

Keep happiness in motion

A
supplement
for daily
joint care



Antinol[®]
PLUS EAB-277[®]



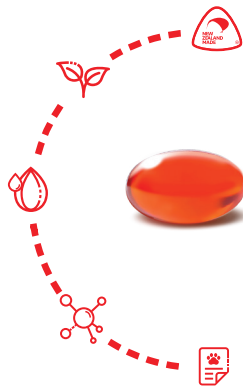
A supplement for daily joint care

Keep happiness in motion

Antinol® Rapid is a potent synergistic blend of 2 marine lipid extracts chosen for their unique enhancement formula called **EAB-277®**.

EAB-277® is the key active ingredient of this advanced formula formulated to promote optimal benefits through its synergistic efficacy contains > 90 free fatty acids full spectrum of Omega 3 including ETA, EPA, DHA as well as other key Polyunsaturated fatty acids (PUFAs) and antioxidants.

The excellency
of Antinol® Plus
EAB-277®



NATURAL

Sourcing + Farming in New Zealand

PRODUCTION PROCESS

Proprietary CO2 Supercritical
Extraction + Stabilization

ADVANCEMENT

of the Synergistic blend Potent +
Patented formula

ENHANCED BIOAVAILABILITY

and Fast Action

EFFICACY PROVEN

by Scientific Researches both
invitro and invivo

The two marine lipids used in Antinol® Plus are proprietary and exclusively produced. The exact combination of 30mg lipid fractions from **Perna canaliculus (New Zealand green lipped mussel)** and 20mg **high phospholipid krill oil** is the result of years of research combining and isolating lipid groups and essential fatty acids to find the optimal nutrient synergy.

Our proprietary high phospholipid krill oil is high in polar lipid enrichment which enhances bioactivity "Potency" of this marine oil blend formula as a result of proven efficacy.

The Antinol® Plus EAB-277® blend has been proven via laboratory tests to be **more effective than either of the individual lipids alone** in inhibiting inflammation markers such as nitric oxide, TNFα, and IL-6.

+ **Perna canaliculus**
(New Zealand)



+ **High Phospholipid Krill Oil**
(Antarctic)



**“Are my
dogs on
Antinol®?
Absolutely
+ Always!”**

[Mattise + Mel, Antinol® 4 Years]

Backed by **science** and extensive research



REVIEWED
INTERNATIONALLY
BY VETERINARIANS



RECOMMENDED
BY VETERINARIANS
GLOBALLY



SAFE TO USE +
DOES NOT INTERACT WITH
OTHER MEDICATIONS



TESTED FOR
STABILITY +
PURITY



THE LEADING JOINT
AND MOBILITY SUPPORT
PRODUCT IN JAPAN

- Suitable for long-term use for disorders or as a preventative + wellness supplement
- Patented and stabilized oil extracts
- 100% natural, free from Heavy metal such as Mercury, Cadmium etc. Clear from toxins
- No synthetic preservatives or fillers
- Fully traceable and sustainable
- No report of contraindications*
- According to safety study no known adverse effects have been reported.

*The safety of this product has not been tested in pregnant or lactating animals.
May contain a minute amount of tropomyosin protein

Antinol® Plus Animal Clinical Studies:

1. Evaluation of Green Lipped Mussel/Krill Oil (EAB-277), Biotaorientalis Extract, and an NSAID for Canine Hip Osteoarthritis Pain



Study Design:

In a prospective, black-randomized, double-blinded, placebo-controlled trial, 101 client-owned dogs with hip OA (one limb more affected than the other) were assigned to one of four groups

1. EAB-277 (n=26)
2. 4CYTE (n=25)
3. meloxicam (n=24)
4. or placebo (n=26)

Osteoarthritis (OA) is a common cause of chronic pain in dogs, yet limited high-quality evidence exists to guide veterinarians on the comparative efficacy of widely marketed joint supplements.

Objective: To compare the analgesic efficacy of a green-lipped mussel plus krill oil extract (EAB-277, Antinol® Rapid), a Biota orientalis extract (4CYTE Epiitalis® Forte), the NSAID meloxicam, and a placebo in dogs with hip OA-associated pain.

Peak vertical force (PVF) via force-plate gait analysis, orthopedic assessment scores (OAS), and hematology/serum chemistry were evaluated at baseline and at 2, 4, and 6 weeks.

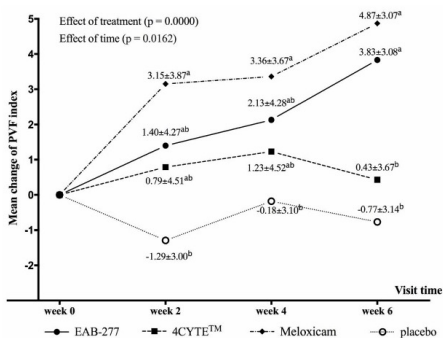


Figure 1

Figure. Mean (±SD) change from baseline in peak vertical force (PVF) of the index limb over 6 weeks. EAB-277 and meloxicam produced significantly greater improvement in limb use than 4CYTE and placebo. Differing superscript letters (a, b) indicate significant between-group differences at each time point. Reproduced from Kampa et al. (2024), Front Vet Sci, distributed under CC BY 4.0.

Results;

By week 6, both the EAB-277 and meloxicam groups showed statistically significant increases in PVF from baseline (mean change ≈3.8% and ≈4.9% of body weight, respectively), while changes in the 4CYTE and placebo groups remained non-significant and were not different from each other. Responder rates (≥2% PVF improvement) at week 6 were 69% for EAB-277, 79% for meloxicam, 40% for 4CYTE, and 8% for placebo. Overall OAS scores at week 6 were significantly lower (indicating less impairment) in the EAB-277, meloxicam, and 4CYTE groups compared with placebo. No adverse events or clinically significant hematologic/biochemical abnormalities were observed.

Conclusion: **EAB-277 produced objectively measurable improvements in limb function comparable in magnitude to the NSAID meloxicam**, while the Biota orientalis-based supplement (4CYTE) did not differ from placebo on the primary objective outcome measure, despite some benefit on subjective assessment scores.

2. Study of the effectiveness of glucosamine and chondroitin sulfate, marine based fatty acid compounds (PCSO-524® and EAB-277®), and carprofen for the treatment of dogs with hip osteoarthritis:

A prospective, block-randomized, double-blinded, placebo-controlled clinical trial



Study Design:

There were 15 dogs per group under treatment over 6 weeks.

1. Dasuquin
2. Carprofen
3. PCSO-524®
4. EAB-277®
5. Placebo

This 75 dogs' study at Khon Kaen University, Thailand was investigating the effectiveness of these compounds for the treatment of dogs with degenerative osteoarthritis and also to demonstrate the significantly superior therapeutic effect of PCSO-524® and EAB-277® compared with a placebo.

The study used **objective force plate gait analysis**, **subjective orthopedic assessment scores**, **hematology and blood chemistry profile analysis** and **subjective owner assessment scores**.

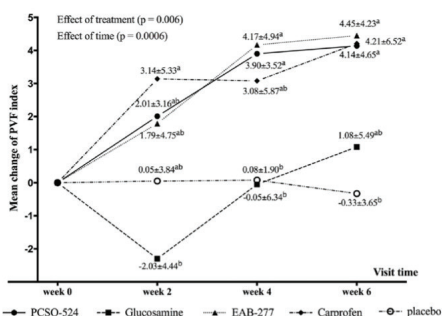


Figure 1

Graphic representation of the mean (± standard deviation) change from baseline in PVF for each group during the study period. Different superscripts (a, b) indicate significant differences between groups for change in PVF.

