Institution: University of Glasgow

Unit of Assessment: Unit 1; Clinical Medicine

Title of case study: Transforming the treatment of atrial fibrillation

1. Summary of the impact

Atrial fibrillation (AF) is the most common chronic heart rhythm disorder, afflicting 1-2% of the total population and up to 10% of individuals aged over 70 years. There is an urgent need for safer and more effective therapies to prevent and treat AF. University of Glasgow researchers have played leading roles in studies that have identified strategies which prevent AF, improved the safety of AF therapies, and proved the clinical efficacy of a novel anticoagulant to reduce the risk of stroke (the major consequence of AF). The findings have rapidly informed recommendations in international guidelines, prompted regulatory amendments of AF therapies and changed prescribing practices. These advances will affect the estimated 12 million Europeans and Americans suffering from AF.

2. Underpinning research

University of Glasgow researchers were among the first to demonstrate the wider health consequences of AF, including risk of heart failure and death, over the long-term using the unrivalled, locally recruited Glasgow Renfrew/Paisley epidemiological study (15,399 middle-aged individuals with 20 year follow-up, MIDSPAN; Stewart *et al.* 2002, *Am J Med*). They went on to describe the economic cost of AF and assess treatments that may prevent the onset of new AF, evaluating the best-treatment of patients with the clinically complex combination of AF and heart failure. They have proved the superiority of a new anticoagulant to prevent stroke in patients with AF and evaluated the best way to diagnose AF in patients presenting with a stroke (where AF may be transient and accurate diagnosis is critical in ensuring prompt anticoagulation therapy).

Treatments that may prevent the onset of new AF: AF is particularly dangerous in heart failure and after a heart attack (myocardial infarction, MI), causing symptomatic worsening, increased risk of hospitalisation, greatly increased risk of stroke and higher mortality. Professors Henry Dargie, Ian Ford and John McMurray showed that the beta-blocker carvedilol reduced the risk of developing arrhythmias, including AF, by 59% in patients with reduced heart (left ventricular, LV) function after MI (CAPRICORN 2005).[1] McMurray was one of the leaders of two studies in heart failure which showed that the angiotensin-receptor blocker (ARB) candesartan and mineralocorticoid-receptor antagonist (MRA) eplerenone reduce the risk of new onset AF by 19% and 42%, respectively (CHARM 2006[2]; EMPHASIS-HF 2012).

Management of AF in patients with heart failure: In a Glasgow-led study published in 2003, Professors John Cleland and Andrew Rankin showed that the combination of a beta-blocker and digoxin provided enhanced control of heart rate and an associated improvement in LV function (heart pumping function) and symptoms compared with the traditional treatment of digoxin alone.[3] A 2011 Glasgow-led study (McMurray and Dr Mark Petrie) showed that radio-frequency ablation was neither effective nor safe in restoring normal rhythm in patients with AF and heart failure – the rate of serious complications was 15% and the procedure was successful in just 50% of patients.[4] McMurray was a lead investigator of a trial (ANDROMEDA) of a new antiarrhythmic drug, dronedarone, which it was hoped would be a safe and effective treatment in patients with AF and heart failure. The study recruited 627 patients with advanced heart failure (New York Heart Association [NYHA] functional class III or IV) plus AF (or at very high risk of developing AF) who were randomised to receive dronedarone or placebo. The trial was stopped early after just 2 months of follow-up due to a doubling of mortality in the patients receiving dronedarone.[5]

New oral anticoagulants to effectively and safely prevent stroke in AF: Vitamin K antagonists (VKAs) such as warfarin have been the mainstay of anticoagulant treatment for 40 years to reduce the risk of stroke in AF patients. However, VKAs have many limitations, particularly an unreliable therapeutic effect resulting from food and drug interactions, placing the patient at risk of bleeding when over-anticoagulated and without stroke protection when under-anticoagulated. McMurray was one of the leaders of the multi-centre ARISTOTLE trial which randomised 18,201 men and women with AF plus one additional risk factor for stroke to the new oral anticoagulant (NOAC)

apixaban or warfarin. The trial results, published in 2011 showed that apixaban was significantly more effective (risk of stroke and death from any cause were reduced by 21% and 11%, respectively) and safer (31% reduction in serious bleeding) than warfarin.[6]

