting in fatal pulmonary edema. Interestingly, in the 3 dogs that died of suspected thrombosis, each had their warfarin administration disrupted in the 72 hours prior to the onset of pulmonary edema, suggesting that warfarin titrated to achieve therapeutic INR may have had a protective effect.[21] The other study included 12 dogs with congenital tricuspid valve dysplasia that underwent bioprosthetic valve replacement.[22] Warfarin was initiated on the second postoperative day and continued for 3 months after surgery, with dose adjustment to target a PT^{INR} of 2.5 (range 2.0–3.0). All dogs also received aspirin (20 mg PO/d, commenced 1–2 wk postoperatively and continued for at least 1 y). Each warfarin dose adjustment involved

changing the total weekly dose by 2–10%. Two of 12 dogs did not survive to discharge; 1 of which was suspected to be due to thrombosis. Another 2 dogs had significant thrombosis within 3 weeks of surgery. The remaining 8 dogs did not have evidence of thrombosis.[22] Given the likely risk of thrombosis created by a valve prosthesis implanted in these dogs, the high long-term survival rate is suggestive of efficacy of the antithrombotic therapy, either or both of the warfarin titrated to a PT^{INR} of 2.5, and daily oral aspirin.[22]

In addition to the aforementioned clinical studies, experimental studies in dogs also provide some information regarding the utility of therapeutic monitoring of warfarin. Similarly, the available studies do not directly address the PICO question, as only a single monitoring test is used (ie, no comparator). Two studies in experimental models associated with a high risk of thrombosis (Quality Fair) reported the use of a combination of warfarin, adjusted to maintain PT 1.5× normal, and aspirin, for 8 weeks postoperatively in dogs undergoing small diameter arterial grafts (carotid and femoral, $n = 18$ dogs), and superior vena cava grafts ($n = 9$ dogs) with autogenous small intestinal submucosa.[23,24] Overall graft patency rates were good; 75% of arterial grafts and 89% of venous grafts.[23,24] Nonetheless it was noted that 1 dog died of hemorrhage, and concurrently had a very high PT.[24] These studies also suggest utility of adjusting warfarin based on PT, and support that marked elevations of PT are sensitive to signify risk of hemorrhage.[23,24]

While individual studies rarely report the thromboplastin reagent used in the PT test, 1 experimental study in dogs at risk of thrombosis specifically reported the use of bovine brain thromboplastin combined with adsorbed bovine plasma (referred to as Thrombotest).[25] Variation in the thromboplastin reagent used in the PT accounts for the majority of test variability, and is the reason that the INR was developed to standardize PT measurement in human medicine. Although this study did not directly address the PICO question because it did not compare 1 monitoring test to another, or no monitoring, it nonetheless provided useful information.[25] This study used the Thrombotest PT to monitor 3 regimens of warfarin therapy in healthy Labrador retriever dogs undergoing mitral valve disc implantation. Dogs in this study also received variable regimens of UFH.[25] The authors noted that stable anticoagulation was very difficult to maintain and all 3 treatment regimens were ineffective at preventing thrombosis.[25]

Another experimental study in healthy dogs evaluated the effect of 3 loading doses of warfarin on the PT^{INR} in dogs undergoing bilateral iliac grafting, however did not directly address the PICO question as patient centered outcomes (ie, postprocedure patency of the grafts) were not reported.[26] Nonetheless, this study was included in the worksheet because both PT and aPTT were measured. PT increased in a dose-dependent fashion, whereas the aPTT was not significantly increased with treatment (compared to baseline) and showed no dose dependent change. As such, this study is evidence that aPTT is unlikely to be a useful monitoring test for warfarin.[26]

Cats

No studies in cats specifically addressed the PICO question. Only 1 experimental study in cats at risk of thrombosis (Quality Poor) documented the therapeutic monitoring of warfarin therapy in this species.[27] Like the dog studies, this study did not specifically address the PICO question as only 1 monitoring test was described. Three cats were treated with orally administered sodium warfarin; the doses were not reported but were adjusted to achieve a PT 2–4 times the control level, at which time carotid endarterectomy was performed. The duration of warfarin administration varied from 3–7 days prior to surgery, and included 2–5 doses of warfarin.[26] Despite this, all 6 carotid arteries thrombosed within 30 minutes of endarterectomy. Another treatment group of 3 cats in the same study were treated with warfarin, as above, and a single oral dose of aspirin (10 mg/kg), and again all 6 carotid arteries experienced rapid thrombosis after endarterectomy.[27] This study suggests that marked prolongation of PT by warfarin did not predict therapeutic efficacy in this model.

