Institution: Royal Veterinary College
Unit of Assessment: A 6 Agriculture, Veterinary and Food Science
Title of case study: Improving diagnosis and treatment of canine heart disease

1. Summary of the impact (indicative maximum 100 words)

RVC research has helped transform differential diagnosis of canine heart disease, in first opinion veterinary practice, by demonstrating the value of peptide biomarkers and collaborating with diagnostics companies to ensure the findings have been translated into commercial assay kits available around the world. Contributions to major clinical trials have complemented this through improvements in canine cardiac disease treatment. This has benefitted dogs and their owners through improved and prolonged canine health; and has additionally delivered new guidance for professional practice, and economic value through increased therapeutic product sales and novel diagnostic services.

2. Underpinning research (indicative maximum 500 words)

Research led by Adrian Boswood, (appointed as Lecturer in Internal Medicine in 1996 and progressing to Professor of Veterinary Cardiology in 2008), has focused on improving management of small animal cardiac conditions through enhanced differential diagnosis, increasing prognostic accuracy and earlier identification of, and introduction of treatment for, sub-clinical disease. Boswood has published work which clearly defined risk factors for progression [1] in a heterogeneous population of dogs presenting to primary care practices in the UK.

His research has focused particularly on the potential of natriuretic peptides as biomarkers and their combination with other parameters, to refine prognosis and management. Although increased concentration of atrial natriuretic peptide (ANP) was known to be associated with heart failure, its short plasma half-life and instability after collection made it impractical to use as a biomarker, and Boswood proposed that a proANP assay could have practical value. The RVC research team, collaborated with the biotechnology business, Guildhay Ltd, demonstrating that an ELISA for a proANP fragment could distinguish normal dogs from those with heart failure [2]. After further discussion between Boswood and Guildhay it was suggested that an assay for NTproBNP would be superior to a proANP assay. Such an assay was developed and shown to discriminate between respiratory and cardiac disease in dogs presenting with difficulty breathing [3], thus offering a valuable diagnostic for first opinion practice. The Guildhay assay acted as the prototype for the Idexx assay that is now marketed and used internationally.

Prospective studies of dogs in primary care practice determined the prognostic value – in predicting mortality - of measuring NT-proBNP in dogs presenting with a heart murmur, indicative of degenerative mitral valve disease (DMVD), in partnership with Idexx Laboratories and CEVA Animal Health [4]. This work has been extended to show enhanced prognostic value of combining NT-proBNP with high sensitivity cardiac troponin I in serial blood samples to identify dogs progressing to cardiac death [1].

Boswood's recognition as a key opinion leader in cardiology clinical trial design and analysis has positioned him to contribute in a major way to international multicentre trials. The outcome of the QUEST trial [5] is recognised as one of the most compelling pieces of evidence for the, then unexpected (based on mode of action), beneficial effects of the calcium sensitiser, pimobendan, on survival of dogs with DMVD when evaluated relative to treatment which was considered at that time to be the gold standard; benazepril. In 2002 Boswood was one of four members of the clinical trial committee and one of two academics who led the design of the study protocol. His input (with that of lead author Professor Jens Haagstrom, of the Swedish University of Agricultural Sciences) meant this study overcame shortcomings of previous trials addressing survival as an end-point and produced compelling evidence for the benefit of pimobendan. In particular, it had the highest event rate of any of the published studies due to the care taken in defining three related endpoints *a*

priori; was appropriately powered to address the relative benefits of the two drugs; and offered the most comprehensive consideration of co-variates of any studies involving DMVD in the dog. As such it is considered to provide the best current evidence for benefit of treatment in slowing disease progression.

Boehringer Ingelheim invited Boswood to be involved in the subsequent 'PROTECT' trial: to contribute to study design, screen cases for inclusion, undertake an interim analysis, advise on the continuation and conclusion of the study, and participate in the publication committee, as supervisor for the statistical analysis and corresponding author. PROTECT examined the effect of pimobendan administration in the preclinical phase of dilated cardiomyopathy in Doberman Pinschers. At its inception, the value of inotropic drugs in asymptomatic dogs was considered highly controversial. The study demonstrated a significant prolongation to the time to onset of congestive heart failure or sudden death in the dogs receiving pimobendan: the first cardiology study to demonstrate clear benefit of therapy in a pre-clinical period [6]. It was also the first to demonstrate a survival benefit in dogs identified through screening of an apparently normal population.