Results;

Overall, the results of this study indicate that **there appear to be benefits of carprofen, PCSO-524®, and EAB-277® for the treatment of OA-pain in dogs based on the measurement of PVF.** Glucosamine/chondroitin and placebo (sunflower oil) did not appear to be associated with positive treatment effects based on the measurement of PVF.

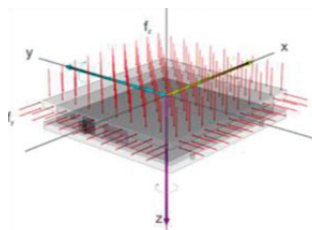
At 4 and 6 weeks after treatment, **the change in PVF of both PCSO-524® and EAB-277® were similar to that of the carprofen group.** The PVF of placebo group remained unchanged (-0.33 ± 3.65) as expected after study completed (6 weeks). The changes in PVF (significant when compared to baseline) in this study with carprofen after 2, 4, and 6 weeks were 3.14 ± 5.33 , 3.08 ± 5.87 , and 4.21 ± 6.52 , respectively.

These values are similar to those of a recent study⁽²⁸⁾ which found an increase in PVF of 3.2 ± 0.8 after 2 weeks treatment of carprofen. In that study, most enrolled dogs had hip OA, and the baseline PVF for index limb was similar in both studies (62.1 ± 13.5 and 60.7 ± 13.5).

Our result is also similar to another OA study⁽²²⁾ using the NSAID treatment firocoxib where the change in PVF of the index limb was reported to be 3.03 ± 4.67 and 3.25 ± 4.13 at 2 and 4 weeks. treatment, respectively.

Other Diagnostic Tools:

- 1) Gait analysis: Objective measurement
- 2) Provide quantitative weight bearing force
 - Force plates
 - Pressure sensitive mats



3.

A Randomized Placebo Controlled Trial - Preliminary Study of the effects of PCSO-524[®] and EAB-277[®] on Renal Protective Function in the case of long term NSAID use for osteoarthritis in dogs.

This study at Kasetsart University, Thailand is designed to **determine the potential efficacy of PCSO-524[®] on renal (kidney) protection in the long term (4 week) NSAID treatment of dogs.**

This clinical trial is being conducted on 100 owned client dogs divided into five groups: (i) NSAID: Meloxicam (Metacam, Boehringer Ingelheim Animal Health), (ii) PCSO-524[®], (iii) EAB-277[®], (iv) a combination of PCSO-524[®] with Meloxicam and (v) Placebo.

The full parameters of renal function evaluation will be conducted to monitor the renal function of the dogs in each group including the newly innovative biomarkers (SDMA test, Idexx) and the CRP inflammatory cytokine test. The study also will show the effects of EAB-277[®] on renal function.

Results;

The results showed that the combination of PCSO-524[®] with the various NSAID formulas **provided no negative effect to the dogs' kidneys** during their treatment with NSAIDs.

The results of this Renal study will include in the Meloxicam study manuscript which is under preparation process to submit Peer Review Journal.

Remarks; Unpublished data

4.

The Effect of EAB-277® on Heart Rate Variability (HRV) in Dogs with Tracheal Collapse.

This preliminary project funds veterinary students at Chiang Mai University, Thailand.

The hypothesis is **to study the effects of EAB-277® to see if it will help decrease HRV impairment due to systemic inflammatory processes** which could induce the dysfunction of the sympathetic nervous system as well as the parasympathetic nervous system.

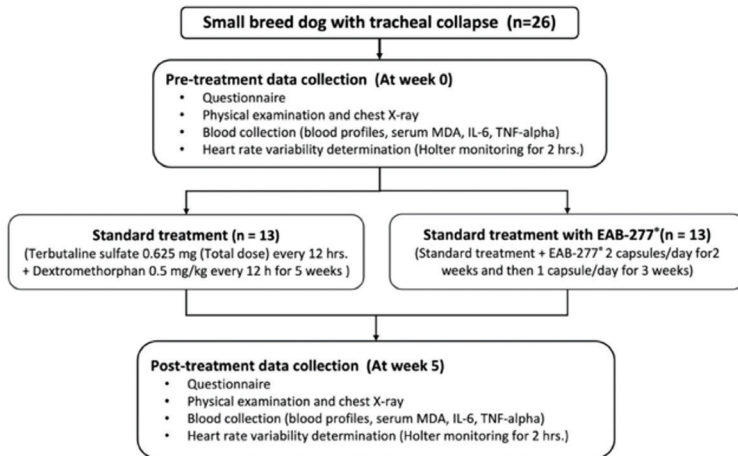


FIGURE 1 | Schematic representation of the study protocol. At pre-treatment, all dogs underwent chest X-ray, blood collection, Holter recording for 2-h. Then, dogs were divided into two groups to receive the standard treatment or standard treatment combined with polyunsaturated fatty acid EAB-277® from Green-Lipped Mussel blend for the 5 weeks. At post-treatment, all dogs underwent the re-assessment of chest X-ray, blood collection, Holter recording for 2-h to investigate cardiac sympathovagal balance, plasma oxidative stress, and inflammatory marker measurement. MDA, Malondialdehyde.

Ten small breed dogs will be used in this study and will be divided into two groups.

- The first group of five dogs comprises canine tracheal collapse patients given **standard treatment** for one month.
- The second group of five dogs comprises canine tracheal collapse patients given the **standard treatment plus EAB-277®** for one month.

Blood from all dogs will be collected for testing of morphology, blood chemistry and measurement of heart rate variability.

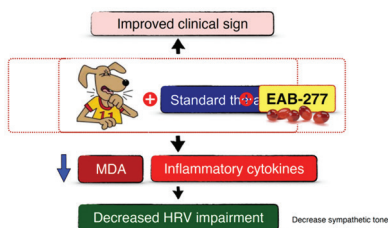
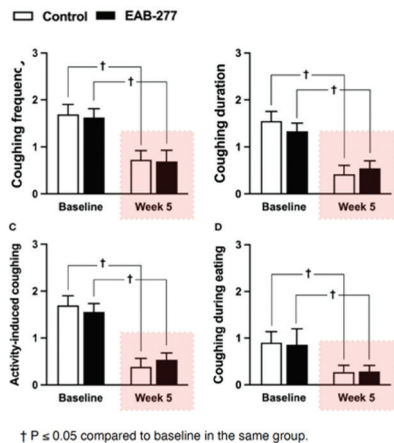


The project has been completed. However, since the results showed improvement in the EAB-277® group based on owner assessments, the study has been expanded to add objective inflammatory biomarker data which is expected to show the relation between clinical improvement and the reduction in the level of inflammation in the body based on scientific evidence developed in the study.

This expanded study was completed at the end of the third quarter of 2021 and has been published in *Frontiers in Veterinary Science*, a peer reviewed journal, in 2022.

This study demonstrated the beneficial effects of **EAB-277[®] supplementation combined with standard therapy on heart rate variability** in dogs with tracheal collapse.

Both standard treatment alone and standard treatment combined with EAB-277[®] **improved all clinical signs** as evaluated by the questionnaire.



The major findings of this study are as follows.

- First, EAB-277[®] supplementation for 5 weeks **did not affect the physical examination results, radiographic findings, or blood profile parameters** in the tracheal collapse dogs.
- Second, EAB-277[®] supplementation for 5 weeks **decreased oxidative stress and inflammatory marker compared to standard therapy** as indicated by serum MDA, canine serum IL-6 and canine TNF- α in tracheal collapse dogs.
- Third, EAB-277[®] supplementation for 5 weeks attenuated sympathovagal imbalance by **increasing parasympathetic activity** in tracheal collapse dogs.
- Fourth, using a questionnaire or evaluating TD/TI by chest X-ray was not accurate in evaluating the improvement of tracheal collapse in dogs.

