Journal of Veterinary Cardiology (2019) **25**, 7—13

ELSEVIER

Journal of Veterinary Cardiology ESVC

www.elsevier.com/locate/jvc

Case Report

Use of rivaroxaban for treatment of cranial vena cava syndrome secondary to transvenous pacemaker lead thrombosis in a dog☆,☆☆

B. Lozada Miranda, DVM, R. Walton, DVM, D.N. LeVine, DVM, PhD, A. Blong, DVM, W. Ware, DVM, MS, J. Ward, DVM*

Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Iowa State University, 1809 S. Riverside Drive, Ames, IA 50011, USA

Received 23 March 2019; received in revised form 2 July 2019; accepted 18 July 2019

KEYWORDS
Anticoagulant;
Factor X;
Proteinuria;
Protein-losing nephropathy;
Canine

Abstract A six-year-old Brussels griffon was presented for cervical swelling three months after implantation of a transvenous pacemaker. Transthoracic echocardiography demonstrated a thrombus associated with the pacemaker lead, partially obstructing right atrial inflow. The laboratory findings were consistent with protein-losing nephropathy. Initial medical therapy consisted of rivaroxaban (0.68 mg/kg orally every 24 hours), clopidogrel (2.5 mg/kg orally every 24 hours), and enalapril (0.5 mg/kg orally every 12 hours). Resolution of cervical and thoracic edema was noted within two weeks of initiating therapy. Recheck echocardiography two months and one year later revealed decreasing thrombus size despite worsening

☆ A unique aspect of the Journal of Veterinary Cardiology is the emphasis of additional web-based images permitting the detailing of procedures and diagnostics. These images can be viewed (by those readers with subscription access) by going to http://www.sciencedirect.com/science/journal/17602734. The issue to be viewed is clicked and the available PDF and image downloading is available via the Summary Plus link. The supplementary material for a given article appears at the end of the page. Downloading the videos may take several minutes. Readers will require at least Quicktime 7 (available free at http://www.apple.com/quicktime/download/) to enjoy the content. Another means to view the material is to go to http://www.doi.org and enter the doi number unique to this paper which is indicated at the end of the manuscript.

☆☆ A unique aspect of the Journal of Veterinary Cardiology is the emphasis of additional web-based materials permitting the detailing of procedures and diagnostics. These materials can be viewed (by those readers with subscription access) by going to http://www.sciencedirect.com/science/journal/17602734. The issue to be viewed is clicked and the available PDF and image downloading is available via the Summary Plus link. The supplementary material for a given article appears at the end of the page. To view the material is to go to http://www.doi.org and enter the doi number unique to this paper which is indicated at the end of the manuscript.

* Corresponding author.
E-mail address: jward@iastate.edu (J. Ward).

https://doi.org/10.1016/j.jvc.2019.07.002

proteinuria. To the authors' knowledge, this is the first documented use of rivaroxaban for successful medical treatment of cranial vena cava syndrome caused by intracardiac pacemaker lead thrombosis in a hypercoagulable patient.

A six-year-old, 7.3 kg, spayed female Brussels griffon was presented to the Cardiology Service at Iowa State University Lloyd Veterinary Medical Center (ISU-LVMC) for a five-day history of ventral cervical swelling. Approximately three months before presentation, the dog was diagnosed with third-degree atrioventricular block and underwent successful implantation of a single-lead transvenous pacemaker system at another institution (left jugular approach; active fixation lead; Medtronic Sensia generator; a variable ventricular pacing rate of 80—130 beats per minute). Three days before presentation at ISU-LVMC, the dog was evaluated by a referring veterinarian who prescribed carprofen (1.7 mg/kg PO q 12 hr) and diphenhydramine (1.7 mg/kg PO q 12 hr), with no improvement noted by the owner.

Physical examination revealed moderate symmetric subcutaneous pitting edema of the ventral cervical and thoracic region from the mandible to xyphoid, accompanied by inspiratory stertor and stridor. The jugular lead insertion and pulse generator sites in the left cervical region were well healed, with no evidence of an open wound or local swelling. The remainder of the physical examination was unremarkable. Thoracic radiographs revealed normal positioning of the pacemaker generator and lead, with no other important findings.

