

Impact case study (REF3b)

Institution: Imperial College London
Unit of Assessment: 01 Clinical Medicine
Title of case study: Development of Beta Blockers for the Treatment of Heart Failure
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Beta-blockers are now a worldwide mainstay of heart failure treatment recommended in all international guidelines for chronic heart failure: this is a reversal of previous practice since they were completely contraindicated in this condition up to the late 1990s. Imperial College researchers were pivotal in defining beta-adrenoceptor/beta-blocker mechanisms in failing human hearts and translating the benefits into clinical practice. Imperial College researchers designed and led the COMET and SENIORS beta-blocker trials for heart failure and the UK arm of the COPERNICUS trial. These studies helped establish beta blockers in modern heart failure management: these are now the 4th most commonly prescribed drugs worldwide.</p>
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>Key Imperial College London researchers: Professor Sian Harding, Professor of Cardiac Pharmacology (1980-present) Professor Philip Poole-Wilson, Simon Marks Chair of Cardiology (1976-2008) Professor Andrew Coats, Visiting Professor (2003-2005) Dr Marcus Flather, Honorary Reader (2003-2011)</p> <p>In the early 1990s observations were made that the failing human heart was unresponsive to catecholamines (adrenaline and noradrenaline) produced by the body, contributing to the inability of patients to exercise (or finally, to undertake any physical activity). This was a strong independent predictor of mortality in these patients. The group of Professor Harding and Professor Poole-Wilson at Imperial contributed understanding of this process in a series of papers in which they developed methods to obtain contracting single cardiac muscle cells from the human heart and to track their responses to catecholamine stimulation (1, 2). They showed that the stimulatory contractile response to catecholamines was reduced in individual cardiac cells from failing heart (compared to normal), but that each cell could respond to catecholamines through both stimulatory β_1-adrenoceptors (β_1ARs) and the protective β_2ARs (2). However, clinical attempts to stimulate the failing heart through the β_1ARs alone produced short-term benefit but long-term increases in mortality, and were discontinued.</p> <p>Beta-blockers prevent the action of catecholamines on the βARs: they were contraindicated for heart failure up to the late-1990's because they initially worsened cardiac contraction further. However after the failure of beta-stimulants, the role of beta-blockers was revisited, guided by the research at Imperial and other laboratories. Professor Poole-Wilson, Professor Coats and Dr Flather at Imperial and the Royal Brompton Hospital designed and led pioneering randomised clinical trials which defined the use of these agents in heart failure such as Carvedilol Or Metoprolol European Trial (COMET, 2003), Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure (SENIORS, 2005) (3, 4) and led and designed the UK arm of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS, 2002) trial. Overall, the trials showed that although there was an initial depression of cardiac function in the heart failure patients treated with beta-blockers, continued use not only restored function but improved it.</p> <p>This had a major impact not only on the quality of life for individuals with heart failure, improving exercise tolerance and symptoms, but importantly, reduced mortality by 30-40%, a benefit consistent across the trials. Specifically, COPERNICUS (led in the UK by Professor Coats at Imperial) showed general efficacy of beta-blockers in heart failure; COMET (designed and led by Professor Poole-Wilson at Imperial) showed that the combined α_1, β_1AR and β_2AR blocker carvedilol reduced mortality more than the β_1AR selective metoprolol (3), and SENIORS (designed and led by Dr Flather at Imperial) extended beta-blocker use to the elderly (4). Insights from the SENIORS and COPERNICUS trials supported the use of beta-blockers in both elderly and the most severe/advanced heart failure patient groups, previously avoided with a relative</p>

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contraindication. The trials also demonstrated that beta-blockers were the first treatment for chronic heart failure which reduced sudden cardiac death angiotensin converting enzyme (ACE) inhibitors had reduced congestive/pump failure death but not sudden arrhythmic death).

