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Evaluation of point-of-care coagulation tests as alternatives to anti-Xa activity for monitoring the anticoagulant effects of rivaroxaban in healthy dogs

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Abstract

Objective: To evaluate a panel of coagulation assays for their potential utility in rivaroxaban monitoring as alternatives to the rivaroxaban-specific anti-Xa activity (RIVA).

Design: Prospective experimental study.

Setting: University research laboratory.

Animals: Five healthy neutered male Beagles.

Interventions: Dogs were administered a median dose of 1.8 mg/kg rivaroxaban (range, 1.6–1.8 mg/kg) orally once daily for 2 consecutive days as part of a pharmacodynamic study. Blood was collected from a preplaced jugular catheter at time points relative to their rivaroxaban administration (0, 2, 4, 8, 24, 36, and 48 h) for measurement of RIVA, prothrombin time (PT), activated partial thromboplastin time, RapidTEG, and thrombin generation variables.

Measurements and main results: One hundred forty data points were available for analysis. There was poor correlation between RIVA and RapidTEG variables: R time (R) (min) ($r = 0.554$, $P < 0.0001$), K time (K) (min) ($r = -0.204$, $P = 0.016$), alpha angle (degrees) ($r = 0.152$, $P = 0.073$), Maximum amplitude (MA) (mm) ($r = 0.106$, $P = 0.215$), and G value (G) (dynes/s) ($r = 0.108$, $P = 0.205$). A good correlation was noted between thrombin generation variables and RIVA: lag time (min) ($r = 0.827$, $P < 0.0001$), peak (nM) ($r = -0.752$, $P < 0.0001$), and endogenous thrombin potential (nM·min) ($r = -0.762$, $P < 0.0001$). There was an excellent correlation between PT and RIVA ($r = 0.915$, $P < 0.0001$) and a good correlation between activated partial thromboplastin time and RIVA ($r = 0.772$, $P < 0.0001$).

Abbreviations: aPTT, activated partial thromboplastin time; dPT, dilute PT; PPP, platelet poor plasma; PT, prothrombin time; RIVA, rivaroxaban specific anti-Xa activity; TEG, thromboelastography; TG, thrombin generation

Conclusions: Of all the coagulation tests investigated, the PT correlated best with RIVA. There is potential for PT being a convenient second-line monitoring option in dogs receiving rivaroxaban, but further work is necessary to validate other PT assays. Thromboelastography performed with strong activators correlated poorly with anti-Xa activity.

KEYWORDS
anticoagulant, antithrombotic, canine direct oral anticoagulants, thromboembolism

1 | INTRODUCTION

Thromboembolism is an important and potentially life-threatening complication of several disease states in dogs.[1–5] Antithrombotic medications are prescribed either for the treatment of confirmed thrombosis or as thromboprophylaxis in patients with a perceived prothrombotic tendency.[6] Several antithrombotic options may be considered in dogs, but there are knowledge gaps with respect to optimal dosing schemes for these drugs.[6] Anticoagulants are an important class of drugs that interfere with clotting cascade function, limiting thrombin generation (TG) and hence fibrin formation.[7] Several factors may be considered in individual patients when prescribing anticoagulants. These include, but are not limited to, the associated disease state, if venous or arterial thrombosis is suspected, drug cost, frequency of dosing, route of administration, and requirement for therapeutic monitoring. However, the requirement for therapeutic monitoring can vary considerably between drugs. Warfarin, for example, has a narrow therapeutic index, and frequent monitoring is recommended to avoid inadvertent bleeding events. Therapeutic monitoring is also advisable when using unfractionated heparin in dogs, because optimal dosing appears to vary between individual dogs.[6] A previous study identified that unfractionated heparin dose adjustment, based upon interpretation of the unfractionated heparin-specific anti-Xa activity, was associated with improved outcome in dogs with immune-mediated hemolytic anemia compared to a fixed dosing scheme.[8] In people, some anticoagulant options (eg, low-molecular-weight heparins) have a very predictable pharmacological profile, which circumvents the need for routine therapeutic monitoring. The pharmacokinetics and pharmacodynamics of low-molecular-weight heparins unfortunately are less predictable in dogs, meaning routine therapeutic monitoring is also sensible.[9]