Transthoracic echocardiography revealed a 1.5 cm $\times$ 1 cm ellipsoid structure of homogenous echotexture attached to the pacing lead within the right atrium (see Fig. 1 and Video 1). Color Doppler imaging revealed partial obstruction to right atrial inflow associated with the lesion, as well as mild tricuspid valve regurgitation associated with the lead crossing the valve. The cause of the ventral cervical and thoracic edema was presumed to be cranial vena cava syndrome (CVCS) secondary to presence of an obstructive lesion (thrombus or vegetation) attached to the pacemaker lead.

Serum biochemistry analysis revealed mild hypoalbuminemia (2.3 g/dL; reference range: 2.7—4.0 g/dL) and hypocalcemia (9.6 mg/dL; reference range: 9.7—11.3 mg/dL). Serum creatinine (1.0 mg/dL; reference range: 0.5—1.5 mg/dL) and blood urea nitrogen (25 mg/dL, reference range: 10—30 mg/dL) levels were normal. A complete blood count was unremarkable. Urinalysis revealed 4 + proteinuria, and the ratio of urine protein to urine creatinine (UPC) was 1.86 (reference range $<$ 0.2 according to International Renal Interest Society staging guidelines). Samples were submitted for blood cultures, urine culture, and

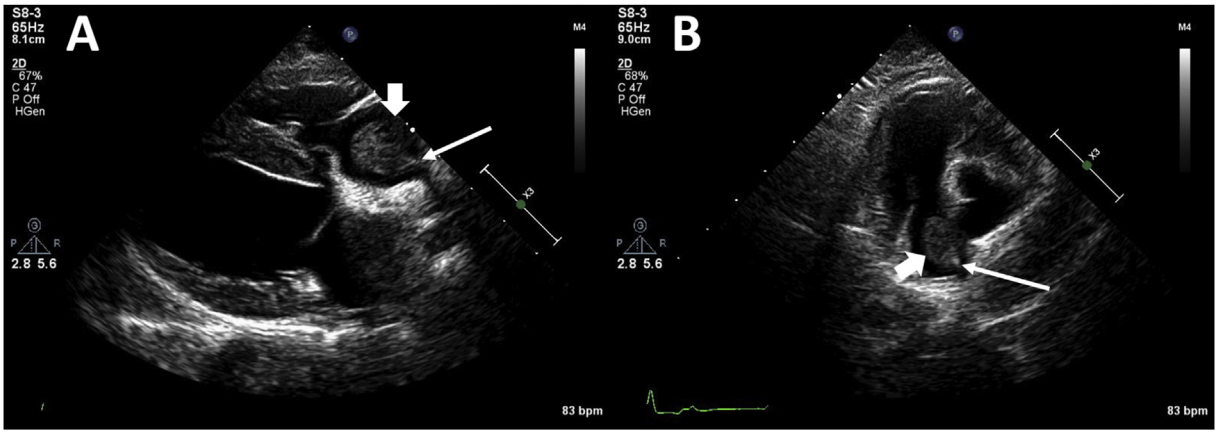

Fig. 1 Still B-mode echocardiographic images from the right parasternal long-axis four-chamber (A) and left cranial (B) views of a six-year-old Brussels griffon with clinical signs of cranial vena cava syndrome. A 1.5 cm $\times$ 1.0 cm ellipsoid lesion (thrombus) is present within the right atrium (thick arrows), attached to a transvenous pacemaker lead (thin arrows).

vector-borne infectious disease testing.[a,b] Given the concern for protein-losing nephropathy (PLN) as a primary cause for thrombus formation, treatment with enalapril (0.5 mg/kg PO q 12 hr), clopidogrel (2.5 mg/kg PO q 24 hr), and rivaroxaban (0.68 mg/kg PO q 24 hr) was initiated. Pending urine and blood cultures, amoxicillin/clavulanic acid (17 mg/kg PO q 12 hr) was also prescribed for two weeks. Computed tomography angiography was offered to further characterize the size and extent of pacemaker lead thrombi in the right atrium and cranial vena cava but was declined by the owners.