In parallel to the clinical trials, the Imperial group made a number of seminal observations which gave a mechanism for the more beneficial effect of the β_2 AR blocker carvedilol. They showed that the β_2 AR (unlike the β_1 AR) was coupled to the inhibitory G-protein G_i . Importantly, beta-blockers like carvedilol were not simply inert inhibitors but were actively steering the β_2 AR to this protective coupling with inhibitory G-protein (5). Most recently they have shown that cardiodepressant but cardioprotective coupling of the β_2 AR underpins a naturally occurring condition (Takotsubo Syndrome), and that beta-blockers are taking advantage of this mechanism (6).

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

- (1) Harding, S.E., Brown, L.A., Wynne, D.G., Davies, C.H., Poole-Wilson, P.A. (1994). Mechanisms of beta-adrenoceptor desensitisation in the failing human heart. *Cardiovasc Res*, 28, 1451-1460 [DOI](#). Times cited: 61 (as at 5th November 2013 on ISI Web of Science). Journal Impact Factor: 5.94.
- (2) del Monte, F., Kaumann, A.J., Poole-Wilson, P.A., Wynne, D.G., Pepper, J., Harding, S.E. (1993). [Coexistence of functioning beta1- and beta2-adrenoceptors in single myocytes from human ventricle](#). *Circulation*, 88, 854-863. [DOI](#). Times cited: 84 (as at 5th November 2013 on ISI Web of Science). Journal Impact Factor: 15.20.
- (3) Poole-Wilson, P.A., Swedberg, K., Cleland, J.G.F., Di Lenarda, A., Hanrath, P., et al. (2003). Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet*, 362, 7-13. [DOI](#). Times cited: 756 (as at 5th November 2013 on ISI Web of Science). Journal Impact Factor: 39.06.
- (4) Flather, M.D., Shibata, M.C., Coats, A.J.S., Van Veldhuisen, D.J., Parkhomenko, A. et al. (2005). Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur. Heart J*, 26, 215-225. [DOI](#). Times cited: 472 (as at 5th November 2013 on ISI Web of Science). Journal Impact Factor: 14.09.
- (5) Gong, H., Sun, H., Koch, W.J., Rau, T., Eschenhagen, T., Ravens, U., Heubach, J.F., Adamson, D.L., & Harding, S.E. (2002). Specific beta(2)AR blocker ICI 118,551 actively decreases contraction through a G(i)-coupled form of the beta(2)AR in myocytes from failing human heart. *Circulation*, 105, 2497-2503. [DOI](#). Times cited: 63 (as at 5th November 2013 on ISI Web of Science). Journal Impact Factor: 15.20.
- (6) Paur, H., Wright, P.T., Sikkil, M.B., Tranter, M.H., Mansfield, C., O'Gara, P., Stuckey, D.J., Nikolaev, V.O., Diakonov, I., Pannell, L., Gong, H., Sun, H., Peters, N.S., Petrou, M., Zheng, Z., Gorelik, J., Lyon, A.R., Harding, S.E. (2012). High Levels of Circulating Epinephrine Trigger Apical Cardiodepression in a beta2-Adrenergic Receptor/Gi-Dependent Manner: A New Model of Takotsubo Cardiomyopathy. *Circulation*, 126 (6), 697-706. [DOI](#). Times cited: 18 (as at 5th November 2013 on ISI Web of Science). Journal Impact Factor: 15.20.

Key funding:

- Wellcome Trust (1997-1998; £43,172), Principal Investigator (PI) S. Harding, A pilot study for the use of a transgenic mouse line to investigate beta-adrenoceptor subtype interactions in single cardiac myocytes.
- Wellcome Trust (1997-1999; £78,053), PI S. Harding, Cyclic AMP-dependent arrhythmias and inhibitory G-protein in failing human heart.
- Wellcome Trust (1999-2001; £149,568), PI S. Harding, Use of the transgenic mouse overexpressing the β_2 -adrenoceptor as a model to investigate aspects of β -adrenoceptor desensitisation in the failing human heart.
- Wellcome Trust (1999-2001; £133,601), PI S. Harding, Investigation of a novel negative inotropic effect of beta-2 adrenoceptor agonists in ventricular myocytes from human and animal heart.
- Wellcome Trust (2003-2005; £120,098), PI S. Harding, β -blocker mediated coupling of the

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β 2AR to Gi in failing human heart: short and long-term consequences.