Another study evaluated the PDs of warfarin in healthy cats.[28] Although studies in healthy animals do not specifically address the PICO questions, it was of interest in that it documented wide interindividual PK/PD variation, prompting the authors to suggest that individual dose algorithms would be warranted to ensure optimal warfarin dosing in cats.[28] Of note, the authors of the aforementioned study had used individually adjusted doses, yet still had therapeutic failure.[27] Studies such as this led to the consensus recommendation that warfarin should not be used as an anticoagulant in cats.

Knowledge gaps

In order to directly address the PICO question, additional studies comparing different tests for therapeutic warfarin monitoring, with long-term follow-up of safety and efficacy outcomes, would be ideal; these are unlikely to ever be performed. The authors believe that the emergence of LMWHs and, more recently, direct oral anticoagulants as safer and effective alternatives for anticoagulation make it unlikely that researchers will undertake future investigations of warfarin in dogs and cats.

PICO QUESTION: Unfractionated heparin monitoring

In dogs and cats with a risk of arterial/venous thrombosis being treated with UFH **(P),** does the use of 1 coagulation test for therapeutic monitoring **(I)** compared with no therapeutic monitoring or using another coagulation test type **(C)** reduce the risk of complications and improve any outcomes? **(O)**

Guidelines

4.3 | Unfractionated heparin

a. We recommend anti-Xa activity for UFH monitoring in dogs because evidence supporting the use of other monitoring tests (eg, ACT, aPTT, TEG, and Sonoclot) is limited at this time.

Evidence summary

Dogs

There are sparse data regarding the clinical impact of therapeutic monitoring of UFH in dogs. The available data suggest that there is a benefit of (a) adjusting doses based upon therapeutic monitoring and (b) that anti-Xa activity is the criterion standard for UFH monitoring. Other hemostatic tests may have a role in monitoring UFH, although clinical utility needs to be demonstrated.

The PICO question is supported by 1 LOE 1 (Fair) study.[29] Helmond et al performed a randomized, prospective, controlled, clinical trial in dogs with immune-mediated hemolytic anemia (IMHA).[29] These dogs were either managed with a constant dose of UFH (150 U/kg SC q 6 h for the first 7 days, followed by q 8 h, $n = 7$ dogs) or individually adjusted doses of UFH based on a nomogram derived from anti-Xa activity ($n = 8$ dogs), until discontinuation on day 35. The study compared median survival times of the respective groups, with a 180 day follow-up. The individually adjusted UFH dosing group had improved survival (median >180 days) compared to the constant dose group (median 68 days).[29] The dosing schemes utilized in both groups were not associated with hemorrhagic complications. Thrombotic complications were noted with increased frequency in the constant dose group compared to the individually adjusted dosing group.[29] Overall, this is a useful study supporting the PICO question, indicating that UFH monitoring with anti-Xa activity and dose adjustment to achieve the target range of 0.35–0.7 IU/mL in clinical patients at high risk of thrombosis resulted in improved outcome compared to fixed UFH dosing without monitoring.[29]

Consistent with the need for individual dose adjustment, another prospective case series of fixed UFH dosing (300 U/kg SC q 6 h) in dogs with IMHA found inconsistent achievement of target anti-Xa activity.[30] Nonetheless, this study did not directly address the PICO question, as it lacked a comparator group and did not adjust UFH doses in response to anti-Xa measurements.

Numerous studies in healthy dogs, although not directly addressing the PICO question (ie, not performed in dog at risk of thrombosis, and not evaluating clinically relevant outcomes), have compared anti-Xa activity as the criterion standard to other tests for monitoring the anticoagulant effects of UFH. Comparator tests included aPTT and thrombin time (TT)[31]; PT and aPTT[32]; PT, aPTT, and TEG[33]; PT, aPTT, and Sonoclot[34]; PT and aPTT with a point-of-care analyzer[35]; aPTT and antithrombin activity[36]; and aPTT and TEG with various activators.[37] These studies demonstrate that of the traditional coagulation tests, aPTT correlates best with anti-Xa activity, and that strong activators are necessary in order for viscoelastic coagulation tests to be useful for UFH monitoring.

Cats

No studies in cats directly addressed the PICO question. The only identified study that conducted therapeutic monitoring in cats receiving UFH did not address the PICO question as it was performed in healthy cats, and there was no comparison group (ie, all cats underwent therapeutic monitoring with anti-Xa activity).[38] As such, the available evidence suggests that anti-Xa is the most appropriate test for monitoring UFH therapy at this time.

