

Institution: Royal Veterinary College (RVC)		
Unit of Assessment: A 6 Agriculture, Veterinary and Food Science		
Title of case study: Extending high quality life of dogs with asymptomatic canine mitral valve disease		
Period when the underpinning research was undertaken: 2008 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Adrian Boswood	Lecturer in Internal Medicine -> Chair in Veterinary Cardiology/Professor	01/11/1996 – present
Jonathan Elliott	Lecturer -> Professor in Veterinary Pharmacology	01/07/1990 – present
David Brodbelt	Lecturer in Companion Animal Epidemiology -> Professor of Evidence-based Veterinary Medicine	01/04/2005 – present
Period when the claimed impact occurred: 01/08/2013 - 31/12/2020		
Is this case study continued from a case study submitted in 2014? N		
1. Summary of the impact (indicative maximum 100 words)		
<p>Degenerative mitral valve disease (DMVD), which can lead to congestive heart failure, reduced quality of life and premature death, affects around 1 in 30 dogs. The “EPIC” study has now demonstrated and quantified the benefit of treatment in the preclinical phase, with pimobendan (sold as Vetmedin®), as a 15-month prolongation of the asymptomatic phase of DMVD. As a consequence, Boehringer Ingelheim (BI) has obtained regulatory approval to extend the drug indications to preclinical DMVD, leading to a substantial increase in annual growth in product sales. Diagnosis of the “B2” preclinical phase via an algorithm (subject of a filed patent application), based on clinical measures routinely recorded in general practice and serum biomarkers, thus avoiding the need for specialist echocardiography, has been shown to be 80% accurate and is under development as an app for primary practitioners, with further support from BI.</p>		
2. Underpinning research (indicative maximum 500 words)		
<p>Since 2004, Professor Boswood’s group has undertaken systematic prospective longitudinal research investigating canine DMVD. Their work underpinned the REF2014 impact case study establishing diagnostic and prognostic value of biomarkers in identifying dogs with clinical signs due to heart failure, leading to their commercialisation. Boswood played a leading role in the QUEST and PROTECT studies that provided the evidence-base for developing uses of pimobendan. Key questions addressed by research led by Boswood which underpins the current impact case study were (i) which dogs with murmurs typical of mitral valve disease were at greatest risk of progressing to congestive heart failure (CHF); and (ii) whether preclinical intervention could delay this progression.</p> <p>From 2008, the focus of Boswood’s work turned to the pre-clinical stage of DMVD. He initially examined the value of combining case history, physical examination and diagnostic information - factors routinely measured in primary care practice - to generate estimates of a patient’s risk of developing progressive disease and cardiac death [1].</p> <p>To demonstrate the wide applicability of this approach of identifying DMVD cases, without the requirement for expert echocardiographic evaluation, a prospective study involving 893 dogs was undertaken through the VetCompass™ practice network, where general practitioners examined the cases and recorded the data [2,3]. This work, which incorporated cardiac biomarkers (NT-pro-BNP and cardiac troponin I) identified a number of factors predictive of a higher risk of death [2] and a higher risk of progression to the point where the introduction of</p>		

therapy was deemed necessary [3]. This knowledge can now assist primary care practitioners to identify dogs in stage B of DMVD (evidence of disease but no signs of heart failure) at high risk of developing CHF.

The EPIC trial [4] was a large international multicentre, prospective, randomised, placebo-controlled study, its design informed by previously published work of RVC and others showing that B2 dogs (evidence of cardiac enlargement) were at a higher risk of death within 6 months of diagnosis than B1 dogs (no such evidence) [5]. EPIC demonstrated that administration of pimobendan to B2 stage dogs significantly lengthened the time to onset of clinical signs or delayed cardiac death (composite primary endpoint) by 15 months. The precision of the study design, separating B1 and B2 stages, enabled demonstration of a convincing benefit of therapy in the preclinical stage of DMVD, thus addressing the key question in this clinical field. Boswood was the primary investigator taking responsibility (with 2 other lead-investigators) for the protocol and contributing to all stages of trial design, recruitment of cases, analysis of results, publication and dissemination of the findings. The study was unique in terms of its large size and the wide geographical distribution of investigating sites.

To broaden the impact of the findings of the EPIC study and reduce the need for specialist echocardiography referral, a further multicentre international study, HAMLET, was designed by the group [6]. HAMLET used historical and physical examination findings and biomarker levels to identify the B2 stage of DMVD. From 1904 dogs enrolled, an algorithm was derived using 8 factors to differentiate dogs in stages B1 and B2, then confirmed by the gold standard of echocardiography.