There is growing interest in direct oral anticoagulants (eg, rivaroxaban and dabigatran) in people. These drugs are convenient because they are oral medications, administered once per day, and with predictable in vivo effects precluding the need for routine therapeutic monitoring. Rivaroxaban is gaining interest as a potential anticoagulant option in dogs.[10–12] One study described an anticoagulant effect that persisted for about 24 hours in healthy dogs that received 2 mg/kg of rivaroxaban twice daily.[11] Lower doses (0.5–1 mg/kg once daily) of rivaroxaban have also been described in sick dogs, although the degree of in vivo anticoagulation achieved in these dogs was not known with certainty.[10,12] The most suitable method of monitoring the anticoagulant effect of rivaroxaban in dogs is via the rivaroxaban-specific anti-Xa activity (RIVA).[13] Therapeutic monitoring of rivaroxaban can provide insight into the suitability of the rivaroxaban dosing in individual patients and allows for dose adjustment if necessary. Timely dose adjustment with RIVA is difficult, however, because it is usually only available as a test at reference laboratories. As such, alternative coagulation tests providing more immediate and accurate results would be beneficial in the critical care setting. Changes in other coagulation tests, specifically prothrombin time (PT), activated partial thromboplastin time (aPTT), and TG variables, were noted in the aforementioned study of healthy dogs receiving rivaroxaban.[11] Interestingly, tissue factor–activated thromboelastography (TEG) variables were unchanged in these dogs. The mode of TEG activation may impact its utility as a therapeutic monitoring tool, as has been noted previously for dogs receiving unfractionated heparin.[14] Robust activation of TEG with tissue factor and kaolin (ie, Rapid TEG) correlated best with the anti-Xa activity and aPTT in this study of normal dogs receiving unfractionated heparin. The utility of RapidTEG for rivaroxaban monitoring has not been evaluated in dogs to our knowledge.

The aim of this study therefore was to assess the correlation between RIVA with alternative hemostatic tests (PT, aPTT, RapidTEG variables of clot reaction speed [R, K, and alpha angle], RapidTEG variables of clot strength [MA and G], and TG variables [lag time, peak, and endogenous thrombin potential]) in dogs administered rivaroxaban orally. We hypothesized that RapidTEG variables would correlate best with RIVA.

2 | MATERIALS AND METHODS

2.1 | Animals

Blood samples obtained from 5 healthy neutered male Beagles enrolled in a rivaroxaban pharmacodynamic study were utilized.[*] This pharmacodynamic study investigated the impact of administering 20 mg of rivaroxaban[†] once daily for 2 consecutive days with either (a) no food, (b) a high-calorie commercial dog food,[‡] (c) 0.5 g of sucralfate,[§] or (d) 10 mg of omeprazole[**] on the apparent anticoagulant intensity as assessed by RIVA. A 14-day minimum washout period was imposed between each study stage. The median weight of the dogs was 11.4 kg

(range, 11–12.6 kg), and the median dose of rivaroxaban administered was 1.8 mg/kg (range, 1.6–1.8 mg/kg).

All dogs were deemed healthy prior to the study based on physical examination and baseline clinicopathological testing (CBC, serum chemistry analysis, baseline coagulation profile [PT, aPTT, D-dimers, and fibrinogen], and voided urine sample). The study protocol was approved by the Institutional Animal Care and Use Committee of North Carolina State University.

2.2 | Procedures

One day prior to the start of each study stage, the dogs were sedated after a 12-hour fast with 5 μg/kg of dexmedetomidine[††] and 0.3 mg/kg butorphanol[‡‡] intravenously to facilitate the placement of a 20-Ga, 12-cm single-lumen jugular catheter[§§] via a modified Seldinger technique.[15] Atipamezole,[***] of an equivalent volume to the dexmedetomidine, was administered intramuscularly after successful jugular catheter placement. When fully recovered from their sedation, the dogs had ad libitum access to water and were fed a commercial maintenance dog food[†††] on a twice daily schedule. The catheters were maintained by flushing them with saline 4 times daily until the end of the study.

Blood samples were obtained from the preplaced jugular catheters at 7 time points corresponding to 0, 2, 4, 8, 24, 36, and 48 hours relative to the first rivaroxaban administration. After 48 hours, the dogs had their jugular catheters removed and were returned to their normal housing. Blood was collected from the jugular catheters as previously described.[16] Briefly, a 3-syringe technique was used to remove 6 mL of blood from the catheter, reserved as a purge sample. Then, an additional 6 mL of blood was collected into plastic tubes containing 3.2% sodium citrate[‡‡‡] to give a ratio of 1:9 citrate to whole blood.

