Institution: University of Dundee
Unit of Assessment: UoA1 Clinical Medicine
Title of case study: Spironolactone as a Treatment to extend life in Heart Failure Patients

1. Summary of the impact

Our research with spironolactone has advanced treatment in heart failure. We conducted the first "proof of concept" study to show that spironolactone had beneficial cardiac effects in man. In patients with heart failure, we demonstrated that it reduced cardiac sympathetic activity and arrhythmias. Spironolactone was pioneered in Dundee as a treatment to reduce deaths in chronic heart failure. This treatment is now recommended (Level A evidence; Class I recommendation) for the treatment of symptomatic heart failure in all guidelines including the 2010 NICE guidelines. It is also now a standard in the 2010 NHS Quality Improvement Scotland standards.

2. Underpinning research

A major advance in the treatment of heart failure was the development in the 1980s of the neurohormonal hypothesis of heart failure (i.e. heart failure develops and progresses because endogenous neurohormonal systems such as the renin-angiotensin-aldosterone system that are activated by the initial injury to the heart exert a deleterious effect on the circulation). The success of angiotensin converting enzyme inhibitors (ACE inhibitors), which were shown in 1987 to reduce deaths in heart failure, provided support for this hypothesis. The expectation thereafter was that ACE inhibitors would suppress aldosterone to such an extent that adding spironolactone to an ACE inhibitor would not add therapeutic value and could be hazardous.

The underpinning research and development work that challenged this contention was funded by the British Heart Foundation and Scottish Hospital Endowments Research Trust and carried out at the University of Dundee under the leadership of Prof Allan **Struthers** (Division of Cardiovascular and Diabetes Medicine, Ninewells Hospital and Medical School, Dundee) with assistance from Dr (now Prof) Chim **Lang** (at the time a Lecturer in the Department) in collaboration with Michael Arnott and Norman Kennedy (Department of Medical Physics). The original impetus for our work was that corticosterone was a known inhibitor of uptake for noradrenaline in non-cardiac tissue. This made us wonder whether aldosterone (a related steroid hormone) would alter noradrenaline kinetics in a different tissue, the myocardium.

We began by showing this was indeed the case in animals and went on to confirm the same effect in man [i]. This was a major finding since cardiac noradrenergic/sympathetic activity is well known to produce arrhythmias and hasten death in patients with heart failure. In 1995 we published seminal work showing that spironolactone not only reduced cardiac adrenergic activity but also reduced ventricular arrhythmias when added to ACE inhibitors in patients with heart failure [i]. This was the first demonstration of a beneficial cardiac effect of spironolactone in man. Hitherto, spironolactone was thought of only as a diuretic and our work changed thinking about this familiar drug. These encouraging results, along with data from others showing that spironolactone might reduce myocardial fibrosis in rats, were a major factor in persuading Searle to launch the large, multicentre Randomized ALdactone Evaluation Study (RALES) trial. An important contribution of the Dundee paper was based on the fact that cardiac arrhythmias are the main cause of sudden cardiac death in man; our observation that spironolactone reduced cardiac arrhythmias and adrenergic activity suggested for the first time that spironolactone might indeed reduce sudden cardiac deaths [i-iv]. This hypothesis was subsequently confirmed by the 1999 RALES study and then by the 2003 Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS).

The findings of EPHESUS raised the question of whether spironolactone would be beneficial in patients with mild or asymptomatic heart failure. Our subsequent publication in *Heart* [v] was the first study to show beneficial effects in mild to asymptomatic congestive heart failure on a key mechanism underlying its benefits—that is, endothelial function. Spironolactone also improved

other markers of prognosis (including brain/B-type naturietic peptide) in patients with asymptomatic or mild congestive heart failure when added to optimal treatment including β blockade.

3. References to the research

i. Barr CS, **Lang** CC, Hanson J, Arnott M, Kennedy N, **Struthers** AD (1995) Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. *Am. J Cardiol.* **76**, 1259-1265 (DOI: 10.1016/S0002-9149(99)80353-1).

ii. MacFadyen RJ, Barr CS, **Struthers** AD (1997) Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. *Cardiovasc. Res.* **35**, 30-34 (DOI:10.1016/S0008-6363(97)00091-6).

iii. MacFadyen RJ, Lee AFC, Morton JJ, Pringle SD, **Struthers** AD (1999) How often are angiotensin II and aldosterone concentrations raised during chronic ACE inhibitor treatment in cardiac failure? *Heart* **82**, 57-61 (DOI:10.1136/hrt.82.1.57).

iv. Shah NC, Pringle SD, Donnan PT, **Struthers** AD (2007) Spironolactone has antiarrhythmic activity in ischaemic cardiac patients without cardiac failure. *J. Hypertension.* **25**, 2345-2351 (DOI: 10.1097/HJH.0b013e3282e9a72d).

v. Macdonald JE, Kennedy N, **Struthers** AD (2004) Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other prognostic markers in patients with mild heart failure already taking optimal treatment. *Heart* **90**, 765-770 (DOI:10.1136/hrt.2003.017368).