Knowledge gaps

The emergence of LMWHs and direct oral anticoagulants as safe and effective alternatives to UFH in dogs and cats has already resulted in a shift in research investigations toward these newer anticoagulant drugs. As such, existing knowledge gaps regarding the optimal use of UFH in veterinary patients, including its monitoring, may go unfilled. Nonetheless, the use of UFH for anticoagulation of patients undergoing extracorporeal therapies remains widespread in veterinary practice but is poorly described in the primary literature; rather addressed in review articles or mentioned briefly in primary literature describing other aspects of these therapies.[39–41] Future investigations to optimize UFH therapy in veterinary patients are perhaps best targeted to animals being treated with extracorporeal therapies. In these patients, alternatives to anti-Xa activity are likely required given the dynamic nature of these therapies and hence the need for frequent and serial assessment of the potency of anticoagulation.

PICO QUESTION: Unfractionated heparin monitoring

In dogs and cats with a risk of arterial/venous thrombosis being treated with UFH **(P)**, does targeting a specific anti-Xa range **(I)** compared with anti-Xa activity outside this range **(C)** reduce the risk of complications and improve any outcomes? **(O)**

Guidelines

4.3 | Unfractionated heparin

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

Evidence summary

Dogs

Few studies specifically examine the safety or efficacy of achieving a specific anti-Xa activity in dogs at risk of thrombosis receiving UFH therapy. In addition to extrapolation from human medicine, the target anti-Xa activity range is derived from an experimental model of induced femoral vein thrombosis in healthy dogs (LOE 3, Fair), in which achievement of this range after SC UFH dosing was associated with a proven antithrombotic effect.[42] Subsequently, a prospective-blinded study performed in dogs with IMHA (LOE 1, Fair) identified improved clinical outcome when this anti-Xa activity range was used to adjust

UFH in individual patients, compared to constant dosing.[29] This provides further supporting data to suggest the anti-Xa activity range for UFH of 0.35–0.7 IU/mL is an appropriate therapeutic target.

Cats

No information exists specifically addressing the PICO question in cats (ie, examining the safety or efficacy of achieving a specific anti-Xa activity in cats at risk of thrombosis receiving UFH). One study in 5 healthy cats receiving 250 U/kg UFH SC every 6 hours described reliable achievement of anti-Xa activity in the 0.3–0.7 U/L range on day 3 and day 5 of treatment (4 h postdose).[38] Two of the 5 cats experienced bruising, bleeding around their intravenous catheters, and epistaxis while receiving UFH in the target anti-Xa range.[38] As such, it was considered that an anti-Xa target of 0.35-0.7 U/mL is reasonable in cats until more evidence is available.

Knowledge gaps

As outlined in Domain 2, further studies in dogs with naturally occurring disease are needed to determine the role of UFH as an antithrombotic in dogs, particularly when compared to LMWH and direct oral anticoagulants. Such studies should involve therapeutic drug monitoring with anti-Xa activity to ensure valid comparisons of safety and efficacy. Future studies in cats are unlikely to be prioritized given the apparently uncommon clinical use of UFH in this species.

PICO QUESTION: Low molecular weight heparin monitoring

In dogs and cats with a risk of arterial/venous thrombosis being treated with LMWH **(P),** does the use of 1 coagulation test for therapeutic monitoring **(I)** compared with no therapeutic monitoring or using another coagulation test type **(C)** reduce the risk of complications and improve any outcomes ? **(O)**