2.3 | Blood Sample handling and analysis

After a standardized 30-minute rest period at room temperature (approximately 23°C) after collection, a RapidTEG[§§§] was performed using a proprietary tissue factor and kaolin assay by a single operator (LR) using a previously described technique.[13] Briefly, after the rest period 1 mL of citrated whole blood was gently mixed with the RapidTEG reagents. Then, 340 µL of this mixed sample was added to a standardized TEG pin and cup containing 20 µL of calcium chloride that was prewarmed to 37°C. Each RapidTEG was performed for 90 minutes. Samples were randomized to 6 different channels on 3 TEG machines. RapidTEG variables (R, K, alpha angle, MA, and G) were recorded at this point.

The remaining citrated whole blood was centrifuged at 4,000 × *g* for 15 minutes at room temperature to yield citrated platelet poor plasma (PPP) and packed red cells. The citrated PPP was harvested and frozen at −80°C for later batch analysis of RIVA and the remaining coagulation tests (PT, aPTT, and TG) at the Comparative Coagulation Laboratory at Cornell University. These remaining tests were all performed within 1 month of collection and storage. The frozen PPP samples were thawed at 37°C immediately before being assayed. The coagulation screening tests (PT and aPTT) were performed in an automated, mechanical endpoint clot detection instrument[****] with commercial reagents.[††††,‡‡‡‡] The anticoagulant action of rivaroxaban was measured in a chromogenic substrate assay based on its Factor Xa inhibitory activity (anti-Xa). The assay is configured with a bovine-activated factor X reagent added in excess to the test plasma and a chromogenic substrate of Factor Xa.[§§§§] In this assay, residual, uninhibited Factor Xa cleaves the chromogenic substrate such that the inverse of the color change in the reaction mixture is proportional to the drug concentration in the test plasma. Results are expressed as ng/mL anti-Xa activity, based on calibration standard containing known rivaroxaban concentrations in human plasma.[*****] Assay controls, consisting of rivaroxaban spiked-human plasma,[†††††] were measured before each batch of test samples.

TG was measured by the calibrated automated thrombogram method[17,18] using a dedicated spectrofluorimeter.[‡‡‡‡‡] Samples were activated using the manufacturer's thromboplastin reagent containing 1 pM tissue factor.[§§§§§] Replicate assays were performed according to the manufacturer's instructions in microtiter plates in reaction mixtures containing 80 µL test plasma (diluted 1:2 in imidazole buffered saline) combined with 20 µL of the activating reagent and 20 µL of a fluorogenic substrate/calcium trigger reagent.[******] The TG measurements for each sample were calibrated against reactions run in parallel that contained the test plasma and a thrombin α2 macroglobulin complex reagent.[††††††] The parameters lag time (min), peak thrombin (nM), and overall endogenous thrombin potential representing the area under the curve were calculated by the thrombinoscope software.[‡‡‡‡‡‡]

2.4 | Statistical analysis

Naïve scatterplots containing data from all dogs, all stages of the pharmacodynamics study, and all time points were composed, comparing RIVA with the other coagulation tests. Pearson's correlations were calculated for RIVA compared to PT, aPTT, RapidTEG variables, and TG variables. Perfect correlation is represented by +1 or −1, with 0 demonstrating no correlation. Significance was set at a P-value < .05. Provided significance was first met, the corresponding strength of correlation was then stratified based on the absolute r values, with 0–0.19 as very weak, 0.2–0.39 as weak, 0.4–0.59 as moderate, 0.6–0.79 as strong, and 0.8–1 as very strong.[19] All analyses were performed by a statistician (EG) using commercial software.[§§§§§§]

3 | RESULTS

Over the course of the pharmacodynamics study, 140 different data points were available for analysis. The scatterplots for RIVA compared to the other coagulation tests, along with the Pearson's correlation (r) and significance (P), are shown in Figures 1–3. Overall, there was