Regarding clinical signs evaluated by questionnaire, **this study found improvement in clinical signs in tracheal collapse dogs after treatment compared to pre-treatment in both groups**, including a decrease in the frequency and duration of coughing, coughing induced by activities such as exercise, and eating and drinking.

A limitation of the questionnaire used in this study was the wide range of response scores and had much personal information, which could affect the reliability of the results.

This suggests that a questionnaire might not be appropriate as a prognostic tool for routine follow-up and routine examination in tracheal collapse dogs.

5.

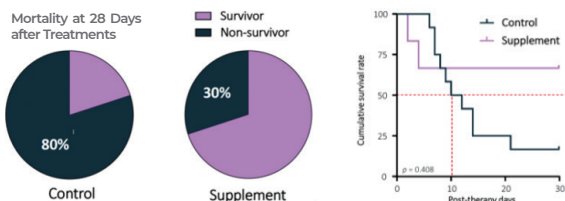
Supplementary effect of EAB-277® in Combination with Prednisolone against Immune-Mediated Hemolytic Anemia in Dogs.

This preliminary project funds veterinary students at Chiang Mai University, Thailand to determine the effects of EAB-277® in combination with Prednisolone against immune-mediated hemolytic anemia in dogs. Ten dogs will be separated into two groups (five dogs in each group).

- The first group of dogs with immune-mediated hemolytic anemia will be treated with **Prednisolone**.
- The second group of dogs with immune-mediated hemolytic anemia will be treated with **EAB-277® as the adjunctive treatment combined with the standard therapy.**

The results are expected to result in the reduction of the Prednisolone dosage in immune-mediated hemolytic anemia cases.

The results demonstrate that The mortality rate of dogs in the control group (80%) was higher than the supplement group (30%) (Figure 1a,b).



Immune-mediated hemolytic anemia (IMHA) is a common autoimmune disorder in dogs with a high fatality rate and it remains a therapeutic challenge.

The marine lipid extract, EAB-277®, is a natural anti-inflammatory nutraceutical product. However, the effects of EAB-277® in IMHA dogs has rarely been investigated.

The objective of this study is to assess the clinical effects of EAB-277® and prednisolone dose-tapering for supplemental therapy in IMHA dogs.

Prednisolone was given to 18 anemic IMHA dogs according to a standard regimen. Six dogs were supplementally treated with EAB-277® for 28 days and the remaining twelve dogs were a control group of untreated supplementations.

The Kaplan-Meier curve was used to demonstrate the survival time from a certain date to the time of IMHA dog death (Figure 1c).

The results show that the killing ability of IMHA was time-dependent.

In the control group, the survival time was 11 post-therapeutic days and the survival rate markedly declined to $16.7 \pm 10.7\%$ at 28-day post-therapeutic observation, whereas the survival rate of dogs in the supplement group was $66.7 \pm 19.2\%$ throughout the study period (log-rank test, $p = 0.408$).

When compared to pre-therapy, the supplement group's blood profiles improved ($p < 0.05$). The EAB-277® treated group showed a moderate decrease in the incidence rate (4.20 times) of prednisolone tapering compared to the control group.

The dosage reduction of prednisolone in supplement group was more than that in the control group ($p < 0.0001$).

Our results suggest that

EAB-277® supplementation may enhance clinical outcomes and lessen prednisolone dose-tapering in canine IMHA therapy.

6. Tracheal Collapse Study in Small Dogs.

These 40 small dog studies at the Mahidol Research Centre of the Mahidol Veterinary School, Thailand is designed to evaluate the efficacy of EAB-277® (Antinol® Plus) in reducing inflammation in tracheal collapse cases which is very common in small dog breeds causing the dog to have difficulty in breathing.

At present the common treatments prescribed for canine tracheal collapse are cough depressants, bronchodilators and steroids to control inflammation.

The objective of this study is to prove the anti-inflammatory efficacy of Antinol® Plus as an adjunctive supplement to the standard treatments in tracheal collapse cases to demonstrate Antinol's superior therapeutic effects, including increased exercise tolerance and less coughing.

Study Design:

There were 40 client owned dogs enrolled over 8 weeks in this study by split into 2 treatment groups as followed

- Control Group:
Standard treatment + Placebo
- Treatment group:
Standard treatment + EAB-277® supplementing

Results;

The treatment group showed improvement in respiratory effort and appetite compared to the placebo group after received the supplement on day 28 compared to day 14 ($P=0.017$ and 0.021).

Fluoroscopically, comparisons of diameter changing of tracheal height within groups showed a significant improvement in the treatment group at thoracic inlet region ($P=0.047$) when compared the changing diameter on day 14 to day 0.

Conclusion and clinical importance;

EAB-277®, the additional supplement for manage tracheal collapse in dogs can improve the quality of life and decrease percent change obtained from fluoroscopy.

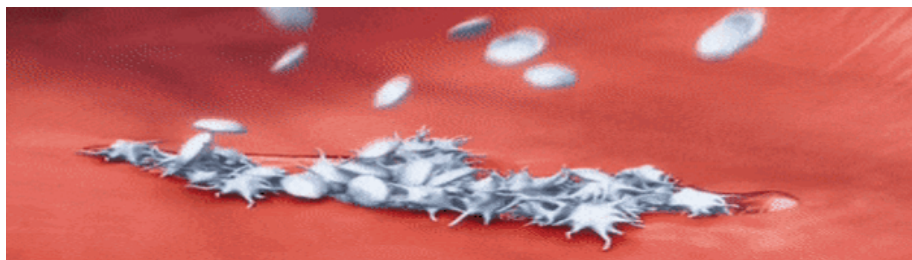
Remarks; Unpublished data



7.

Effects of marine based fatty acid compound EAB-277® on coagulopathy in dogs.

This preliminary project funds veterinary students at Kasetsart University, Thailand to investigate **whether long term supplementation of the marine based fatty acid compound EAB-277® affects blood coagulation**. If there is an effect, the study seeks to learn how long the canine patient needs to be withdrawn from the supplementation of EAB-277® prior to a surgical operation to reduce the risk of bleeding during the operation.



This preliminary study is being conducted by veterinary students on **nine dogs with a recommended dose** based on lean body weight and will **continue for three months**.

Blood samples will be collected to record

- The base line of hematology coagulation parameters
- Activated prothrombin time (apTT)
- Prothrombin time (PT)
- Thrombin time (TT)
- Collagen-epinephrine closure time (CEPI-CT)
- Collagen-ADP closure time (CADP-CT)

before prescribing EAB-277® at the outset and one, two and three months after treatment.

If there is no coagulopathy effect shown, all dogs will continue with EAB-277® and will be monitored for the above parameters on a weekly basis.

If coagulopathy is shown, then from that point EAB-277® will be withdrawn and the dogs will be followed on a weekly basis until their coagulation parameters have returned to normal.

Results;

The study demonstrated that **consumption of EAB-277® at 20 mg per kg (4 times of loading dose) continuously for 3 months did not prolong coagulation**. Although some dogs showed the higher collagen-epinephrine closure time (CEPI-CT) than Human reference range, it can not conclude that EAB-277® prolong coagulation in dogs as there is no report of Canine CEPI-CT moreover the delayed coagulation was interpreted based on > 300 sec. However the normal reference range for dogs and cats should be defined by studying in larger samples sizes.

Remarks; Unpublished data

8.

Safety Study of EAB-277® (Antinol® Plus) in Dogs.

