Institution: University of Birmingham

Unit of Assessment: UoA2

Title of case study: Heart failure: Improving the quality of life and survival of heart failure patients through Cardiac Resynchronisation Therapy

1. Summary of the impact

Heart failure affects more than 22 million people worldwide, including 6 million in Europe and 5 million in the United States, with approximately 500,000 new patients diagnosed each year.

The cardiac resynchronisation in heart failure trial (CARE-HF) demonstrated that, in patients with heart failure and cardiac dyssynchrony, use of an implantable pacemaker to improve heart contraction led to a 37% reduction in the risk of death and hospitalisations and significant improvements in patient quality of life. The benefits are in addition to those of standard pharmacologic therapy. As a result of the CARE-HF trial, international and NICE guidelines have recommended the use of cardiac resynchronization therapy in patients with heart failure and dyssynchrony resulting in an increased use of cardiac resynchronisation throughout the world and significant improvements in quality of life and survival for heart failure patients.

2. Underpinning research

Heart failure affects more than 22 million people worldwide, including 6 million in Europe and 5 million in the United States, with approximately 500,000 new patients diagnosed each year (http://www.medtronic.com/physician/care_hf/faqs.html). Despite improvements in pharmacological treatment, many patients with heart failure have severe and persistent symptoms and their prognosis remains poor. Early studies of an implantable pacemaker - cardiac resynchronization therapy (CRT) suggested that it was a promising new intervention for patients with heart failure, left ventricular systolic dysfunction and ventricular dyssynchrony with evidence that CRT decreased symptoms, improved exercise capacity, quality of life, and ventricular function. The COMPANION trial (2004) showed that CRT alone or combined with an implantable defibrillator reduced the composite end point of death from any cause or hospitalization during a mean follow-up of 16 months; however, the decrease in the risk of death was not significant with CRT alone (P=0.06). Meta-analyses left lingering uncertainty about the effects of cardiac resynchronization on the risk of complications and death.

From 2001 to 2005, a team from the University of Birmingham (Professor Nick ***Freemantle***, Professor of Clinical Epidemiology and Biostatistics, UoB up to April 2011; Dr Melanie **Calvert**, Reader in Epidemiology, UoB) led the design and analysis of the landmark Cardiac Resychronisation in Heart Failure Trial (CARE-HF) and its extension study. The CARE-HF trial (PI Cleland, University of Hull; funded by Medtronic Ltd; design & analysis ***Freemantle*, Calvert**) was a multi-centre, international, randomised controlled trial to evaluate long-term effects of CRT on the mortality and morbidity of patients with heart failure due to left ventricular systolic dysfunction and cardiac dyssynchrony who were receiving standard pharmacologic therapy. A total of 813 patients were recruited between January 2001 and March 2003 at 82 centres across 12 European countries. Patients were randomly assigned to receive medical therapy alone or with CRT and followed for a mean of 29.4 months.

The primary end point was the time to death from any cause or unplanned hospitalisation for a major cardiovascular event. The principal secondary end point was death from any cause. The primary end point was reached by 159 patients in the cardiac-resynchronization group, as compared with 224 patients in the medical-therapy group (39 percent vs. 55 percent; hazard ratio, 0.63; 95 percent confidence interval, 0.51 to 0.77; P<0.001). There were 82 deaths in the CRT group, as compared with 120 in the medical-therapy group (20 percent vs. 30 percent; hazard ratio 0.64; 95 percent confidence interval, 0.48 to 0.85; P<0.002). As compared with medical therapy, CRT reduced the interventricular mechanical delay, the end-systolic volume index, and the area of the mitral regurgitant jet; increased the left ventricular ejection fraction; and improved symptoms and the quality of life (P<0.01 for all comparisons). This landmark trial thus demonstrated significant improvements in survival and quality of life in patients randomised to CRT. These

benefits are in addition to those afforded by standard pharmacologic therapy and it was recommended that the implantation of a cardiac-resynchronization device should routinely be considered in such patients. The results were published in the New England journal of Medicine [1] and have been cited 2715 times *accessed via Scopus online 30th July 2013*. The observed benefits in survival and quality of life were sustained over time [2].