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- **Struthers** AD, Barr CS: Does spironolactone produce beneficial effects over and above an ACE inhibitor in chronic heart failure?; Scottish Hospitals Endowment Research Trust (1992-1993) £23,190.
- **Struthers** AD, Fraser C: Does aldosterone blockade produce beneficial effects over and above an ACE inhibitor in chronic heart failure?; British Heart Foundation (1992-1994) £21,210.
- **Struthers** AD, Pringle S, Morton JJ: The Identification of Angiotensin II Reactivation in Heart Failure patients taking ACE Inhibitors; Scottish Home & Health Department (1995-1996) £41,526.
- **Struthers** AD, MacFadyen RJ, Pringle S: Spironolactone induced bradycardia at dawn: what is the mechanism and does it reduce ischaemia?; Scottish Home & Health Department (1996-1998) £120,140.
- **Struthers** AD, Kennedy N: Will spironolactone reduce cardiac deaths in mild chronic heart failure?; Tenovus/Northwood Trust (2000-2002) £109,961.
- **Struthers** AD, Pringle S, Donnan P: Does Aldosterone Blockade improve endothelial dysfunction in patients with coronary artery disease but without heart failure?; British Heart Foundation (2004-2006) £104,071.

4. Details of the impact

Our underpinning research addressed the challenge of heart failure, which is a global health issue. It led to the recognition that aldosterone antagonists such as spironolactone have beneficial effects in individuals with various kinds of heart failure. It is now widely recognised that aldosterone antagonists improve survival among patients with chronic, severe systolic heart failure and heart

failure after myocardial infarction. Consequently, current guidelines recommend the use of an aldosterone-receptor antagonist in these patients. This has led to significant patient benefit.

Aldosterone antagonist treatment is now recommended in National Institute for Health and Case Excellence (NICE) guidelines, specifically those on chronic heart failure ([1]; issued in 2010). In preparing this Guideline, NICE gave detailed consideration to our previous work, as follows: "….studies were identified comparing aldosterone antagonists plus optimal medical management with placebo plus optimal medical management in patients with chronic heart failure. Barr (1995) [i] compared spironolactone with placebo in a population with chronic heart failure (CHF) secondary to coronary heart disease. Macdonald (2004) [v] compared spironolactone with placebo in a population with mild heart failure, defined as patients whose CHF had been at least [New York Heart Association] NYHA class II at diagnosis, but optimising their treatment had improved the patients' condition substantially into a stable and less symptomatic one….." (Section 5.2.3.2, p96; tabulated on p103). This contributed to the following recommendation (R29) for second-line treatments: "….consider adding one of the following if a patient remains symptomatic despite optimal therapy with an ACE inhibitor and a beta-blocker: an aldosterone antagonist licensed for heart failure (especially if the patient has moderate to severe heart failure [NYHA14 class III-IV], or has had a myocardial infarct within the past month)….".

In recognition of the influence of his work on heart failure, Prof **Struthers** was appointed as a member of the Steering Group of the NHS Quality Improvement Scotland Heart Disease project, which led in 2010 to the publication of Clinical Standards for Heart Disease [2]. These apply throughout the NHS in Scotland and recommend (Standard Statement 15, p28) that "Patients with heart failure are commenced on medication to reduce symptoms and improve prognosis, unless contraindicated….15.5 Patients with left ventricular systolic dysfunction and persistent New York Heart Association class III heart failure and who have been New York Heart Association class IV in the last 6 months receive spironolactone except where contraindicated…..".

In a further recent development [3], the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) randomised, double-blind trial evaluated the effects of another aldosterone antagonist, eplerenone, in patients with chronic systolic heart failure and mild symptoms. The decision to undertake this study was based upon the outcomes of the RALES and EPHESUS studies, both of which were influenced by our work [i-iv]. The results of this Pfizer-funded study indicated that eplerenone, as compared with placebo, reduced both the risk of death and the risk of hospitalization among patients with systolic heart failure and mild symptoms.

An aldosterone antagonist is now recommended (Level 1 recommendation) for use in all patients with systolic heart failure including patients with mild NYHA II heart failure. Clinical practice guidelines making this recommendation include the 2012 European Society of Cardiology guidelines [4,5] and the 2011 National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand guidelines [6,7].

Aldosterone antagonist treatment has been shown to be cost effective: the incremental cost-effectiveness ratio for aldosterone antagonist therapy when added to standard therapy (ACE inhibitor plus β-blocker) in patients with heart failure has been calculated to be ~US$500 per life year gained [8].

Finally, the most recent development (April 2013) has been the addition of the use of spironolactone for heart failure to the World Health Organization Model List of Essential Medicines, which is updated every two years using a transparent evidence-based process endorsed by the WHO Expert Committee on Selection and Use and serves as a guide for the development of national and institutional essential medicine lists throughout the world [9].

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

1. National Clinical Guideline Centre (2010) Chronic heart failure: the management of chronic heart failure in adults in primary and secondary care London: National Clinical Guideline Centre. Available from: http://guidance.nice.org.uk/CG108/Guidance/pdf/English.
2. NHS Quality Improvement Scotland (2010) Clinical Standards on Heart Disease (ISBN 1-84404-590-0).

3. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group (2011). Eplerenone in patients with systolic heart failure and mild symptoms. *N. Engl. J. Med*. **364**, 11–21 (DOI: 10.1056/NEJMoa1009492).

4. 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 and 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).

5. Letter of Corroboration from the Chairman of the 2012 European Society of Cardiology Guideline on Heart Failure.

6. Krum, H, Jelinek MV, Stewart S, Sindone A, Atherton JJ. (2011) 2011 update to National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006 *Med. J. Aust.* **194**, 405-409 (https://www.mja.com.au/journal/2011/194/8/2011-update-national-heart-foundation-australia-and-cardiac-society-australia-and).

7. 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.

8. Banka G, Heidenreich PA, Fonarow GC (2013) Incremental cost-effectiveness of guideline-directed medical therapies for heart failure. *J. Am. Coll. Cardiol.* **61**, 1440-6. (DOI: 10.1016/j.jacc.2012.12.022).

9. WHO Model Lists of Essential Medicines; available at: http://www.who.int/medicines/publications/essentialmedicines/en/.