Institution: University of Leeds

Unit of Assessment: UOA2

Title of case study: Reducing mortality following acute myocardial infarction (AMI)

1. Summary of the impact

Patients with evidence of heart failure following acute myocardial infarction (AMI) have a particularly poor prognosis, with substantially increased risk of death and subsequent cardiovascular events. The Acute Infarct Ramipril Efficacy (AIRE) Randomised Controlled Trial (RCT) was an international trial designed and led by the University of Leeds. AIRE demonstrated, for the first time, that early treatment of patients with clinical evidence of heart failure following AMI with the angiotensin converting enzyme inhibitor (ACEI) ramipril significantly improved survival and quality of life compared with placebo treated patients. The strategy of early initiation of ACEI is now a cornerstone in the management of patients suffering from AMI, leading to a global improvement in post-AMI outcomes.

2. Underpinning research

Cardiovascular disease, in particular acute myocardial infarction (AMI) and its complications, is the principal cause of premature mortality worldwide (World Health Organisation September 2011, www.who.int/cardiovascular_diseases/en). Whilst contemporary mechanical reperfusion strategies significantly improve survival following AMI, left ventricular dysfunction and heart failure develops in at least 40% of patients after AMI resulting in poorer outcomes, highlighting the importance of effective management of heart failure in these patients.

The AIRE RCT (**1**) was conceived, designed and led by staff at the University of Leeds (Professor SG Ball, British Heart Foundation Chair (Leeds 1990-2010); Professor **AS Hall** (Leeds 1992-)), and built upon evidence from earlier studies demonstrating the efficacy of angiotensin converting enzyme inhibitors (ACEI) in reducing mortality in patients with severe heart failure. A reduction in sympathetic activity and decreased adverse cardiac remodelling were believed to contribute to the beneficial effects of ACEI in heart failure, suggesting likely benefits for patients with heart failure following AMI. The AIRE study (named after the river running through the city of Leeds) evaluated the effect of early initiation of ACEI (ramipril) therapy on subsequent mortality in patients sustaining an AMI with clinical evidence of heart failure in a large multicentre, international prospective RCT. AIRE was the first RCT specifically designed to evaluate the efficacy of ACEI therapy on mortality and morbidity in this high-risk group of patients with AMI. Previously, investigators had been reluctant to adopt this strategy because of fears over a negative effect of ACEI therapy in high risk patients. The AIRE study demonstrated a significant reduction in post-AMI mortality in patients randomised to ramipril, reported in a series of high citation Lancet publications (**1, 2, 3**), providing vital evidence that the use of early and prolonged ACEI therapy improved outcomes; this has led to a global change in the clinical management of AMI.

In patients suffering an AMI the study randomly allocated patients with evidence of heart failure to placebo or ramipril. Two thousand and six patients were recruited across 14 countries and on a background of optimal therapy were prescribed placebo (982 patients), or 5 mg ramipril (1004 patients) twice per day. At an average follow-up of 15 months (minimum 6 months), there were 170 deaths (17%) in the ACEI group and 222 deaths (23%) in the placebo group, representing a relative risk reduction for all-cause mortality of 27% (95% CI 11-40%) (**1**). An evaluation of secondary (time to death or re-infarction, severe resistant heart failure or stroke) and tertiary (mode of death) outcomes, demonstrated that ACEI reduced sudden cardiac death by approximately 30% (95% CI 8-47%), which appeared to be largely attributable to a reduction in progressive heart failure (**4**). In an analysis of longer-term mortality in the UK cohort of AIRE, 3 years after cessation of study treatment (minimum follow-up period of 42 months), the relative risk reduction for long-term mortality in those randomised to ACEI was 34% [95% CI 11–51%], corresponding to an extra 114 patients surviving at 5 years per 1000 patients treated with ACEI for an average of 1 year

following AMI (**2**). A subsequent meta-analysis, including data from AIRE, confirmed that ACEI treatment in patients sustaining an AMI with LV dysfunction/heart failure reduced early and longer-term mortality, and reduced the composite endpoint of mortality or subsequent cardiovascular events (including recurrent AMI and readmission for heart failure), supporting the benefit of long-term ACEI in high-risk patients (**3**).

More recent work from Leeds (**Hall A** and **Gale** (Leeds Senior Lecturer 2007-, NIHR Clinician Scientist)) in the EMMACE-2 study (Evaluation of Methods and Management of Acute Coronary Events-2) examined outcomes in 2,499 unselected patients with acute coronary syndromes. Results of this study demonstrated that ACEI treatment is equally beneficial in patients with and without diabetes sustaining an AMI, which was not found to be the case for aspirin (**5)**.