Guidelines

4.4 | Low molecular weight heparin

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

Evidence summary

Dogs

Four LOE 3 studies, in experimental models of thrombosis, directly address the PICO question in dogs, but they have different comparator groups and involve the IV administration of LMWH, which is in contrast to the standard of SC administration in clinical cases.[43–46] Libersan et al (LOE 3, Good) demonstrated that dogs treated with a fixed IV dose of enoxaparin (bolus then continuous rate infusion) started before the end of a 90 minute period of coronary artery occlusion, and throughout reperfusion, had a decreased infarct size by 50% relative to dogs in the control group, suggesting improved reperfusion and decreased reocclusion with thromboprophylaxis.[43] In this model, anti-Xa activity was the most sensitive monitoring test to the anticoagulant effect of enoxaparin, with all dogs achieving an anti-Xa activity in the range of 0.6–0.75 IU/mL. An increased aPTT was also observed in the enoxaparin-treated group during treatment, compared to baseline, as was an increased TT, although the latter was not significantly increased compared to control-treated dogs.[42] Another of these studies that supports the PICO question (LOE 3, Poor) also evaluated reocclusion after coronary thrombolysis in dogs.[44] In that study, enoxaparin treatment did not significantly alter PT or aPTT, when given alone or in combination with an antiplatelet agent (GPIIb/IIIa receptor antagonist), when compared to baseline or the saline-treated group (negative control).[44] Enoxaparin treatment did achieve a significant increase in anti-Xa activity (to the range of 0.58–1.54 IU/mL) and was associated with a decreased incidence of reocclusion, increased time to reocclusion, and decreased thrombus mass compared to control dogs.[44] Ignasiak et al (LOE 3, Good) evaluated the effects of IV enoxaparin in an electrolytic model of venous thrombosis; low-dose enoxaparin was compared to high dose enoxaparin, and a control group.[45] Time to reocclusion was longest in the high-dose group compared to the low-dose group, which in turn was longer than in the control group. Similarly, there were dose-dependent prolongations in aPTT and TT, but PT remained unchanged.[45] The same group of authors also reported the effects of enoxaparin administration to dogs in an electrolytic model of arterial and venous thrombosis (LOE 3, Good).[46] Anti-Xa activity was not reported by these authors, but enoxaparin treatment resulted in a dose dependent decrease in the time to formation of an occlusive thrombus and increased surgical blood loss that was predicted by increases in the aPTT, TT, and ACT.[46] Of these hemostatic parameters, TT was most sensitive to the anticoagulant effects of enoxaparin.[46] Consistent with previous studies, there was no effect on PT in any of the enoxaparin treatment groups.[46] Taken together these studies suggest that anti-Xa activity is likely the most sensitive monitoring test to the anticoagulant effects of LMWHs; however, aPTT and TT are generally increased by IV LMWH therapy.[43–46] Additionally, 1 study even suggests utility of ACT when LMWH is given as an IV infusion.[46]

One LOE 1 (Fair) study was considered neutral to the PICO question because it did not adequately address patient centered outcomes.[47] In this prospective clinical trial in 18 dogs at risk of venous thrombosis, 6 dogs were randomized to each of 3 groups; a low-dose UFH group (300 U/kg IV CRI for 24 h), a high-dose UFH group (100 U/kg IV bolus followed by 900 U/kg CRI for 24 h), and a dalteparin group (100 U/kg SC q 12 h for 3 doses).[47] Monitoring tests (aPTT and anti-Xa activity) were measured at baseline and then 4 and 28 hours after the initiation of anticoagulation.[47] This study is considered neutral to PICO question because there was minimal change in the aPTT and anti-Xa activity in dalteparin-treated dogs. One dog in the dalteparin group had a clinically significant increase in aPTT at 1 time point (aPTT = 31 s, 1.9× baseline, 28 h after commencing dalteparin).[47] Similarly, the majority of dogs in the dalteparin group had an anti-Xa ≤0.1 IU/mL at all time points, except 1 dog, which had an anti-Xa activity of 0.4 IU/mL at 28 hours.[47] Since studies by other authors document peak dalteparin

activity in dogs 2 hours postdose,[31] it is highly likely that Scott et al missed the peak anti-Xa activity with their 4-hour time point.

Numerous studies evaluated the effects of LMWHs on coagulation tests in healthy dogs, and thus did not directly address the PICO question. Nonetheless, they are discussed briefly here, as some useful information can be gained. Mischke et al have published multiple studies documenting that anti-Xa activity is the most sensitive test of the anticoagulant effect of LMWHs in healthy dogs, concluding that the screening tests they evaluated (aPTT and TT) were not suitable for monitoring LMWH therapy in dogs.[31,48] Other authors studying enoxaparin in healthy dogs have also documented reliable attainment of therapeutic anti-Xa activity.[49–52] Brainard et al evaluated the effects of enoxaparin in healthy dogs on TEG and dynamic viscoelastic coagulometry (Sonoclot).[50] The most reliable changes with enoxaparin therapy on viscoelastic tests parameters were prolongation of R in TEG, and ACT and clot rate in dynamic viscoelastic coagulometry.[50] Gara-Boivin et al also documented that increasing dalteparin doses result in decreased endogenous thrombin potential, however the endogenous thrombin potential was much less sensitive than anti-Xa in that study.[51]