This study at Chulalongkorn University, Thailand was proposed to evaluate the safety of EAB-277® in dogs which is required for veterinary product registration purposes. Initially a total of 40 mature beagles of 8 months in age or older were divided equally into four groups:

(i) placebo, (ii) recommended loading dose of two capsules per day, (iii) administration of six capsules once per day and (iv) administration of twenty capsules once per day



9.

Safety Study of EAB-277® (Antinol® Plus) in Cats.

This study at Chulalongkorn University, Thailand has been proposed to evaluate the safety of EAB-277® in cats which is required for veterinary product registration purposes. A total of 36 cats of 8 months in age or older were divided equally into four groups: (i) placebo, (ii) recommended dose of 1 capsule per day, (iii) administration of 3 capsules once per day and (iv) administration of 10 capsules once per day.



Results;

Animals used in the current study composed of **twenty healthy mature beagle dogs** (12 female and 8 male), body weight 9.50 ± 0.75 kg and twelve healthy mature domestic cats (8 female and 4 male), body weight 3.25 ± 0.50 kg. All animals had the body condition scores of 2 to 3 (on a 5-point scale) at the beginning of study.

Physical examination of all studied population composing of body temperature (38.4 – 38.8 °C), capillary refill time (CRT, 1 or 2 second) and fecal score (2.5 to 3.5) (on a 5-point scale) were all normal. No animals had neither constipation nor diarrhea.

Studied dogs and cats maintained their initial body condition without significant weight loss or gain. No abnormalities and illness sign of any system (ocular, nervous, musculoskeletal and integumentary systems) were observed. Blood parasite was not found for both dogs and cats.

Both dogs and cats of all four treatment groups preferred consumption of the PUFAs supplement capsules even the empty ones. No association was detected between the dose treatments and the dependent variables including blood hematology, blood chemistry, blood clotting factors, and PLI values.

Remarks; Unpublished data

References

- Franklin SP, Park RD, Egger EL. Metacarpophalangeal and metatarsophalangeal osteoarthritis in 49 dogs. *J Am Anim Hosp Assoc.* (2009) 45:112–7. doi:10.5326/0450112
- Rychel JK. Diagnosis and treatment of osteoarthritis. *Top Companion Anim Med.* (2010) 25:20–5. doi:10.1053/j.tcam.2009.10.005
- Johnston SA. Osteoarthritis. Joint anatomy, physiology, and pathobiology. *Vet Clin North Am Small Anim Pract.* (1997) 27:699–723. doi:10.1016/S0195-5616(97)50076-3
- Wright A, Amadio DM, Cernicchiaro N, Lascelles BDX, Pavlock AM, Roberts C, et al. Identification of canine osteoarthritis using an owner-reported questionnaire and treatment monitoring using functional mobility tests. *J Small Anim Pract.* (2022) 63:609–18. doi:10.1111/jsap.13500
- Moreau M, Dupuis J, Bonneau NH, Desnoyers M. Clinical evaluation of a nutraceutical, carprofen and meloxicam for the treatment of dogs with osteoarthritis. *Vet Rec.* (2003) 152:323–9. doi:10.1136/vr.152.11.323
- Sanderson RO, Beata C, Flipo RM, Genevois JP, Macias C, Tacke S, et al. Systematic review of the management of canine osteoarthritis. *Vet Rec.* (2009) 164:418–24. doi:10.1136/vr.164.14.418
- Edamura K, King JN, Seewald W, Sakakibara N, Okumura M. Comparison of oral robenacoxib and carprofen for the treatment of osteoarthritis in dogs: a randomized clinical trial. *J Vet Med Sci.* (2012) 74:1121–31. doi:10.1292/jvms.11-0529
- Vasseur PB, Johnson AL, Budberg SC, Lincoln JD, Toombs JP, Whitehair JC, et al. Randomized, controlled trial of the efficacy of carprofen, a nonsteroidal antiinflammatory drug, in the treatment of osteoarthritis in dogs. *J Am Vet Med Assoc.* (1995) 206:807–11.
- Mansa S, Palmer E, Grondahl C, Lonaas L, Nyman G. Long-term treatment with carprofen of 805 dogs with osteoarthritis. *Vet Rec.* (2007) 160:427–30. doi:10.1136/vr.160.13.427
- Brown DC, Boston RC, Coyne JC, Farrar JT. Ability of the canine brief pain inventory to detect response to treatment in dogs with osteoarthritis. *J Am Vet Med Assoc.* (2008) 233:1278–83. doi:10.2460/javma.233.8.127
- Bhathal A, Spryszak M, Louizos C, Frankel G. Glucosamine and chondroitin use in canines for osteoarthritis: a review. *Open Vet J.* (2017) 7:36–49. doi:10.4314/ovj.v7i1.6