At a recheck appointment two weeks later, physical examination showed complete resolution of the cervical and thoracic edema. The results of infectious disease testing and cultures had become available, and all tests were negative. Echocardiography revealed that the pacemaker lead thrombus was still present but no longer causing atrial inflow obstruction. Blood work showed worsening hypoalbuminemia (1.7 g/dL) and proteinuria (UPC: 6.01). Creatinine and blood urea nitrogen concentrations remained normal. Systemic hypertension was documented for the first time, with a Doppler blood pressure reading of 192 mmHg. Abdominal radiographs and ultrasound were unremarkable. Antithrombotic therapy with rivaroxaban and clopidogrel was continued. For treatment of progressive PLN and systemic hypertension, telmisartan (0.7 mg/kg PO q 24 hr) was added to enalapril, and a prescription renal diet and omega-3 fatty acid supplementation were recommended.

Two months later, echocardiography revealed a noticeable decrease in thrombus size (0.9 × 0.7 cm; see Fig. 2 and Video 2). On recheck serum chemistry analysis, hypoalbuminemia had resolved (2.7 g/dL), but new mild azotemia was noted (blood urea nitrogen: 64 mg/dL, creatinine: 1.7 mg/dL). Proteinuria persisted with a UPC of 3.4, and systemic hypertension persisted with a Doppler blood pressure of 180 mmHg. Given the infeasibility of renal biopsy concurrent to antithrombotic therapy, mycophenolate mofetil (12.9 mg/kg PO q 12 hr) was initiated as a therapeutic trial for possible immunopathogenesis of the dog's glomerular disease. Previous doses of enalapril, clopidogrel, and rivaroxaban were continued; the dose of telmisartan was increased to 0.7 mg/kg PO q 12 hr. At subsequent follow-up visits for management of PLN, the dose of telmisartan was further uptitrated (to a final total daily dose of 3.0 mg/kg PO), and mycophenolate was discontinued owing to gastrointestinal side-effects, with no clinically relevant change in UPC.

A recheck echocardiogram performed one year after initial presentation to ISU-LVMC revealed that the pacemaker lead thrombus had continued to decrease in size (0.5 × 0.5 cm). The UPC ratio remained elevated at 3.14; mild azotemia persisted (blood urea nitrogen: 47 mg/dL, creatinine: 1.9 mg/dL); and systemic blood pressure was 165 mmHg. Because the patient was doing clinically well and displaying no hemorrhagic side-effects from antithrombotic therapy, medical treatment with clopidogrel, rivaroxaban, enalapril, and telmisartan was continued. At the time of writing, the patient continues to be clinically stable with no recurrence of CVCS and no overt clinical signs associated with PLN. The owners were counseled to observe the patient for bleeding complications as potential side-effects of concurrent clopidogrel and rivaroxaban use. Routine rechecks of UPC, systemic blood pressure, and serum chemistry analysis were recommended to monitor for both beneficial and adverse effects of concurrent angiotensin-converting enzyme inhibition and angiotensin receptor blockade.

Discussion

Cranial vena cava syndrome is an uncommonly reported complication of transvenous pacemaker placement in dogs. Cranial vena cava syndrome is a manifestation of impaired right atrial inflow secondary to extraluminal compression, intraluminal obstruction, or intraluminal constriction of the cranial vena cava [1]. Obstruction of venous return increases cava hydrostatic pressure, resulting in an increase in net fluid flow to the interstitial space. Clinically, CVCS is appreciated as dependent edema of the head, neck, or forelimbs, with or without pleural effusion. Pleural effusion results if interstitial fluid pressure exceeds lymphatic drainage or increased pressure in the cranial vena cava extends into the thoracic duct [2].

In dogs with transvenous pacemakers, the presence of the lead in the right atrium and cranial vena cava can lead to CVCS owing to either intraluminal obstruction (in the case of lead thrombus or vegetation) or constriction (in the case of stricture/stenosis). The causative relationship between cranial vena cava thrombosis and stricture formation in patients with transvenous

[a] Canine SNAP Test Plus, IDEXX Laboratories, Westbrook, Maine, USA.

[b] Canine Comprehensive Vector-Borne Disease Panel, Vector Borne Disease Diagnostic Laboratory, NC State College of Veterinary Medicine, Raleigh, North Carolina, USA.