Other quality indicators

Boswood, A. Elliott, J and Brodbelt, D. Identification of diagnostic tests predictive of progression of mitral valve disease in the dog. £92,798. 2008-2011. Petplan Charitable Trust.

References [2] and [3], won the BSAVA Petsavers Award for the best clinical paper of their year in the Journal of Small Animal Practice.

3. References to the research (indicative maximum of six references)

1. Hezzell, MJ, Boswood, A, Chang, YM, Moonarmart, W, Souttar, K, Elliott J. 2012 The combined prognostic potential of serum high-sensitivity cardiac troponin I and N-terminal pro-B-type natriuretic peptide concentrations in dogs with degenerative mitral valve disease. Journal of Veterinary Internal Medicine; 26(2):302-11. DOI: 10.1111/j.1939-1676.2012.00894.x.

2. Boswood, A, Attree, S, Page, K. 2003 Clinical validation of a proANP 31-67 fragment ELISA in the diagnosis of heart failure in the dog. Journal of Small Animal Practice; 44(3):104-108 DOI: 10.1111/j.1748-5827.2003.tb00128.x

3. Boswood, A, Dukes-McEwan, J, Loureiro, J, James, RA, Martin, M, Stafford-Johnson, M, Smith, P, Little, C, Attree, S. 2008 The diagnostic accuracy of different natriuretic peptides in the investigation of canine cardiac disease. Journal of Small Animal Practice 49(1): 26-32 DOI: 10.1111/j.1748-5827.2007.00510.x

4. Moonarmart, W, Boswood, A, Fuentes, VL, Brodbelt, D, Souttar, K, Elliott, J. 2010 N-terminal pro B-type natriuretic peptide and left ventricular diameter independently predict mortality in dogs with mitral valve disease. Journal of Small Animal Practice; 51(2): 84-96 DOI: 10.1111/j.1748-5827.2009.00889.x

5 . Häggström, J, Boswood, A, O'Grady, M, Jöns, O, Smith, S, Swift, S, Borgarelli, M, Gavaghan, B, Kresken, JG, Patteson, M, Ablad, B, Bussadori, CM, Glaus, T, Kovacević, A, Rapp, M, Santilli, RA, Tidholm, A, Eriksson, A, Belanger, MC, Deinert, M, Little, CJ, Kvart, C, French, A, Rønn-Landbo, M, Wess, G, Eggertsdottir, AV, O'Sullivan, ML, Schneider, M, Lombard, CW, Dukes-McEwan, J, Willis, R, Louvet, A, DiFruscia, R. 2008 Effect of pimobendan or benazepril hydrochloride on survival times in dogs with congestive heart failure caused by naturally occurring myxomatous mitral valve disease: the QUEST study. Journal of Veterinary Internal Medicine; 22(5):1124-35 DOI: 10.1111/j.1939-1676.2008.0150.x

6. Summerfield, NJ, Boswood, A, O'Grady, MR, Gordon, SG, Dukes-McEwan, J, Oyama, MA, Smith, S, Patteson, M, French, AT, Culshaw, GJ, Braz-Ruivo, L, Estrada, A, O'Sullivan, ML, Loureiro, J, Willis, R, Watson, P. 2012 Efficacy of Pimobendan in the prevention of congestive heart failure or sudden death in Doberman Pinschers with preclinical cilated cardiomyopathy (The PROTECT Study). Journal of Veterinary Internal Medicine; 26:1337-1349 DOI: 10.1111/j.1939-1676.2012.01026.x

4. Details of the impact (indicative maximum 750 words)

Cardiac disease is one of the most common conditions presented to the veterinarian. It has been estimated that up to 15% of dogs presented to a practice may show some signs of cardiac disease

and this increases to over 40% in dogs older than 7 years of age. DMVD, which is progressive and incurable, accounts for around 75% of all cases of canine congestive heart failure. A number of breeds show a predisposition - such as Cavalier King Charles Spaniels (most animals eventually affected and high proportion at younger age), Chihuahuas, fox terriers, Boston terriers and miniature poodles, pinschers and schnauzers. Dobermans and a number of other large breeds have disproportionately high rates of dilated cardiomyopathy.