- Monteiro-Stegall BP, Steagall PV, Lascelles BD. Systematic review of nonsteroidal anti-inflammatory drug-induced adverse effects in dogs. *J Vet Intern Med.* (2013) 27:1011–9. doi:10.1111/jvim.12127
- Aragon CL, Hofmeister EH, Budberg SC. Systematic review of clinical trials of treatments for osteoarthritis in dogs. *J Am Vet Med Assoc.* (2007) 230:514–21. doi:10.2460/javma.230.4.514
- Beale BS. Use of nutraceuticals and chondroprotectants in osteoarthritic dogs and cats. *Vet Clin North Am Small Anim Pract.* (2004) 34:271–89, viii. doi:10.1016/j.cvsr.2003.09.008
- McCarthy G, O'Donovan J, Jones B, McAllister H, Seed M, Mooney C. Randomised double-blind, positive-controlled trial to assess the efficacy of glucosamine/chondroitin sulfate for the treatment of dogs with osteoarthritis. *Vet J.* (2007) 174:54–61. doi:10.1016/j.tvjl.2006.02.015
- Cupta RC, Canerdy TD, Lindley J, Konemann M, Minniear J, Carroll BA, et al. Comparative therapeutic efficacy and safety of type-II collagen (UC-II), glucosamine and chondroitin in arthritic dogs: pain evaluation by ground force plate. *J Anim Physiol Anim Nutr.* (2012) 96:770–7. doi:10.1111/j.1439-0396.2011.01166.x
- Scott RM, Evans R, Conzemius MG. Efficacy of an oral nutraceutical for the treatment of canine osteoarthritis. A double-blind, randomized, placebocontrolled prospective clinical trial. *Vet Comp Orthop Traumatol.* (2017) 30:318–23. doi:10.3415/vcot-17-02-0020
- Fernandez-Martin S, Gonzalez-Cantalapiedra A, Munoz F, Garcia-Gonzalez M, Permuy M, Lopez-Pena M. Glucosamine and chondroitin sulfate: is there any scientific evidence for their effectiveness as disease-modifying drugs in knee osteoarthritis preclinical studies? A systematic review from 2000 to 2021. *Animals.* (2021) 11:1608. doi:10.3390/ani11061608
- Mongkon N, Soontornvipart K. Preliminary study of the clinical outcome of using PCSO-524 polyunsaturated fatty acid compound in the treatment of canine osteoarthritis and degenerative spinal diseases. *Thai J Vet Med.* (2012) 42:311–7.
- Soontornvipart K, Mongkhon N, Nganvongpanit K, Kongtawelert P. Effect of PCSO-524 on OA biomarkers and weight-bearing properties in canine shoulder and coxofemoral osteoarthritis. *Thai J Vet Med.* (2015) 45:157–65.
- Kwananocha I, Vijarnsorn M, Kashemsant N, Lekcharoensuk C. Effectiveness of disease modifying osteoarthritis agents and carprofen for treatment of canine osteoarthritis. *Thai J Vet Med.* (2016) 46:363–71
- Vijarnsorn M, Kwananocha I, Kashemsant N, Jarudecha T, Lekcharoensuk C, Beale B, et al. The effectiveness of marine based fatty acid compound (PCSO524) and firocoxib in the treatment of canine osteoarthritis. *BMC Vet Res.* (2019) 15:349. doi:10.1186/s12917-019-2110-7
- Suzuki Y, Fukushima M, Sakuraba K, Sawaki K, Sekigawa K. Krill oil improves mild knee joint pain: a randomized control trial. *PLoS ONE.* (2016) 11:e0162769. doi:10.1371/journal.pone.0162769
- Lafamme DP. Development and validation of a body condition score system for dogs. *Canine Pract.* (1997) 22:10–5.
- Chow SC, Shao J, Wang H. *Sample Size Calculations in Clinical Research*, 2nd ed. Boca Raton, FL: Chapman and Hall/CRC; (2003). doi:10.1201/9780203911341
- Hercrook CA, Pinchbeck G, Giejda A, Clegg PD, Innes JF. Validation of a client-based clinical metrology instrument for the evaluation of canine elbow osteoarthritis. *J Small Anim Pract.* (2009) 50:266–71. doi:10.1111/j.1748-5827.2009.00765.x
- Hielm-Bjorkman AK, Rita H, Tulamo RM. Psychometric testing of the Helsinki chronic pain index by completion of a questionnaire in Finnish by owners of dogs with chronic signs of pain caused by osteoarthritis. *Am J Vet Res.* (2009) 70:727–34. doi:10.2460/ajvr.70.6.727
- Brown DC, Boston RC, Farrar JT. Comparison of force plate gait analysis and owner assessment of pain using the Canine Brief Pain Inventory in dogs with osteoarthritis. *J Vet Intern Med.* (2013) 27:22–30. doi:10.1111/jvim.12004
- Moreau M, Lussier B, Ballaz L, Troncy E. Kinetic measurements of gait for osteoarthritis research in dogs and cats. *Can Vet J.* (2014) 55:1057–65.
- Waxman AS, Robinson DA, Evans RB, Hulse DA, Innes JF, Conzemius MG. Relationship between objective and subjective assessment of limb function in normal dogs with an experimentally induced lameness. *Vet Surg.* (2008) 37:241–6. doi:10.1111/j.1532-950X.2008.00372.x