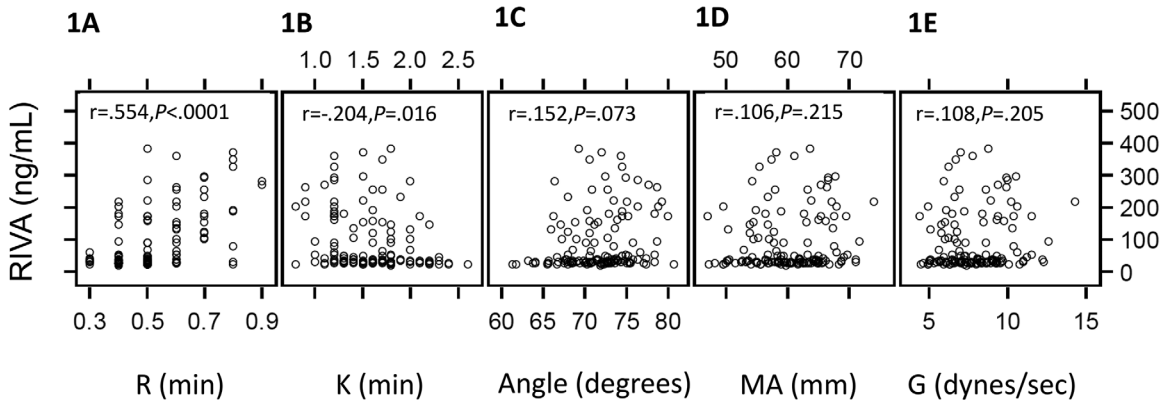

FIGURE 1 Scatterplot showing the relationship between the rivaroxaban-specific anti-Xa activity (RIVA [ng/mL]) and RapidTEG variables. (A) R time (min); (B) K (min); (C) alpha angle (degrees); (D) maximum amplitude (MA) (mm); and (E) G (dynes/s). The correlation (*r*) and the associated significance (*P*-value) are displayed at the top of each graph

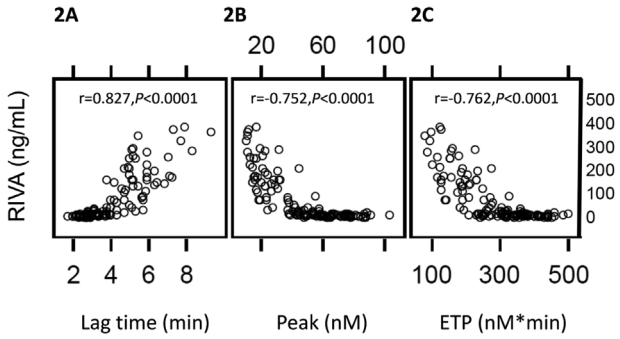

FIGURE 2 Scatterplot showing the relationship between the rivaroxaban-specific anti-Xa activity (RIVA [ng/mL]) and thrombin generation variables. (A) Lag time (min); (B) peak (nM); (C) endogenous thrombin potential (ETP) (nM·min). The correlation (*r*) and the associated significance (*P*-value) are displayed at the top of each graph

moderate correlation between RIVA and the RapidTEG R time (min) ($r = 0.554$, $P < 0.0001$), a weak correlation with K (min) ($r = -0.204$, $P = 0.016$), and no correlation with alpha angle (degrees) ($r = 0.152$, $P = 0.073$) (Figure 1). There was also no correlation between RIVA and RapidTEG variables of clot strength (Figure 1), MA (mm) ($r = 0.106$, $P = 0.215$), and G (dynes/s) ($r = 0.108$, $P = 0.205$).

A stronger correlation was noted between TG variables and RIVA (Figure 2). There was a very strong, positive correlation between RIVA and the lag time (min) ($r = 0.827$, $P < 0.0001$). A strong, negative correlation was noted between RIVA and peak (nM) ($r = -0.752$, $P < 0.0001$) and the endogenous thrombin potential (nM·min) ($r = -0.762$, $P < 0.0001$). A strong correlation was also noted between RIVA and aPTT ($r = 0.772$, $P < 0.0001$) (Figure 3). PT correlated very strongly with RIVA ($r = 0.915$, $P < 0.0001$) and was the strongest correlation of all the coagulation tests investigated in this study (Figure 3). Most data points for RIVA and PT are clustered at lower levels. Only 18 of 140 data points are contained with the human therapeutic RIVA activity range of 150–250 ng/mL. The correlation between PT and RIVA within this specific range is very weak ($r = 0.174$, $P < 0.0001$).