As described above in the study by Scott et al,[47] not all studies in healthy dogs have shown that LMWH therapy reliably prolongs anti-Xa activity in dogs. Pouzot-Nevoret et al administered 0.8 mg/kg enoxaparin SC every 6 hours to healthy Beagle dogs for a total of 9 doses.[53] These authors documented no significant change in PT, aPTT, rotational thromboelastometry parameters, fibrinogen concentration, or antithrombin activity during the 48-hour dosing period. Anti-Xa activity was increased but only 3 hours after the second and third injections, and only reached target activity (0.5–1.0 IU/mL) in 3/8 dogs.[53] Although not discussed by the authors, the reason for the apparent inability to attain target anti-Xa may well be due to the timing of sample collection (ie, missing a possible 2-h postdose peak). Additionally, in an experimental model of venous thromboembolism, Morris et al concluded that the antithrombotic effect of enoxaparin and dalteparin is not entirely dependent on anti-Xa activity.[42] Interestingly, however, that study used once daily dosing of dalteparin and twice daily dosing of enoxaparin, which is a lower frequency of both LMWHs than recommended in these guidelines (see Domain 3). A clinical case series (not directly addressing the PICO question due to lack of a comparator group) has also documented difficulty in attaining the therapeutic anti-Xa range for dalteparin in dogs.[54] The exact timing of blood sampling for measurement of anti-Xa activity was not reported in that manuscript due to its retrospective nature; however, common institutional practice was to test 2 hours postdose.[54] The limited number of clinical studies in dogs receiving LMWH makes it impossible to determine whether or not achieving target anti-Xa activity is more difficult to diseased patients.

Another body of literature that should be considered when evaluating the anticoagulant effects of LMWHs in dogs but did not directly address the PICO question are those studies that although performed in experimental models of thrombosis, either just conducted 1 type of coagulation monitoring test (ie, no comparison), or did not include clinically relevant outcomes. Similarly to many of the studies in healthy dogs, Hong et al found that treating dogs with IV enoxaparin (0.6 μg/kg IV loading dose, followed by 6.0 μg/kg/min CRI) did not result in an increase in aPTT compared to baseline, despite reducing repeat thrombosis after coronary artery thrombolysis.[55] The same research group did however document aPTT prolongation with a much higher dose of dalteparin (400 IU/kg SC), achieving an approximately 1.5× increase in aPTT 2 hours postdose.[56] Another group, using an experimental model of thrombosis, documented that anti-Xa, anti-IIa, and aPTT increased in a dose dependent fashion in dogs receiving enoxaparin, but did not evaluate clinically relevant outcomes.[57]

Cats

No studies in cats specifically address the PICO question. Seven studies were identified in which cats were administered LMWH; 1 in diseased cats,[58] 4 in healthy cats,[38,59–61] and 1 in an experimental model of venous thrombosis.[62] Each of these studies is addressed below.

One clinical case series of 57 cats at risk of thrombosis treated with the LMWH dalteparin did not perform therapeutic monitoring; however, coagulation testing was reported in some cats.[58] Of the 7 cats that had aPTT measured after dalteparin administration, 1 cat with a normal aPTT pretreatment developed aPTT prolongation 7 days after commencing dalteparin; sample timing was not reported.[58] Four cats in this case series had clinical bleeding reported; however, only 1 (with hematuria) had clotting times measured, and aPTT was within reference interval.[58] Other studies retrieved in the search for cats receiving LMWH did not address the PICO question because they involved healthy cats.[38,59–61]

Alwood et al administered dalteparin (100 IU/kg SC q12h) and enoxaparin (1 mg/kg SC q12h) in a prospective, cross-over study in healthy cats (n = 5).[38] Monitoring tests included PT, aPTT, anti-Xa, and TEG (no activator). Sampling time points for monitoring tests in this study included baseline, 4 hours postdose on day 3 and 5, and trough on day 3 and 5.[38] Anti-Xa activity was highest at the 4-hour time points, but remained below therapeutic ranges in the majority of circumstances. PT was not increased at any time point. Although aPTT was increased above baseline in some cases, it was not prolonged beyond the reference interval in LMWH-treated cats. Some cats treated with LMWH developed hypocoagulable TEGs, however there was marked interindividual variation. Changes in anti-Xa activity were also relatively inconsistent after LMWH in this study; mean anti-Xa activity was below the target range in the majority of cats at 4 hours and below the lower limits of detection at 12 hours.[38] Similarly, Vargo et al documented that PT, aPTT, and antithrombin were unaffected by LMWH therapy in healthy cats (n = 8) at a dose of 100 IU/kg SC every 12 h for 13 doses.[59] These authors also found unreliable attainment of therapeutic anti-Xa activity, 4 hours postdose, returning to baseline 6 hours postdose.[59] Given that the earliest sampling time points in these studies was at 4 hours postdose, they incompletely informed optimal therapeutic monitoring of LMWH therapy in cats.