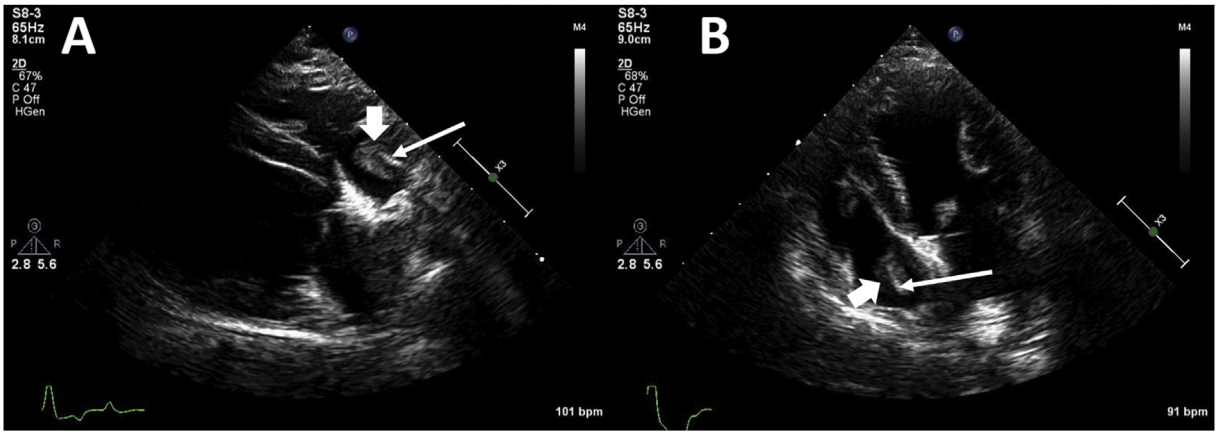

Fig. 2 Still B-mode echocardiographic images from the right parasternal long-axis four-chamber (A) and left cranial (B) views of the same patient after two months of antithrombotic treatment with rivaroxaban and clopidogrel. The thrombus (thick arrows) attached to the pacemaker lead (thin arrows) is still visible within the right atrium, but has decreased in size.

pacemaker leads is not entirely clear. In canine experimental models and some previous case reports, lead-induced endothelial trauma has been linked to deposition of a fibrous connective sheath around the lead, resulting in stricture formation and subsequent thrombus formation [2,3]. In other cases, primary lead-associated thrombosis secondary to redundant pacemaker lead [4], sepsis [5], or an underlying prothrombotic disease [6] causes CVCS in the absence of a stricture.

Treatment strategies reported for CVCS include surgical removal of the lead and associated thrombi, balloon angioplasty, antithrombotic medications, or combinations of these therapies. Successful treatment for CVCS has consisted of balloon angioplasty alone [7] or in combination with clopidogrel and low-molecular-weight heparin, with or without tissue plasminogen activator [8]. Of the dogs successfully treated for caval strictures, the goal of anticoagulant therapy was to reduce the incidence of thrombus formation after balloon angioplasty or to address ongoing thrombus formation caused by the stricture. Additional reports describe cases of CVCS where medical or surgical treatment was unsuccessful. One case report describes a dog with stricture formation of the cranial vena cava with an associated thrombus, with no apparent predisposing factors for thrombus formation. A combination of balloon angioplasty, thoracic duct ligation, and antiplatelet therapy was unsuccessful in resolving clinical signs [2]. Another study reported three dogs with CVCS secondary to lead thrombosis, with no identified underlying disease predisposing to hypercoagulability; multiple treatment strategies were attempted without success, including enoxaparin with acetylsalicylic acid, enoxaparin with recombinant tissue plasminogen activator, and surgical removal of the lead and thrombi [9].

The case reported here describes successful medical treatment of CVCS secondary to lead thrombosis in a dog. A unique aspect of the present case was the use of a synthetic direct factor Xa inhibitor, rivaroxaban, as the anticoagulant of choice. Direct factor Xa inhibitors bind directly and reversibly to free factor Xa, the prothrombinase complex, and clot-associated factor Xa, thereby preventing thrombin generation and limiting thrombin-induced positive feedback activation [10]. In human medicine, the use of rivaroxaban and other direct factor Xa inhibitors has been recommended as an efficacious alternative to warfarin for the prevention of strokes and embolism in patients with atrial fibrillation [11].