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

1. **López-Alvarez J, Elliott J, Pfeiffer D, Chang YM, Mattin M, Moonarmart W, Hezzell MJ, Boswood A.** (2015) Clinical severity score system in dogs with degenerative mitral valve disease. *Journal of Veterinary Internal Medicine*. 29(2):575-81. <https://doi.org/10.1111/jvim.12544>
2. **Mattin MJ, Boswood A, Church DB, Brodbelt DC.** (2019) Prognostic factors in dogs with presumed degenerative mitral valve disease attending primary-care veterinary practices in the United Kingdom. *Journal of Veterinary Internal Medicine*. 33(2):432-444. <https://doi.org/10.1111/jvim.15251>
3. **Mattin MJ, Brodbelt DC, Church DB, Boswood A.** (2019) Factors associated with disease progression in dogs with presumed preclinical degenerative mitral valve disease attending primary care veterinary practices in the United Kingdom. *Journal of Veterinary Internal Medicine*. 33(2):445-454. <https://doi.org/10.1111/jvim.15390>
4. **Boswood A,** Häggström J, Gordon SG, Wess G, Stepien RL, Oyama MA, Keene BW, Bonagura J, MacDonald KA, Patteson M, Smith S, Fox PR, Sanderson K, Woolley R, Szatmári V, Menaut P, Church WM, O'Sullivan ML, Jaudon JP, Kresken JG, Rush J, Barrett KA, Rosenthal SL, Saunders AB, Ljungvall I, Deinert M, Bomassi E, Estrada AH, Fernandez Del Palacio MJ, Moise NS, Abbott JA, Fujii Y, Spier A, Luethy MW, Santilli RA, Uechi M, Tidholm A, Watson P. (2016) Effect of Pimobendan in Dogs with Preclinical Myxomatous Mitral Valve Disease and Cardiomegaly: The EPIC Study-A Randomized Clinical Trial. *Journal of Veterinary Internal Medicine*. 30(6):1765-1779. <https://doi.org/10.1111/jvim.14586>
5. **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. <https://doi.org/10.1111/j.1939-1676.2012.00894.x>
6. **Wilshaw J,** Rosenthal SL, Wess G, Dickson D, Bevilacqua L, Dutton E, Deinert M, Abrantes R, Schneider I, Oyama MA, Gordon S, **Elliott J,** Xia D, **Boswood A.** (2020) A prospective

multicenter study to determine the accuracy of history, physical examination, biochemical parameters and biomarkers to identify dogs with stage B2 degenerative mitral valve disease: The HAMLET study. Research Communications of the 30th ECVIM-CA Online Congress. Abstract ESVC-O-8 pp 3078-79. <https://doi.org/10.1111/jvim.15924> [Full paper from this study was published in *Journal of Veterinary Internal Medicine* in March 2021, <https://doi.org/10.1111/jvim.16083>]

Other Quality Indicators

Professor Boswood received the 2015 JSAP achievement award for outstanding contributions to the Journal of Small Animal Practice and 2015 Petplan Charitable Trust Scientific award, both of which recognise the high quality of his clinical research in the field of canine cardiology.

The EPIC trial (reference 4) was in the top 1% of articles for its field, based on the field weighted citation index. The invitation to Boswood to lead the design of the EPIC trial stemmed from the success of the PROTECT and QUEST trials which preceded EPIC. Boswood's ability to secure the involvement of many cardiologists of international repute in both EPIC and HAMLET studies is evidence of the esteem in which he is held for the design, analysis and reporting of clinical research undertaken in multi-centre trials. The quality of evidence provided by the EPIC study is rated as level 1 evidence of the benefit of pimobendan in stage B2 DMVD dogs by the 2019 ACVIM consensus statement (see below), an additional quality indicator.

Underpinning references 2,3 and 5 resulted from a competitively won research grant awarded by Petplan Charitable Trust, one of the few UK based charitable funders of companion animal clinical research. References 2 and 3 have citation indices which currently place them in the top 10% for their field.

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

The beneficiaries in this case include Boehringer Ingelheim (commercial company benefiting from expanding claims and therefore use of an existing product), veterinary general practitioners (who can target treatment on dogs with asymptomatic DMVD to those where there is now good evidence they will benefit), and the owners and dogs with preclinical DMVD whose health and wellbeing will be improved by application of this treatment at the right stage of their disease. Up to 1 in 30 dogs in the UK and Europe attend veterinary practices having heart murmurs consistent with DMVD ([Egenvall et al. 2006](#); [Mattin et al. 2015](#)).