Whilst the CARE-HF trial demonstrated reduced morbidity and mortality, CRT is relatively costly thus it was essential to establish the incremental cost-effectiveness of using the device compared to standard care. Within trial and life-time simulation model based cost-effectiveness analyses were led from the University of Birmingham (***Freemantle*; Calvert**; Professor Stirling ***Bryan***, Professor of Health Economics, UoB, up to August 2008; Dr Lily ***Yao***, Senior Lecturer in Health Economics, UoB, up to February 2013; Professor Lucinda **Billingham**, Professor of Biostatistics, UoB) in conjunction with CARE-HF investigators from elsewhere (Cleland, Daubert). The aim of the within trial cost-effectiveness analysis was to evaluate the incremental cost per QALY gained and incremental cost per life year gained of CRT plus medical therapy compared to medical therapy alone. It. CRT was associated with increased costs (€4316, 95% CI: 1327 to 7485), survival (0.10 years, 95% CI: -0.01 to 0.21), and QALYs (0.22, 95% CI: 0.13 to 0.32). The incremental cost-effectiveness ratio was €19 319 per QALY gained (95% CI: 5482 to 45 402) and €43 596 per life-year gained (95% CI: -146 236 to 223 849) [3]. A further long term cost-effectiveness analysis used a lifetime simulation model developed based upon individual patient data from the CARE-HF trial to examine the additional effect of CRT with an implantable cardioverter-defibrilator (ICD) function, which further reduces risk of death. Both CRT + medical therapy and CRT-ICD + medical therapy were cost-effective at a notional willingness to pay threshold of €29 400 (£20,000) but the latter to a lesser extent [4]. There were also contributions to cost-effectiveness analyses for the Nordic region and Greece (***Freemantle*, Calvert**).

The CARE-HF trial has resulted in a further 24 publications (including Birmingham authors ***Freemantle;* Calvert;** Dr Puvanendran ***Tharmanathan*,** doctoral student, UoB up to December 2008**;** Matthew ***Richardson***, research fellow, UoB up to April 2012; Aparna ***Shankar*,** research associate, UoB up to August 2008) on topics including quality of life [5], neurohormonal effects, procedure success rate and predictors of outcome.

3. References to the research

1. Cleland J, Daubert J-C, Erdmann E, ***Freemantle N,*** Gras D, Kappenberger L et al . CARE-HF Study Investigators (inc. **Calvert M**). The effect of cardiac resynchronization on morbidity and mortality in heart failure *N Engl J Med* 2005; 352(15) :1539-1549. http://www.ncbi.nlm.nih.gov/pubmed/15753115
2. Cleland JG, **Calvert MJ,** Verboven Y, ***Freemantle N.*** Effects of cardiac resynchronization therapy on long-term quality of life: an analysis from the CArdiac Resynchronisation-Heart Failure (CARE-HF) study. *Am Heart J*. 2009 ;157(3):457-66. Epub 2009 Jan 20. http://www.ncbi.nlm.nih.gov/pubmed/19249415
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4. ***Yao G, Freemantle N,* Calvert MJ, *Bryan S,*** Daubert JC, Cleland JG. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. *Eur Heart J.* 2007;28(1) : 42-51. Epub 2006 Nov 16. http://www.ncbi.nlm.nih.gov/pubmed/17110403
5. **Calvert MJ, *Freemantle N,*** Cleland JGF. The impact of chronic heart failure on health-related quality of life data acquired in the baseline phase of the CARE-HF study. *Eur J Heart Fail.* 2005; 7(2) : 243-51. http://www.ncbi.nlm.nih.gov/pubmed/15701474