4 | DISCUSSION

This study aimed to assess the correlation between the RIVA with several hemostatic tests that could potentially serve as a gauge for anticoagulant intensity in dogs receiving rivaroxaban. In contrast to viscoelastic monitoring of unfractionated heparin,[14] TEG performed with robust activation was a poor surrogate for RIVA. PT correlated strongly with RIVA and may prove to be a convenient second-line monitoring option in dogs receiving rivaroxaban. TG variables may also provide some insight into the anticoagulant intensity of rivaroxaban achieved in individual dogs.

Interest in rivaroxaban as an anticoagulant option in dogs and cats is growing. Rivaroxaban is an example of a direct oral anticoagulant. Its mechanism of action involves direct competitive inhibition of clotting factor Xa, both in its clot-bound and free forms, and does not rely on endogenous anticoagulants (eg, antithrombin) to achieve its anticoagulant effect.[11,20] Factor Xa is in itself an important therapeutic target because it is centrally located within the clotting cascade, at the convergence of the extrinsic and intrinsic pathways, and complexes with Factor Va to form prothrombinase.[7] Prothrombinase catalyzes the conversion of prothrombin to thrombin, hence facilitating a thrombin burst and leading to fibrin clot formation.[21] Rivaroxaban is a convenient anticoagulant option in people because its pharmacokinetics and pharmacodynamics are very predictable in most patients.[21,22] Rivaroxaban appears to be a well-tolerated drug in both healthy and sick dogs.[10–12] A dose of about 2 mg/kg twice daily was associated with a sustained anticoagulant effect in healthy dogs.[11] Practically, rivaroxaban may be cost prohibitive in larger dogs following this dosing scheme, and lower doses with reduced frequency appear to be commonplace in clinical practice.[10,12] However, a knowledge gap currently exists with respect to the optimal dosing of rivaroxaban in sick dogs. It is certainly plausible that a standard fixed dose of rivaroxaban will not be appropriate for all dogs based upon our experience of unfractionated heparin in sick dogs.[8,23] Therapeutic monitoring, via RIVA, would provide insight into the in vivo anticoagulant intensity achieved in individual patients receiving rivaroxaban. Reliance on RIVA is problematic in the critical

