Institution: University of Dundee
Unit of Assessment: UoA1 Clinical Medicine
Title of case study: BNP as a Diagnostic and Risk Stratifying Test in Cardiology
1. Summary of the impact

Our research on brain/B-type naturietic peptide (BNP) has helped to diagnose both types of heart failure (systolic and diastolic heart failure) and to identify high-risk aortic stenosis patients for surgery. We were first to demonstrate the value of BNP as a biomarker for left ventricular systolic dysfunction, isolated diastolic dysfunction and for aortic stenosis. BNP testing is now recommended in Guidelines as a screening test for patients with suspected heart failure (Class I recommendation) and in the current European Society of Cardiology consensus statement for diagnosis of diastolic heart failure. The European Society of Cardiology Guidelines have also introduced BNP testing in the management of patients with aortic stenosis (Class IIb recommendation).

2. Underpinning research

Around 900,000 people in the UK have heart failure. Both the incidence and prevalence of heart failure increase steeply with age. Heart failure accounts for a total of 1 million inpatient bed days and 5% of all emergency medical admissions to hospital with readmission rates among the highest for any common condition in the UK. Financially, this adds up to some 2% of healthcare costs, about two thirds of which are hospital costs. The costs of GP consultations have been estimated at £45 million per year with an additional £35 million for GP referrals to outpatient clinics. Community based drug therapy for heart failure costs the NHS around £129 million per year.

The diagnosis of heart failure is difficult because its symptoms are non-specific and the physical signs are often not obvious; however, early and accurate diagnosis is important so that patients can start appropriate life-saving treatment. The British Heart Foundation-funded research and development work underpinning this case study was led by Professor Allan **Struthers** (Division of Cardiovascular and Diabetes Medicine, Ninewells Hospital and Medical School, Dundee) with assistance from Motwani (British Heart Foundation research fellow) and Chim **Lang** (at the time a Lecturer in the Department) in collaboration with Norman Kennedy (medical physicist, Ninewells Hospital). We were the first to show that plasma levels of BNP could be used in clinical practice to detect left ventricular systolic dysfunction [i]. We followed this with a study of the diagnostic role of BNP in a community population in another Lancet publication [ii]. The latter publication provided the evidence leading to National and International Guidelines recommending BNP testing in patients with suspected heart failure in the community.

Our work on BNP as a biomarker of left ventricular wall stress led us to show for the first time that BNP was elevated in patients with the other form of heart failure (isolated diastolic dysfunction) [iii]. The diagnosis of heart failure with preserved ejection fraction (HFpEF) due to diastolic dysfunction is difficult, especially in patients with multiple co-morbidities. To aid diagnosis, the use of plasma BNP as a biomarker which is elevated in elevated left ventricular wall stress has been recommended in Guidelines including the European Society of Cardiology consensus statement on HFpEF. This test and is used as an inclusion criterion in most ongoing studies of HFpEF including the on-going Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist (TOPCAT) study (see section 4).

Aortic stenosis is the most common valvular disease in Western countries. Identification of subgroups of symptomatic patients with aortic stenosis who may benefit from early surgery is a clinical challenge. Our 1997 American Heart Journal publication was the first study to show elevated plasma BNP in aortic stenosis [iv]. This observation led to international investigations which provided the evidence underpinning the latest European Society of Cardiology

recommendation on BNP testing in asymptomatic severe aortic stenosis to select patients for aortic valve replacement.

In further recent related work, we have expanded the diagnostic role for BNP into other populations of patients. We have recently described for the first time how BNP could be used in primary prevention to detect patients with silent asymptomatic heart disease such as left ventricular hypertrophy and silent coronary artery disease [v].

3. References to the research

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iii. **Lang** CC, Prasad N, McAlpine HM, MacLeod C, Lipworth BJ, MacDonald TM and **Struthers** AD (1994) Increased levels of brain natriuretic peptide in patients with isolated diastolic dysfunction. *Am. Heart J.* **127**, 1635-636 (DOI: 10.1016/0002 8703(94)90401-4).

iv. Prasad N, Bridges N, **Lang** CC, Clarkson P, **Struthers** AD, MacDonald TM (1997) Brain natriuretic peptide plasma concentrations in patients with aortic stenosis. *Am. Heart J.* **133**, 477-479 (DOI: 10.1016/S0002-8703(97)70196-0).

v. Nadir MA, Rekhraj S, Wei L, Lim TK, Davidson J, MacDonald TM, **Lang** CC, Dow E, **Struthers** AD (2012) Improving the Primary Prevention of Cardiovascular events by using Biomarkers to identify Individuals with Silent Heart Disease. *J. Am. Coll. Cardiology* **60**, 960-8 (DOI: 10.1016/j.jacc.2012.04.049).

Funding

- **Struthers** AD, Pringle TH, McNeil G: The potential use of natriuretic peptide in clinical cardiology; British Heart Foundation (1993-1995) £65,644.
- Cowie M, Coats A, **Struthers** AD: Sensitivity, specificity and predictive value of natriuretic peptide levels in detecting ventricular dysfunction in those with a new primary care diagnosis of heart failure; British Heart Foundation (1995-1997) £10,205.
- **Struthers** AD, Pringle S, Goudie B, Sullivan F: Improving the diagnosis of heart failure in general practice; British Heart Foundation (2001-2004) £108,206.
- **Struthers** AD, Pringle S, Goudie B, Sullivan, Donnan P: Near patient BNP and portable echocardiography in general practice; British Heart Foundation (2004-2006) £124,670.
- **Struthers** AD, **Lang** CC, MacDonald T, Houston G: The potential to improve primary prevention by using BNP as an indicator of silent pan-cardiac target organ damage: the 5P study; British Heart Foundation (2007-2013) £323,958.

