Institution: University of Glasgow

Unit of Assessment: Unit 2; Public Health, Health Services and Primary Care

Title of case study: Practice-changing clinical trials expand the treatment options for heart disease

1. Summary of the impact

Randomised placebo-controlled trials (RCTs) are the most robust way to demonstrate the effectiveness of medical therapies. The University of Glasgow's Robertson Centre for Biostatistics (RCB) is internationally renowned for its biostatistical input and leading roles on landmark RCTs of cardiovascular therapies. The findings of the BEAUTIFUL and SHIFT studies underpinned European and UK regulatory approval for a novel use of the heart-rate-lowering drug ivabradine, potentially preventing thousands of hospital admissions for heart failure every year. The IONA trial supported UK approval of generic versions of another heart drug (nicorandil), thereby enhancing cost-effectiveness for the NHS. The BEAUTIFUL, SHIFT, DOT-HF and CAPRICORN trials provided the evidence base for US, European and UK guideline recommendations, steering best practice for treatment of patients with heart disease worldwide.

2. Underpinning research

The University of Glasgow RCB is a world-renowned centre of excellence in the collaborative conduct of national and international multicentre clinical trials, particularly those involving cardiovascular therapies/devices. The RCB comprises statisticians, trial managers and IT staff who make key contributions to the design and protocols of RCTs. In addition, they co-ordinate trial implementation, conduct interim and final analyses, and interpret the clinical outcome data. To complement this, RCB investigators have extensive experience of the clinical context and epidemiology of cardiovascular disease. Such robust methodologies have contributed to the RCB's position as a leading UK Clinical Research Collaboration registered Clinical Trials Unit (since 2007) and formed the foundation of its role in the highly successful National Institute for Health Research Stroke Research Network. RCTs performed by the RCB that underpin this case study include CAPRICORN (2001),[1] IONA (2002),[2] BEAUTIFUL (2008),[3] SHIFT (2010)[4] and DOT-HF (2011).[5]

Carvedilol improves survival in patients with a history of heart attack

In the mid-1990s, it was unclear whether beta-blockers were beneficial when given in addition to angiotensin-converting-enzyme (ACE) inhibitors to patients with severe cardiac disease (e.g. patients such as those who had just experienced a heart attack and were at high risk of subsequent cardiovascular events). Professor Ian Ford was on the Steering Committee of CAPRICORN, which was designed and analysed in collaboration with the RCB. This RCT examined the effect of the beta-blocker carvedilol in 1,959 patients from 17 countries worldwide with abnormal heart function (left ventricular dysfunction) following a heart attack. Treatment with carvedilol (on top of background ACE inhibitor therapy) led to a 23% reduction in mortality during follow-up (average 1.3 years), supporting the use of beta-blockers in this patient population.[1]

Nicorandil is cardioprotective in patients with stable angina

Stable angina is a form of chest pain or discomfort that occurs upon exertion and results from poor blood flow through the arteries of the heart. The pioneering IONA study was designed, conducted and analysed by the RCB, with Ford serving on the Steering Committee. This RCT assessed the effects of nicorandil (a drug that maintains blood flow to the heart) on morbidity and mortality among 5,126 patients, recruited from across the UK, with stable angina pectoris. The findings of IONA (2002) showed a 17% reduction in the risk of coronary events and deaths in patients being treated with nicorandil compared with placebo.[2]

Ivabradine reduces cardiovascular events in heart failure patients with elevated heart rate

Elevated heart rate is an established risk factor for cardiovascular events. BEAUTIFUL was the first RCT to examine the effect of ivabradine (a drug that lowers heart rate) on cardiovascular events. This study involved 10,917 patients with coronary disease and left ventricular dysfunction who were recruited internationally. Whilst ivabradine did not affect the composite primary endpoint in the general trial population, the results established the importance of a heart rate over 70 beats per minute (bpm) in identifying high-risk patients and those who might benefit from heart-rate-

lowering therapy.[3] The ground-breaking SHIFT study of 6,558 patients demonstrated the ability of ivabradine to reduce cardiovascular death or hospital admission for heart failure by 18% among individuals with a heart rate above 70bpm.[4] SHIFT was the first RCT to provide robust evidence that lowering heart rate can specifically reduce the incidence of cardiovascular events, and provide an additional therapy on top of the maximally tolerated beta-blocker dose to further improve outcomes for patients with heart failure. Ford had key roles on the Executive Committees of BEAUTIFUL and SHIFT, which were designed and analysed with considerable involvement of the RCB.