Mischke et al have subsequently determined that peak anti-Xa activity occurs 90 minutes to 2 hours after SC administration of

dalteparin and enoxaparin.[60,61] In 1 study, these investigators administered a single SC dose of 50, 100, or 200 IU/kg dalteparin ($n = 6$ cats per group), and documented dose-dependent maximum anti-Xa activity and low interindividual variation.[60] An early T_{max} (91–110 min postinjection) and predictable maximum concentration based on dose suggested rapid absorption into circulation and high bioavailability.[60] A similar study in healthy cats evaluated single dose (1 mg/kg SC) and multiple dose (0.75 mg/kg IV q6h for 4 d) enoxaparin.[61] Anticoagulant effect of enoxaparin in this study was monitored with anti-Xa activity, aPTT, TT, and TEM.[61] Peak anti-Xa activity occurred at 2 hours and was within target range in all cats after their second dose, with no appreciable accumulation thereafter. Ratios of aPTT and TT (measured/baseline) did increase significantly with enoxaparin treatment, but only slightly, with some reagents more sensitive to the anticoagulant effects of enoxaparin than others.[61] For example, the maximal value of median aPTT ratio was only 1.27 (ie, a 1.27× increased aPTT above baseline at the time of peak anti-Xa activity). Based on these findings, the authors concluded that conventional coagulation tests are unsuitable for monitoring LMWH treatment.[61] More marked changes were seen in TEM, to a greater extent in nonactivated than intrinsically activated TEM; however, there was also marked interindividual variation. Nonetheless, anti-Xa activity was the most sensitive of these tests to LMWH dose and hence most likely to reflect its anticoagulant activity.[61]

One study of enoxaparin in a venous stasis model in cats used anti-Xa monitoring; however, there was no comparator group and hence it did not directly address the PICO question.[62] Cats ($n = 10$) received 1 mg/kg enoxaparin SC every 12 hours for 5 days (10 doses), and underwent induction of thrombosis (via venous stasis) at either 4 hours after their 10th enoxaparin dose ($n = 5$), or 12 hours after their final dose ($n = 5$). Like previous investigators,[38,59] these investigators measured anti-Xa activity at the 4-hour and 12-hour time points under the assumption that these were peak and trough. Cats in both groups had significant inhibition of thrombus formation with decreased normalized thrombus weight compared to control cats.[62] Interestingly, plasma anti-Xa activities were quite variable at the 4-hour time point (median 0.75 IU/mL; range 0.35 to 1.4 IU/mL), and unmeasurable in the 12-hour group. Hemorrhagic complications did not occur in any cat prior to euthanasia. This study demonstrated that even at the time that anti-Xa activity was unmeasurable (12 hours postdose), anticoagulant effect of enoxaparin persisted.[62]

Knowledge gaps

The use of LMWHs is now widespread in veterinary medicine yet our understanding of the most appropriate way to monitor and adjust therapy is extrapolated from human medicine and based on limited studies in healthy dogs and cats or experimental models of disease. Ideally, prospective randomized clinical trials in dogs and cats at risk of thrombosis would compare the safety and efficacy of fixed dose LMWH with individually adjusted doses based on peak anti-Xa activity, and/or other coagulation tests (eg, aPTT with appropriate reagents, or viscoelastic tests). Such trials are warranted given differences in LMWH PK/PDs among people, dogs, and cats; most significantly, the much earlier attainment of maximal plasma activities after SC administration and the more rapid elimination in small animals.

PICO QUESTION: Low molecular weight heparin monitoring

In dogs and cats with a risk of arterial/venous thrombosis being treated with LMWH **(P),** does targeting a specific anti-Xa range **(I)** compared with anti-Xa activity outside this range **(C)** reduce the risk of complications and improve any outcomes? **(O)**

Guidelines

4.4 | Low molecular weight heparin

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

Evidence summary

Dogs

Two LOE 3 studies support the PICO question.[63,64] Mestre et al found a protective effect of IV enoxaparin dosing that achieved an anti-Xa activity of 0.55 U/mL in a dog model of tissue plasminogen activator (tPA)-induced coronary thrombus lysis.[63] In this model, the addition of enoxaparin to tPA resulted in an improvement in recanalization (from 2/5 with tPA only, to 5/5 with tPA and enoxaparin), and smaller thrombus weight.[63] Mischke et al also showed a benefit of achieving target anti-Xa activity in dog model of thromboplastin-induced acute disseminated intravascular coagulation.[64] This study indicated that low dose dalteparin, achieving anti-Xa activities between 0.27 ± 0.01 (5 min after the start of therapy) and 0.36 ± 0.02 IU/mL (2 h after the start of therapy) were not sufficient to stop the intravascular consumptive coagulopathy.[64] In contrast, high-dose dalteparin, achieving anti-Xa activities between 0.62 ± 0.08 and 0.9 ± 0.07 resulted in a cessation of the consumptive coagulopathy in this model.[64] Note that this model used IV dosing of dalteparin; the low-dose group received 20 anti-FXa U/kg as an IV bolus followed by 16.7 U/kg/h as a CRI, while the high dose group received 40 anti-FXa U/kg as an IV bolus followed by 33.3 U/kg/h as an IV CRI.[64] Although not directly addressing the PICO question, studies in healthy dogs targeting an anti-Xa activity of 0.5–1.0 IU/mL, have demonstrated safety at this dose, with no hemorrhagic complications noted.[31,49]