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); Mark Petrie (Honorary Reader, 2009-present). ***Positions in large multi-centre trials:*** CAPRICORN: Dargie, Chairman of steering committee, Ford, steering committee member, McMurray, endpoint committee Chair. ARISTOTLE: McMurray, executive committee member. CHARM trial series: McMurray, executive committee member. EMPHASIS-HF: McMurray, executive steering committee member. ANDROMEDA: McMurray, steering committee member ***External collaborators****:* Members of trial committees; see original articles for details.

3. References to the research

1. McMurray J *et al*. Antiarrhythmic effect of carvedilol after acute myocardial infarction: results of the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial. *J Am Coll Cardiol* 2005; 45: 525–530 doi:10.1016/j.jacc.2004.09.076.
2. Ducharme A *et al*. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: assessment of Reduction in Mortality and morbidity (CHARM) program. *Am Heart J* 2006; 151: 985–991 doi:10.1016/j.ahj.2005.06.036.
3. Khand AU *et al*. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol* 2003; 42: 1944–1951 doi:10.1016/j.jacc.2003.07.020.
4. MacDonald MR *et al*. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart* 2011; 97: 740–747 doi:10.1136/hrt.2010.207340.
5. Køber L *et al*. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008; 358: 2678–2687 doi:10.1056/NEJMoa0800456.
6. Granger CB *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365: 981–992 doi:10.1056/NEJMoa1107039.

4. Details of the impact

AF is an enormous and growing medical problem. AF accounts for 1 in 5 of all strokes, and doubles an individual's risk of both heart failure and premature death. The cost of AF to the NHS in 2000 was conservatively estimated to be £459 million (approximately 1% of NHS expenditure) with an additional £111 million in nursing home costs. Consequently, the treatment of AF is an NHS health priority. AF treatment strategies focus on rhythm control (with antiarrhythmic drugs or interventions that are safe) and thromboembolism prophylaxis with anticoagulant drugs to prevent stroke (ideally maximising effectiveness and minimising risk of bleeding). University of Glasgow research has had an overwhelming influence in the prevention and treatment of AF.

Impact on international and national clinical guidelines: Key University of Glasgow studies[1–6] have contributed to the evidence-base for recommendations made by the European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF) and American Heart Association (AHA), the world's most influential cardiovascular societies with estimated professional memberships of 30,000, 43,000 and 73,000, respectively. The ESC, ACCF/AHA and Heart Rhythm Society (HRS) guidelines, as well as Australian and Canadian Cardiovascular Society (CCS) guidelines on the management of AF and heart failure (published since 2008) make the following high level recommendations based on key trials led or co-led by University of Glasgow investigators as follows:

- The use of beta-blockers, ARBs and MRAs for prevention of new onset AF (primary prevention) in patients with heart failure (ESC AF 2010[a], ACCF/AHA/HRS 2011[b], ESC AHT 2013[c]) based on findings from CAPRICORN[1], CHARM[2] and EMPHASIS-HF.
- The use of beta-blockers as first-line therapy to control ventricular rate in patients with AF,

heart failure and low LV ejection fraction (LVEF). The addition of a digoxin where monotherapy is inadequate to control the rapid heart rate in patients with AF and heart failure (ESC AF 2010[a], ACCF/AHA/HRS 2011[b]) based on findings from Khand *et al.*[3]