Pimobendan has been the leading drug used to treat CHF due to DMVD since 2012. The EPIC trial discovered that administration of pimobendan to dogs in preclinical stage B2 prolonged a healthy good quality life by 15 months on average. This enabled BI, in 2017, to obtain regulatory approval to extend the datasheet indications to include dogs with a mitral valve disease murmur and enlarged heart, (stage B2) in Australia, Japan, all EU Countries and China [a]. This extension was widely publicised in the veterinary press and through BI and the RVC [b]. As the first clinical trial to demonstrate unequivocal benefit of therapy in the preclinical stage of DMVD, the work received considerable media attention including international news channel coverage and inclusion in several national daily newspapers and been included in resources prepared by the "Cardiac Education Group" [b]. During this REF period, this case has generated 18,371 unique visitors to the RVC website. The mass media combined coverage exceeds >18,000,000 across countries including UK, USA, Italy, Thailand and India. It has featured in veterinary professional outlets online and/or in print, including Vet Times (circulation 18,000; online 528,256 users); vetsurgeon.org (14,356 online users) and veterinarypracticenews.com (57,000 users). It has also reached dog owning public via mass media such as the Daily Telegraph (circulation 2,600,000; online 8,300,000 users) and Times of India (2,800,000 online users) [b].

The work was recognised as a significant advance in the management of DVMD, by its acceptance into the American College of Veterinary Internal Medicine (ACVIM) consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs [c]. These guidelines credit EPIC with the ability to identify dogs that are likely to benefit

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substantially from treatment before the onset of clinical signs of heart failure and recommend the use of pimobendan at this stage. The guidelines identify the EPIC trial as the only class 1 category (randomised controlled clinical trial) evidence for a treatment benefit in stage B2, and identify the level of evidence as “strong”. The guidelines also re-defined the B2 stage by adopting EPIC’s specific inclusion criteria, which in turn were informed by RVC research.

The EPIC study additionally demonstrated that treatment enabled dogs to live longer and spend a lower proportion of their life in CHF, and that the risk of a dog experiencing heart failure was reduced by approximately one third, all of which contribute to enhanced quality of life for the dogs and their owners ([Freeman et al, 2005](#)).

[Text removed for publication]

The RVC research into how B2 can be identified in primary care practice without requiring expert echocardiographic evaluation, stimulated BI to support the RVC-led international multicentre HAMLET study [a]. Based on the study results, RVC filed a patent application on 7 April 2020 for an algorithm to determine the probability that a dog is in stage B2 and, therefore, whether it is likely to benefit from pimobendan [d]. [Text removed for publication]. The use of this app will enable primary care practitioners to target pimobendan treatment on those asymptomatic dogs with mitral valve murmurs that are most likely to benefit, without the need to refer them to expert cardiologists to determine which dogs are in stage B2.

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

All corroborating evidence has been uploaded unless stated as held by the RVC.

a. Letter from Boehringer Ingelheim corroborating: the EPIC study’s involvement in the extension claim for Vetmedin® chewable tablets in Australia, Japan, all EU Countries and China for treating dogs in B2 in 2017 [Text removed for publication]

b. Details of press coverage and cardiac education resources:

- <https://www.vettimes.co.uk/news/licence-extended-for-vetmedin/>
- http://cardiaceducationgroup.org/wp-content/uploads/2016/12/CEG_Recommendations_EPIC_121316.pdf
- <https://wiley.altmetric.com/details/12340122/news>
- <https://www.vettimes.co.uk/news/pimobendan-study-outcome-a-revolution-for-vet-cardiology/>
- <https://www.vettimes.co.uk/news/top-tier-study-shows-pimobendan-mvd-delay/>
- <https://www.vettimes.co.uk/news/global-clinical-trial-shows-pimobendans-effectiveness/>
- <https://www.vetsurgeon.org/news/b/veterinary-news/posts/new-canine-heart-disease-campaign>
- <https://www.veterinarypracticenews.com/popular-ways-of-treating-congestive-heart-failure-in-dogs/>
- <https://www.telegraph.co.uk/science/2016/10/27/pet-dogs-could-live-15-months-longer-by-taking-a-simple-pill/>
- <https://timesofindia.indiatimes.com/life-style/relationships/pets/new-drug-could-let-your-pet-dogs-live-longer/articleshow/55176936.cms>
- RVC website and media statistics from Google Analytics, Meltwater/Signal PR systems, and RVC social channels [Held by RVC].

c. Keene BW, Atkins CE, Bonagura JD, Fox PR, Häggström J, Luis Fuentes V, Oyama MA, Rush JE, Stepien R, Uechi M (2019) ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs. *Journal of Veterinary Internal Medicine* 33(3) 1127-1140 <https://onlinelibrary.wiley.com/doi/10.1111/jvim.15488>

d. Paperwork for patent filed for the HAMLET algorithm: Letter from J.A. Kemp, description, abstract, claims, drawings, form 1, form 9A and filing receipt.