Cats

No studies directly address the PICO question. As described above for PICO question 6, there is considerable variation in the anti-Xa activity achieved in cats after SC administration of LMWH in different studies, most likely due to variation in test timing. Alwood et al administered dalteparin (100 IU/kg SC q12h) and enoxaparin (1 mg/kg SC q12h) in a prospective, cross-over study in healthy cats ($n = 5$).[38] Mean anti-Xa activity 4 hours after enoxaparin (0.48 U/mL) was just below the human therapeutic range of 0.5–1.0 U/mL; however, mean trough

anti-Xa was below the lower limits of detection. Mean anti-Xa activity was even lower after dalteparin treatment, with only 1 cat attaining therapeutic anti-Xa at a single time point.[38] Similarly, Vargo et al reported unreliable attainment of target anti-Xa 4-hours postdose in healthy cats administered 100 IU/kg SC dalteparin every 12 hours for 13 doses, with anti-Xa activity returning to baseline 6 hours postdose.[59] Mischke et al have subsequently determined that peak anti-Xa activity occurs 90 minutes to 2 hours after SC administration of dalteparin and enoxaparin.[60,61] In 1 study, these investigators administered a single SC dose of 50, 100, or 200 IU/kg dalteparin (n = 6 cats per group), and documented dose-dependent maximum anti-Xa activity and low interindividual variation.[60] The lowest dose resulted in peak anti-Xa activity of 0.43 ± 0.10 (below the human target range), the intermediate dose achieved peak anti-Xa activity of 1.00 ± 0.10 (at the high end of the human target dose range), and the high dose achieved maximum anti-Xa of 1.92 ± 0.17, with T_{max} 91–110 minutes postinjection, suggesting high bioavailability and rapid absorption into circulation.[60] A similar study in healthy cats evaluated single-dose (1 mg/kg SC) and multiple-dose (0.75 mg/kg IV q6h for 4 d) enoxaparin.[61] Peak anti-Xa activity occurred at 2 hours and was within target range in all cats after their second dose, with no appreciable accumulation thereafter. The findings of these 2 studies led Mischke et al to conclude that routine monitoring of anti-Xa activity may not necessary in cats; however, they encourage further studies to confirm the predictability of anti-Xa after LMWH therapy in diseased cats.[60,61]

Knowledge gaps

Clinical studies of anti-Xa monitoring of LMWH therapy in dogs and cats, with naturally occurring disease, at risk of thrombosis are required to better address the PICO question. Even if it is ultimately concluded that routine anti-Xa monitoring is not required in dogs or cats receiving LMWHs, there is still likely to be a need in special patient populations. Even in human medicine, where routine monitoring is not performed, anti-Xa activity monitoring is still indicated in pregnancy, children, those with extremes of body weight, renal insufficiency, and overdose situations.[65–68]

PICO QUESTIONS 8 AND 9: Rivaroxaban monitoring

In dogs and cats with a risk of arterial/venous thrombosis being treated with rivaroxaban **(P)**, does the use of a 1 coagulation test for therapeutic monitoring **(I)** compared with no therapeutic monitoring or using another coagulation test type **(C)** reduce the risk of complications and improve any outcomes? **(O)**

In dogs and cats with a risk of arterial/venous thrombosis being treated with rivaroxaban **(P)**, does targeting a specific anti-Xa range **(I)** compared with anti-Xa activity outside this range **(C)** reduce the risk of complications and improve any outcomes? **(O)**

Guidelines

Guidelines for rivaroxaban monitoring were not formulated given the lack of literature addressing the PICO questions.