Implantable devices to enable early detection of fluid accumulation in heart failure patients
Progressive worsening of heart failure results in fluid accumulation in the lungs and peripheral tissues, which requires emergency hospitalisation and urgent in-patient intensification of therapy to relieve fluid overload. Contrary to expectations, the DOT-HF trial determined that implantation of expensive devices to detect fluid accumulation at an early stage and intensify treatment as an out-patient resulted in higher rather than lower rate of heart failure hospitalisation (and no improvement in any other outcome). This negative result was important as it challenged the rationale that the use of expensive technology to detect and manage fluid overload could improve patient outcomes in patients with heart failure.[5]

In summary, the RCB held leading roles in these four major projects providing vital, independent analysis in all of these practice-changing trials – an important point given that the individual members of steering committees and trial management groups differed across all four trials.

Key University of Glasgow researchers: Ian Ford (Professor of Statistics/Biostatistics [1992–present] all trials above); Michele Robertson (Consultant statistician [1994–2008], Senior statistician, [2008–2010], Assistant Director Commercial Biostatistics [2010–present]; CAPRICORN, BEAUTIFUL and SHIFT); Henry Dargie (Professor of Cardiology [1994–1999], Honorary Senior Research Fellow [1999–present]; Steering committee CAPRICORN, IONA); William Hillis (Professor of Cardiovascular and Exercise Medicine [1997–2008]; Steering committee IONA). **External collaborators**: Members of the Executive Committees (SHIFT, BEAUTIFUL) and Steering Committees (IONA, CAPRICORN, DOT-HF); see original articles for details.

3. References to the research

1. The CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*, 2001; 357: 1385–1390. doi:10.1016/S0140-6736(00)04560-8
2. The IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet*, 2002; 359: 1269–1275. doi:10.1016/S0140-6736(02)08265-X
3. Fox K, *et al.* on behalf of the BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet*, 2008; 372: 807–816. doi:10.1016/S0140-6736(08)61170-8
4. Swedberg K, *et al.* on behalf of the SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*, 2010; 376: 875–885. doi:10.1016/S0140-6736(10)61198-1
5. The DOT-HF invesitgators. Intrathoracic impedance monitoring, audible patient alerts, and outcome in patients with heart failure. *Circulation,* 2011; 124:1719-26. doi: 10.1161/CIRCULATIONAHA.111.043042

4. Details of the impact

Cardiovascular disease, resulting from damage to the heart, blood vessels or both, is the leading cause of death worldwide. Current estimates suggest that more than 7000 European and American adults die of cardiovascular disease every day. Heart disease, a major form of cardiovascular disease, is a broad term used to describe heart failure, heart attack and angina, all of which present a substantial economic burden to healthcare services. For example, in 2010–2011, it is estimated that the NHS spent in excess of £2 billion on patients with heart failure, with around 70%

of this expenditure reflecting hospitalisation. Medical therapy limits heart disease progression and patients are typically treated with a lifelong prescription of multiple classes of drugs. Since 2008, landmark clinical trials with leadership involvement of the RCB have led to the expansion of therapeutic options for patients with heart failure.

Regulatory approval

Conducting well-designed RCTs to determine whether medications are safe and effective is the lynchpin of gaining regulatory approval for their use in patients. Ivabradine (brand name, Procoralan) was originally approved by the European Medicines Agency (EMA) in 2005 specifically for the treatment of long-term angina among people with normal heart rhythm. The findings of BEAUTIFUL prompted the manufacturer of this drug (leading French pharmaceutical company Servier) to apply for an extension to the original indication (angina).[a] In October 2009, the EMA approved ivabradine as an add-on therapy (on top of beta blockers) for the treatment of long-term angina in patients with coronary artery disease and normal heart rhythm.[b] The BEAUTIFUL study (CL3-056) was extensively cited as key supporting evidence for clinical benefit and acceptable safety profile in this application (sections I.2.2 and I.2.3). In March 2012, the EMA Committee for Medicinal Products for Human Use (CHMP) granted a further request by Servier to extend the indications for ivabradine to include patients with chronic heart failure.[b] The SHIFT study (CL3-16257-063) was cited as the sole supporting evidence in the CHMP assessment report (sections 1.1, 2.1, 2.3, 2.4 and 3). Consequently, the CHMP recommendation for this novel use of ivabradine (variation C.I.6.a; section 4) was based entirely on information made available by the SHIFT investigators.

Commenting on the key role of the RCB in this approval process, Servier's Director of the Division for Medical Affairs stated that '*The internationally recognised combination of outstanding biostatistical skill, knowledge of the disease area and experience in large cardiovascular clinical outcome trials…highlighted the synergy between the [RCBs] expertise and our own research aims in developing treatments for heart disease…[the] findings of BEAUTIFUL and particularly SHIFT were pivotal in Servier's successful application to the EMA in 2012 to extend the original licence for ivabradine in stable angina to include heart failure'*.[a]

The Scottish Medicines Consortium (SMC) is responsible for assessing new treatments for use within NHS Scotland. The SMC approved the restricted use of ivabradine for chronic heart failure in September 2012, citing SHIFT as the sole evidence base for this decision.[c] In November 2012, the UK National Institute for Health and Care Excellence (NICE) approved ivabradine for this application throughout the NHS.[d] The NICE technical appraisal document (TA 267) cites SHIFT in the evidence as the "*only randomised controlled trial that assessed the effect of ivabradine in people with heart failure*" (section 3.1). Regulatory approval of ivabradine in 2012 was widely reported by major UK media outlets, including the *Telegraph*, *Guardian*, *Mail Online* and *Daily Mirror*, reaching a potential audience of approximately 9 million.[e] Specialist coverage included NHS Choices, theheart.org, and the British Heart Foundation.