Direct factor Xa inhibitors represent an emerging class of antithrombotic medications in veterinary medicine. Although studies evaluating the clinical use of rivaroxaban in veterinary patients are limited, several molecular and pharmacokinetic studies support its use in dogs. A study comparing the binding site of rivaroxaban on human factor Xa to canine factor Xa revealed that 13 of the 14 (93%) amino acids interacting with rivaroxaban were identical to the canine isoform, suggesting the drug is potentially effective in dogs [12]. Furthermore, an in vitro study has confirmed the anticoagulant effect of rivaroxaban on canine plasma [13]. Pharmacokinetic studies have shown that plasma concentrations of rivaroxaban increase linearly with increasing doses and that rivaroxaban demonstrates an average of 60—80% oral bioavailability in dogs [14]. An in vivo study in healthy dogs showed that rivaroxaban (2 mg/kg PO) provides an anticoagulant effect lasting almost

24 h, with some interindividual variability [15]. In addition, a preliminary clinical study suggested that rivaroxaban (0.89 mg/kg PO q 24 hr) may be a valid treatment option for hypercoagulability associated with primary immune-mediated hemolytic anemia in dogs [16].

A recent consensus statement regarding antithrombotic use in dogs and cats (Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care) suggested that factor Xa inhibitors appear to be safe and well tolerated in veterinary patients and may be preferred over unfractionated heparin and warfarin [17,18]. The panel recommended a rivaroxaban dose of 1—2 mg/kg/day in dogs. Based on the current literature, the consensus panel concluded that insufficient evidence exists to formulate guidelines for monitoring factor Xa inhibitor therapy or to strongly recommend the use of rivaroxaban over low-molecular-weight heparins in dogs [18,19]. One of the potential major benefits of direct factor Xa inhibitors over other anticoagulants relates to context and specificity of factor Xa binding. Indirect factor Xa inhibitors, such as low-molecular-weight heparins, that potentiate the action of antithrombin only bind and inhibit factor Xa that exists free in the plasma. Direct factor Xa inhibitors are also able to inhibit prothrombinase-bound and clot-associated factor Xa, making a drug such as rivaroxaban an effective method of preventing thrombus growth [10]. Other benefits of factor Xa inhibitors over low-molecular-weight heparins include ease of administration (oral versus subcutaneous) and decreased cost [5].

In the case reported here, rivaroxaban therapy was initiated before publication of consensus guidelines; the dose of 0.68 mg/kg/day was prescribed based on limited previous clinical trial data and the available tablet size. No therapeutic monitoring was performed in this case. Continued use of rivaroxaban was justified based on improvement in clinical signs of CVCS, reduction of the thrombus size on echocardiography, and absence of clinical bleeding. It remains unknown whether and what type of testing is appropriate to monitor the anticoagulant effects of factor Xa inhibitors in dogs [17,18].

A single case series has documented the use of rivaroxaban (0.5—1.1 mg/kg PO q 24 hr) for treatment of pulmonary or systemic thromboembolic disease in four dogs [5]. In each case, a low-molecular-weight heparin (dalteparin or enoxaparin) was prescribed initially, but antithrombotic therapy was eventually switched to rivaroxaban owing to cost and owner non-compliance with injectable medication. All four dogs were also concurrently receiving antiplatelet therapy (clopidogrel with or without aspirin). Three of the cases had underlying prothrombotic diseases (PLN or immune-mediated pancytopenia), and the thromboelastography results were suggestive of hypercoagulability; the thrombus size decreased in two of these three dogs after rivaroxaban therapy. The fourth case described a thrombus associated with a pacemaker lead, similar to the present case report. However, positive urine culture and blood cultures in this patient revealed bacterial septicemia (*Escherichia coli* and *Enterococcus*), suggesting that the lesion on the pacemaker was likely an infective vegetation rather than a thrombus. This patient clinically improved with a combination of aggressive antibiotic therapy and rivaroxaban; it is therefore difficult to assess the true value of rivaroxaban therapy in that case. Imaging was not repeated to assess changes in the pacemaker lead lesion over time [5].