Diagnosis can be challenging: Clinical signs of cardiac disease may be absent or indistinguishable from those of other conditions, particularly respiratory disease. Indications from physical examination may be inconclusive, especially in a distressed, anxious or uncooperative patient and thoracic radiographs difficult to interpret. Detection of a heart murmur is not conclusive. Cardiac ultrasound, which usually requires referral to a specialist, is often necessary to fully characterise the disease. However, a cardiac biomarker can be used in first opinion practice as part of the diagnostic workup and guide decisions about additional testing, the need for referral and treatment.

[text removed for publication]. The RVC team has continued to work in partnership with Idexx to provide evidence for the clinical value of this test and to identify ways of enhancing this.

Prior to 2008, ACE inhibitors were the primary drug class used in treatment for canine DMVD. The QUEST trial demonstrated compelling evidence (91% improvement) that pimobendan in conjunction with conventional therapy could prolong life. Accompanying the publication of the trial results, an editorial, by Mark Oyama of University of Pennsylvania, commented: “I … currently consider pimobendan the single most important addition to the medical therapy of dogs with symptomatic DMVD and dilated cardiomyopathy since becoming a veterinary cardiologist more than a decade ago. … the study by Haggstrom et al is to be commended not only for its ambition and meticulous reporting but also for its ultimately successful multicentered design”[d].

An American College of Veterinary Internal Medicine Consensus Statement, which disseminates good practice via cardiology specialists in the USA and Europe, to which RVC contributed, was rapidly issued reflecting these findings [e].

The trial results have transformed sales of the drug (as Vetmedin) during the REF impact period. In its 2009 Annual Report, Boehringer Ingelheim (BI) reported for Vetmedin, double digit growth in Europe, compared with the previous year; year on year growth in the USA exceeding 50%; and market leader position in the cardiovascular segment in Japan, from launch in 2008 [f]. [text removed for publication]
The QUEST trial also showed significant improvement in quality of life. As dogs may be euthanized when their symptoms are perceived to be overwhelmingly debilitating, rather than dying naturally of disease, this was a critical factor in transforming the approach to management of this condition and, of course, represents a hugely positive outcome for affected dogs and their owners.

Boswood’s contributions to the QUEST and PROTECT trials have led to BI’s requesting his assistance in designing and leading an even larger trial – EPIC [h] - aiming at identifying if pre-symptomatic use can delay the onset of signs of clinical disease in DMVD. He is principal investigator on the study and was one of three international cardiologists involved in writing the protocol. The study involves 36 centres in 11 countries, is the largest prospective veterinary cardiology study to date and has already successfully recruited its target of 360 patients.
[text removed for publication]

As an international opinion leader in veterinary cardiology, Boswood has contributed to the dissemination of research findings thereby contributing to changes in professional practice. In addition to invited conference presentations, including those to the British Veterinary Association Congress (2011) [j] and international CEVA cardio symposium (2011) [k]; he is featured in CEVA’s on-line CPD ‘cardio-academy e-learning programme [l]. In the twenty month period from launch in March 2011, Boswood’s first cardio-academy presentation received 2,196 visits from a total of 4,200 veterinary cardiology specialists from 8 European countries, registered on the site [m].

5. Sources to corroborate the impact (indicative maximum of 10 references)

a. [text removed for publication]

b. [text removed for publication]

c. [text removed for publication]

d. http://onlinelibrary.wiley.com/doi/10.1111/j.1939-1676.2008.0157.x/full [accessed 14 Aug 2013]

e. http://onlinelibrary.wiley.com/doi/10.1111/j.1939-1676.2009.0392.x/pdf [accessed 14 Aug 2013]

f. http://www.boehringer-ingelheim.com/content/dam/internet/opu/com_EN/document/01_news/04_Annual_Report/AR_2009_english.pdf Page 109 of 167. [accessed 14 Aug 2013]

g. [text removed for publication]

h. https://www.epictrial.com [accessed 14 Aug 2013]

i. [text removed for publication]

j. http://www.bva.co.uk/news/2366.aspx [accessed 14 Aug 2013]

k.http://cardiosymposium2011.ceva.com/ [accessed 14 Aug 2013]

l. http://www.cardioacademy.cevalearn.com/en/Programme/Sessions/1-Pathophysiology-of-Mitral-Valve-Disease [accessed 14 Aug 2013]

m. Information supplied by Ceva Sante Animale, by email dated 9 November 2012. Held by RVC.