- Wellcome Trust (2006-2007; £103,000); PI S. Harding, Role of protein kinase A-dependent G-protein switching of the β 2-adrenoceptor in depression of cardiac contraction.
- British Heart Foundation (BHF; 2002-2004; £162,720), PI S. Harding, Dual coupling of the β 2-adrenoceptor to stimulatory and inhibitory G-proteins in failing human heart: implications for beta-blocker therapy.
- BHF (2006-2008; £103,514), PIs S. Harding and A. Williams, Sarcoplasmic reticulum Ca²⁺-release channel phosphorylation state and function in the failing heart.
- BHF (2006-2008; £105,000), PI C. Terracciano, Regulation of Na⁺/Ca²⁺-exchanger activity by the beta2-adrenoceptor in normal and failing heart.
- BHF (2006-2008; £105,000), PI S. Harding, Mechanisms of cardiac depression via the beta2AR.
- BHF (2010-2017; £878,000), PI J. Gorelik and S. Harding, cAMP/cGMP localisation in cardiovascular tissue by a new nanoscale multifunctional scanning technique.

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

Impacts include: health and welfare, public policy and services, practitioner and services

Main beneficiaries include: patients, practitioners, NHS, NICE, American Heart Association (AHA), American College of Cardiology (ACC), European Society of Cardiology (ESC)

Heart failure occurs in 1-2% of the adult population rising to 16.4% in men over the age of 75. The overall prevalence is 0.9% in men and 0.7% in women, giving estimated total of 750,000 people in the UK [1]. The most recent National Audit report (2011) shows that there are roughly 68,000 hospital admissions for acute heart failure per annum [1]. Most cases of heart failure are due to coronary heart disease (approximately 70%) and many heart failure patients have or have had hypertension. Although there has been an overall decline in mortality from coronary heart disease, the number of patients with heart failure is increasing. More than 80% of patients who die in the weeks, months and years after a heart attack will first develop heart failure, which is the underlying cause of their mortality. Survival rates in epidemiological series are worse than for breast and prostate cancer, with annual mortality ranging from 10% to 50% depending on severity, with a high risk of sudden death. Newly diagnosed patients have a 40% risk of dying within a year of diagnosis. Providing services to patients with heart failure costs the NHS an estimated £625 million per year. Heart failure is in the top ten diagnoses for use of hospital bed days and places.

The heart failure burden is set to increase, due to the increased age, diabetes and obesity in the general population, and because it is now possible to rescue patients who would previously have died during myocardial infarction (MI) using improved treatments [1]. Beta-blockers both improve symptoms and produce 30-40% benefits in terms of mortality. In England and Wales 65% of patients are prescribed a beta-blocker, and it is considered that this figure should be improved. Their use is now mandatory in heart failure where once it was completely contraindicated: a dramatic reversal of practice. The National Heart Failure Audit 2010 demonstrated that heart failure patients discharged home on beta-blockers, and particularly if the beta-blocker was increased to >50% of the target dose, had better survival and reduced rehospitalisation for heart failure at follow up. Particularly, the routine treatment of MI patients with beta-blockers is found to lengthen life and reduce symptoms in the heart failure population [1].

The initial uptake of beta-blockers to treat heart failure was slow, because the initial loss of cardiac function during dosage meant that GPs were reluctant to prescribe these drugs. Adoption came following the findings of the clinical trials and subsequent publication of the international guidelines. The NICE 2010 guidelines for chronic heart failure were predicated on the findings from the Imperial led randomised controlled trials (as discussed above) and recommendations now include the use of beta blockers in older adults with heart failure due to left ventricular systolic dysfunction (as shown in the SENIORS trial), as well as previously undertreated patient subgroups with heart failure including chronic obstructive pulmonary disease (COPD), peripheral vascular disease, diabetes mellitus and erectile dysfunction [2; see page 95]. The American guidelines AHA/ACC (2009) [3] recommend beta-blockers in a number of stages for heart failure e.g. p410. "Use of 1 of