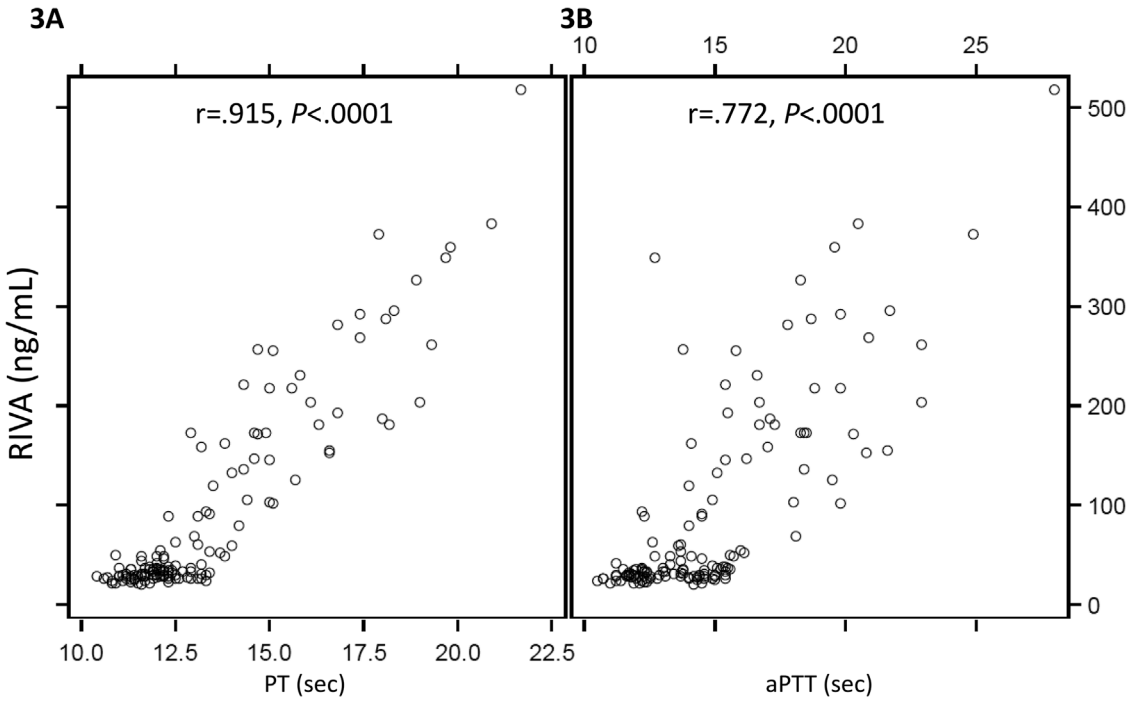

FIGURE 3 Scatterplot showing the relationship between the rivaroxaban specific anti-Xa activity (RIVA [ng/mL]) and conventional coagulation tests. (A) Prothrombin time (PT) (min); (B) activated partial thromboplastin time (aPTT) (min). The correlation (*r*) and the associated significance (*P*-value) are displayed at the top of each graph

care setting, however, because it is a test performed at reference laboratories, meaning timely dose adjustment is unlikely. Alternative coagulation tests that correlate well the gold standard would be desirable.

PT has been considered a useful alternative to anti-Xa activity monitoring in people.[21–23] Prolongation of conventional screening tests (PT and aPTT) was noted in a study of healthy dogs receiving rivaroxaban.[11] Interestingly, tissue factor–activated TEG was not significantly impacted by rivaroxaban administration in these same dogs. The mode of activation for TEG is a relevant consideration for anticoagulant therapeutic monitoring. A study in healthy dogs receiving unfractionated heparin identified that TEG performed with strong activators was necessary for anticoagulant monitoring and correlated well with the unfractionated heparin anti-Xa activity.[13] Based on these data, the potential utility of traditional coagulation diagnostics (ie, PT and aPTT) as well as strongly activated TEG (RapidTEG) as surrogates for anti-Xa activity was investigated in this present study. Despite robust activation, TEG correlated poorly with RIVA in this study. PT had an excellent correlation with RIVA, however, and therefore has potential as a readily available, affordable alternative option to RIVA in dogs receiving rivaroxaban.

It is important to interpret the PT results with some caution, however. Despite an overall very strong correlation between PT and RIVA in this study, the correlation was very weak within the therapeutic target activity used in people. The number of data available for comparison was considerably lower within this range, so the apparent poor correlation may be a product of low numbers in the sample. Further work examining the apparent correlations between PT and RIVA below, above, and within this target activity range would be helpful. The PT utilized in this study was performed at a specialist veterinary coagulation laboratory. Therefore, the results of this study cannot necessarily be extrapolated to all PT assays, especially point-of-care monitoring devices. Further work is necessary to investigate the correlation between alternative PT assays with RIVA to corroborate the findings here. Interestingly, in people, not all studies necessarily agree that PT is a good surrogate for anti-Xa, with variability in both laboratories and reagents.[22–25] Thromboplastin reagents used for PT can have considerable variation in sensitivity to rivaroxaban related to the variability of their tissue factor and phospholipid content.[24] However, the variability of PT reagents for anticoagulant monitoring is not a new issue. PT is the monitoring test of choice for warfarin, but variability in reagents led to the development of the international normalized ratio to standardize interpretation of results. Even when an international normalized ratio is utilized for rivaroxaban, disparate results compared to anti-Xa may still be encountered.[22,24] To that end, a recent systematic review recommended against PT as a screening test for people receiving rivaroxaban, with strong preference for anti-Xa monitoring.[25] An additional challenge when using PT involves determining the desired degree of PT prolongation in patients receiving rivaroxaban, because this may also be dependent on the methodology used to measure PT. Further work is needed to understand these issue more comprehensively in dogs. An alternative approach described in people is the use of dilute PT (dPT), which may create a more physiological in vitro environment compared to standard PT.[26–28] There are conflicting reports, however, regarding the suitability of dPT assays as a surrogate for RIVA in people.[26,27] Dilute PT has been investigated in healthy cats receiving

rivaroxaban[29] but to the authors' knowledge has not been examined in dogs. Future work investigating the role of dPT as a rivaroxaban therapeutic monitoring option in dogs would be warranted.