31. McLaughlin RM. Kinetic and kinematic gait analysis in dogs. *Vet Clin North Am Small Anim Pract.* (2001) 31:193–201. doi: 10.1016/S0195-5616(01)50045-5
32. Conzemius MG, Torres BT, Muir P, Evans R, Krotscheck U, Budsberg S. Best practices for measuring and reporting ground reaction forces in dogs. *Vet Surg.* (2022) 51:385–96. doi: 10.1111/VSU.13772
33. Conzemius MG, Evans RB. Caregiver placebo effect for dogs with lameness from osteoarthritis. *J Am Vet Med Assoc.* (2012) 241:1314–9. doi: 10.2460/javma.241.10.1314
34. Venator KP, Frye CW, Gamble LJ, Waikshlag JJ. Assessment of a single intraarticular stifle injection of pure platelet rich plasma on symmetry indices in dogs with unilateral or bilateral stifle osteoarthritis from long-term medically managed cranial cruciate ligament disease. *Vet Med.* (2020) 11:31–8. doi: 10.2147/VMR.20238598
35. Chervier, C.; Cadore, J.L.; Rodriguez-Pineiro, M.I.; Deputte, B.L.; Chabanne, L. Causes of anaemia other than acute blood loss and their clinical significance in dogs. *J. Small Anim. Pract.* 2012, 53, 223–227. [Google Scholar] [CrossRef] [PubMed]
36. Borchert, C.; Herman, A.; Roth, M.; Brooks, A.C.; Friedenberg, S.G. RNA sequencing of whole blood in dogs with primary immune-mediated hemolytic anemia (IMHA) reveals novel insights into disease pathogenesis. *PLoS ONE* 2020, 15, e0240975. [Google Scholar] [CrossRef]
37. Balch, A.; Mackin, A. Canine immune-mediated hemolytic anemia: Pathophysiology, clinical signs, and diagnosis. *Compend. Contin. Educ. Vet.* 2007, 29, 217–225. [Google Scholar] [PubMed]
38. Morley, P.; Mathes, M.; Guth, A.; Dow, S. Anti-erythrocyte antibodies and disease associations in anemic and nonanemic dogs. *J. Vet. Intern. Med.* 2008, 22, 886–892. [Google Scholar] [CrossRef] [PubMed]
39. Kjølgaard-Hansen, M.; Goggs, R.; Winberg, B.; Chan, D.L. Use of serum concentrations of interleukin-18 and monocyte chemoattractant protein-1 as prognostic indicators in primary immune-mediated hemolytic anemia in dogs. *J. Vet. Intern. Med.* 2011, 25, 76–82. [Google Scholar] [CrossRef] [PubMed]
40. Cui, B.; Blois, S.L.; Bedard, C.; Wood, R.D.; Abrams-Ogg, A.C.; Beauchamp, G.; Wood, G.A. Serum interleukin 17 concentrations in dogs with immune-mediated hemolytic anemia. *J. Vet. Intern. Med.* 2021, 35, 217–225. [Google Scholar] [CrossRef]
41. Archer, T.M.; Mulligan, C.; Narayanan, L.; Riggs, C.; Fellman, C.; Thomason, J.M.; Wills, R.W.; Boothe, D.M.; Cruz-Espindola, C.; Harmon, R.; et al. Effects of oral administration of 5 immunosuppressive agents on activated T-cell cytokine expression in healthy dogs. *J. Vet. Intern. Med.* 2020, 34, 1206–1213. [Google Scholar] [CrossRef] [Green Version]
42. Swann, J.W.; Skelly, B.J. Systematic review of evidence relating to the treatment of immune-mediated hemolytic anemia in dogs. *J. Vet. Intern. Med.* 2013, 27, 1–9. [Google Scholar] [CrossRef]
43. Swann, J.W.; Skelly, B.J. Evaluation of immunosuppressive regimens for immune-mediated haemolytic anaemia: A retrospective study of 42 dogs. *J. Small Anim. Pract.* 2011, 52, 353–358. [Google Scholar] [CrossRef]
44. Swann, J.W.; Garden, O.A.; Fellman, C.L.; Glanemann, B.; Goggs, R.; LeVine, D.N.; Mackin, A.J.; Whitley, N.T. ACVIM consensus statement on the treatment of immune-mediated hemolytic anemia in dogs. *J. Vet. Intern. Med.* 2019, 33, 1141–1172. [Google Scholar] [CrossRef] [Green Version]
45. Wolyniak, C.J.; Brenna, J.T.; Murphy, K.J.; Sinclair, A.J. Gas chromatography-chemical ionization-mass spectrometric fatty acid analysis of a commercial supercritical carbon dioxide lipid extract from New Zealand green-lipped mussel (*Perna canaliculus*). *Lipids* 2005, 40, 355–360. [Google Scholar] [CrossRef]
46. Doggrell, S.A. Lyprinol-is it a useful anti-inflammatory agent? *Evid. Based Complement. Altern. Med.* 2011, 2011, 307121. [Google Scholar] [CrossRef] [Green Version]
47. Vijarnsom, M.; Kwananocha, I.; Kashemsant, N.; Jarudecha, T.; Lekcharonsuk, C.; Beale, B.; Peirone, B.; Lascelles, B.D.X. The effectiveness of marine based fatty acid compound (PCSO-524) and Firocoxib in the treatment of canine osteoarthritis. *BMC Vet. Res.* 2019, 15, 349. [Google Scholar] [CrossRef] [Green Version]
48. Mongkon, N.; Soontornvipart, K. Preliminary Study of the Clinical Outcome of Using PCSO-524 Polyunsaturated Fatty Acid Compound in the Treatment of Canine Osteoarthritis and Degenerative Spinal Diseases. *Thai J. Vet. Med.* 2013, 42, 311–317. [Google Scholar]
49. Kongwut, S.; Soontornvipart, K.; Sarikaphuti, M.; Makoom, P.; Nganvongpanit, K. Effect of Serum IL-1 β of PCSO-524 and Firocoxib in Dogs Undergoing Medial Patellar Luxation Repair. *Thai J. Vet. Med.* 2015, 45, 639–643. [Google Scholar]
50. Garden, O.A.; Kidd, L.; Mexas, A.M.; Chang, Y.M.; Jeffery, U.; Blois, S.L.; Fogle, J.E.; MacNeill, A.L.; Lubas, G.; Birkenheuer, A.; et al. ACVIM consensus statement on the diagnosis of immune-mediated hemolytic anemia in dogs and cats. *J. Vet. Intern. Med.* 2019, 33, 313–334. [Google Scholar] [Green Version]
51. Sun, P.L.; Jeffery, U. Effect of dilution of canine blood samples on the specificity of saline agglutination tests for immune-mediated hemolysis. *J. Vet. Intern. Med.* 2020, 34, 2374–2383. [Google Scholar] [CrossRef]
52. Paes, G.; Paepe, D.; Meyer, E.; Kristensen, A.T.; Duchateau, L.; Campos, M.; Daminet, S. The use of the rapid osmotic fragility test as an additional test to diagnose canine immune-mediated haemolytic anaemia. *Acta Vet. Scand.* 2013, 55, 74. [Google Scholar] [CrossRef] [Green Version]
53. Baum, K.; Telford, R.D.; Cunningham, R.B. Marine oil dietary supplementation reduces delayed onset muscle soreness after a 30 km run. *Open Access J. Sports Med.* 2013, 4, 109–115. [Google Scholar] [CrossRef] [Green Version]
54. Pampa, K.L.; Fallon, K.E.; Bensoussan, A.; Papalia, S. The effects of Lyprinol((R)) on delayed onset muscle soreness and muscle damage in well trained athletes: A double-blind randomised controlled trial. *Complement. Ther. Med.* 2011, 19, 311–318. [Google Scholar] [CrossRef]
55. Liu, S.; Hu, W.; Fang, Y.; Cai, Y.; Zhang, J.; Liu, J.; Ding, Y. Extraction of oil from wet Antarctic krill (*Euphausia superba*) using a subcritical dimethyl ether method. *RSC Adv.* 2019, 9, 34274–34282. [Google Scholar] [CrossRef] [PubMed] [Green Version]
56. Yin, F.-W.; Zhou, D.-Y.; Liu, Y.-F.; Zhao, Q.; Zhou, X.; Song, L.; Qi, H.; Zhu, B.-W. The Forms of Fluoride in Antarctic Krill (*Euphausia superba*) Oil Extracted with Hexane and its Removal with Different Absorbents. *J. Aquat. Food Prod. Technol.* 2017, 26, 835–842. [Google Scholar] [CrossRef]
57. Mickleborough, T.D.; Sinex, J.A.; Platt, D.; Chapman, R.F.; Hirt, M. The effects PCSO-524(R), a patented marine oil lipid and omega-3 PUFA blend derived from the New Zealand green lipped mussel (*Perna canaliculus*), on indirect markers of muscle damage and inflammation after muscle damaging exercise in untrained men: A randomized, placebo controlled trial. *J. Int. Soc. Sports Nutr.* 2015, 12, 10. [Google Scholar] [CrossRef] [PubMed] [Green Version]
58. Piek, C.J.; Junius, G.; Dekker, A.; Schrauwen, E.; Slappendel, R.J.; Teske, E. Idiopathic immune-mediated hemolytic anemia: Treatment outcome and prognostic factors in 149 dogs. *J. Vet. Intern. Med.* 2008, 22, 366–373. [Google Scholar] [CrossRef] [PubMed]
59. Mistry, N.; Mazer, C.D.; Sled, J.G.; Lazarus, A.H.; Cahill, L.S.; Solish, M.; Zhou, Y.Q.; Romanova, N.; Hare, A.G.M.; Doctor, A.; et al. Red blood cell antibody-induced anemia causes differential degrees of tissue hypoxia in kidney and brain. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2018, 314, R611–R622. [Google Scholar] [CrossRef] [Green Version]

