Institution: University of Glasgow

Unit of Assessment: Unit 1; Clinical Medicine

Title of case study: Landmark advances in outcomes for patients with heart failure

1. Summary of the impact

Approximately 26 million people live with heart failure worldwide. University of Glasgow researchers have been instrumental in proving the value, in landmark clinical trials, of bisoprolol, candesartan and eplerenone - three of the four classes of drug that reduce mortality, reduce hospitalisation rates and improve quality of life for patients with heart failure. These trials led directly to revision of clinical guidelines on heart failure management globally (including in Europe, USA, UK, Australia and Canada, all published since 2008). The Glasgow researchers have established heart failure as a healthcare priority and encouraged the introduction of specialist heart failure nurses, saving the NHS an estimated £8 million per year. Collectively, these advances have transformed the treatment and survival rates of heart failure patients worldwide.

2. Underpinning research

The University of Glasgow has been a world-renowned centre of heart failure research for 30 years, making seminal contributions to the modern understanding of the causes, epidemiology, diagnosis and treatment of heart failure, as well as training many of the UK's leading experts in this area. Glasgow investigators conducted some of the first studies of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients, studies showing non-ACE generation of angiotensin II (rationale for combining ACE inhibitors and ARBs) and a proof of concept study for using a mineralocorticoid receptor antagonist (MRA) in mild heart failure. This resulted in their leadership roles on large-scale randomised clinical trials demonstrating the value of each of the effective drug treatments for heart failure: beta-blockers, ACE inhibitors, ARBs and MRAs. These drugs act to limit aspects of either the renin-angiotensin aldosterone system or the sympathetic nervous system, both of which are abnormally regulated in patients with heart failure.

Beta-blockers: In the mid-1990s, University of Glasgow researcher Prof Henry Dargie chaired and led the first definitive and ground-breaking trial establishing the benefit of beta-blockers in heart failure (CIBIS-2).[1] This randomised study revealed that patients with heart failure treated with the beta-blocker bisoprolol had a 32% reduction in annual all-cause mortality compared with a group treated with a placebo. The striking mortality benefit with bisoprolol, which was independent of heart failure cause, led to early cessation of the CIBIS-2 trial. A further study from the group confirmed the positive value of another beta-blocker, carvedilol, in patients with reduced heart function (left ventricular systolic dysfunction; LVSD) following a heart attack (CAPRICORN, 2001).

ACE inhibitors and ARBs: In a parallel trial (1999), University of Glasgow researcher Prof John Cleland was on the steering committee of the largest multi-centre trial with an ACE inhibitor in patients with symptomatic heart failure (ATLAS),[2] demonstrating the importance of adequate dosing (showing a 24% reduction in hospitalisation rates with higher doses of ACE inhibitors [~35 mg per day]) than were routinely being prescribed. The University of Glasgow's Prof John McMurray was a lead investigator in the innovative series of CHARM trials (2003-2004). The trials examined the effect of the ARB candesartan in three distinct groups of patients with heart failure: those with reduced left ventricular function intolerant of ACE inhibitors (CHARM-Alternative), similar patients also taking an ACE inhibitor (CHARM-Added)[3] and, uniquely at the time, heart failure patients with preserved function (CHARM-Preserved). In CHARM-Alternative and CHARM-Added, candesartan significantly reduced death from cardiovascular causes or hospitalisation for worsening heart failure (by 23% and 15% in CHARM-Alternative and –Added, respectively) and improved symptoms and quality of life. Patients with heart failure in CHARM-Preserved had no clear improvement when taking candesartan compared with placebo. A further trial co-led by McMurray also demonstrated the benefit of the ARB valsartan in patients with LVSD, heart failure or both following a heart attack (VALIANT).[4]

MRAs: In 2010, McMurray was one of the leaders of the EMPHASIS-HF randomised controlled

trial, which assessed the value of adding the MRA eplerenone to standard heart failure therapy (ACE inhibitor or ARB plus beta-blocker) in patients with mild heart failure.[5] The design of this trial was based upon CHARM-Added. Treatment with eplerenone led to a striking 37% overall reduction in the composite outcome of cardiovascular mortality or heart failure hospitalisation (and a 24% reduction in the risk of death from any cause and a 22% reduction in hospitalisation for any reason). The magnitude of reduction on all-cause hospitalisation in EMPHASIS-HF was (and still is) the greatest of any major trial of a heart failure drug to date; the overwhelming benefit of eplerenone in this patient group led to early cessation of the trial.

The University of Glasgow investigators have also shown that all of these treatments are cost-effective and have also been leaders in key trials establishing (i) the value of the biomarker B-type natriuretic peptide (BNP) as a diagnostic test for heart failure[6], (ii) the positive benefit of specialist heart failure nurses in reducing hospitalisation rates and improving patient outcomes[7] and (iii) the neutral effect of rosuvastatin in patients with chronic heart failure (CORONA, 2007), irbesartan in patients with preserved function (I-Preserve, the design of which was informed by CHARM-Preserved, 2008), nesiritide in acute HF (ASCEND-HF, 2011) and darbepoetin in chronic heart failure (RED-HF, 2013) all of which have led to changes in guidelines, clinical practice or both and further demonstrate the breadth of University of Glasgow research into treatments for heart failure.