the 3 beta blockers proven to reduce mortality (i.e., bisoprolol, carvedilol, and sustained release metoprolol succinate) is recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (see Table 3). (Level of Evidence: A)". The recently updated ESC (2012) guidelines [4] states in their section 7.2 Treatments recommended in potentially all patients with systolic heart failure "The pivotal trials with beta-blockers were conducted in patients with continuing symptoms and a persistently low EF, despite treatment with an ACE inhibitor and, in most cases, a diuretic. Despite this, there is consensus that these treatments are complementary and that a beta-blocker and an ACE inhibitor should both be started as soon as possible after diagnosis of HF-REF. This is in part because ACE inhibitors have a modest effect on LV remodelling whereas beta-blockers often lead to a substantial improvement in EF. Furthermore, beta-blockers are anti-ischaemic, are probably more effective in reducing the risk of sudden cardiac death, and lead to a striking and early reduction in overall mortality" (page 1804). In the section "Key evidence supporting the use of beta-blockers" page 1805-6, they extensively reference the COPERNICUS, SENIORs and COMET trials.

Professor Poole-Wilson was a key opinion-leader in the adoption of beta-blockers into clinical practice for heart failure. He gave many presentations on the use and mechanism of benefit of beta-blockers, showing experimental and clinical data from groups at Imperial, which contributed to the widespread adoption. From his experience with the COPERNICUS and COMET trials, as well as the underpinning Imperial research on the protective role of the β_2 AR, he argued strongly for carvedilol as a drug of choice. Carvedilol is now a widely used drug for this condition [8].

NICE has adopted the use of beta-blockers in systolic heart failure as a 'Quality Standard (2011)' [5; see page 18] "Proportion of people with chronic heart failure due to left ventricular systolic dysfunction who are prescribed beta-blockers licensed for heart failure". It is also used as an incentivisation metric for GPs in their 'Quality and Outcome Framework (QOF)' [6; page 12] "In those patients with a current diagnosis of heart failure due to left ventricular systolic dysfunction who are currently treated with an ACE-I or ARB, the percentage of patients who are additionally currently treated with a beta-blocker licensed for heart failure". For all indications, more than 191.5 million prescriptions for beta blockers were filled in 2010, making them part of standard therapy [7] and the 4th most commonly prescribed drug for all indications [8].

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

- [1] NICOR: 2010-2011 Annual Report on the National Heart Failure Audit <http://www.ucl.ac.uk/nicor/audits/heartfailure/additionalfiles/pdfs/annualreports/annual11.pdf>. Archived on 5th November 2013.
- [2] NICE guidelines, Management of chronic heart failure in adults in primary and secondary care, updated 2010 <http://guidance.nice.org.uk/CG108/Guidance/pdf/English>. Archived on 5th November 2013.
- [3] AHA/ACC Focused Update Incorporated Into the ACC/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults Guidelines (2009). *Circulation*, 119, 391-479. [DOI](#).
- [4] ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. ESC Guidelines (2012). *Eur Heart J*, 33 (14), 1787-1847. [DOI](#).
- [5] NICE Centre for Clinical Practice, CHF Quality Standards Programme. <http://www.nice.org.uk/media/D6F/93/CHFQualityStandard.pdf>. Archived on 5th November 2013.
- [6] 2013/14 general medical services (GMS) contract quality and outcomes framework (QOF) <http://www.nhsemployers.org/Aboutus/Publications/Documents/qof-2013-14.pdf>. Archived on 5th November 2013.
- [7] McMurray, J.J. (2010). Clinical practice. Systolic heart failure. *N Engl J Med*, 362(3), 228-38. [DOI](#)
- [8] Shah, S.M., Carey, I.M., DeWilde, S., Richards, N., Cook, D.G. (2008). Trends and inequities in beta-blocker prescribing for heart failure. *Br J Gen Pract*, 58 (557), 862-869. [DOI](#)