60. Zoia, A.; Gerou-Ferriani, M.; Drigo, M.; Caldin, M. Case-control study of plasma mean platelet component concentration and survival analysis for dogs with immune-mediated hemolytic anemia. *J. Am. Vet. Med. Assoc.* 2018, **252**, 1384–1392. [Google Scholar] [CrossRef]
61. Lawson, C.; Smith, S.A.; O'Brien, M.; McMichael, M. Neutrophil Extracellular Traps in Plasma from Dogs with Immune-mediated Hemolytic Anemia. *J. Vet. Intern. Med.* 2018, **32**, 128–134. [Google Scholar] [CrossRef] [Green Version]
62. Mekritirat, T.; Rueangsri, T.; Keeratichandacha, W.; Soonsawat, S.; Boonyapakorn, C.; Pongkan, W. Polyunsaturated Fatty Acid EAB-2771(R) Supplementation Improved Heart Rate Variability and Clinical Signs in Tracheal Collapse Dogs. *Front. Vet. Sci.* 2022, **9**, 880952. [Google Scholar] [CrossRef]
63. Doganci, A.; Eigenbrod, T.; Krug, N.; De Sanctis, G.T.; Hausding, M.; Erpenbeck, V.J.; Haddad, E.B.; Lehr, H.A.; Schmitt, E.; Bopp, T.; et al. The IL-6R alpha chain controls lung CD4⁺CD25⁺ Treg development and function during allergic airway inflammation in vivo. *J. Clin. Investig.* 2005, **115**, 313–325. [Google Scholar] [CrossRef] [Green Version]
64. Valencia, X.; Stephens, G.; Goldbach-Mansky, R.; Wilson, M.; Shevach, E.M.; Lipsky, P.E. TNF downmodulates the function of human CD4⁺CD25^{hi} T-regulatory cells. *Blood* 2006, **108**, 253–261. [Google Scholar] [CrossRef]
65. Swann, J.W.; Woods, K.; Wu, Y.; Glanemann, B.; Garden, O.A. Characterisation of the Immunophenotype of Dogs with Primary Immune-Mediated Haemolytic Anaemia. *PLoS ONE* 2016, **11**, e0168296. [Google Scholar] [CrossRef] [Green Version]
66. Kampa, N.; Kaenkangpoo, D.; Jitpean, S.; Srithunyarat, T.; Seesupa, S.; Hoisang, S.; Yongvanit, K.; Kamlangchai, P.; Tuchpramuk, P.; Lascelles, B.D.X. Study of the effectiveness of glucosamine and chondroitin sulfate, marine based fatty acid compounds (PCSO-524 and EAB-277), and carprofen for the treatment of dogs with hip osteoarthritis: A prospective, block-randomized, double-blinded, placebo-controlled clinical trial. *Front. Vet. Sci.* 2023, **10**, 1033188. [Google Scholar] [CrossRef]
67. Swann, J.W.; Sziadovits, B.; Threlfall, A.J.; Garden, O.A.; Chang, Y.M.; Church, D.B.; Glanemann, B. Randomised controlled trial of fractionated and unfractionated prednisolone regimens for dogs with immune-mediated haemolytic anaemia. *Vet. Rec.* 2019, **184**, 771. [Google Scholar] [CrossRef]
68. Sri-Jayantha, L.S.; Doornink, M.T.; Urie, B.K. Increased risk of select glucocorticoid adverse events in dogs of higher body weight. *Can. Vet. J.* 2022, **63**, 32–38. [Google Scholar]
69. Weingart, C.; Thielemann, D.; Kohn, B. Primary immune-mediated haemolytic anaemia: A retrospective long-term study in 61 dogs. *Aust. Vet. J.* 2019, **97**, 483–489. [Google Scholar] [CrossRef]
70. Elkholy, D.A.; Brodbelt, D.C.; Church, D.B.; Pelligand, L.; Mwacimba, K.; Wright, A.K.; O'Neill, D.G. Side Effects to Systemic Glucocorticoid Therapy in Dogs Under Primary Veterinary Care in the UK. *Front. Vet. Sci.* 2020, **7**, 515. [Google Scholar] [CrossRef]
71. Swann, J.W.; Skelly, B.J. Canine autoimmune hemolytic anemia: Management challenges. *Vet. Med.* 2016, **7**, 101–112. [Google Scholar] [CrossRef] [Green Version]
72. Alvarez, A.M.; Mukherjee, D. Liver abnormalities in cardiac diseases and heart failure. *Int. J. Angiol.* 2011, **20**, 135–142. [Google Scholar] [CrossRef] [Green Version]
73. Jamiokorn, U.; Vibchok-anun, S. Effects of Dietary Polyunsaturated Fatty Acid Supplement on Healthy Beagle Dogs. *Thai J. Vet. Med.* 2014, **44**, 505–511. [Google Scholar]
74. Clarke D.L. Interventional radiology management of tracheal and bronchial collapse. *Vet. Clin North Am Small Anim Pract.* (2018) 48765–79. doi:10.1016/j.cvsm.2018.05.010
75. Hedlund C.S. Tracheal collapse. *Probl Vet Med.* (1991) 3:229–38. 3. Tappin SW. Canine tracheal collapse. *J Small Anim Pract.* (2016) 579–17. doi:10.1111/jsap.12436
76. Tappin SW. Canine tracheal collapse. *J Small Anim Pract.* (2016) 579–17. doi:10.1111/jsap.12436
77. Maggioro A.D. Tracheal and airway collapse in dogs. *Vet Clin North Am Small Anim Pract.* (2014) 44:117–27. doi:10.1016/j.cvsm.2013.09.004
78. Papaioannou V, Pneumatikos I, Maglaveras N. Association of heart rate variability and inflammatory response in patients with cardiovascular diseases: current strengths and limitations. *Front Physiol.* (2013) 4:174. doi:10.3389/fphys.2013.00174
79. Cooper TM, McKinley PS, Seeman TE, Choo TH, Lee S, Sloan RP. Heart rate variability predicts levels of inflammatory markers: evidence for the vagal anti-inflammatory pathway. *Brain Behav Immun.* (2015) 4994–100. doi:10.1016/j.bbi.2014.12.017
80. Yan M, Mehta JL, Zhang W, Hu C. LOX-1, oxidative stress and inflammation: a novel mechanism for diabetic cardiovascular complications. *Cardiovasc Drugs Ther.* (2011) 25:451–9. doi:10.1007/s10557-011-6342-4
81. Hussain T, Tan B, Yin Y, Blachier F, Tossou MC, Rahu N. Oxidative stress and inflammation: what polyphenols can do for us? *Oxid Med Cell Longev.* (2016) 2016:7432797. doi:10.1155/2016/7432797
82. Khoubnasabjafari M, Ansari K, Jouyban A. Reliability of malondialdehyde as a biomarker of oxidative stress in psychological disorders. *Bioimpacts.* (2015) 5:123–7. doi:10.15171/bi.2015.20
83. Cygankiewicz I, Zareba W. Heart rate variability. *Handb Clin Neurol.* (2013) 117:379–93. doi:10.1016/B978-0-444-53491-0.00031-6
84. Chueinta P, Pongkan W, Boonyapakorn C. Clinical applications of heart rate variability in dogs. *Vet Integr Sci.* (2019) 17:195–220.
85. Lahdenoja O, Hurnanen T, Kaisti M, Koskinen J, Tuominen J, Vähä-Heikkilä M, et al. Cardiac monitoring of dogs via smartphone mechanocardiography: a feasibility study. *Biomed Eng Online.* (2019) 18:47. doi:10.1186/s12938-019-0667-9
86. Thio C.H.L., van Roon A.M., Lefrandt J.D., Gansevoort RT, Snieder H. Heart rate variability and its relation to chronic kidney disease: results from the PREVEND study. *Psychosom Med.* (2018) 80:307–16. doi:10.1097/PSY.0000000000000556
87. Chou Y.H., Huang W.L., Chang C.H., Yang C.H., Kuo T.B.J., Lin S.L., et al. Heart rate variability as a predictor of rapid renal function deterioration in chronic kidney disease patients. *Nephrology.* (2019) 24:806–13. doi:10.1111/neph.13514
88. Serrao NF Jr., Porta A, Minatel V, Castro AAM, Catai AM, Sampaio LMM, et al. Complexity analysis of heart rate variability in chronic obstructive pulmonary disease: relationship with severity and symptoms. *Clin Auton Res.* (2020) 30:157–64. doi:10.1007/s10286-019-00659-z
89. Li Y, Wang J, Li X, Jing W, Omorodion I, Liu L. Association between heart rate variability and Parkinson's disease: a meta-analysis. *Curr Pharm Des.* (2021) 27:2056–67. doi:10.2174/18715273196662009051222217. Lucini D, Pagani M. Heart rate variability, autonomic regulation and myocardial ischemia. *Int J Cardiol.* (2020) 312:22–3. doi:10.1016/j.ijcard.2020.03.012
90. Tan JPH, Beilharz JE, Vollmer-Conna U, Cvejic E. Heart rate variability as a marker of healthy ageing. *Int J Cardiol.* (2019) 275:101–3. doi:10.1016/j.ijcard.2018.08.005
91. Alfonso A, Le Sueur ANV, Geraldies SS, Guimaraes-Okamoto PTC, Tsumeni MH, Santana DF, et al. Heart rate variability and electrocardiographic parameters predictive of arrhythmias in dogs with stage IV chronic kidney disease undergoing intermittent haemodialysis. *Animals.* (2020) 10:1829. doi:10.3390/ani10101829
92. Petrie JP. Practical application of holter monitoring in dogs and cats. *Clin Tech Small Anim Pract.* (2005) 20:173–81. doi:10.1053/j.ctsap.2005.05.006