- The contraindication of dronedarone for the treatment of AF in patients with advanced heart failure (NYHA class III-IV) or with recently unstable (decompensated within the last month) HF (ESC AF 2010[a], ESC AF 2012[d], ESC HF 2012[e], ACCF/AHA/HRS 2011[f]/2013[g], Australia and New Zealand 2011[h], CCS 2012[i]) based on findings from ANDROMEDA[5]
- The use of apixaban (as one of three NOACs) in all AF patients at high risk of stroke; and furthermore, due to the superior safety profile of apixaban (versus warfarin), the use of apixaban (as one of three NOACs) is recommended in AF patients at lower, intermediate risk of stroke(ESC AF 2012[d], CCS 2012[f]) – recommendations based on findings from ARISTOTLE[6]

The University of Glasgow led-study by MacDonald *et al.*[4] has also been prominently cited in the leading European guidelines in the on-going controversy surrounding the use of radio-frequency ablation to treat AF. The University of Glasgow findings have exerted considerable caution within the clinical community that this complex, invasive and expensive new procedure has limited effectiveness and safety in patients with AF and HF (EHRA/HRS 2012[j], ESC HF 2012[e]).

Dissemination and implementation of guideline recommendations: The major international guideline societies have a robust strategy for disseminating guidelines. In 2012, the ESC guideline on AF (2010[a]) was downloaded 75,151 times and its 2012 focused update[d] 40,810. Up to 31 July 2013, these numbers were 25,554 and 39,385, respectively.[k] Pocket versions and foreign (non-English) language versions have been produced and widely disseminated.

Regulatory approval and guidance

Conducting well-designed randomised controlled trials to determine whether medications are safe and effective is the cornerstone of gaining regulatory and healthcare provider approval for their use in patients, as well as ensuring that treatments are targeted to the most appropriate populations.

ARISTOTLE underpins regulatory approval of apixaban

ARISTOTLE[6] was a landmark trial because it demonstrated conclusively that apixaban was both safer and more effective than the gold standard (warfarin), causing less bleeding, preventing more strokes and reducing the risk of death. As warfarin reduces stroke risk by 60–70%, these remarkable research findings constitute the only major breakthrough in anticoagulant therapy in over 40 years of investigation. Consequently, ARISTOTLE was pivotal in gaining marketing authorisation for apixaban from the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).

Apixaban (brand name, Eliquis) was originally approved by the EMA in May 2011 for the prevention of venous thromboembolism following orthopaedic surgery. The findings of ARISTOTLE prompted the manufacturers of this drug (Bristol-Myers Squibb and Pfizer) to apply for an extension to the original indication. In September 2012, the EMA Committee for Medicinal Products for Human Use (CHMP) approved apixaban (2.5 mg and 5 mg) for "*prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors.*"[l] In the accompanying assessment report, ARISTOTLE (study 'CV185030') was extensively cited as one of two key studies in the supporting evidence for clinical efficacy and safety.[l] FDA approval of apixaban for use in AF followed in December 2012, with ARISTOTLE also underpinning this licence application.[m] European and US regulatory approval of apixaban was widely reported by major international media outlets, including the *New York Times*, *Forbes* and *PharmaTimes*, highlighting the pivotal role of ARISTOTLE in gaining these marketing licences.[n]

ARISTOTLE prompts NHS funded prescribing of apixaban

Treatment of AF to prevent stroke is a NHS National Priority Project in primary care. The UK National Institute for Health and Care Excellence (NICE) technology appraisals provide guidance on whether new therapeutic options should be funded within the NHS, focusing on value for money by weighing up costs and benefits. The findings of ARISTOTLE[6] prompted NICE to approve apixaban as a cost-effective therapy for preventing stroke among patients with AF (NICE technology appraisal TA275; February 2013).[o] ARISTOLE was the sole randomised controlled trial

of apixaban to meet the inclusion criteria for TA275. An economic model showed an incremental cost-effectiveness ratio (ICER, used to evaluate the cost impact of medical interventions) of £12,757 per quality adjusted life-year (QALY, an indicator of improved health) for apixaban versus warfarin. The approval by NICE was reported by various media outlets.[p] Therefore, through their key involvement in ARISTOTLE, University of Glasgow researchers have directly influenced the expansion of NHS-funded treatment for AF patients.