4. Details of the impact

Impact on Public Policy

CARE-HF has been used as key evidence supporting the use of cardiac resynchronization therapy in a series of international guidelines at both regional (Europe [1]) and national level, in countries as diverse as Australia [2], Brazil [3], Canada [4], Czech Republic [5], New Zealand [2,6], and USA [7,8,9]. Examples include:

1) European Society of Cardiology Guidelines for the Diagnosis and Treatment of Heart Failure, were initially published in 2005 and later revised during the 2008-13 impact period, in both 2008 and 2012 [1]. These guidelines all cite CARE-HF as a source of key evidence for recommending the use of cardiac resynchronization therapy in patients with moderate to severely symptomatic heart failure (Section 9.2.1, reference 157 in 2012 revision)
2) American College of Cardiology Foundation/American Heart Association Guidelines for the Diagnosis and Management of Heart Failure in Adults 2005 and 2009 [9]. CARE-HF is cited as one of the trials providing strong evidence supporting the use of CRT in selected patients (Section 4.3.1.3.4., reference 101).
3) Guidelines for the prevention, detection and management of chronic heart failure in Australia published in 2011 [2] (Section 8.1; pg 36, reference 204). These guidelines cite CARE-HF (reference 204) as supporting use of biventricular pacing for patients with: NYHA symptoms Class III/IV despite optimal medical therapy; dilated heart failure with an ejection fraction less than or equal to 35%; QRS duration greater than or equal to 120 ms; sinus rhythm.

The 2012 expert consensus statement on cardiac resynchronization therapy in heart failure from EHRA/HRS cites evidence from the CARE-HF trial as influencing a number of recommendations including around use of biomarkers in assessing heart failure (Section 1.2.2, reference 8), around considerations for patients with CRT and concomitant atrial fibrillation (Section 6.2, reference 264), and concerning the cost-effectiveness of CRT (Section 6.8, references 348, 350) [10]. This consensus statement is endorsed by the governing bodies of *European Association of Cardiovascular Imaging, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, European Heart Rhythm Association,* and *Heart Rhythm Society*.

Impact on Clinical Practice and Patient Health

There has been impact on UK patients throughout the 2008-2013 impact period, resulting from both the UK guidelines included above and also the incorporation of the research into NICE guidance just prior to the impact period. In the UK, CARE-HF provided evidence that underpins the NICE Technology Appraisal Guidance: Cardiac resynchronisation therapy for the treatment of heart failure, 2007 [11] and which recommended the use of CRT in selected patients with left ventricular dysfunction. CARE-HF was one of 4 RCTs considered by the NICE Appraisal Committee on CRT-P versus optimal pharmacological therapy alone (see p7-15). In addition the strict clinical inclusion criteria was adopted by the committee as a requirement in clinical practice (see pages 14/15):

"The Committee noted that in one of the large studies (CARE-HF) additional evidence of mechanical dyssynchrony from echocardiography was required in patients with a QRS duration of between 120 ms and 150 ms, and was therefore persuaded that such a requirement would be appropriate to use in clinical practice." (p14)

"The Committee also understood from the clinical specialists that confirmation of the presence of mechanical dyssynchrony by echocardiography was considered appropriate in patients with electrical dyssynchrony as indicated by a QRS duration of between 120 ms and 149 ms. The Committee noted that this approach was the same as the inclusion criteria for the CARE-HF trial." (p15)

The publication of the CARE-HF Trial was a substantial contribution within the overall portfolio of evidence which has seen the use of CRT substantially increased throughout Europe. Eucomed data, based on reports from major device manufacturers, suggest an increase in CRT (+/-ICD) use across Europe rising from 86 units per million inhabitants in 2008 to 141 units per million inhabitants in 2012 [12]. In the UK new CRT implants have increased significantly following the publication of the CARE-HF trial in 2005 [12] and are now over 100/million population [13].

5. Sources to corroborate the impact

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