93. Hsieh BM, Beets AK. Coughing in small animal patients. *Front Vet Sci.* (2020) 6:513. doi: 10.3389/fvets.2019.00513
94. Williams J, editor. Management of tracheal collapse. World Small Animal Veterinary Association World Congress Proceedings. Cape Town (2014).
95. Della Maggiore A. An update on tracheal and airway collapse in dogs. *Vet Clin North Am Small Anim Pract.* (2020) 50:419–30. doi: 10.1016/j.cvsm.2019.11.003
96. Shei RJ, Adamic EM, Chapman RF, Mickleborough TD. The effects of PCSO524(R), a patented marine oil lipid derived from the New Zealand green lipped mussel (*Perna canaliculus*), on pulmonary and respiratory muscle function in non-asthmatic elite runners. *Int J Exerc Sci.* (2018) 11:669–80.
97. Vijansorn M, Kwananocha I, Kashemsant N, Jarudecha T, Lekcharonsuk C, Beale B, et al. The effectiveness of marine based fatty acid compound (PCSO524) and firocoxib in the treatment of canine osteoarthritis. *BMC Vet Res.* (2019) 15:349. doi: 10.1186/s12917-019-2110-7
98. Zhu B, Zhang Y, Herrup K. Testing the neuroprotective properties of PCSO524((R)) using a neuronal cell cycle suppression assay. *Mar Drugs.* (2019) 17:79. doi: 10.3390/md17020079
99. Mickleborough TD, Sinex JA, Platt D, Chapman RF, Hirt M. The effects PCSO-524(R), a patented marine oil lipid and omega-3 PUFA blend derived from the New Zealand green lipped mussel (*Perna canaliculus*), on indirect markers of muscle damage and inflammation after muscle damaging exercise in untrained men: a randomized, placebo controlled trial. *J Int Soc Sports Nutr.* (2015) 12:10. doi: 10.1186/s12970-015-0073-z
100. Doggrell SA. Lyprinol-is it a useful anti-inflammatory agent? *Evid Based Complement Alternat Med.* (2011) 2011:307121. doi: 10.1093/ecam/hep030
101. Mickleborough TD, Vaughn CL, Shei RJ, Davis EM, Wilhite DP. Marine lipid fraction PCSO-524 (lyprinol/omega XL) of the New Zealand green lipped mussel attenuates hyperpnea-induced bronchoconstriction in asthma. *Respir Med.* (2013) 107:1152–63. doi: 10.1016/j.rmed.2013.04.010
102. Mongkon N, Sontornvipart K. Preliminary study of the clinical outcome of using PCSO-524 polyunsaturated fatty acid compound in the treatment of canine osteoarthritis and degenerative spinal diseases. *Thai J Vet Med.* (2012) 42:311–7. 31. Mateos R, Lecumberri E, Ramos S, Goya L, Bravo L. Determination of malondialdehyde (MDA) by high-performance liquid chromatography in serum and liver as a biomarker for oxidative stress: application to a rat model for hypercholesterolemia and evaluation of the effect of diets rich in phenolic antioxidants from fruits. *J Chromatogr B Analyt Technol Biomed Life Sci.* (2005) 827:76–82. doi: 10.1016/j.jchromb.2005.06.035
103. Pongkan W, Pintana H, Jaiwongkam T, Kredphoo S, Sivasinprasasn S, Chattipakorn SC, et al. Vildagliptin reduces cardiac ischemic-reperfusion injury in obese orchietomized rats. *J Endocrinol.* (2016) 231:81–95. doi: 10.1530/JOE-16-0232.33. Pongkan W, Jitnapakarn W, Phetnoi V, Punyapornwithaya V, Boonyapakorn C. Obesity-induced heart rate variability impairment and decreased systolic function in obese male dogs. *Animals.* (2020) 10:1383. doi: 10.3390/ani10081383
104. Bogucki S, Noszczyk-Nowak A. Short-term heart rate variability (HRV) in healthy dogs. *Pol J Vet Sci.* (2015) 18:307–12. doi: 10.1515/pjvs-2015-0040.35. von Borell E, Langbein J, Despres G, Hansen S, Leterrier C, Marchant-Forde J, et al. Heart rate variability as a measure of autonomic regulation of cardiac activity for assessing stress and welfare in farm animals – a review. *Physiol Behav.* (2007) 92:293–316. doi: 10.1016/j.physbeh.2007.01.007
105. Lima AH, Forjaz CL, Silva GQ, Meneses AL, Silva AJ, Ritti-Dias RM. Acute effect of resistance exercise intensity in cardiac autonomic modulation after exercise. *Arq Bras Cardiol.* (2011) 96:498–503. doi: 10.1590/S0066-782X2011005000043
106. Latchman PL, Mathur M, Bartels MN, Axtell RS, De Meersman RE. Impaired autonomic function in normotensive obese children. *Clin Auton Res.* (2011) 21:319–23. doi: 10.1007/s10286-011-0116-8
107. Kenneth S, Edward A, Keith W. Duncan and Prasses's Veterinary Laboratory Medicine Clinical Pathology. 4 ed. Ames, IA: Iowa State Press. (2003).
108. Regier PJ, Grosso FV, Stone HK, van Santen E. Radiographic tracheal dimensions in brachycephalic breeds before and after surgical treatment for brachycephalic airway syndrome. *Can Vet J.* (2020) 61:971–6.
109. Jepsen-Grant K, Pollard RE, Johnson LR. Vertebral heart scores in eight dog breeds. *Vet Radiol Ultrasound.* (2013) 54:3–8. doi: 10.1111/j.1740-8261.2012.01976.x
110. Vezzosi T, Puccinelli C, Tognetti R, Pelligrà T, Citi S. Radiographic vertebral left atrial size: a reference interval study in healthy adult dogs. *Vet Radiol Ultrasound.* (2020) 61:507–11. doi: 10.1111/vru.12896
111. Zawadzki M, Janosch C, Szechinski J. Perna canaliculus lipid complex PCSO524 demonstrated pain relief for osteoarthritis patients benchmarked against fish oil, a randomized trial, without placebo control. *Mar Drugs.* (2013) 11:1920–35. doi: 10.3390/md11061920
112. Malik M. Producing consistent estimates of the power spectral density of NN sequences. *Circulation.* (1997) 96:2082–3.
113. Shukla RS, Aggarwal Y. Time-domain heart rate variability-based computer-aided prognosis of lung cancer. *Indian J Cancer.* (2018) 55:61–5. doi: 10.4103/ijc.IJC_395_17
114. Kleiger RE, Stein PK, Bigger JT Jr. Heart rate variability: measurement and clinical utility. *Ann Noninvasive Electrocardiol.* (2005) 10:88–101. doi: 10.1111/j.1542-474x.2005.10101.x
115. Pongkan W, Pintana H, Sivasinprasasn S, Jaiwongkam T, Chattipakorn SC, Chattipakorn N. Testosterone deprivation accelerates cardiac dysfunction in obese male rats. *J Endocrinol.* (2016) 229:209–20. doi: 10.1530/JOE-16-0002
116. Sivasinprasasn S, Sa-Nguanmoo P, Pongkan W, Prachayasakul W, Chattipakorn SC, Chattipakorn N. Estrogen and DPP4 inhibitor, but not metformin, exert cardioprotection via attenuating cardiac mitochondrial dysfunction in obese insulin-resistant and estrogen-deprived female rats. *Menopause.* (2016) 23:894–902. doi: 10.1097/GME.0000000000000640
117. Pavithran P, Nandeeshha H, Shaiyapriya V, Bobby Z, Madanmohan T. Short-term heart variability and oxidative stress in newly diagnosed essential hypertension. *Clin Exp Hypertens.* (2008) 30:486–96. doi: 10.1080/10641960802251875
118. Pongkan W, Jinawong K, Prachayasakul W, Jaiwongkam T, Kredphoo S, Tokuda M, et al. D-allulose provides cardioprotective effect by attenuating cardiac mitochondrial dysfunction in obesity-induced insulin-resistant rats. *Eur J Nutr.* (2020). doi: 10.1007/s00394-020-02394-y
119. Balasubramanian P, Asirvatham-Jeyaraj N, Monteiro R, Sivasubramanian MK, Hall D, Subramanian M. Obesity-induced sympathoexcitation is associated with Nrf2 dysfunction in the rostral ventrolateral medulla. *Am J Physiol Regul Integr Comp Physiol.* (2020) 318:R435–r44. doi: 10.1152/ajpregu.00206.2019