3. References to the research

1. The Acute Infarction Ramipril Efficacy (AIRE) study investigators (including **Hall A**). Effect on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993; 342: 821-828.
The first study to show the beneficial effect of early ACEI treatment in patients sustaining an AMI with clinical evidence of heart failure.

2. **Hall AS**, Murray GD, Ball SG. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. *Lancet* 1997; 349:1493-97.
Research showing long-term beneficial effect of ACEI in patients sustaining an AMI with clinical evidence of heart failure.

3. Flather M, Yusuf S, Kober L, Pfeffer M, **Hall AS**, Murray G, Torp-Pedersen C, Ball S, Pogue J, Moye L, Braunwald E. Long term ACE-inhibitor therapy in patients with heart failure or left ventricular dysfunction: a systematic overview of data from individual patients. *Lancet* 2000; 355: 1575-81.
A systematic review confirming the important role of ACEI post AMI.

4. Cleland JGF, Erhardt L, Murray G, **Hall AS**, Ball SG. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure. A report from the AIRE Study Investigators. *European Heart Journal* 1997; 18:41-51.
Analysis of secondary and tertiary outcomes in AIRE demonstrating that ACEI reduced sudden cardiac death and progression of heart failure.

5. Cubbon RM, **Gale CP**, Rajwani A, Abbas A, Morrell C, Das R, Barth JH, Grant PJ, Kearney MT, **Hall AS**. Aspirin and mortality in patients with diabetes sustaining acute coronary syndrome. *Diabetes Care* 2008; 31: 363-5.
Data showing beneficial effect of ACEI in patients with and without diabetes sustaining an AMI.

4. Details of the impact

The AIRE study, which was conceived, designed and led by staff at Leeds, showed *for the first time* the benefits of early initiation of ACEI therapy for high-risk patients with clinical signs of heart failure after AMI. This and subsequent research has led to the global introduction of a simple and effective treatment, improving survival and quality of life for many thousands of patients.

Impact on health and welfare

For patients surviving AMI, the debilitating syndrome of heart failure secondary to left ventricular dysfunction is a common problem. The body's production of angiotensin after AMI acts initially as a protective mechanism to preserve blood pressure; however, prolonged angiotensin production causes cell death. It had been proposed that ACEI therapy would mitigate these effects but investigators were cautious about using the drugs in these high-risk patients. The AIRE study was

the first trial to show survival benefits of the ACEI ramipril in these patients. A long-term follow up study by Leeds of the trial's UK patients showed that these beneficial effects persisted years later.

The international adoption of the strategy of early ACEI after AMI has made it a fundamental part of routine treatment. In addition to significantly changing clinical practice, the use of this simple and cost effective treatment has contributed to the substantial decline in mortality associated with AMI seen over the last two decades. For instance, figures from the USA National Registry of Myocardial Infarction Investigators indicates that in-hospital mortality after an AMI fell by 24% from 1990 to 2006 [**A**]. This trend due to improved care for AMI, including the adoption of early secondary prevention such as ACEI treatment, is reflected in data from other countries around the world. In the UK, a study looking at trends in 3 year mortality in 3 month survivors of AMI in the UK, demonstrated that between 1991 and 2002 the use of ACEI increased from 11% to 71% and during the same period mortality fell by 28% [**B**]. More recent data from the UK Myocardial Ischaemia National Audit Project (covering England, Wales and Belfast) showed a continued increase in the prescription of ACEI, from just over 80% of patients with AMI in 2003 to 94% of patients with AMI in 2011/12 [**C,** figure 15]. In 2011/12 there were 79,433 individuals sustaining an AMI; in England, 95% of patients received ACEI treatment, Wales 90% and Belfast 98% [**C**; table 7]. At a UK population level there has been a year-on-year fall in the percentage of patients with AMI who die within 30 days of admission to hospital [**C**; figures 19 and 20]. The observed improvements in mortality are not solely attributable to use of ACEI; however, ACEI therapy is a fundamental element of modern treatment strategies for AMI [**D-F**]. The AIRE study has had major reach and significance, as evidenced by its recognition as one of the "Landmark Heart Failure Treatment Trials" [**D**] which made "a fundamental contribution to international clinical guidelines, implementation of which has delayed or prevented morbidity and death for millions of people worldwide." [**E**]. "Two decades later the results of this study still have a major impact on current guidelines underscoring that this study significantly changed treatment of cardiovascular high-risk patients." [**F**].