4. Details of the impact

Our BNP research has helped to hasten the diagnosis of heart failure

There are considerable clinical difficulties involved in diagnosing heart failure by symptoms alone. Our early work on BNP published in the Lancet 1993 and in 1997 lead to intense research into the utility of BNP in the diagnosis of heart failure which has confirmed its accuracy. As a result, all current Guidelines including the European Society of Cardiology 2012 Guidelines advocate the measurement of plasma concentrations of BNP in the diagnosis of chronic heart failure, either in combination with, or as an alternative to, an electrocardiogram [1,2]. The availability of BNP as a

diagnostic test has important implications. Firstly, when applied early in the diagnostic process in patients with suspected cardiac failure, a negative BNP test can help rule out congestive heart failure and thus avoid unnecessary tests and referral to clinics. Secondly, BNP assessment can hasten the correct diagnosis of heart failure allowing prompt delivery of evidence based treatment and thereby reduce the morbidity and mortality associated with heart failure [3]. The inclusion of BNP testing in the recent 2010 NICE Guidelines [4] will have a major clinical impact [5]. These Guidelines was supported by a 2009 Health Technology Assessment which showed that BNP testing is cost-effective and that measuring BNP is the single most useful test to add to the diagnostic process in primary care [3]. A costing report for implementing the 2010 NICE guidance on BNP testing to rule out heart failure estimated that there will be a £3.8 million net saving and a 23% reduced risk per patient of being admitted to hospital within the first six months with the implementation of BNP testing [5].

Our BNP research has helped to introduce BNP as a biomarker to identify at-risk patients for clinical trials

We were the first to utilize BNP as a biomarker to identify patients with left ventricular systolic dysfunction for therapy (angiotensin converting enzyme inhibitors). This concept is currently adopted in clinical trials to identify at risk heart failure patients for study inclusion. Examples of trials that used BNP to select patients are the Eplerenone or Placebo in Addition to Standard Heart Failure Medicines (EMPHASIS-HF) trial and the ongoing PARADIGM study (Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality of Patients With Chronic Heart Failure) [6].

Our BNP research has helped to diagnose HFpEF / diastolic dysfunction

We were also the first to show that BNP was elevated and related to diastolic filling in patients with isolated diastolic dysfunction. Half of patients with heart failure have preserved ejection fraction with similar morbidity and mortality to heart failure with reduced ejection fraction. Diagnosis of HFpEF is challenging, especially in patients with multiple co-morbidities. The diagnosis of heart failure with reduced ejection fraction now requires coupling exertional dyspnoea and a normal left ventricular ejection fraction with objective measures of diastolic dysfunction such as the measurement of plasma BNP. This use of BNP is now recommended by most experts for the diagnosis of HFpEF [7] and as an inclusion criterion in studies of HFpEF such as the TOPCAT study of aldosterone antagonist therapy for adults with heart failure and preserved systolic function [8]. The current NICE Guidelines also recommend BNP testing in heart failure as “Earlier diagnosis and treatment of associated conditions (such as hypertension) in patients with HFpEF who are found to have raised BNP levels is likely to result in a decrease in the number of these patients needing hospital admission” [3].

Our BNP research has helped in the management of asymptomatic aortic stenosis

Identification of subgroups of symptomatic patients with aortic stenosis who may benefit from early surgery is a clinical challenge. We were the first to demonstrate elevated plasma BNP in aortic stenosis and this led to international investigations of the prognostic value of BNP in aortic stenosis which underpin the latest 2012 European Society of Cardiology recommendation for BNP testing in asymptomatic severe aortic stenosis to select patients for aortic valve replacement (Level C, Class IIb recommendation) [9].

Our BNP research has prompted the development of commercial assays for BNP

The success of BNP testing in routine clinical settings is attested by the fact that BNP tests is available on both mainframe laboratory systems as well as point-of-care analysers. Tests for measuring BNP are now offered by all major *in vitro* diagnostics players including companies such as Abbott, Alere, Roche, Siemens, OCD and Beckman-Coulter. In a report on point-of-care diagnostic testing world markets, it was stated that in terms of ‘market drivers ranked in order of impact’, BNP testing was placed third out of twelve drivers [10] demonstrating that these commercial BNP assays have a direct economical impact [11].

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

1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; ESC Committee for Practice Guidelines (2012) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur. Heart J.* **33**, 1787-1847 (DOI:10.1093/eurheartj/ehs104).
2. Letter of Corroboration from the Chairperson, European Society of Cardiology Clinical Practice Guidelines Task Force.
3. National Heart Foundation of Australia (2011) Guidelines for the prevention, detection and management of chronic heart failure in Australia, updated 2011. ISBN 978-1-921748-71-4; available at: http://www.heartfoundation.org.au/SiteCollectionDocuments/Chronic_Heart_Failure_Guidelines_2011.pdf
4. Letter of Corroboration from the Chair, National Heart Foundation of Australia, Cardiac Society of Australia and New Zealand, Chronic Heart Failure Guidelines Expert Writing Panel.
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6. Paradigm HF Trial: http://clinicaltrials.gov/ct2/show/NCT01035255
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9. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS) (2012) Guidelines on the management of valvular heart disease (version 2012) *Eur. Heart J.* **33**, 2451–2496 (DOI: 10.1093/eurheartj/ehs109).
10. TriMark Publications, LLC (2013) Point of Care Diagnostic Testing World Markets July 2013. Sample available at: https://www.trimarkpublications.com/product_images/samples/pocdiagnosticssample.pdf.
11. Letter of Corroboration from the Commercial Director, Axis-Shield /Alere.