Evidence summary

Dogs

No literature in dogs directly addressed the PICO question. Most of the rivaroxaban literature documents in vitro and in vivo PKs in dog plasma and healthy dogs and thus did not address the population of interest for the PICO question.[69–73] Nonetheless, some studies in healthy dogs did evaluate monitoring of rivaroxaban therapy and thus are briefly described below. Conversy et al performed an in vivo randomized, placebo-controlled study in 24 healthy Beagle dogs to evaluate the ability of different coagulation tests to detect the anticoagulant activity of 1 or 2 oral doses of 2 mg/kg rivaroxaban PO.[74] In that study, the authors reported that rivaroxaban-specific anti-Xa activity was much more sensitive to detect the anticoagulant activity of rivaroxaban in dogs than PT, aPTT, or TEG. Rate index and lag time of thrombin generation also showed good sensitivity for the anticoagulant effect of rivaroxaban. The authors used their findings to make some suggestions about the potential of using anti-Xa to determine inadequate anticoagulation and PT to determine excessive anticoagulation from rivaroxaban; however, further studies are needed in dogs at risk of thrombosis.[74] Other authors have also documented a lack of change in hemostatic parameters (PT, aPTT, and TEG) in healthy dogs administered rivaroxaban at 1 mg/kg PO every 24 hours for 1 week.* Another study in healthy dogs administered rivaroxaban reported in abstract form, had similar findings to Conversy et al, with tissue factor activated TEG correlating poorly with anti-Xa.† The same authors have also reported that rivaroxaban-specific anti-Xa activity was not affected when rivaroxaban was administered concurrently with food, sucralfate or omeprazole.‡ Consistent with the purported potential of PT to detect excessive anticoagulation due to rivaroxaban, a case series reported in abstract form documented a mildly prolonged PT in 1/9 dogs that had clotting times measured after inadvertent rivaroxaban exposure; that dog ingested a 3.3 mg/kg rivaroxaban dose.§

To date, only 2 studies have described the administration of rivaroxaban to dogs with or at risk of thrombosis. One case series of 4 dogs did not report therapeutic monitoring of rivaroxaban therapy.[75] The other was a prospective, multicenter, positive-controlled, unblinded clinical trial (LOE 1, Fair) in which dogs with IMHA were block randomized to receive 1 of 2 protocols for thromboprophylaxis for 3 months; either rivaroxaban (0.5–1.0 mg/kg PO q24h) and low dose aspirin (1 mg/kg PO q24h), or clopidogrel (2–3 mg/kg PO q24h) and low dose aspirin (1 mg/kg PO q24h).[76] Coagulation tests (PT and aPTT) were performed at baseline, and then at 7, 14, 30, and 90 days therefore. No significant prolongation in PT or aPTT was noted from baseline in dogs receiving rivaroxaban at any recheck.[76] These findings are consistent with the previously reported poor sensitivity of PT and aPTT for detecting the anticoagulant effect of rivaroxaban. Unfortunately, anti-Xa activity was not monitored in that study.

In people, the predictable PK and PD profile of rivaroxaban means that fixed oral doses can be used and therapeutic monitoring is rarely required. Nonetheless, therapeutic monitoring has suggested dose reductions in some people with renal impairment and has also been useful in overdose situations.[77] Additionally, peak anti-Xa activity was independently related to the incidence of major and nonmajor clini-

cally relevant bleeding events in a Japanese study of people with atrial fibrillation, suggesting that monitoring and dose adjustment could be implemented to reduce bleeding complications.[78]

Cats

No literature in cats directly addressed the PICO question. Only 1 study was retrieved that described rivaroxaban PKs and PDs in 6 healthy cats.[79] Oral administration of single and multiple-dose rivaroxaban to healthy cats resulted in dose-dependent prolongations of dilute PT (ie, a PT assay using diluted thromboplastin) and increases in anti-Xa activity.[79] Additionally, a case series reported in abstract form documented 2 cases of rivaroxaban overdose in cats.[§] One cat received 5.6 mg/kg and remained asymptomatic, while the other ingested 46.7 mg/kg of rivaroxaban was noted to bruise easily, had a prolonged PT (26 s [reference interval 15–20 s]), and required a blood transfusion but recovered.[§]

Knowledge gaps

Rivaroxaban PDs are currently an area of significant research interest in the veterinary community. Randomized clinical trials are required to determine the role of therapeutic monitoring of rivaroxaban to optimize the safety and efficacy of this oral anticoagulant in dogs and cats at risk of thrombosis.

CONCLUSION

Systematic evidence evaluations regarding therapeutic monitoring of thromboprophylatic drugs yielded 4 detailed guidelines specific for the use of aspirin, warfarin, UFH, and the LMWHs in dogs and cats. As in other CURATIVE domains, significant knowledge gaps were highlighted, indicating the need for substantial additional research in this field. Ongoing investigation of the role of therapeutic monitoring of antithrombotic therapies will undoubtedly facilitate improved outcomes for our dog and cat patients at risk of thrombosis.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

FOOTNOTES

[*] Murphy LA, et al. A prospective evaluation of rivaroxaban on hemostatic parameters in apparently healthy dogs. J Vet Emerg Crit Care 2018; 28(S1):S10. https://doi.org/10.1111/vec.12758 [Abstract]

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[§] Bates N, Edwards N. Apixaban and rivaroxaban ingestion in cats and dogs. Clin Toxicol. 2018; 56(6):475-475. [Abstract]

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