The importance of AIRE in contributing to the routine adoption of ACEI therapy in patients sustaining an AMI is evidenced by the continuing citation of this study in international clinical guidelines. The first recommendation for the routine adoption of ACEI therapy in patients with AMI who develop signs and symptoms of heart failure or who have reduced left ventricular ejection fraction, the protocol used in the AIRE study, was in the American College of Cardiology/ American Heart Association guidelines in 1996, which cited AIRE as supporting evidence. Since the publication of AIRE, ACEI use after AMI has become standard practice globally and is established as a class IA recommendation by, for instance, the American College of Cardiology Foundation/American Heart Association [**G**] and the European Society of Cardiology [**H**] guidelines for management of acute myocardial infarction. The AIRE Study is an underpinning reference for this therapeutic strategy in both guidelines. In the UK, the National Institute for Health and Care Excellence (NICE) recommendation for secondary prevention following AMI, published in 2007, has guided clinical practice during the current REF period and emphasised the prescription of ACEI as a key priority [**I**, page 10]. This guidance cites Leeds research on the efficacy of long term ACEI therapy as supporting clinical evidence for the recommendation that: "After an MI, all patients with preserved left ventricular function or with left ventricular systolic dysfunction should continue treatment with an ACE inhibitor indefinitely, whether or not they have symptoms of heart failure." [**I,** page 127]. Furthermore, cost effectiveness analysis based on AIRE contributed to the conclusion that long-term ACEI was cost effective in patients with and without left ventricular dysfunction [**I,** pages 145-151]. A partial update of these guidelines released in June 2013 for consultation continues to emphasise ACEI as a key priority in secondary prevention in patients with AMI and includes additional priority recommendations on correct dosing of ACEI in acknowledgement of their ongoing importance [**J**]. The updated guidance emphasises the importance of rapidly achieving the target dose, based on relevant clinical evidence, including AIRE, for specific ACEI (e.g. ramipril 10 mg/day, as per AIRE): "Titrate the ACE inhibitor dose upwards at short intervals (for example, every 12–24 hours) before the person leaves hospital until the maximum tolerated or target dose is reached. If this is not possible, this should be completed within 4–6 weeks of hospital discharge." [**J**].

5. Sources to corroborate the impact

[A] Rogers WJ, et al. Trends in presenting characteristics and hospital mortality among patients with ST-elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am. Heart J 2008; 156: 1026–34.

[B] Hardoon et al. Trends in longer-term survival following an acute myocardial infarction and prescribing of evidenced-based medications in primary care in the UK from 1991: a longitudinal population-based study. J Epidemiol Community Health. 2011 September; 65(9): 770–774.

[C] Myocardial Ischaemia National Audit Project (MINAP). How the NHS cares for patients with heart attack. Annual public report 2011/12.
http://www.ucl.ac.uk/nicor/audits/minap/publicreports/pdfs/2012minappublicreportv2.pdf

[D] Letter of corroboration from Professor of Heart Failure and Consultant Cardiologist, Heart Failure Unit, Kings College Hospital, London, UK, confirming the AIRE study's fundamental contribution to international clinical guidelines, implementation of which has delayed or prevented morbidity and death for millions of people worldwide.

[E] Letter of corroboration from Professor of Vascular Medicine, Service d'Hypertension et de Médecine Vasculaire, Hopital Européen Georges Pompidou, Paris, France, confirming the AIRE study's fundamental contribution to international clinical guidelines.

[F] Letter of corroboration from Professor of Medicine/Cardiology, Department of Internal Medicine I, University Hospital Aachen, Germany, confirming the lasting impact of the AIRE study on current guidelines.

[G] O'Gara et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;127:e362-e425.
Available from: http://circ.ahajournals.org/content/127/4/e362.full.pdf+html. ACE inhibitor recommendations and reference to AIRE (table 12, p e389; p e390; table 14, p e400; AIRE referenced p e412, references 421 and 430).

[H] Van de Werf F, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2008; 29: 2909-45.
Available from: http://eurheartj.oxfordjournals.org/content/29/23/2909.full.pdf+html. ACE inhibitor recommendations (table 15, p 2924; table 22, p 2933; AIRE referenced on p 2944, reference 213)

[I] The National Institute for Health and Clinical Excellence (NICE). MI: secondary prevention. Secondary prevention in primary and secondary care for patients following a myocardial infarction (CG48; 2007).
Available from: http://guidance.nice.org.uk/CG48/Guidance/pdf/English. ACE inhibitor recommendations (p 10; p 127); Cost effectiveness of ACE inhibitors in patients after MI with LV dysfunction including reference to AIRE (pp 145-151).

[J] The National Institute for Health and Clinical Excellence (NICE). Post myocardial infarction Secondary prevention in primary and secondary care for patients following a myocardial infarction. Partial update of NICE CG48: Methods, evidence and recommendations. June 2013 Available from: http://www.nice.org.uk/nicemedia/live/13502/64153/64153.pdf. Updated guidance on ACEI in section 7.3 (pp 219-318). AIRE cited in: table 49 (p 228); table 61 (p 269) and references to AIRE (reference numbers 16, 24, 123, 169, 365).