ANDROMEDA highlights need to restrict use of dronedarone
The ANDROMEDA[5] trial highlighted a potential danger of the antiarrhythmic drug dronedarone among patients with heart failure. This finding led NICE to restrict use of dronedarone within the NHS in December 2012.[q] NICE recommended that "*dronedarone should not be used in people with unstable NYHA class III or IV heart failure and to refer to the recommendation in the SPC about the use of dronedarone in people with LVEF less than 35%.*" The NICE contraindication followed similar warnings from the EMA and FDA.

Changes in prescribing trends for AF – patients receive NOACs
Regulatory approval and incorporation into clinical guidelines have led to rapid uptake of NOACs including apixaban. The superior safety profile of NOACs has also supported their use in AF patients at lower risk of stroke, a group previously considered unsuitable for anticoagulation with warfarin. As a result, these new drugs are already being prescribed to 6–12% of eligible patients in Europe and the USA.[r,s] Conversely, prescription of dronedarone is decreasing, particularly among patients with heart failure (4% prescription rate in Europe).[s] Underuse of anticoagulation therapy is a recognised problem in the NHS. However, the availability of NOACs should now increase the proportion of patients receiving treatment that is both more effective and safe than warfarin and, in turn, drive a large public-health benefit in terms of stroke reduction.

5. Sources to corroborate the impact

a. ESC guidelines for the management of AF, 2010 (Khand *et al.* Ref 171 p2415, ANDROMEDA Ref 117 p2405, CHARM Ref 149 p2414)
b. ACCF/AHA/HRS focused updates incorporated, 2011 (Khand *et al.* Ref 754, p162, CAPRICORN Ref 858 p168, CHARM Ref 898 p171)
c. ESC guideline for the management of arterial hypertension, 2013 (EMPHASIS-HF Ref 578 p44)
d. ESC guidelines focused update management of AF, 2012 (ARISTOTLE Ref 4, p2726/2729)
e. ESC Guidelines for the diagnosis and treatment of heart failure, 2012 (ANDROMEDA Ref 176 p33, MacDonald *et al.* Ref 175 p32)
f. ACCF/AHA/HRS Focussed update on the management of patients with AF, 2011 (ANDROMEDA Ref 30, p110)
g. ACCF/AHA task Force on Practice Guidelines – management of patients with AF, 2013 (ANDROMEDA p1920)
h. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand guideline update, 2011. (ANDROMEDA Ref 21 p406)
i. Canadian Cardiovascular Society atrial fibrillation guidelines focused update, 2012 (ARISTOTLE Ref 20, p128-130, ANDROMEDA Ref 54 p133)
j. EHRA/HRS consensus statement on CRT, 2012 (MacDonald *et al.* Ref 323 p1267)
k. Download data for 2010 and 2012 ESC AF guidelines are available on request.
l. EMA approval of apixaban for AF, 2012: CHMP statement and EMA assessment report. ARISTOTLE [study CV185030] cited throughout, specific page numbers available on request.
m. FDA approval of apixaban for AF, 2012: press release
n. Media coverage of apixaban approval for AF, 2012: Forbes, New York Times, PharmaTimes
o. NICE recommendation on apixaban for AF (TA275), 2013 (p14/1725–26)
p. Media coverage of NICE TA275 on apixaban, 2013: PharmaTimes, Telegraph, Reuters
q. NICE recommendation on restricted use of dronedarone for AF (TA197), 2012 (p4/9/22/26-27)
r. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC guidelines on atrial fibrillation: primary results of PREFER in AF) (data for 2012–2013)
s. PINNACLE-AF registry shows early patterns for new atrial fibrillation treatments (data for 2011)