The dog in the present case report was diagnosed with PLN as the presumed cause of its pacemaker lead thrombus. Dogs with severe PLN have been shown to have hemostatic abnormalities consistent with hypercoagulability, such as lower levels of antithrombin and higher thromboelastographic clot strength, compared with clinically normal dogs [20]. Several retrospective studies have documented propensity for thrombus formation in dogs with PLN [21,22]. Because of this, dogs with proteinuria characterized by UPC $\geq$2.5 and hypoalbuminemia are considered to be at risk of venous and arterial thromboembolic disease, and prophylactic antithrombotic therapy is recommended [23,24]. In humans, rivaroxaban is used to treat venous thromboemboli in patients with low antithrombin secondary to nephrotic syndrome and is thought to be superior to other antithrombotic therapies in this setting owing to its ability to function despite low serum antithrombin levels [25]. For this reason, factor Xa inhibitors such as rivaroxaban may be the preferred anticoagulant option in patients with PLN.

Presence of an intravascular device such as pacemaker leads is a risk for thrombus formation, and lead thrombosis is a known complication of transvenous pacemaker implantation. Because underlying hypercoagulability increases risk of lead thrombosis, the authors advocate performing an UPC ratio to screen dogs for preexisting proteinuria before transvenous pacemaker implantation.

The present case report illustrates successful medical management of CVCS secondary to lead thrombosis in a patient with PLN. Rivaroxaban appears to be a safe and potentially effective option for treating pacemaker lead thrombosis and may obviate the need for more invasive

treatments such as balloon angioplasty or surgical removal of the pacing system. Therapy in this case involved a combination of anticoagulant treatment (rivaroxaban) with an antiplatelet medication (clopidogrel), so the individual antithrombotic benefit of rivaroxaban versus clopidogrel cannot be assessed. Further prospective studies are needed to develop recommendations for monitoring rivaroxaban treatment and to compare rivaroxaban with other antithrombotic treatments in dogs with hypercoagulability or identified thrombi.

Conflicts of Interest Statement

The authors do not have any conflicts of interest to disclose.

Acknowledgments

This study was not supported by any grant or other funding source.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvc.2019.07.002.

Video table

Video number	Title	Description
1	Echocardiogram at diagnosis	Two-dimensional echocardiogram from a right parasternal long-axis four-chamber view. A large, ellipsoid, echocardiographically homogeneous lesion is seen within the right atrium, attached to a transvenous pacemaker lead. The electrocardiographic rhythm is a third-degree atrioventricular block with right ventricular pacing.
2	Recheck echocardiogram	Two-dimensional echocardiogram from a right parasternal long-axis four-chamber view. The lead-associated lesion is still visible within the right atrium but is reduced in size.