Generic drug formulations can significantly lower health costs and improve access to treatment once brand-name drugs come off patent. Data from IONA was cited in the evidence base supporting the marketing of generic nicorandil in the UK. This application was approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) in November 2010.[f]

Clinical guidelines

RCB research has underpinned high-level recommendations in the leading international and national guidelines on the management of patients with heart disease.

The joint American College of Cardiology Foundation and American Heart Association (ACCF/AHA, estimated professional membership of 73,000) guideline on the management of heart failure was published in June 2013.[g] The CAPRICORN study of carvedilol is cited in this guideline and underpins the following highest level (Level I) recommendations:

- *In patients with heart attack (myocardial infarction; MI) and reduced heart output (ejection fraction; EF), evidence-based beta blockers* ***should be used*** *to prevent heart failure.*

- *Use of 1 of the 3 beta blockers proven to reduce mortality is **recommended** for all stable patients.*

Similarly, the DOT-HF results have been included in the evidence base to form guideline recommendations on device therapy for management of chronic (Stage C) heart failure.

In May 2012, the European Society of Cardiology (ESC; estimated professional membership of 80,000) published guidelines on the diagnosis and treatment of heart failure.[h] These guidelines cite SHIFT, BEAUTIFUL and CAPRICORN. Data from SHIFT and BEAUTIFUL underpin the following recommendations on the use of ivabradine:

- ***Should be considered** to reduce the risk of heart failure hospitalisation in patients in sinus rhythm with an EF ≤35%, a heart rate remaining ≥70 bpm, and persisting symptoms (NYHA class II–IV) despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and an MRA (or ARB).* SHIFT is cited as the sole underpinning evidence.
- ***Should be considered** in patients in sinus rhythm who cannot tolerate a beta-blocker, to relieve angina (effective antianginal treatment and safe in HF).* SHIFT and BEAUTIFUL are the only studies cited.
- *The addition of ivabradine is **recommended** when angina persists despite treatment with a beta-blocker (or alternative), to relieve angina (effective antianginal treatment and safe in HF)*. SHIFT and BEAUTIFUL are the only studies cited.

Data from CAPRICORN underpins the following recommendation for carvedilol:

- *A beta-blocker is **recommended** in patients with an EF ≤40%, after stabilization, to reduce the risk of death and recurrent myocardial infarction*. CAPRICORN is the only study cited.

More than 158,000 copies of this guideline have been downloaded from the ESC website, making it the leading downloaded guideline in the ESC series in 2012.[i] These data are complemented by a further 28,500 downloads of the ESC pocket guideline version, with a worldwide readership including South America, India and China.

The Scottish Intercollegiate Guidelines Network (SIGN) develops evidence-based clinical guidelines for NHS Scotland. In February 2013, SIGN published a guideline on acute coronary syndromes.[j] CAPRICORN is cited as the sole evidence in support of the following highest level recommendation:

- *Patients with clinical myocardial infarction should be maintained on long term beta blocker therapy*.

In summary, these landmark clinical trials with leadership involvement of the RCB (described in section 2) have widened therapeutic options for patients with heart failure worldwide.

5. Sources to corroborate the impact

a. Statement from Servier Director of the Division for Medical Affairs
b. EMA approval of licence extension for ivabradine, 2009 and 2012
c. SMC No. 805/12, 2012
d. NICE TA267, 2012
e. Media coverage of regulatory approval of ivabradine, 2012: Telegraph, Guardian, Mail Online and Daily Mirror
f. MHRA approval of generic nicorandil, 2010
g. ACCF/AHA guideline on heart failure, 2013 Recommendations for treatment of stage B HF; CAPRICORN (ref 346), Table 12, p261 and Table 19, p275; DOT-HF (table 28, p109 data supplement) referenced on p277
h. ESC guideline on heart failure, 2012 Other treatments for systolic HF, p1808, SHIFT (ref 112); Alternatives to beta-blockers, p1822, SHIFT and BEAUTIFUL (ref 122); Recommendations for acute HF, p1829, CAPRICORN (ref 223).
i. ESC 2012 guideline download data up to June 2013 – were obtained directly through correspondence with the ESC, copies of the data are available on request
j. SIGN guideline 93 on acute coronary syndromes, 2013 Beta blocker therapy, p24, CAPRICORN (ref 169)