Key University of Glasgow researchers: John Cleland (Senior Lecturer, 1994–1999; then University of Hull and Imperial College, London); John McMurray (Professor of Cardiology, 1999–present); Henry Dargie (Professor of Cardiology 1994-1999; Honorary Senior Research Fellow 1999–present); Ian Ford (Professor of Statistics/Biostatistics, 1992–present); Theresa McDonagh (Senior Lecturer, 1999–2004; then Imperial and King's College, London). ***Positions in large multi-centre trials:*** CIBIS-2: Dargie, Chairman of scientific committee and writing committee member (1 of 2). ATLAS: Cleland, steering committee member. CHARM trial series: McMurray, executive committee member and Principal Investigator, CHARM-Added. VALIANT: McMurray, Co-chair of executive committee. EMPHASIS-HF: McMurray, executive steering committee member. ***External collaborators****:* Members of trial committees; see original articles for details.

3. References to the research

1. CIBIS-2 Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; 353: 9–13. doi: 10.1016/S0140-6736(98)11181-9.
2. ATLAS Study Group. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 1999; 100: 2312–2318. doi: 10.1161/01.CIR.100.23.2312
3. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; 362:767–771. doi: 10.1016/S0140-6736(03)14283.
4. Valsartan in Acute Myocardial Infarction Trial (VALIANT) Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; 349:1893–1906. doi: 10.1056/NEJMoa032292.
5. EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; 364:11–21. doi: 10.1056/NEJMoa1009492.
6. McDonagh TA, *et al.* Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 1998; 351: 9–13. doi: 10.1016/S0140-6736(97)03034-1
7. Blue L, *et al.* Randomised controlled trial of specialist nurse intervention in heart failure. *BMJ* 2001; 323715-718. doi:10.1136/bmj.323.7315.715

4. Details of the impact

Heart failure is a complex syndrome in which the heart is unable to pump sufficient blood to meet the demands of the body. The incidence of heart failure increases with age, and the condition progressively leads to a significant debilitation of physical capacity and quality of life. Heart failure is associated with high mortality and more than 50% of patients die within 5 years of diagnosis. The condition represents a substantial economic burden to health services, with nearly 17 million

people living with a heart failure diagnosis in the UK, USA and Europe. In 2010/2011 the cost of heart failure management in the NHS was in excess of £2 billion; approximately 70% of this expenditure was due to hospitalisation costs. Drugs can limit progression of the disease and patients are typically treated with multiple drugs that are prescribed for the rest of their lives.

Impact on international and national heart failure clinical guidelines

Key University of Glasgow studies (detailed in sections 2 and 3) have provided the evidence-base for current clinical recommendations made by the European Society of Cardiology (ESC) and by the American College of Cardiology Foundation and American Heart Association (ACCF/AHA) for the management of heart failure. The ESC, ACCF and AHA are the most prominent and influential cardiovascular societies in the world, with estimated professional memberships of 30,000, 43,000 and 73,000 respectively. Owing to his internationally renowned reputation and expertise in the field, McMurray held the highly prestigious position of Chair of the 2012 ESC guideline committee and the only European member of the writing committee for the 2013 ACCF/AHA guidelines. The 2012 ESC[a] and 2013 ACCF/AHA[b] guidelines, through rigorous peer-review, make the highest level of recommendations, citing University of Glasgow studies in the key evidence base for the following drug therapies in patients with heart failure:

- ACE inhibitors and beta-blockers to be used in all patients with heart failure (based on evidence including the ATLAS[2], CIBIS-2[1] and CAPRICORN studies).
- ARBs in patients intolerant of ACE inhibitors or those who remain symptomatic on beta-blockers and ACE inhibitors (based on evidence including VALIANT[4] and the CHARM[3] trials).
- MRAs as the third disease-modifying drug in patients who remain symptomatic despite ACE inhibitor (or ARB) and beta-blocker (based on evidence from EMPHASIS-HF[5]).

The landmark demonstration of the lifesaving benefits of the MRA eplerenone in patients with heart failure is the biggest breakthrough in the drug management of heart failure since that of beta-blockers and is the most recent change in these new international guidelines.

The ESC and ACCF/AHA guidelines dominate the evidence-based best practice for treatment of heart failure and their recommendations are mirrored in the majority of current national guidelines. Examples published since 2008 include the National Institute for Health and Care Excellence (NICE), in the UK (2010[c]), the Canadian Cardiovascular Society (CCS, 2012[d]) and the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand (2011[e]). Approval of these therapies by NICE not only reflects their clinical efficacy but their cost-effectiveness, confirming they represent 'good value for money' for the NHS. The influence of neutral or negative trials which recommend the discontinuation of harmful drug therapies must not be underestimated. Evidence from the CORONA study led to removal of the statin therapy recommendation in patients with heart failure in the current NICE guidelines.[c] In summary, the recommendations based on University of Glasgow research outlined above affect the clinical management of heart failure worldwide. These have contributed to the reduction in mortality and hospitalisation rates (by approximately 25% and 40% respectively) recorded in the past 2 decades, with mortality rates post-2008 continuing to follow this trend.