References

[1] Cote E, Nicastro A. Cranial vena cava syndrome. Compend Continuing Educ Pract Vet 2002;24:701—10.
[2] Mulz JM, Kraus MS, Thompson M, Flanders JA. Cranial vena caval syndrome secondary to central venous obstruction associated with a pacemaker lead in a dog. J Vet Cardiol 2010;12:217—23.
[3] Fishbein MC, Tan KS, Beazell JW, Schulman JH, Hirose FM, Criley JM. Cardiac pathology of transvenous pacemakers in dogs. Am Heart J 1977;93:73—81.
[4] Stauthammer C, Tobias A, France M, Olson J. Caudal vena cava obstruction caused by redundant pacemaker lead in a dog. J Vet Cardiol 2009;11:141—5.
[5] Yang VK, Cunningham SM, Rush JE, de Laforcade A. The use of rivaroxaban for the treatment of thrombotic complications in four dogs. J Vet Emerg Crit Care 2016;26:729—36.
[6] Ward JL, Defrancesco TC, Tou SP, Atkins CE, Griffith EH, Keene BW. Complication rates associated with transvenous pacemaker implantation in dogs with high-grade atrioventricular block performed during versus after normal business hours. J Vet Intern Med 2015;29:157—63.
[7] Van De Wiele CM, Hogan DF, Green HW, Parnell NK. Cranial vena caval syndrome secondary to transvenous pacemaker implantation in two dogs. J Vet Cardiol 2008;10:155—61.
[8] Cunningham SM, Ames MK, Rush JE, Rozanski EA. Successful treatment of pacemaker-induced stricture and thrombosis of the cranial vena cava in two dogs by use of anticoagulants and balloon venoplasty. J Am Vet Med Assoc 2009;235:1467—73.
[9] Murray JD, O'Sullivan ML, Hawkes KCE. Cranial vena caval thrombosis associated with endocardial pacing leads in three dogs. J Am Anim Hosp Assoc 2010;46:186—92.
[10] Samama MM. The mechanism of action of rivaroxaban — an oral, direct Factor Xa inhibitor — compared with other anticoagulants. Thromb Res 2011;127:497—504.
[11] January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. Aha/acc/hrs focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American heart association task force on clinical practice guidelines and the heart rhythm society. Circulation 2019;140:e125—51.
[12] Roehrig S, Straub A, Pohlmann J, Lampe T, Pernerstorfer J, Schlemmer KH, Reinemer P, Perzborn E. Discovery of the novel antithrombotic agent 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl) thiophene-2-carboxamide (BAY 59-7939): an oral, direct factor Xa inhibitor. J Med Chem 2005;48:5900—8.
[13] Conversy B, Blais MC, Dunn M, Gara-Boivin C, Carioto L, Del Castillo JRE. Rivaroxaban demonstrates in vitro anticoagulant effects in canine plasma. Vet J 2013;198:437—43.
[14] Weinz C, Buetehorn U, Daehler HP, Kohlsdorfer C, Pleiss U, Sandmann S, Schlemmer KH, Schwarz T, Steinke W. Pharmacokinetics of BAY 59-7939 - an oral, direct Factor Xa inhibitor - in rats and dogs. Xenobiotica 2005;35:891—910.
[15] Conversy B, Blais MC, Dunn M, Gara-Boivin C, del Castillo JRE. Anticoagulant activity of oral rivaroxaban in healthy dogs. Vet J 2017;223:5—11.
[16] Morassi A, Bianco D, Park E, Nakamura RK, White GA. Evaluation of the safety and tolerability of rivaroxaban in dogs with presumed primary immune-mediated hemolytic anemia. J Vet Emerg Crit Care 2016;26:488—94.

[17] Brainard BM, Buriko Y, Good J, Ralph A, Rozanski EA. Consensus on the rational use of antithrombotics in veterinary critical Care (CURATIVE): domain 5-discontinuation of anticoagulant therapy in small animals. J Vet Emerg Crit Care 2019;29:88—97.
[18] Blais MC, Bianco D, Goggs R, Lynch AM, Palmer L, Ralph A, Sharp CR. Consensus on the rational use of antithrombotics in veterinary critical Care (CURATIVE): domain 3—defining antithrombotic protocols. J Vet Emerg Crit Care 2019;29:60—74.
[19] Sharp CR, Lynch AM, Hons B, Dvm AMK, Dvm JMT. Consensus on the rational use of antithrombotics in veterinary critical Care (CURATIVE): domain 4 — refining and monitoring antithrombotic therapies. J Vet Emerg Crit Care 2019:75—87.
[20] Donahue SM, Brooks M, Otto CM. Examination of hemostatic parameters to detect hypercoagulability in dogs with severe protein-losing nephropathy. J Vet Emerg Crit Care 2011;21:346—55.
[21] Slauson DO, Gribble DH. Thrombosis complicating renal amyloidosis in dogs. Vet Pathol 1971;363:352—63.
[22] Littman MP, Dambach DM, Vaden SL, Giger U. Familial protein-losing enteropathy and protein-losing nephropahty in soft coated wheaten terriers: 222 cases. J Vet Intern Med 2000;14:68—80.
[23] Littman MP, Daminet S, Grauer GF, Lees GE, van Dongen AM. Consensus recommendations for the diagnostic investigation of dogs with suspected glomerular disease. J Vet Intern Med 2013;27:S19—26.
[24] deLaforcade A, Bacek L, Blais MC, Goggs R, Lynch A, Rozanski E. Consensus on the rational use of antithrombotics in veterinary critical Care (CURATIVE): domain 1—defining populations at risk. J Vet Emerg Crit Care 2019;29:37—48.
[25] Zhang L, Zhang H, Zhang J, Tian H, Liang J, Liu Z. Rivaroxaban for the treatment of venous thromboembolism in patients with nephrotic syndrome and low AT-III: a pilot study. Exp Ther Med 2018;15:739—44.