TG was also examined in this current study. TG variables did correlate quite well with anti-Xa activity, which appears similar to previous work in other healthy dogs.[13] Although the changes in TG variables do support the achievement of anticoagulation, it is unlikely that TG would be a sensitive enough test to use in place of anti-Xa. The availability of TG testing is also limited to a few institutions currently, further limiting the applicability of this modality as a surrogate for the gold standard in dogs. In the emergency setting in people where the turnaround time for anti-Xa activity is also too slow, newer methodologies are being explored for point-of-care assessment of anticoagulation (eg, prior to emergency surgery). Optical sensing of anticoagulants in whole blood using laser speckle rheology technology has been described and was shown to be superior to viscoelastic testing in a pilot study in people.[30] Although this is in the early stages of development in people, this novel alternative to anti-Xa activity may become more widespread eventually.

This study has some limitations that are worthy of comment. Although 140 data points were available for analysis, these blood samples were obtained from 5 healthy neutered male Beagles. These dogs therefore may not be representative of a larger population of dogs (eg, different sex, neuter status, breed, age, and disease states). Further clinical trials are necessary to examine therapeutic monitoring in a greater number of dogs, especially those with systemic disease. As mentioned previously, all coagulation diagnostics, with the exception of RapidTEG, were performed by a specialist veterinary coagulation laboratory. It is therefore not possible to extrapolate these data directly to similar coagulation tests performed at other centers.

To conclude, this study identified that PT correlated strongly with RIVA in a population of healthy dogs receiving rivaroxaban. PT performed better than all other coagulation tests investigated here and was vastly superior to TEG even when strong activators were used. PT therefore has a potential as a useful alternative to anti-Xa, but further work is necessary to validate these results with a wider array of PT assays. Ultimately, an understanding of whether point-of-care coagulation diagnostics, rather than coagulation assays performed at reference laboratories, would facilitate timely dose adjustment of rivaroxaban in sick dogs is needed.

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Notes

* Lynch AM, Ruterbories L, Griffith EH, et al. Rivaroxaban pharmacodynamics are unaffected by concurrent feeding or gastroprotectant administration in healthy dogs. J Vet Emerg Crit Care 2018;28(S1):S8.
† Xarelto (rivaroxaban) 20 mg tablets, Bayer HealthCare AG, Leverkussen, Germany.
‡ Hill's a/d, Hill's Pet Nutrition Inc, Topeka, KS.
§ Sucralfate, Nostrum Laboratories Inc, Kansas City, MO.
** Prilosec, Proctor & Gamble, Cincinnati, OH.
†† Dexdomitor (dexmedetomidine), Zoetis, Kalamazoo, MI.
‡‡ Torbugesic (butorphanol tartrate), Zoetis, Kalamazoo, MI.
§§ Mila International Inc, Florence, KY.
*** Antisedan (atipamezole), Zoetis, Kalamazoo, MI.
††† Maintenance dog food, Exclusive, Dearing, KS.
‡‡‡ S-Monovette vacutainers, Sardtedt, Numbrecht, Germany.
§§§ RapidTEG, Haemonetics Corp, Braintree, MA.
**** STA Compact, Diagnostica Stago, Parsippany, NJ.
†††† Thromboplastin LI, Helena Diagnostics, Beaumont, TX.
‡‡‡‡ Dade Actin FS, Siemens Health Diagnostics, Marburg, Germany.
§§§§ STA-Liquid anti-Xa, Diagnostica Stago, Parsippany, NJ.
***** STA-Rivaroxaban Calibrator, Diagnostica Stago, Parsippany, NJ.
††††† STA-Rivaroxaban Controls, Diagnostica Stago, Parsippany, NJ.
‡‡‡‡‡ CAT (Thrombinoscope), Diagnostica Stago, Assieres, France.
§§§§§ PPP-reagent low, Diagnostica Stago, Parsippany, NJ.
****** FluCa buffer, Diagnostica Stago, Parsippany, NJ.
†††††† Thrombin calibrator, Diagnostica Stago, Parsippany, NJ.
‡‡‡‡‡‡ Thrombinoscope Software, Diagnostica Stago, Assieres, France.
§§§§§§ SAS software (version 9.4), Cary, NC.

ETHICAL APPROVAL

This study was approved by the IACUC at the College of Veterinary Medicine, North Carolina State University, Raleigh, NC.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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