Dissemination and implementation of heart failure guideline recommendations

A robust process of dissemination has ensured that the above guideline recommendations form the basis of current clinical heart failure treatment. Since their publication in May 2012, the ESC guidelines on heart failure management have become the most downloaded guideline in the 2012 ESC series (158,000 copies).[f] A further 28,500 pocket version guidelines of the ESC heart failure guideline have been accessed and French, Spanish, Chinese and Polish-language editions published. Beyond Europe, users are located in South America, India and China, thereby demonstrating the global reach of these recommendations.[f] A similar process of dissemination is operated by the AHA through their 'Get with the guidelines – heart failure overview' programme.

Patients with heart failure are receiving the guideline recommended first-line therapies

In the UK, implementation of these recommendations is assessed annually by the National Heart Failure audit. The 2011/2012 audit reported that, of the patients discharged from hospital in

England and Wales with heart failure, 84% were prescribed an ACE inhibitor and/or an ARB, 78% were prescribed a beta-blocker and 45% were prescribed an MRA thereby indicating adherence to the guideline recommendations based on University of Glasgow research.[g] In a primary care setting, financial incentives standardise delivery of front-line heart failure drug therapies to patients via the Quality Outcomes Framework (QOF) for all practices on the General Medical Services contract.[h] Two QOF indicators have been in existence since 2008 for the on-going management of heart failure patients. QOF data (April 2011–March 2012) indicate that 83% of patients in England with a current diagnosis of heart failure are being treated with an ACE inhibitor or an ARB, 60% of whom are additionally treated with a beta-blocker.[i] In the US, the government Health and Human Services department operates a standardised clinical quality measurement for hospitals, on which performance is rated and made publically available. The current measure (2012) stipulates that patients with heart failure are discharged with a valid prescription for ACE inhibitors and ARBs, and directly cites the Glasgow evidence base (citing CHARM-Alternative and VALIANT[4]).[j] Approximately 77% of all US hospitals are accredited to this scheme, administered by the governmental agency The Joint Commission. In 2012 The Joint Commission annual report noted that accredited hospitals reached an average 97% compliance with the heart failure measure.[k]

An estimated 7 million people in the UK and US currently live with a diagnosis of heart failure. Taken together, the above figures indicate the widespread delivery of the recommended first-line therapies within this patient population.

Advances in diagnosis and community based management of patients with heart failure

University of Glasgow clinical heart failure researchers were among the first to show the potential role of BNP as a diagnostic test for heart failure[6], which is now used universally to improve accurate and earlier diagnosis of heart failure[a, b]. A major advancement in the day-to-day care of heart failure patients has been achieved through Specialist Heart Failure Nurses (SHFNs), the concept and benefit behind which was pioneered in the UK in a 2001 Glasgow-led trial[7] (alongside two complementary trials conducted in US and Australia). As a result of the trial of specialist heart failure nurses (SHFNs), there are now more than 400 SHFNs in the UK, supported by the NHS and the British Heart Foundation. SHFNs help to reduce hospital admissions by 35% and save the NHS approximately £8 million per year.[l]

5. Sources to corroborate the impact

a. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (2012). Table of recommended treatments and key evidence sections; citing: CIBIS-2 (ref 92), ATLAS (ref 90), VALIANT (ref 120), CHARM series (refs 108, 111), EMPHASIS-HF (ref 100), CAPRICORN (ref 223) p1806-1809 & 1829.
b. ACCF/AHA Guideline for the management of heart failure (2013). Recommended treatments and key evidence sections, p47&p49-55; citing: CIBIS-2 (ref 117), ATLAS (ref 445), VALIANT series (refs 345&120), CHARM series (refs 450&589), EMPHASIS-HF (ref 426), CAPRICORN (ref 346); data supplements 18-20 p79-85, CORONA (ref 207).
c. NICE Chronic Heart Failure (2010). ATLAS (ref 75), CIBIS-2 (ref 86), CHARM (105); p38-46.
d. CCS update, Heart Failure management guidelines update: Focus on Acute and Chronic Heart Failure (2012). CIBIS-2 (ref 70), VALIANT (ref 63), CHARM (64), EMPHASIS-HF (67); recommended therapies p174.
e. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand update, Guidelines for the prevention, detection and management of chronic heart failure in Australia (2011). Recommended therapies p406; citing EMPHASIS-HF (ref 16).
f. Download data for ESC 2012 heart failure guidelines (reference a. above) were obtained directly through correspondence with the ESC and are available on request.
g. National Heart Failure Audit Report, April 2011-March 2012.
h. 2013/14 general medical services (GMS) contract quality and outcomes framework (QOF).
i. QOF 2011–2012 *Cardiovascular disease primary prevention*, England, (HF3 and HF4).
j. US Department of Health and Human Services (HHS).
k. The Joint Commission Annual Report on quality and safety 2012.
l. BHF Specialist Nurses Report 2008 – *Changing the face of cardiac care*